Synjardy

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
PSUSA/10388 /202404	Periodic Safety Update EU Single assessment - empagliflozin, empagliflozin / metformin	12/12/2024	07/02/2025	SmPC	• In view of available data on the risk of "necrotizing fasciitis of the perineum (Fournier´s gangrene)" from the literature and spontaneous reports of Fournier´s gangrene reported in non-diabetic population and in view of a plausible mechanism of action, the PRAC considers that there is sufficient evidence to justify an amendment of the

[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).

					product information in order to indicate that this ADR can occur irrespective of the indication. The PRAC concluded that the product information of products containing empagliflozin should be amended accordingly. • In view of the available data on phimosis from spontaneous reports and the plausible mechanism of action, PRAC considers there is sufficient evidence to justify an amendment of the product information to hightlight that genital infections may result in phimosis that can require circumcision. The PRAC concluded that the product information of products containing empagliflozin should be amended accordingly. • In view of the available data on haematocrit increased/polycythaemia from the literature and spontaneous reports and the plausible mechanism of action, the PRAC considers there is sufficient evidence to justify an amendment of section 4.4 of the SmPC to reflect that patients with pronounced elevations in haematocrit should be monitored and investigated for underlying haematological disease. The PRAC concluded that the product information of products containing empagliflozin should be amended accordingly. • In view of the available data on prolonged ketoacidosis and prolonged glucosuria from the literature and spontaneous reports, the PRAC considers there is sufficient evidence to justify an amendment of section 4.4 of the SmPC related to the warning on ketoacidosis to indicate that ketoacidosis may be prolonged after discontinuation of empagliflozin in some patients. The PRAC concluded that the product information of products

					containing empagliflozin should be amended accordingly.
WS/2713	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	28/11/2024	n/a		
II/0078	Extension of indication to include the treatment of children aged 10 years and above with type 2 diabetes for Synjardy, based on the final results from study 1218-0091 (DINAMO) - A double-blind, randomised, placebo-controlled, parallel group trial to evaluate the efficacy and safety of empagliflozin and linagliptin over 26 weeks, with a double-blind active treatment safety extension period up to 52 weeks, in children and adolescents with type 2 diabetes mellitus. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 16.1 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	19/09/2024	04/11/2024	SmPC and PL	Please refer to Scientific Discussion "h-3770-II-78-en"
IB/0081/G	This was an application for a group of variations.	21/08/2024	n/a		

	B.II.z - Quality change - Finished product - Other variation B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation				
N/0079	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	29/07/2024	04/11/2024	PL	
WS/2571	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	13/06/2024	n/a		
IG/1700/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.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	16/01/2024	n/a		
WS/2567	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	05/10/2023	n/a		

	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation				
IB/0074	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	13/09/2023	n/a		
WS/2450/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. Update of sections 4.2, 4.4 and 5.1 of the SmPC in order to modify administration instructions to the elderly, amend an existing warning for the elderly and remove the warning for 'Cardiac Failure' in order to align with the Jardiance Product Information; the Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. Update of section 4.4 of the SmPC in order to introduce a rewording related to use in patients with type 1 diabetes in order to align with the Jardiance Product Information; the Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	20/07/2023	30/08/2023	SmPC and PL	This variation concerned the alignment of Glyxambi and Synjardi's SmPC and Package Leaflet with that of Jardiance's, following the approval of Jardiance in the treatment of heart failure. This indication was based on the submission of data from trials EMPEROR-Preserved and EMPEROR-Reduced trial, in which most patients were elderly (≥65 years old). After the completion of both EMPEROR trials, where 483 patients aged 85 years and older were included, it has been agreed that the information on the use of empaglifozin in elderly patients is no longer limited. For more information, please refer to the Summary of Product Characteristics.

