Vokanamet

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
IA/0077/G	This was an application for a group of variations. 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	16/12/2024	n/a		

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

	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				
WS/2719	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. The final report from study PCSCVM003617 was listed as a category 3 study in the RMP. It is a Real-World Database Study of Canagliflozin Utilization in Type 1 Diabetes Patients Over Time among European Countries. The RMP version 12.1 has also been submitted. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	05/09/2024	n/a		Please refer to Scientific Discussion Invokana, Vokanamet EMEA/H/C/WS2719
WS/2619/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.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	05/09/2024		SmPC and PL	

IG/1779	A.7 - Administrative change - Deletion of manufacturing sites	02/08/2024	n/a		
IG/1752/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 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	21/06/2024	n/a		
II/0072	Update of section 4.6 of the SmPC in order to update information on pregnancy based on literature and post-marketing data. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	07/12/2023	27/06/2024	SmPC	SmPC new text The following changes in the SmPC, Section 4.6, are suggested by the MAH (new text is underlined): A limited amount of data from the use of metformin in pregnant womenA large amount of data from the use of metformin in pregnant women (more than 1,000 exposed outcomes) from a register-based cohort study and published data (meta-analyses, clinical studies, and registries) does not indicate an increased risk of congenital malformations. Animal studies with metformin do not indicate harmful effects with respect to pregnancy, embryonic or foetal development, parturition, or postnatal development (see section 5.3).
PSUSA/10077 /202303	Periodic Safety Update EU Single assessment - canagliflozin, canagliflozin / metformin	30/11/2023	n/a		PRAC Recommendation - maintenance

II/0067/G	This was an application for a group of variations. Please refer to the Recommendations section C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	15/06/2023	27/06/2024	SmPC and PL	SmPC new text For more information, please refer to the Summary of Product Characteristics.
WS/2368	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Please refer to the Recommendations section C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	15/06/2023	27/06/2024	SmPC	SmPC new text Diabetic ketoacidosis may be prolonged after discontinuation of canagliflozin in some patients, i.e. it may last longer than expected from the plasma half-life of canagliflozin (see section 5.2). Prolonged glucosuria has been observed along with persistent DKA. Insulin deficiency may contribute to prolonged diabetic ketoacidosis and has to be corrected when verified. For more information, please refer to the Summary of Product Characteristics.
N/0070	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	29/05/2023	27/06/2024	PL	
IAIN/0069	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)	05/05/2023	n/a		

N/0068	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/02/2023	27/06/2024	PL	
II/0064	Please refer to the Recommendations section C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	29/09/2022	n/a		N/A
IB/0065/G	This was an application for a group of variations. 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.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 corresponding test method as a result of a safety or quality issue	27/09/2022	n/a		
N/0063	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	04/03/2022	27/06/2024	PL	
IA/0062	B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the	29/11/2021	n/a		

	relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer				
IAIN/0061/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.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	30/08/2021	n/a		
N/0060	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	23/03/2021	27/06/2024	PL	
PSUSA/10077 /202003	Periodic Safety Update EU Single assessment - canagliflozin, canagliflozin / metformin	12/11/2020	14/01/2021	SmPC and PL	Based on available data on post-marketing cases of urinary tract infection (UTI), which reported discontinuation of canagliflozin treatment in the majority of post-marketing cases, the PRAC considers that the information on these ADRS, which are already labelled in the product information of products containing canagliflozin, canagliflozin/metformin, should be changed to reflect the information on treatment interruption.
IB/0058	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	18/12/2020	n/a		

IA/0059	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	14/12/2020	n/a		
IA/0057/G	This was an application for a group of variations. B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	28/09/2020	n/a		
II/0051	Update of sections 4.4, 4.8 5.1 and 6.6 of the Summary of Product Characteristics based upon new safety data from the Phase 3 study: Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation Trial (CREDENCE) (DNE3001). Furthermore minor editorial changes in other sections of the SmPC. The Package Leaflet is updated accordingly. The RMP version 8.5 has also been agreed. In addition, the list of local representatives in the Package Leaflet has been revised. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	28/05/2020	16/11/2020	SmPC and PL	
IA/0055/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.I.b.1.d - Change in the specification parameters	25/03/2020	n/a		

	and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)				
PSUSA/10077 /201903	Periodic Safety Update EU Single assessment - canagliflozin, canagliflozin / metformin	14/11/2019	06/02/2020	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10077/201903.
IB/0054	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	30/01/2020	n/a		
IAIN/0053	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	22/11/2019	16/11/2020	SmPC, Annex II, Labelling and PL	
II/0050/G	This was an application for a group of variations. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	31/10/2019	n/a		
IB/0052	B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	16/10/2019	n/a		

IA/0049	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	16/07/2019	n/a		
IB/0048	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	04/07/2019	n/a		
IB/0046/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation	28/05/2019	n/a		
IA/0045/G	This was an application for a group of variations. 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.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	21/03/2019	n/a		
IA/0044	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	04/03/2019	06/02/2020	SmPC and PL	
IB/0042/G	This was an application for a group of variations.	08/02/2019	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 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.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/0043/G	This was an application for a group of variations. B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) 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	31/01/2019	n/a		

II/0041	Provision of the final CSR for Study RRA-21651; a retrospective, observational, new-user cohort study using 4 administrative claims databases in the US, undertaken to investigate the incidence of diabetic ketoacidosis among patients with type 2 diabetes mellitus treated with SGLT2 inhibitors or other antihyperglycemic agents. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	17/01/2019	n/a		Overall, the study confirms the higher incidence of DKA with SGLT2i treatment compared to other AHA except treatment with insulin. The MAH did not propose any changes to the product information. However, no new information was gathered from the trial that would warrant an update of the product information. Overall, the benefit-risk balance of Vokanamet, remains positive.
R/0039	Renewal of the marketing authorisation.	18/10/2018	18/12/2018	SmPC and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Vokanamet in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
II/0040	Submission of the final Study Report for the non-interventional PASS Study RRA-21430; Acute Pancreatitis Retrospective Observational Epidemiology Cohort Study - Acute pancreatitis in patients with T2DM who are new users of canagliflozin as compared with new users of other AHAs: a retrospective cohort study using large claims databases in the US. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	29/11/2018	n/a		The study did not show any constant association between treatment and the occurrence of acute pancreatitis and it might be concluded that in real life there are no comparable distinct treatment cohorts to prove such a safety concern. Hence, based on the study results no final conclusion on pancreatitis risk can be drawn and no update of the product information is warranted at present.

PSUSA/10077 /201803	Periodic Safety Update EU Single assessment - canagliflozin, canagliflozin / metformin	04/10/2018	n/a		PRAC Recommendation - maintenance
II/0034	Modification of the indication in section 4.1 as well as update of sections , 4.4, 4.8 and 5.1 of the SmPC in order to update the safety and efficacy information on cardiovascular events following final results from CANVAS Program (DIA3008 and DIA4003); the Package Leaflet is updated accordingly. Study DIA3008 is phase 3 Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of JNJ-28431754 on Cardiovascular Outcomes in Adult Subjects With Type 2 Diabetes Mellitus Study DIA4004 is phase 4 Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of Canagliflozin on Renal Endpoints in Adult Subjects With Type 2 Diabetes Mellitus The RMP version 7.3 in Rev.2 of the GVP module V has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to bring the PI in line with the latest QRD template version 10. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/07/2018	27/08/2018	SmPC, Annex II and PL	Based on the recent completion of studies DIA3008 (CANVAS) and DIA4003 (CANVAS-R), the European Union Summaries of Product Characteristics (SmPCs) for the canagliflozin/ metformin immediate release fixed-dose combination (VOKANAMET) have been revised to update the efficacy and safety information with data from these 2 studies. The wording in section 4.1 of SmPC has been amended, CHMP considered as adequate the enhancement of the wording of the indication by deleting ". . . to improve glycaemic control" from this section (as this restriction does no longer adequately reflect the demonstrated effects). The wording "treatment of . . . type 2 diabetes" was considered more relevant as it encompasses both glycaemic control and results of clinical outcomes such as cardiovascular complications , with a reference to section 5.1 of the SmPC. This is aligned with the labelling of other oral antihyperglycaemic agents. The Section 4.4 of the SmPC has been updated with editorial change; the paragraph on lower limb amputations was shifted upwards. In Section 4.8 of the SmPC, existing safety information was updated to reflect the results of the CANVAS studies. Furthermore, a paragraph providing detailed information on lower limb amputation and a paragraph describing the time course of eGFR during canagliflozin treatment were included. Section 5.1 of SmPC has been updated to include the data on CANVAS program, please refer to SmPC for details of

