Xigduo

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/2544	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.4 and 4.8 of the SmPC in order to add a new warning on 'Vitamin B12	08/02/2024		SmPC and PL	Metformin may reduce vitamin B12 serum levels. The risk of low vitamin B12 levels increases with increasing metformin dose, treatment duration, and/or in patients with risk factors known to cause vitamin B12 deficiency. In case of suspicion of vitamin B12 deficiency (such as anaemia or neuropathy), vitamin B12 serum levels should

[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).

	decrease/deficiency' and to change the frequency of 'Vitamin B12 decrease/deficiency' in the list of adverse drug reactions (ADRs) from frequency 'very rare' to 'common'. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI and to update the contact details of the local representative in the Netherlands in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				be monitored. Periodic vitamin B12 monitoring could be necessary in patients with risk factors for vitamin B12 deficiency. Metformin therapy should be continued for as long as it is tolerated and not contraindicated and appropriate corrective treatment for vitamin B12 deficiency provided in line with current clinical guidelines.
IG/1693	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	06/02/2024		SmPC and PL	
IG/1630	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)	26/06/2023	n/a		
IG/1616	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	30/05/2023		Annex II and PL	
WS/2382	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	12/01/2023	03/02/2023	SmPC and PL	

IG/1558	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	06/10/2022	n/a		
WS/2279/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.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.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	07/07/2022	n/a		
WS/2234/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. A.7 - Administrative change - Deletion of manufacturing sites 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	02/06/2022	n/a		

	variation				
WS/2230	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	22/04/2022	n/a		
IG/1479/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites	26/01/2022	03/02/2023	Annex II and PL	
PSUSA/10294 /202101	Periodic Safety Update EU Single assessment - dapagliflozin / metformin	02/09/2021	n/a		PRAC Recommendation - maintenance
IG/1410/G	This was an application for a group of variations. B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.b - Replacement or addition of a	17/06/2021	n/a		

	manufacturing site for the FP - Primary packaging site				
IG/1367	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	15/03/2021	n/a		
IG/1343	B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	05/02/2021	03/02/2022	Annex II and PL	
WS/1853/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.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.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	03/09/2020	n/a		

	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.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				
PSUSA/10294 /202001	Periodic Safety Update EU Single assessment - dapagliflozin / metformin	03/09/2020	n/a		PRAC Recommendation - maintenance
WS/1843/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.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.III.1.a.3 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the	23/07/2020	n/a		

	relevant Ph. Eur. Monograph - New certificate from a new manufacturer (replacement or addition)				
WS/1742	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	14/05/2020	n/a		
IG/1200/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites 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	07/02/2020	30/09/2020	Annex II and PL	
IG/1199	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	07/02/2020	n/a		
WS/1715/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.	16/01/2020	n/a		

	B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation 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				
IG/1171	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	11/12/2019	30/09/2020	SmPC and PL	
WS/1697	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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	17/10/2019	n/a		
WS/1637	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.4 (Special warnings and precautions for use) and 4.8 (Undesirable effects) of the SmPC of dapagliflozin-containing products with respect to the Fournier's gangrene class labelling language, following results from the DECLARE study	17/10/2019	30/09/2020	SmPC and PL	Information on Fournier`s gangrene in section 4.8 was updated with the frequency 'very rare', based on the DECLARE study and information was added under 'Description of selected adverse reactions' ; a reference to section 4.8 was added in SmPC section 4.4. The Package Leaflet was updated accordingly.

	(a Multicentre, Randomized, Double-Blind, Placebo-Controlled cardiovascular outcome trial in Patients with Type 2 Diabetes). The Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
PSUSA/10294 /201901	Periodic Safety Update EU Single assessment - dapagliflozin / metformin	05/09/2019	n/a		PRAC Recommendation - maintenance
WS/1539	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.1 , 4.2, 4.4, 4.8, and 5.1 of the SmPC of Forxiga, Edistride, Xigduo and Ebymect to modify the indication and to reflect new data based on final results from study D1693C00001 (DECLARE). This was a multi-centre, randomised, double-blind, placebo-controlled study to evaluate the effect of dapagliflozin on cardiovascular (CV) and renal outcomes in patients with T2DM with or without established CV disease. The Package Leaflets (PL) are updated accordingly. The dapagliflozin Risk Management Plan (RMP) and dapagliflozin/metformin RMP have also been updated to version 17 and version 11 respectively. The Worksharing applicant took the opportunity to make editorial changes and bring the PI in line with	27/06/2019	25/07/2019	SmPC and PL	Please refer to the Scientific Disdcussion 'EMEA/H/C/xxxx/WS/1539'

