Invokana

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
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-	05/09/2024	n/a		Please refer to Scientific Discussion Invokana, Vokanamet EMEA/H/C/WS2719

[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).

	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				
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	21/06/2024	n/a		

	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				
PSUSA/10077 /202303	Periodic Safety Update EU Single assessment - canagliflozin, canagliflozin / metformin	30/11/2023	n/a		PRAC Recommendation - maintenance
II/0062	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	28/06/2024	SmPC	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	28/06/2024	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/0064	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	29/05/2023	28/06/2024	PL	
N/0063	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/02/2023	28/06/2024	PL	

II/0060	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
N/0059	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	04/03/2022	28/06/2024	PL	
II/0058	B.II.d.3 - Variations related to the introduction of real-time release or parametric release in the manufacture of the finished product	03/02/2022	n/a		
II/0055	Update of sections 4.2, 4.4 and 5.1 of the SmPC to amend posology information concerning the treatment of patients with eGFR between ≥30 and <45 mL/min/1.73 m2, whether or not albuminuria is present, based on further analysis of previously submitted CANVAS data (studies DIA3008 and DIA4003). The Applicant has also taken the opportunity to make minor editorial changes to SmPC section 4.5. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	14/10/2021	15/11/2021	SmPC	In a pooled analysis of patients (N = 348) with a baseline eGFR <45 mL/min/1.73 m2, canagliflozin provided a modest reduction in HbA1c compared to placebo, with 0.23% for canagliflozin 100 mg and 0.39% for canagliflozin 300 mg. There is experience with canagliflozin for the treatment of diabetic kidney disease (eGFR ≥30 mL/min/1.73 m2) both with and without albuminuria. While both groups of patients benefitted, patients with albuminuria may benefit more from treatment with canagliflozin. For more information, please refer to the Summary of Product Characteristics.
IAIN/0057/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	27/08/2021	n/a		

	or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient 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				
N/0056	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	15/07/2021	15/11/2021	PL	
PSUSA/10077 /202003	Periodic Safety Update EU Single assessment - canagliflozin, canagliflozin / metformin	12/11/2020	11/01/2021	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/0054	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		
II/0052/G	This was an application for a group of variations. B.II.d.1.f - Change in the specification parameters and/or limits of the finished product - Deletion of a specification parameter which may have a significant effect on the overall quality of the finished product B.II.d.1.f - Change in the specification parameters	10/12/2020	n/a		

	and/or limits of the finished product - Deletion of a specification parameter which may have a significant effect on the overall quality of the finished product B.II.d.2.b - Change in test procedure for the finished product - Deletion of a test procedure if an alternative method is already authorised B.II.d.2.b - Change in test procedure for the finished product - Deletion of a test procedure if an alternative method is already authorised B.II.d.2.b - Change in test procedure for the finished product - Deletion of a test procedure if an alternative method is already authorised B.II.d.2.b - Change in test procedure for the finished product - Deletion of a test procedure if an alternative method is already authorised B.II.d.3 - Variations related to the introduction of real-time release or parametric release in the manufacture of the finished product B.II.d.3 - Variations related to the introduction of real-time release or parametric release in the manufacture of the finished product B.II.d.3 - Variations related to the introduction of real-time release or parametric release in the manufacture of the finished product B.II.d.3 - Variations related to the introduction of real-time release or parametric release in the manufacture of the finished product				
IA/0053	B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	28/09/2020	n/a		

II/0046	Update of sections 4.1 , 4.2, , 4.4, 4.8, 5.1 and 6.6 of the Summary of Product Characteristics to modify the therapeutic indication for INVOKANA (canagliflozin) based upon new clinical efficacy and safety data from the Phase 3 study: Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation Trial (CREDENCE) (DNE3001). This study provides data on the use of Invokana in addition to standard of care in diabetic kidney disease patients. 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. The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP). 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	26/06/2020	SmPC and PL	Please refer to Scientific Discussion Invokana-II-0046
IA/0050/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 and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	25/03/2020	n/a		

IB/0049	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		
PSUSA/10077 /201903	Periodic Safety Update EU Single assessment - canagliflozin, canagliflozin / metformin	14/11/2019	13/01/2020	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10077/201903.
IAIN/0048	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	22/11/2019	26/06/2020	SmPC, Annex II, Labelling and PL	
II/0045/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/0047	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		
IAIN/0043	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	04/03/2019	21/10/2019	SmPC and PL	

IB/0042/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or 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	08/02/2019	n/a		
II/0040	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	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. No new information was gathered from the trial that would warrant an update of the product information. Overall, the benefit-risk balance of Invokana, remains positive.

