

## Vokanamet

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification <sup>1</sup> issued on	Commission Decision Issued <sup>2</sup> / amended on	Product Information affected <sup>3</sup>	Summary
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,	09/02/2017	20/04/2017	SmPC and PL	Please refer to the assessment report: SGLT2 inhibitors - EMEA/H/A-20/1442

<sup>1</sup> 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.

<sup>2</sup> 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.

<sup>3</sup> SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

	<p>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.</p> <p>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.</p> <p>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.</p> <p>As the request results from the evaluation of data resulting from pharmacovigilance activities, the CHMP opinion has been adopted on the basis of a recommendation of the Pharmacovigilance Risk Assessment Committee.</p>				
PSUSA/10077 /201609	Periodic Safety Update EU Single assessment - canagliflozin, canagliflozin / metformin	06/04/2017	n/a		PRAC Recommendation - maintenance
IA/0026/G	<p>This was an application for a group of variations.</p> <p>A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites</p>	09/03/2017	n/a		

	<p>(excluding manufacturer for batch release)</p> <p>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</p> <p>B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test</p> <p>B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure</p>				
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	<p>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.</p> <p>The notification for the procedure is appended to this opinion.</p>	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 from an already approved manufacturer	25/11/2016	n/a		
II/0016	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	<p>This was an application for a group of variations.</p> <p>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</p> <p>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</p> <p>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</p> <p>B.I.a.2.a - Changes in the manufacturing process of</p>	04/11/2016	n/a		

	the AS - Minor change in the manufacturing process of the AS				
II/0018/G	<p>This was an application for a group of variations.</p> <p>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</p> <p>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</p> <p>B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation</p> <p>B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation</p> <p>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</p> <p>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</p> <p>B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other</p>	27/10/2016	n/a		

	<p>variation</p> <p>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</p> <p>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</p> <p>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</p> <p>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</p>				
PSUSA/10077 /201603	Periodic Safety Update EU Single assessment - canagliflozin, canagliflozin / metformin	27/10/2016	n/a		PRAC Recommendation - maintenance
II/0019	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 $\geq 10$ 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	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		
II/0012	<p>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.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p>	30/06/2016	12/12/2016	SmPC and PL	<p>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:</p> <p>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".</p> <p>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".</p> <p>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 <sup>14</sup>C-canagliflozin in healthy male subjects (study DIA1021), the value of V<sub>d,ss</sub> for unchanged [<sup>14</sup>C]-Canagliflozin should read 83.5 L instead of 119 L.</p>

A20/0007	<p>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.</p> <p>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.</p> <p>The notification for the procedure is appended to this recommendation.</p>	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.	27/11/2015	n/a		

	<p>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</p> <p>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</p> <p>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 with its corresponding test method as a result of a safety or quality issue</p>				
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	<p>This was an application for a group of variations.</p> <p>B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation</p> <p>B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation</p>	17/08/2015	n/a		
IB/0008/G	<p>This was an application for a group of variations.</p> <p>B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any</p>	21/07/2015	n/a		

	<p>manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products</p> <p>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</p>				
IB/0005/G	<p>This was an application for a group of variations.</p> <p>B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation</p> <p>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation</p> <p>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation</p> <p>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</p>	03/07/2015	n/a		
IG/0526/G	<p>This was an application for a group of variations.</p> <p>A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release</p> <p>B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site</p>	04/03/2015	20/08/2015	Annex II and PL	
II/0002	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance	23/10/2014	20/08/2015	SmPC	

	data				
--	------	--	--	--	--