IA/0073	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)	14/07/2023	n/a		
WS/2492	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	15/06/2023	n/a		
IG/1617	B.I.a.1.i - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a new site of micronisation	01/06/2023	n/a		
WS/2410	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	16/03/2023	n/a		
WS/2377	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 and 4.8 of the SmPC in order to add a new warning on Vitamin B12 decrease or	02/03/2023	30/08/2023	SmPC and PL	

	deficiency and to update the list of adverse drug reactions (ADRs) in accordance with the recent update of the PI for Glucophage, which is the reference label for the compound metformin, and following the request by MHRA on 20 June 2022 for all products containing metformin; the Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI and to update the list of local representatives in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
WS/2406	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	09/02/2023	n/a		
PSUSA/10388 /202204	Periodic Safety Update EU Single assessment - empagliflozin, empagliflozin / metformin	01/12/2022	n/a		PRAC Recommendation - maintenance
IB/0066/G	This was an application for a group of variations. B.II.d.1.g - Change in the specification parameters and/or limits of the finished product - Addition or replacement (excluding biological or immunological product) of a specification parameter wit its	23/11/2022	n/a		

	corresponding test method as a result of a safety or quality issue 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.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) 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.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.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				
WS/2196	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	10/06/2022	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'; '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	24/03/2022	23/01/2023	SmPC and PL	

	(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				
PSUSA/10388 /202104	Periodic Safety Update EU Single assessment - empagliflozin, empagliflozin / metformin	16/12/2021	04/03/2022	SmPC and PL	Taking into account the PRAC Assessment Report on the PSUR(s) for empagliflozin, empagliflozin / metformin, the scientific conclusions of CHMP are as follows: In view of available data on tubulointerstitial nephritis from the literature and spontaneous reports highly suggestive of causality association including a close temporal relationship and a positive dechallenge, the PRAC considers a causal relationship between empagliflozin, empagliflozin/metformin and tubulointerstitial nephritis is at least a reasonable possibility. The PRAC concluded that the product information of products containing empagliflozin, empagliflozin/metformin should be amended accordingly. In view of available data on the drug-drug interaction between empagliflozin and lithium from clinical trials and the literature suggestive for causal association, including in some cases a close temporal relationship and positive dechallenge/rechallenge and in view of a plausible mechanism of interaction, the PRAC considers a causal relationship between empagliflozin, empagliflozin /

					metformin and drug-drug interaction with lithium is at least a reasonable possibility. The PRAC concluded that the product information of products containing empagliflozin, empagliflozin / metformin should be amended accordingly. The CHMP agrees with the scientific conclusions made by the PRAC.
IB/0063/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. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	10/02/2022	23/01/2023	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 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.
IAIN/0061/G	This was an application for a group of variations. 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.7 - Administrative change - Deletion of	10/12/2021	04/03/2022	Annex II and PL	

	manufacturing sites B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site A.7 - Administrative change - Deletion of manufacturing sites A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release 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				
N/0056	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	31/03/2021	04/06/2021	PL	
IB/0053/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	05/02/2021	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		

IA/0054	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	08/01/2021	n/a		
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 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	19/10/2020	n/a		
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,	04/09/2020	04/06/2021	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

	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				of Product Characteristics.
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	04/06/2021	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.
IB/0051/G	This was an application for a group of variations. 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 the AS -replacement or addition of a site where	28/05/2020	04/06/2021	Annex II and PL	

	batch control/testing takes place 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.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				
IA/0050	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	05/05/2020	n/a		

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		
R/0044	Renewal of the marketing authorisation.	30/01/2020	01/04/2020	SmPC and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Synjardy in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
IG/1221	B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	13/03/2020	n/a		
IAIN/0045	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	22/11/2019	01/04/2020	SmPC	
PSUSA/10388 /201904	Periodic Safety Update EU Single assessment - empagliflozin, empagliflozin / metformin	31/10/2019	n/a		PRAC Recommendation - maintenance
WS/1626/G	This was an application for a group of variations following a worksharing procedure according to	25/07/2019	n/a		

	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				
IA/0041/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 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	07/06/2019	n/a		
IB/0039	B.I.d.1.a.1 - Stability of AS - Change in the re-test period/storage period - Reduction	29/05/2019	n/a		
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	28/03/2019	n/a		

	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				
IAIN/0038	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	22/02/2019	06/06/2019	SmPC and PL	
PSUSA/10388 /201804	Periodic Safety Update EU Single assessment - empagliflozin, empagliflozin / metformin	31/10/2018	n/a		PRAC Recommendation - maintenance
IG/0991	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	04/10/2018	n/a		
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.	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).

