



## Incesync

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
N/0043	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	07/09/2022		PL	
WS/2191	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	10/06/2022	n/a		n/a

<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).



Submission of a consolidated RMP version 11.1 for Vipidia, Vipdomet and Incresync in order to:

- Update the RMPs for Alogliptin, Alogliptin/Pioglitazone fixed dose combination (FDC) and Alogliptin/Metformin fixed dose combination (FDC) to consolidate within a single RMP as committed within the PSUR procedure (PSUSA/00010061/202104).
- Following review of cumulative safety data, removal of a number of safety concerns is done based on GVP Module V, Risk Management Systems (revision 2) guidelines.
- Remove the target follow up Questionnaires of Severe Hypersensitivity and skin reactions, Pancreatitis, Hepatic events and follow up gastrointestinal events and infections from Alogliptin and Alo/Met RMPs.
- Reflect the removal of the inverted black triangle as agreed as part of the alogliptin renewal procedure (EMA/H/C/002178/R/0023) for Alogliptin and the FDC Alogliptin/Metformin. The black triangle was already removed from the FDC Alogliptin/Pioglitazone RMP as part of the Type II variation (EMA/H/C/002178/II/0029).

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

IG/1486/G	<p>This was an application for a group of variations.</p> <p>B.Ia.3.b - Change in batch size (including batch size ranges) of AS or intermediate - Downscaling down to 10-fold</p> <p>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</p>	13/04/2022	n/a		
N/0039	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	25/11/2021	04/04/2022	PL	
PSUSA/10061 /202104	Periodic Safety Update EU Single assessment - alogliptin, alogliptin / metformin, alogliptin / pioglitazone	28/10/2021	n/a		PRAC Recommendation - maintenance
WS/1967/G	<p>This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>C.Iz - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation</p> <p>A.1 - Administrative change - Change in the name and/or address of the MAH</p>	18/03/2021	04/04/2022	SmPC, Annex II, Labelling and PL	
WS/1966	This was an application for a variation following a worksharing procedure according to Article 20 of	14/01/2021	n/a		

	<p>Commission Regulation (EC) No 1234/2008.</p> <p>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</p>				
PSUSA/10061 /202004	<p>Periodic Safety Update EU Single assessment - alogliptin, alogliptin / metformin, alogliptin / pioglitazone</p>	12/11/2020	07/01/2021	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s) for PSUSA/10061/202004.
IB/0036/G	<p>This was an application for a group of variations.</p> <p>B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information</p> <p>B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure</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.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits</p> <p>B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process</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</p>	22/12/2020	n/a		

	control/testing takes place 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				
IB/0034	C.I.7.b - Deletion of - a strength	30/10/2020	07/01/2021	SmPC, Labelling and PL	
IB/0031/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.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits 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 B.II.d.2.a - Change in test procedure for the finished	15/07/2020	n/a		

	<p>product - Minor changes to an approved test procedure</p> <p>B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information</p>				
II/0029	<p>RMP (version 10.1) updates</p> <p>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</p>	13/02/2020	07/01/2021	Annex II and PL	<p>Incesync RMP (version 10.1) includes the following updates:</p> <p>(i) MAH's proposal for removal of aRMMs and consequently the Drug Utilisation Study along with removal of relevant commitment (EMEA/H/C/002182/LEG/009).</p> <p>(ii) RMP updated in the new template in order to implement the GVP Module V Revision 2 template along with revising/removal of the safety concerns as summarised below:</p> <ul style="list-style-type: none"> <li>· The safety concerns for the alogliptin component have been updated.</li> <li>· The safety concerns for the pioglitazone component have been aligned with the consolidated Pioglitazone family RMP (RMP V27.0 as part of the worksharing variation procedure [EMEA/H/C/XXXX/WS/1680]).</li> <li>· The safety concerns for alogliptin/pioglitazone FDC have been updated.</li> </ul> <p>(iii) Targeted Adverse Event (AE) Follow-up Questionnaires related to AEs of severe hypersensitivity skin reactions, hepatic events, pancreatitis, bladder cancer, bone fractures, and macular oedema were also removed.</p> <p>(iv) RMP has also been updated to reflect the removal of the inverted black triangle as agreed as part of alogliptin renewal procedure (EMEA/H/C/002182/R/0019).</p>

					Annex II of the PI has been updated accordingly, as well as local representative for Poland.
IA/0030	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	06/11/2019	n/a		
PSUSA/10061 /201904	Periodic Safety Update EU Single assessment - alogliptin, alogliptin / metformin, alogliptin / pioglitazone	31/10/2019	n/a		PRAC Recommendation - maintenance
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.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits 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 B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.e.6.b - Change in any part of the (primary)	10/10/2019	n/a		

	packaging material not in contact with the finished product formulation - Change that does not affect the product information				
IG/1071/G	<p>This was an application for a group of variations.</p> <p>B.Ia.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.Ia.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size</p> <p>B.Ia.3.b - Change in batch size (including batch size ranges) of AS or intermediate - Downscaling down to 10-fold</p>	28/03/2019	n/a		
IB/0025/G	<p>This was an application for a group of variations.</p> <p>A.7 - Administrative change - Deletion of manufacturing sites</p> <p>B.III.2.a.1 - Change of specification(s) of a former non EU Pharmacopoeial substance to fully comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - AS</p>	01/02/2019	n/a		
PSUSA/10061/201804	Periodic Safety Update EU Single assessment - alogliptin, alogliptin / metformin, alogliptin / pioglitazone	31/10/2018	n/a		PRAC Recommendation - maintenance