	the updated excipient guideline (lactose wording in SmPC section 4.4) . The worksharing procedure leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IG/1067	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	19/03/2019	n/a		
IG/1064	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	01/03/2019	25/07/2019	SmPC and PL	
WS/1380	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.2, 4.4 and 5.1 of the SmPC in order to reflect the final study results from study D1690C00024 (DERIVE); A Multicentre, Double-Blind, Placebo-Controlled, Parallel Group, Randomized, Phase III Study to Evaluate the Glycaemic Efficacy and Renal Safety of Dapagliflozin in Patients with Type 2 Diabetes Mellitus and Moderate Renal Impairment (CKD 3A) Who Have	20/09/2018	12/11/2018	SmPC and PL	Based on the results from study D1690C00024 (DERIVE) the following dosage recommendation in case of renal impairment has been updated in section 4.2 and 4.4. Forxiga, Edistride: dapagliflozin should not be initiated in patients with a glomerular filtration rate [GFR] < 60 mL/min and should be discontinued at GFR persistently below 45 mL/min. No dosage adjustment is required based on renal function. Xigduo, Ebymect: the maximum daily dose of metformin should preferably be divided into 2-3 daily doses. Factors that may increase the risk of lactic acidosis should be reviewed before considering initiation of metformin in

	Inadequate Glycaemic Control. In addition, the Worksharing applicant took the opportunity to implement minor editorial changes in Edistride, Ebymect and Xigduo PI and to update the list of local representatives in the Package Leaflets for Edistride and Ebymect. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				patients with GFR < 60 mL/min. The results of study D1690C00024 (DERIVE) have been reflected in section 5.1 of Edistride, Ebymect, Forxiga and Xigduo
R/0044	Renewal of the marketing authorisation.	26/07/2018	28/09/2018	SmPC, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Xigduo in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
PSUSA/10294 /201801	Periodic Safety Update EU Single assessment - dapagliflozin / metformin	06/09/2018	n/a		PRAC Recommendation - maintenance
WS/1345/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.d.z - Stability of AS - Other variation B.I.d.1.c - Stability of AS - Change in the re-test period/storage period or storage conditions - Change to an approved stability protocol	19/04/2018	n/a		
IG/0892	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder	28/02/2018	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				
PSUSA/10294 /201707	Periodic Safety Update EU Single assessment - dapagliflozin / metformin	08/02/2018	n/a		PRAC Recommendation - maintenance
IG/0894	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	05/02/2018	n/a		
WS/1271/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.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	23/11/2017	20/12/2017	SmPC, Labelling and PL	
WS/1229	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	30/11/2017	n/a		

WS/1259	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	30/11/2017	n/a		
IG/0841	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	24/10/2017	n/a		
WS/1167	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.8 and 5.1 of the SmPC in order to add information regarding two initial combination studies (MB102021 and MB102034) in treatment-naïve patients of dapagliflozin 5 mg + metformin and dapagliflozin 10 mg + metformin, respectively, compared to each component separately. In addition, the Worksharing applicant (WSA) 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	12/10/2017	20/12/2017	SmPC and Labelling	
WS/1196/G	This was an application for a group of variations following a worksharing procedure according to	14/09/2017	n/a		