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				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.
IB/0033	B.III.1.a.3 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - New certificate from a new manufacturer (replacement or addition)	11/04/2018	n/a		
PSUSA/10388 /201704	Periodic Safety Update EU Single assessment - empagliflozin, empagliflozin / metformin	09/11/2017	08/01/2018	SmPC	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10388/201610.
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		
PSUSA/10388 /201610	Periodic Safety Update EU Single assessment - empagliflozin, empagliflozin / metformin	18/05/2017	19/07/2017	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for

					PSUSA/10388/201610.
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		
IA/0029/G	This was an application for a group of variations. 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.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	04/07/2017	n/a		
WS/1171	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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	22/06/2017	08/01/2018	SmPC and PL	

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	08/01/2018	SmPC	
A20/0022	Pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested on 15 April 2016 the PRAC to assess the impact on the benefit-risk balance of canagliflozin containing medicinal products of an increase in amputations, mostly affecting the toes, observed in an ongoing clinical trial (CANVAS) for canagliflozin and a numerical imbalance with regards to amputation events seen in an ongoing renal study CANVAS-R with a similar population as CANVAS. Considering that a class effect cannot be excluded, the European Commission extended on 6 July 2016 the scope of the procedure to include all SGLT2 inhibitors containing medicinal products to allow a review of data from the class. The PRAC was requested to assess the impact thereof on the benefit-risk balance of Invokana, Vokanamet, Forxiga, Edistride, Xigduo, Ebymect, Jardiance and Synjardy and to give its recommendation whether the marketing authorisation of these products should be maintained, varied, suspended or revoked. As the request results from the evaluation of data resulting from pharmacovigilance activities, the	09/02/2017	20/04/2017	SmPC and PL	Please refer to the assessment report: SGLT2 inhibitors - EMEA/H/A-20/1442

	CHMP opinion has been be adopted on the basis of a recommendation of the Pharmacovigilance Risk Assessment Committee.				
II/0015	Modification of the indication for Synjardy to reflect new data on cardiovascular outcomes based on study 1245.25 (EMPA-REG OUTCOME). As a consequence the SmPC sections 4.1, 4.2, 4.4, 4.8, 5.1 have been updated. The Package Leaflet and RMP have been updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to make some editorial changes. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	26/01/2017	03/03/2017	SmPC and PL	Please refer to the Scientific Discussion Synjardy H-C-3770-II-15.
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	19/01/2017	n/a		

	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 the AS -replacement or addition of a site where batch control/testing takes place				
WS/0971	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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		
WS/0953	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.a - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of wording agreed by the competent authority	15/12/2016	n/a		
A31/0013	Pursuant to Article 31 of Regulation (EC) No 726/2004, the European Commission requested on 25 January 2016 the opinion of the European Medicines Agency on the adequacy of the current recommendations for metformin containing products with respect to the use in patients with moderate renal failure, taking into account the available information on the risk of lactic acidosis. The CHMP	13/10/2016	12/12/2016	SmPC and PL	Please refer to the assessment report: Metformin containing medicinal products - EMEA/H/A-31/1432