	elsewhere in this Annex which involve the submission of studies to the competent authority				
II/0039	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.
IB/0041	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)	05/11/2018	21/10/2019	SmPC	
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	26/07/2018	04/09/2018	SmPC and PL	Based on the recent completion of studies DIA3008 (CANVAS) and DIA4003 (CANVAS-R), the European Union Summaries of Product Characteristics (SmPCs)) for canagliflozin (INVOKANA) has 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

	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 update the list of local representatives in the Package Leaflet and 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				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 PL have been updated accordingly. 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.
R/0037	Renewal of the marketing authorisation.	31/05/2018	26/07/2018	SmPC, Annex II, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Invokana in the approved indication remains favourable and therefore recommends the renewal of the marketing authorisation with unlimited validity.
II/0033/G	This was an application for a group of variations. Update of section 5.1 of the SmPC in order to update the safety information on 'Canagliflozin as initial combination therapy with metformin' based on final results from the DIA3011 study, which is Randomized, Double-Blind, 5-Arm, Parallel-Group, 26-Week, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin in Combination With Metformin as Initial Combination Therapy in the Treatment of Subjects With Type 2 Diabetes Mellitus With Inadequate Glycemic Control With Diet and Exercise. Update of section 5.1 of the SmPC in order to update the safety information on 'Add-on combination therapy with Metformin and Dipeptidyl-peptidase-4 Inhibitor' based on final results from the DIA4004 study, which is a Randomized, Double-blind, Placebo Controlled, 2-arm, Parallel-group, 26-week, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin in the Treatment of Subjects with Type 2 Diabetes Mellitus with Inadequate Glycemic Control on Metformin and	15/03/2018	26/07/2018	SmPC	The MAH updated section 5.1 of the SmPC to include new information on two clinical studies of canagliflozin, including data from 1,186 T2DM subjects inadequately controlled by diet and exercise who received co-administration of canagliflozin and metformin XR as initial combination therapy relative to canagliflozin alone or metformin XR alone for 26 weeks (DIA3011) and 213 T2DM subjects who received canagliflozin or placebo add-on to metformin and sitagliptin alone for 26 weeks (DIA4004).

	Sitagliptin Therapy. 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				
IA/0036/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.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.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	11/01/2018	n/a		
N/0035	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	28/11/2017	26/07/2018	PL	
PSUSA/10077 /201703	Periodic Safety Update EU Single assessment - canagliflozin, canagliflozin / metformin	26/10/2017	n/a		PRAC Recommendation - maintenance

IA/0032	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	29/09/2017	26/07/2018	SmPC, Annex II, Labelling and PL	
II/0030	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 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	01/09/2017	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	09/06/2017	n/a		

	pharmaceutical group as the currently approved manufacturer				
II/0026	Update of section 4.4 of the SmPC in order to update the safety information: the term 'and fatal' is added when describing the Diabetic Ketoacidosis cases that have been reported. The Package Leaflet is updated accordingly: term 'rare but serious, sometimes life-threatening and fatal' is added when describing Diabetic Ketoacidosis. In addition, the Marketing authorisation holder (MAH) took the opportunity 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	23/03/2017	28/04/2017	SmPC and PL	
A20/0018	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
IAIN/0028	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		
II/0020	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	10/11/2016	n/a		

	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				
IAIN/0025/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	04/11/2016	n/a		

	manufacturer B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS				
PSUSA/10077 /201603	Periodic Safety Update EU Single assessment - canagliflozin, canagliflozin / metformin	27/10/2016	n/a		PRAC Recommendation - maintenance
II/0023	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	20/04/2017	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/0024	B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	31/08/2016	n/a		

IA/0022/G	This was an application for a group of variations. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test 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 B.II.e.4.a - Change in shape or dimensions of the container or closure (immediate packaging) - Non-sterile medicinal products B.II.f.1.e - Stability of FP - Change to an approved stability protocol	28/07/2016	n/a		
II/0017/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	28/07/2016	n/a		

	manufacturer 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 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				
II/0019	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 Fasted Conditions). The variation leads to no amendments to the Product Information. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	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 been provided for information purposes and no changes to the product information are proposed.

II/0016	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 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	20/04/2017	SmPC and PL	Based on the availability of new postmarketing 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: 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 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.
A20/0011	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	25/02/2016	25/04/2016	SmPC and PL	Please refer to the assessment report: SGLT2 inhibitors - EMEA/H/A-20/1419