	Article 20 of Commission Regulation (EC) No 1234/2008. B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation 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.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)				
PSUSA/10294 /201701	Periodic Safety Update EU Single assessment - dapagliflozin / metformin	01/09/2017	n/a		PRAC Recommendation - maintenance
WS/1198	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	20/07/2017	n/a		
WS/1092	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/07/2017	20/12/2017	SmPC and PL	In study D5553C00003, the combination of dapagliflozin and prolonged release exenatide (a GLP 1 receptor agonist) was compared to dapagliflozin alone and prolonged release exenatide alone in subjects with inadequate glycaemic control on metformin alone (HbA1c ≥ 8% and ≤ 12%). All treatment groups had a reduction in HbA1c compared to baseline. The combination treatment with dapagliflozin 10 mg and prolonged release exenatide group showed superior reductions in HbA1c from baseline compared to

					dapagliflozin alone and prolonged release exenatide alone. Combination therapy of dapagliflozin 10 mg and prolonged release exenatide resulted in significantly greater reductions in fasting plasma glucose, in 2 hour post prandial glucose, in body weight and systolic blood pressure at week 28, as compared to either agent alone. These efficacy results were reflected in section 5.1 of the SmPC. In addition the statement that combination with glucagon like peptide 1 (GLP 1) analogues had not been studied, was removed from section 4.4 as result of the availability of this study.
WS/1055	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	21/04/2017	20/12/2017	SmPC, Labelling and PL	
A20/0024	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	09/02/2017	20/04/2017	SmPC and PL	Please refer to the assessment report: SGLT2 inhibitors - EMEA/H/A-20/1442

	the scope of the procedure to include all SGLT2 inhibitors containing medicinal products to allow a review of data from the class. The PRAC was requested to assess the impact thereof on the benefit-risk balance of Invokana, Vokanamet, Forxiga, Edistride, Xigduo, Ebymect, Jardiance and Synjardy and to give its recommendation whether the marketing authorisation of these products should be maintained, varied, suspended or revoked. 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.				
WS/0921	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	06/04/2017	n/a		
WS/1103	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing	23/03/2017	n/a		

	authorisation, including the RMP - Other variation				
PSUSA/10294 /201607	Periodic Safety Update EU Single assessment - dapagliflozin / metformin	09/02/2017	n/a		PRAC Recommendation - maintenance
WS/1056	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	19/01/2017	20/04/2017	SmPC, Labelling and PL	Based on literature data, information on interaction on the interaction between 1,5-anhydroglucitol assay (monitoring glycaemic control method) and the SGLT2 inhibitors was added in section 4.5 of the Summary Product Characteristics as follows: Interference with 1,5-anhydroglucitol (1,5-AG) assay Monitoring glycaemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycaemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycaemic control.
A31/0018	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

WS/0968	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	10/11/2016	n/a		
PSUSA/10294 /201601	Periodic Safety Update EU Single assessment - dapagliflozin / metformin	02/09/2016	n/a		PRAC Recommendation - maintenance
WS/0931/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.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.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	21/07/2016	n/a		
A20/0012	Pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested on	25/02/2016	28/04/2016	SmPC and PL	Please refer to the assessment report: SGLT2 inhibitors -

	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.				EMEA/H/A-20/1419
IG/0654	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	29/02/2016	n/a		
IG/0653	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	29/02/2016	n/a		

	intermediate used in the manufacture of the AS or manufacturer of a novel excipient				
PSUSA/10294 /201507	Periodic Safety Update EU Single assessment - dapagliflozin / metformin	11/02/2016	n/a		PRAC Recommendation - maintenance
IG/0643	B.II.f.1.e - Stability of FP - Change to an approved stability protocol	12/01/2016	n/a		
WS/0824/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.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation 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 B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	10/12/2015	n/a		
IG/0633	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	09/12/2015	n/a		
PSUSA/10294 /201501	Periodic Safety Update EU Single assessment - dapagliflozin / metformin	10/09/2015	n/a		PRAC Recommendation - maintenance

IG/0576	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	26/06/2015	n/a		
IG/0522	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	12/03/2015	n/a		
IAIN/0009/G	This was an application for a group of variations. B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place 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.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	17/02/2015	11/02/2016	Annex II and PL	