					Cardiovascular outcomes; information on the secondary endpoint all-cause mortality and of the additional endpoint hospitalisation for heart failure as well as renal endpoints is included. The CANVAS Program demonstrated that canagliflozin is not associated with an unacceptable increase in cardiovascular risk (major adverse cardiovascular events (MACE)), as non-inferiority to placebo has been demonstrated. Results of the primary and the key secondary endpoints all-cause mortality and cardiovascular mortality were numerically in favor of canagliflozin. A reduction of heart failure and an improvement of diabetic nephropathy may have contributed to the observed mortality benefits. The PL has been updated accordingly.
II/0033/G	This was an application for a group of variations. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	15/03/2018	28/05/2018	SmPC	
IB/0037/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	21/02/2018	n/a		

	B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation				
IAIN/0036/G	This was an application for a group of variations. B.II.b.5.a - Change to in-process tests or limits applied during the manufacture of the finished product - Tightening of in-process limits 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)	02/02/2018	n/a		
N/0035	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	28/11/2017	28/05/2018	PL	
PSUSA/10077 /201703	Periodic Safety Update EU Single assessment - canagliflozin, canagliflozin / metformin	26/10/2017	n/a		PRAC Recommendation - maintenance
II/0031	Submission of an updated RMP version 7.1 in order to include prior commitments made to PRAC during the PSUR/LEG procedural review of pancreatitis cases and the Article 20 referral procedure reviewing lower limb amputation in relation to the use of SGLT-2 inhibitors. In addition, the updated RMP reflects labelling changes that resulted from a variation to add information regarding fatal DKA cases to the	01/09/2017	n/a		

	existing DKA warning and the Article 31 procedure reviewing metformin-containing medicines. 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				
IB/0029	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	04/07/2017	n/a		
IG/0810/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	09/06/2017	n/a		
IB/0027	B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	24/05/2017	28/05/2018	SmPC	

IB/0028/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.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	12/05/2017	n/a		
II/0023	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/03/2017	28/04/2017	SmPC and PL	
A20/0014	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	09/02/2017	20/04/2017	SmPC and PL	Please refer to the assessment report: SGLT2 inhibitors - EMEA/H/A-20/1442

	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 CHMP opinion has been be adopted on the basis of a recommendation of the Pharmacovigilance Risk Assessment Committee.				
PSUSA/10077 /201609	Periodic Safety Update EU Single assessment - canagliflozin, canagliflozin / metformin	06/04/2017	n/a		PRAC Recommendation - maintenance
IA/0026/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.5.c - Change to in-process tests or limits applied during the manufacture of the finished	09/03/2017	n/a		

	product - Deletion of a non-significant in-process test B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure				
IAIN/0025	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	11/01/2017	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 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.	13/10/2016	12/12/2016	SmPC and PL	Please refer to the assessment report: Metformin containing medicinal products - EMEA/H/A-31/1432
IA/0022	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	25/11/2016	n/a		

	from an already approved manufacturer				
II/0016	To revise RMP (v. 6.0) in order to update the following information: Article 20 procedure on Diabetic Ketoacidosis (DKA) including updates to reflect discussions with PRAC on renal impairment/renal failure; hypersensitivity and DKA, update the information related to revisions to proposed dates for completion of clinical studies and to include additional studies requested as part of the Article 20 DKA review procedure. Additionally, the MAH included in the response document the outcome of variation EMEA/H/C/002649/II/23 or Invokana and EMEA/H/C/002656/II/19 for Vokanamet concerning the completion of study DIA 1055 (a PK/PD study in children >10 years to < 18 years of age. The MAH included also with the response document the outcome of the Article 31 referral (EMEA/H/A-31/1432) procedure regarding metformin-containing products. 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	10/11/2016	n/a		
IAIN/0021/G	This was an application for a group of variations. B.I.a.1.a - Change in the manufacturer of AS or of a	04/11/2016	n/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.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				
II/0018/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.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other	27/10/2016	n/a		

	variation 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.2.b - Changes in the manufacturing process of the AS - Substantial change to the manufacturing process of the AS which may have a significant impact on the quality, safety or efficacy of the medicinal product 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 B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS				