	was requested to assess the impact thereof on the benefit-risk balance of metformin containing products and to give its recommendation whether the marketing authorisation of this product should be maintained, varied, suspended or revoked. The notification for the procedure is appended to this opinion.				
WS/0926	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 4.8 and 5.1 of the SmPC in order to include data from the study 1275.9. In addition, the Worksharing applicant (WSA) took the opportunity to remove optional sentence 'Medicinal product subject to medical prescription' from the Labelling. Moreover, the updated RMP version 8.1 (for Jardiance) and version 6.1 (for Synjardy) have been agreed, as part of this procedure. Furthermore, the WSA took the opportunity to bring the Labelling in line with the latest QRD template version 10. In addition, only for Synjardy, the WSA took the opportunity to make a minor editorial correction in section 4.8 of the SmPC in line with the outcome of EMEA/H/C/PSUSA/00010388/201510 procedure. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	10/11/2016	03/03/2017	SmPC and Labelling	In patients inadequately controlled with metformin and linagliptin 5 mg, treatment with both empagliflozin 10 mg or 25 mg resulted in statistically significant ($p<0.0001$) reductions in HbA1c and body weight compared to placebo. In addition it resulted in clinically meaningful reductions in FPG, systolic and diastolic blood pressure compared to placebo. In a prespecified subgroup of patients with baseline HbA1c greater or equal than 8.5% the reduction from baseline in HbA1c was -1.3% with empagliflozin 10 mg or 25 mg at 24 weeks ($p<0.0001$) compared to placebo. The incidence of hypoglycaemia (overall, minor, major) for empagliflozin as add-on to linagliptin and metformin was similar to that in combinations of empagliflozin with other anti-diabetic medicines.

PSUSA/10388 /201604	Periodic Safety Update EU Single assessment - empagliflozin, empagliflozin / metformin	27/10/2016	n/a		PRAC Recommendation - maintenance
IB/0023	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	10/10/2016	n/a		
WS/0939	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 4.8 and 5.1 of the SmPC in order to include data from study 1276.1 ('A 24-week phase III randomized, double-blind, parallel group study to evaluate the efficacy and safety of twice daily oral administration of empagliflozin + metformin compared with the individual components of empagliflozin or metformin in drug naive patients with type 2 diabetes mellitus'). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	21/07/2016	12/12/2016	SmPC	A factorial design study of 24 weeks duration was conducted to evaluate the efficacy and safety of empagliflozin in drug-naïve patients. Treatment with empagliflozin in combination with metformin (5 mg and 500 mg; 5 mg and 1000 mg; 12.5 mg and 500 mg, and 12.5 mg and 1000 mg given twice daily) provided statistically significant improvements in HbA1c and led to greater reductions in FPG (compared to the individual components) and body weight (compared to metformin). The frequency of patients with hypoglycaemic events (overall, minor or major hypoglycaemia) was similar for empagliflozin and placebo as add on to metformin, and for the combination of empagliflozin with metformin in drug-naïve patients compared to those treated with empagliflozin and metformin as individual components.
PSUSA/10388 /201510	Periodic Safety Update EU Single assessment - empagliflozin, empagliflozin / metformin	26/05/2016	15/07/2016	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10388/201510.
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	25/05/2016	n/a		

	manufacturer of a novel excipient				
A20/0001	Pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested on 10 June 2015 the opinion of the European Medicines Agency on the risk of Diabetic ketoacidosis (DKA) in patients treated with sodium-glucose co-transporter 2 (SGLT2) inhibitors and requested the Agency to assess the impact thereof on the benefit-risk balance of canagliflozin-containing medicinal products (Invokana and Vokanamet), dapagliflozin-containing medicinal products (Forxiga and Xigduo), and empagliflozin-containing medicinal products (Jardiance and Synjardy) and to issue a recommendation on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked. As the request results from the evaluation of data resulting from pharmacovigilance activities, the CHMP opinion should be adopted on the basis of a recommendation of the Pharmacovigilance Risk Assessment Committee. The notification for the procedure is appended to this recommendation.	25/02/2016	28/04/2016	SmPC and PL	Please refer to the assessment report: SGLT2 inhibitors - EMEA/H/A-20/1419
IA/0014	B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	17/02/2016	n/a		

IB/0011/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 B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation 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	07/01/2016	28/04/2016	Annex II and PL	
IB/0010	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	11/12/2015	n/a		

	data				
IB/0009/G	This was an application for a group of variations. 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 B.I.a.1.i - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a new site of micronisation 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.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	19/11/2015	n/a		

	or addition) for the AS or a starting material/intermediate				
WS/0801	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 5.3 and 4.6 of the SmPC in order to update renal development and maturation information after analysis of the non-clinical study 14R018 [n00231757]; in addition, the Worksharing applicant (WSA) took the opportunity to correct minor mistakes in section 5.1 of the SmPC and minor linguistic mistakes in the Spanish product information for Jardiance and in the Finnish, Spanish and Danish product information for Synjardy. The list of local representatives for Spain and Portugal in the Package Leaflet for Jardiance has been updated and the PIs have been brought in line with the latest QRD template version 9.1 for both products. The RMPs have been updated accordingly (final versions Jardiance v.5.1, Synjardy version 3.1). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	22/10/2015	28/04/2016	SmPC, Annex II, Labelling and PL	In a juvenile toxicity study in the rat, when empagliflozin was administered from postnatal day 21 until postnatal day 90, non-adverse, minimal to mild renal tubular and pelvic dilation in juvenile rats was seen only at 100 mg/kg/day, which approximates 11 times the maximum clinical dose of 25 mg. These findings were absent after a 13 weeks drug free recovery period.
WS/0800	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 4.3, 4.4 and 4.5 of the SmPC in	22/10/2015	28/04/2016	SmPC, Annex II and PL	Lactic acidosis is a very rare, but serious (high mortality in the absence of prompt treatment), metabolic complication that can occur due to metformin accumulation. Reported cases of lactic acidosis in patients on metformin have occurred primarily in diabetic patients with significant renal

	order to align the SmPC for Jentadueto and Synjardy to the safety information for the UK metformin label (Glucophage) with regard to tissue hypoxia, lactic acidosis, compromised cardiac or renal function and administration of iodinated contrast agents. In addition, the Worksharing applicant (WSA) took the opportunity to update the list of local representatives for Spain and Portugal in the Package Leaflet for Jentadueto and to bring the PI of Jentadueto in line with the latest QRD template version 9.1. The RMPs (version 3.0 for Synjardy and version 11.0 for Jentadueto) for both products have been updated according to the SmPC changes. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				failure or acute worsening of renal function. Special caution should be paid to situations where renal function may become impaired, for example in case of dehydration (severe diarrhoea or vomiting), or when initiating antihypertensive therapy or diuretic therapy and when starting therapy with a non-steroidal anti-inflammatory drug (NSAID). In the acute conditions listed, metformin should be temporarily discontinued. The intravascular administration of iodinated contrast materials in radiologic studies can lead to renal failure. This may induce metformin accumulation and may increase the risk for lactic acidosis. Therefore, this medicinal product must be discontinued prior to, or at the time of the test and not be reinstituted until at least 48 hours afterwards, and only after renal function has been re-evaluated and has not deteriorated further. Other associated risk factors should be considered to avoid lactic acidosis such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic impairment and any condition associated with hypoxia (such as decompensated cardiac failure, acute myocardial infarction). Patients with heart failure are more at risk of hypoxia and renal insufficiency. In patients with stable chronic heart failure, the combination with metformin may be used with a regular monitoring of cardiac and renal function. For patients with acute and unstable heart failure, the combination is contraindicated due to the metformin component. The risk of lactic acidosis must be considered in the event of non-specific signs such as muscle cramps, digestive disorders as abdominal pain and severe asthenia. Patients

					should be instructed to notify these signs immediately to their physicians if they occur, notably if patients had a good tolerance to the combination including metformin before. The combination should be discontinued, at least temporarily, until the situation is clarified. Reintroduction of the combination should then be discussed taking into account the benefit/risk ratio in an individual basis as well as renal function. In case of lactic acidosis, the patient should be hospitalised immediately. Physicians should alert the patients on the risk and on the symptoms of lactic acidosis.
IAIN/0008/G	This was an application for a group of variations. B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	16/10/2015	28/04/2016	SmPC, Labelling and PL	
IAIN/0007	B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	16/10/2015	28/04/2016	SmPC, Labelling and PL	

IB/0003	B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	23/07/2015	n/a		
IB/0002/G	This was an application for a group of variations. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	22/07/2015	n/a		