R/0023	Renewal of the marketing authorisation.	22/03/2018	25/05/2018	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 Vipidia in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
IB/0022	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	08/01/2018	n/a		
PSUSA/10061 /201704	Periodic Safety Update EU Single assessment - alogliptin, alogliptin / metformin, alogliptin / pioglitazone	26/10/2017	n/a		PRAC Recommendation - maintenance
WS/1235/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.  B.I.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.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	14/09/2017	n/a		
IB/0021/G	This was an application for a group of variations.  B.I.a.2.a - Changes in the manufacturing process of	24/08/2017	n/a		

	<p>the AS - Minor change in the manufacturing process of the AS</p> <p>B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS</p> <p>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</p>				
IB/0018/G	<p>This was an application for a group of variations.</p> <p>C.I.3.a - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Implementation of wording agreed by the competent authority</p> <p>C.I.3.z - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Other variation</p>	11/01/2017	20/12/2017	SmPC, Annex II and PL	
PSUSA/10061/201604	Periodic Safety Update EU Single assessment - alogliptin, alogliptin / metformin, alogliptin / pioglitazone	27/10/2016	n/a		PRAC Recommendation - maintenance
IG/0734/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</p>	13/10/2016	n/a		

	<p>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.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS</p> <p>B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size</p>				
IB/0015	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	28/04/2016	n/a		
WS/0940	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation</p>	28/04/2016	n/a		
IG/0652	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the	22/01/2016	n/a		

	PSMF location				
PSUSA/10061 /201504	Periodic Safety Update EU Single assessment - alogliptin, alogliptin / metformin, alogliptin / pioglitazone	06/11/2015	n/a		PRAC Recommendation - maintenance
IA/0011	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	12/06/2015	n/a		
PSUSA/10061 /201410	Periodic Safety Update EU Single assessment - alogliptin, alogliptin / metformin, alogliptin / pioglitazone	10/04/2015	n/a		PRAC Recommendation - maintenance
PSUV/0008	Periodic Safety Update	20/11/2014	15/01/2015	SmPC and PL	Please refer to Incresync PSUV/08 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation
IAIN/0009	A.1 - Administrative change - Change in the name and/or address of the MAH	07/11/2014	15/01/2015	SmPC, Labelling and PL	
WS/0519	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>The WSA proposed the update of sections 4.4, 4.8, and 5.1 of the SmPC and in order to reflect the results of study 402, a phase 3b, randomised, double-blind, placebo-controlled, event-driven study, designed to demonstrate that no excess risk of a major adverse cardiovascular event (MACE) exists</p>	24/07/2014	15/01/2015	SmPC	Results from study 402, a phase 3b, randomised, double-blind, placebo-controlled, event-driven study, which was designed to demonstrate that no excess risk of a major adverse cardiovascular event (MACE) exists following treatment with alogliptin compared with placebo when added to standard of care in adults with type II diabetes mellitus (T2DM) and acute coronary syndrome (ACS), are included in the SmPC. The primary endpoint of the study was achieved, demonstrating non-inferiority of alogliptin compared with placebo for the primary MACE composite.

	<p>following treatment with alogliptin compared with placebo when added to standard of care in adults with type II diabetes mellitus (T2DM) and acute coronary syndrome (ACS).</p> <p>The MAH took this opportunity to propose amendments to the RMP in order to reflect results from study 402 and to update its structure according to the new European Union (EU) template for RMPs.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p>				Therefore, in general, alogliptin was not associated with an increased risk of cardiovascular disease.
II/0002	<p>The MAH proposed the update of sections 4.4, 4.8, and 5.1 of the SmPC and in order to reflect the results of study 305, a phase 3, randomised, double-blind, active-controlled, 2-year study, designed to assess the efficacy and safety of alogliptin in combination with metformin compared with glipizide in combination with metformin in adults with T2DM. The Package leaflet has been updated accordingly. The MAH took this opportunity to propose consequential amendments to the RMP.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p>	24/07/2014	15/01/2015	SmPC and PL	Results from study 305, a phase 3, randomised, double-blind, active-controlled, 2-year study, designed to assess the efficacy and safety of alogliptin in combination with metformin compared with glipizide in combination with metformin in adults with T2DM, are included in the SmPC. Treatment with alogliptin as add on to metformin therapy showed similar results after two years of treatment to glipizide in combination with metformin treatment. The dose of glipizide used in this trial was relatively low. Furthermore, alogliptin therapy was associated with less hypoglycaemic periods compared to glipizide treatment and the weight of the alogliptin group reduced slightly as the weight of the glipizide group increased slightly. There were no specific safety issues in this trial.
PSUV/0005	Periodic Safety Update	12/06/2014	n/a		PRAC Recommendation - maintenance
IB/0007	C.I.z - Changes (Safety/Efficacy) of Human and	05/05/2014	n/a		

	Veterinary Medicinal Products - Other variation				
II/0006	Update of section 4.4 of the SmPC in order to update the safety information on acute pancreatitis. The Package Leaflet is updated accordingly.  C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	25/04/2014	15/01/2015	SmPC and PL	The scope of this variation was to update section 4.4 of the SmPC to update the safety information on acute pancreatitis following recommendations of an Art 5(3) procedure on GLP-1-based therapies and pancreatic safety. The Package Leaflet is updated accordingly. The benefit/risk balance of Incesync remains unchanged
IG/0401	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	11/02/2014	n/a		