	B.I.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				
PSUSA/10077 /201603	Periodic Safety Update EU Single assessment - canagliflozin, canagliflozin / metformin	27/10/2016	n/a		PRAC Recommendation - maintenance
II/0019	Submission of study DIA 1055 an open-Label, Multicenter, Multiple Oral Dose Study to Evaluate the Pharmacokinetics, Pharmacodynamics and Safety of Canagliflozin in Older Children and Adolescents ≥10 to <18 years of age with Type 2 Diabetes Mellitus and Currently on a Stable Dose of Metformin. The summary of product characteristics in section 5.2 is updated with the description of the study characterising the pharmacokinetics of canagliflozin in paediatric patients. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	15/09/2016	12/12/2016	SmPC	The MAH updated section 5.2 of the SmPC to include information of a paediatric Phase 1 study examined the pharmacokinetics and pharmacodynamics of canagliflozin in children and adolescents ≥ 10 to < 18 years of age with Type 2 Diabetes Mellitus. The observed pharmacokinetic and pharmacodynamic responses were consistent with those found in adult subjects.”
IB/0020	B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	31/08/2016	n/a		
II/0015	Submission of a study DIA1072 (A Single-Dose, Open-Label, Randomized, 4-Way Crossover Pivotal Study to Assess the Bioequivalence of Canagliflozin when Administered as the Monohydrate form to the Hemihydrate form in Healthy Adult Subjects under	21/07/2016	n/a		A new polymorph for canagliflocin (a monohydrate form) was recently discovered. Study DIA1072 was conducted to investigate the bioequivalence between this new form and the hemihydrate form which is used in the currently marketed tablets. The submission of the study results has

	Fasted Conditions) C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				been provided for information purposes and no changes to the product information are proposed.
II/0012	Update of section 4.8 of the SmPC in line with the MAH's updated CDS to add the new ADR 'anaphylactic reaction' with a frequency category of 'rare' under the system organ class category ' immune system disorder', and to change the frequency of the existing ADR 'angioedema' from 'not known' to 'rare'. Further, section 5.2 of the SmPC has been updated to implement a minor change related to the mean steady-state volume of distribution based on the results of Study DIA1021. In addition, the MAH took the opportunity to align the SmPC and the Package Leaflet with the latest QRD template version 9.1, to combine the SmPCs for the 100 mg and 300 mg strengths, and to update the contact details for the local representatives in Denmark in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	30/06/2016	12/12/2016	SmPC and PL	Based on the availability of new post marketing information, the Company Core Data Sheets (CCDSs) for canagliflozin (CANA) immediate release fixed-dose combination (CANA/MET IR FDC) have been updated to modify the adverse drug reaction (ADR) section and the following changes in the SmPC and PIL have been implemented: a) Change to Section 4.8 of the SmPC to add a new System organ class category, Adverse reaction and associated frequency category to Table 1 for SOC - "Immune system disorder", Adverse reaction - "Anaphylactic reaction" with a frequency category of "rare". b) Change to Section 4.8 of the SmPC to change in frequency of the existing adverse reaction of "Angioedema" from "not known" to "rare". c) Section 5.2 Pharmacokinetic properties is updated regarding the mean steady-state volume of distribution of canagliflozin following a single intravenous infusion in healthy subjects in the EU SmPC for CANA/MET IR FDC. The change is based upon an updated analysis from an open-label, single-dose study to assess the absolute oral bioavailability and pharmacokinetics of canagliflozin administered as a 300-mg oral tablet and an intravenous microdose of 10 µg 14C-canagliflozin in healthy male subjects (study DIA1021), the value of Vd,ss for unchanged

					[14C]-Canagliflozin should read 83.5 L instead of 119 L.
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	28/04/2016	SmPC and PL	Please refer to the assessment report: SGLT2 inhibitors - EMEA/H/A-20/1419
PSUSA/10077 /201509	Periodic Safety Update EU Single assessment - canagliflozin, canagliflozin / metformin	14/04/2016	n/a		PRAC Recommendation - maintenance
PSUSA/10077 /201503	Periodic Safety Update EU Single assessment - canagliflozin, canagliflozin / metformin	22/10/2015	16/12/2015	SmPC	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for

					PSUSA/10077/201503.
IB/0010/G	This was an application for a group of variations. 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.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 corresponding test method as a result of a safety or quality issue	27/11/2015	n/a		
PSUSA/10077 /201411	Periodic Safety Update EU Single assessment - canagliflozin, canagliflozin / metformin	25/06/2015	20/08/2015		Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10077/201411.
IB/0009/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	17/08/2015	n/a		

IB/0008/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.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	21/07/2015	n/a		
IB/0005/G	This was an application for a group of variations. 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 B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.II.b.5.f - Change to in-process tests or limits applied during the manufacture of the finished product - Addition or replacement of an in-process test as a result of a safety or quality issue	03/07/2015	n/a		
IG/0526/G	This was an application for a group of variations. A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release B.II.b.1.a - Replacement or addition of a	04/03/2015	20/08/2015	Annex II and PL	

	manufacturing site for the FP - Secondary packaging site				
II/0002	Update of section 4.2 of the SmPC in order to clarify the maximum daily dose of metformin. In addition, the MAH took the opportunity to implement minor changes in Section 5.1 of the SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/10/2014	20/08/2015	SmPC	