	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.				
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/0014/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 corresponding test method as a result of a safety or quality issue B.II.d.1.g - Change in the specification parameters and/or limits of the finished product - Addition or	22/10/2015	n/a		

	replacement (excluding biological or immunological product) of a specification parameter wit its corresponding test method as a result of a safety or quality issue				
IB/0012/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 manufacturing site for the FP - Secondary 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.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.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	03/09/2015	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/0013/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	14/08/2015	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				
IB/0009/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	01/07/2015	n/a		
PSUV/0007	Periodic Safety Update	04/12/2014	n/a		PRAC Recommendation - maintenance
II/0006	Update of section 4.2 of the SmPC to update the safety information related to bone fractures, based on new information collected from the CANVAS (DIA3008). In addition, the MAH implemented some linguistic minor changes in sections 4.2, 4.5, 4.6, 4.8 and 5.1. The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.	25/04/2014	n/a		With this procedure the MAH intended to update the Product Information (PI) for Invokana in order to bring it in line with the PI for Vokanamet, with regards to bone fractures. Based on an analysis of fracture events in the ongoing CV outcome study CANVAS the MAH has included the new AE "bone fractures" as uncommon in section 4.8 of the SmPC and added an explanatory paragraph as follows: "Bone fracture In a cardiovascular study of 4,327 patients with known or

	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				at high risk for cardiovascular disease, the incidence rates of bone fracture were 1.6, 1.6, and 1.1 per 100 patient years of exposure to canagliflozin 100 mg, canagliflozin 300 mg, and placebo, respectively, with the fracture imbalance initially occurring within the first 26 weeks of therapy. In other type 2 diabetes studies with canagliflozin, which enrolled a general diabetes population of approximately 5,800 patients, no difference in fracture risk was observed relative to control. After 104 weeks of treatment, canagliflozin did not adversely affect bone mineral density.”
II/0005	The purpose of this variation is the submission of several Clinical Study Reports (CSRs) that have recently become available. No update of the Product Information is deemed necessary. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/04/2014		SmPC and PL	With this variation clinical study reports of an independent clinical development programme in Japan have been submitted. The MTPC studies were conducted in Japan in accordance with Japanese Good Clinical Practice (GCP). The provision of these reports is deemed as informational data only. Of note, the phase III studies submitted with this variation were conducted with products containing 100 mg and 200 mg canagliflozin (as opposed to the 100 mg and 300 mg canagliflozin doses investigated in the European program). One of the studies submitted investigated the effect of CANA in patients with moderate renal impairment used inclusion criteria for eGFR ranges distinct from the ones used in the European programme. In the phase III studies numbers of patients with an eGFR<60ml/ min/ 1.73 at baseline were too low to draw conclusions on the efficacy in this subgroup. Overall, the two phase III studies showed that CANA exerted good antihyperglycemic efficacy in the Japanese population with the magnitude of effect being in the same range as in the European phase III programme.

					The newly submitted phase III studies did not reveal new safety signals for CANA. Known effects of SGLT2 inhibitors became obvious such as increased formation of ketone bodies, decreased incidence in elevated blood pressure and increased incidence in vulvovaginal candidiasis. Otherwise these newly submitted studies do not contribute relevantly to the safety assessment of CANA due to limitations (low patient number in study 05 and lack of a control group in study 06). Also the newly submitted phase I and II studies cannot provide relevant new information because of low patient number and treatment duration. They are therefore not discussed here under safety aspects. Taken together, the B/R balance of CANA remains unchanged.
II/0003	Update of section 4.5 of the SmPC in order to insert new information relating to Drug/Laboratory test interference of canagliflozin with 1,5-anhydroglucitol (1,5-AG) assays. In addition editorial changes were made to the SmPC (Section 4.8 and 5.2; 300 mg only), significance levels have been added (section 5.1, table 2) and errors were corrected in (section 5.1, tables 2 and 3). In addition, the MAH has corrected typographical errors in Annex II and Annex IIIA. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/04/2014	08/04/2015	SmPC, Labelling and PL	In this variation, the MAH has presented post hoc analysis to determine 1,5-AG levels in archived samples from 20 patients each from the canagliflozin 300 mg and placebo treatment groups of a subset of patients who participated in a Phase 3 study of canagliflozin monotherapy. In this post hoc analysis, serum 1,5-AG levels were decreased with canagliflozin 300 mg compared with placebo after 26 weeks of treatment. As reductions in 1,5-AG indicate poorer glycemic control, findings are in contrast to improvements in HbA1c. The results of this post hoc analysis are consistent with an interference with the measurement of 1,5-AG in the context of SGLT2 inhibition; thus, 1,5-AG assays may provide inaccurate results regarding glycemic control in patients with T2DM treated with an SGLT2 inhibitor, such as canagliflozin. This new information pertains to interference with a

					laboratory assessment and does not affect the benefit risk assessment. The overall benefit-risk relationship remains favorable for canagliflozin when used as recommended in the currently approved indication.
II/0002/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	20/03/2014	n/a		
IB/0004/G	This was an application for a group of variations. B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	28/02/2014	n/a		
IB/0001/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	19/12/2013	n/a		

	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.3.b - Change in batch size (including batch size ranges) of AS or intermediate - Downscaling down to 10-fold B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation				