Jardiance

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/0042	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	22/02/2019		SmPC and PL	
R/0040	Renewal of the marketing authorisation.	13/12/2018	14/02/2019	SmPC, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Jardiance in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

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

PSUSA/10388 /201804	Periodic Safety Update EU Single assessment - empagliflozin, empagliflozin / metformin	31/10/2018	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	14/02/2019	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/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	30/11/2017	n/a		

	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				
IB/0036/G	This was an application for a group of variations. 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.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.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 B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	27/11/2017	n/a		
IA/0035	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	03/08/2017	n/a		

	control/testing takes place				
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		
II/0026	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	22/06/2017	n/a		Comparison between refeeding with glucose or fat" in non-diabetic rats showed that treatment with empagliflozin resulted in a modest and transient burst of ketone in the blood according to the fat contained in the diet at re-feeding, after a fasting period. These findings in animals did not warrant changes to the SmPC.
II/0025	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	22/06/2017	n/a		Study 1245.22 is a non-interventional drug utilisation study to assess the characteristics of patients initiating empagliflozin treatment and evaluate the potential off-label use. In the study period of over 1 year, all empagliflozin initiators were older than 18 years and had at least 1 diagnostic code for diabetes mellitus. No use of empagliflozin was observed during pregnancy or breast-feeding. Overall, the use of empagliflozin was in accordance with the approved indication, only 1 case of off-label use in Type 1 diabetes mellitus was detected. Results from this study did not warrant amendments to the approved 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	08/01/2018	SmPC	
IA/0031	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	28/04/2017	19/07/2017	SmPC	
A20/0023	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.	09/02/2017	20/04/2017	SmPC and PL	Please refer to the assessment report: SGLT2 inhibitors - EMEA/H/A-20/1442

	As the request results from the evaluation of data resulting from pharmacovigilance activities, the CHMP opinion has been be adopted on the basis of a recommendation of the Pharmacovigilance Risk Assessment Committee.				
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 the AS -replacement or addition of a site where batch control/testing takes place	19/01/2017	n/a		
II/0014	Update of section 4.1, 4.4, 4.8 and 5.1 of the SmPC to reflect new data on cardiovascular outcomes, based on the final study report of the phase III clinical trial EMPA-REG OUTCOME. The Package Leaflet and RMP	15/12/2016	19/01/2017	SmPC and PL	Please refer to the published assessment report Jardiance H-C- 2677-II-14: EPAR - Assessment Report – Variation

	have been updated accordingly. The MAH took the opportunity to make some editorial changes and bring the PI in line with the latest QRD template. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IA/0029	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	16/01/2017	n/a		
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		
WS/0926	This was an application for a variation following a worksharing procedure according to Article 20 of	10/11/2016	19/01/2017	SmPC and	In patients inadequately controlled with metformin and linagliptin 5 mg, treatment with both empagliflozin 10 mg or

	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			Labelling	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
II/0021	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	15/09/2016	19/01/2017	SmPC	Results from the study 1245.31 (extension study of the pivotal Phase III studies 1245.20, 1245.23 and 1245.19 part of the initial submission package for empagliflozin) showed in monotherapy and Combination therapy a duration of the empagliflozin effect from 52 weeks to 76 weeks. This is reflected in section 5.1 for the monotherapy and combination therapy as follows: In the double blind placebo controlled extension of these studies, reduction of HbA1c, body weight

					and blood pressure were sustained up to Week 76.
IAIN/0024/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.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	02/09/2016	19/01/2017	Annex II and PL	
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	19/01/2017	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.
A20/0007	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	25/04/2016	SmPC and PL	Please refer to the assessment report: SGLT2 inhibitors - EMEA/H/A-20/1419
IB/0015	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/0013/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 or addition) for	24/11/2015	n/a		

	the AS or a starting material/intermediate				
PSUSA/10219 /201504	Periodic Safety Update EU Single assessment - empagliflozin	06/11/2015	n/a		PRAC Recommendation - maintenance
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	14/12/2015	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.
IB/0010	B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of	30/07/2015	n/a		

	specification limits				
IB/0008/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	24/07/2015	n/a		
PSUSA/10219 /201410	Periodic Safety Update EU Single assessment - empagliflozin	07/05/2015	n/a		PRAC Recommendation - maintenance
II/0005	Submission of the updated ERA and the final study report of a toxicity study on a sediment dwelling organism; the updated RMP version 3.0 has been submitted as part of the application. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	26/02/2015	n/a		
II/0002	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	18/12/2014	14/12/2015	SmPC	
N/0004	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	28/11/2014	14/12/2015	PL	
IAIN/0003/G	This was an application for a group of variations.	28/11/2014	n/a		

	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.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site 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				
IAIN/0001	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	12/06/2014	n/a		