	B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier				
PSUSA/10294 /201407	Periodic Safety Update EU Single assessment - dapagliflozin / metformin	12/02/2015	n/a		PRAC Recommendation - maintenance
WS/0601/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.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	22/01/2015	n/a		
IG/0486	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	28/11/2014	n/a		

	manufacturer of a novel excipient				
T/0005	Transfer of Marketing Authorisation fom Bristol-Myers Squibb/AstraZeneca EEIG to AstraZeneca AB. Transfer of Marketing Authorisation	23/09/2014	03/10/2014	SmPC, Labelling and PL	
WS/0536	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/07/2014	03/10/2014	SmPC	
WS/0510	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/07/2014	03/10/2014	SmPC and PL	
WS/0537	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 5.1 of the SmPC of Xigduo (dapaglifozin and metformin) and Forxiga (dapaglifozin) in order to reflect the long-term findings from 208 weeks (4 years) of administration of dapagliflozin as add-on-to metformin compared	22/05/2014	03/10/2014	SmPC	The up to 4 years safety and efficacy data has been reported in the clinical study report of study D1690C00004. Based on it the MAH has updated section 5.1 of the SmPC of Xigduo (dapaglifozin and metformin) and Forxiga (dapaglifozin) in order to reflect the long-term findings from 208 weeks of administration of dapagliflozin as add-on-to metformin compared with a sulphonylurea (glipizide) as add-on to metformin. The study was designed to show non-inferiority for

	with a sulphonylurea (SU; i.e, glipizide) as add-on to metformin. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				dapagliflozin versus glipizide at 52 weeks and the primary endpoint was met. At the end of the first extension period (LT1) some deterioration of HbA1c was observed, however, less prominent for dapagliflozin with a between treatment difference of 0.18 %. During the LT2 extension, HbA1c continued to rise but slower in the dapagliflozin treated group than in the glipizide treated group, resulting in a between treatment difference of -0.30 % at 208 weeks. Overall about 20 % of patients completed the study without the need for rescue medication in both treatment groups (20 % vs 18 %, dapagliflozin and glipizide respectively) thus managed to maintain an acceptable metabolic control for four years with either dapagliflozin or glipizide. Due to the progressive nature of T2DM it is well known that treatment has to be intensified over time and maintaining effect over four years is considered clinically relevant albeit in a limited proportion of the patients. The data also show that the effect of both treatments on body weight, which had stabilised for both treatments at 52 weeks, was maintained over the study duration resulting in a decrease in body weight (compared to baseline) of about -3.5 kg in the dapagliflozin treated group and a treatment difference of 4.38 kg at week 208. The safety data provided (up to 208 weeks treatment) confirm the safety profile known for dapagliflozin. The most common AEs are related to the increased excretion of urinary glucose, i.e. genital infections and UTI (urinary tract infections); there appears to be no increase in serious UTI over time compared to glipizide treatment. In conclusion, the data provided support the long-term use of dapagliflozin in the treatment of T2DM. The data supporting a maintained efficacy, both with regards to

					HbA1c and body weight, over the 208 week study period for a relevant proportion of patients is considered of relevance for the prescriber and the changes proposed to section 5.1 is therefore accepted. This application was submitted for a Type II variation, following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.
II/0002	Update of sections 4.2, 4.8 and 5.1 of the SmPC in order to reflect the up to 24 weeks safety and efficacy results reported in study D1693C00005 Clinical Study Report (CSR), study that investigated dapagliflozin as add-on therapy to metformin and a sulphonylurea for the treatment of subjects with Type 2 Diabetes who have inadequate glycaemic control on a background combination of metformin and sulphonylurea. The Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/04/2014	03/10/2014	SmPC and PL	The Marketing Authorisation Holder (MAH) submitted study D1693C00005 clinical study report (CSR) in order to provide additional information on the efficacy and safety of dapagliflozin as add-on therapy to metformin and a sulphonylurea (SU). Update of sections 4.2, 4.8 and 5.1 of the SmPC were proposed by the MAH in order to reflect the up to 24 weeks safety and efficacy results reported in the above mentioned study report. In the CHMP view, the data from study D1693C00005 show compelling efficacy results. A placebo-corrected reduction in HbA1c of -0.62 was observed after 24 weeks which is considered a clinically relevant effect. This treatment effect is within the same range as observed in previously reported placebo-controlled studies with dapagliflozin. It can therefore be concluded that dapagliflozin is effective in combination with metformin and a sulphonylurea. The additional effect on body weight and blood pressure is noted and welcomed. The safety profile reported in this study is similar to the already known safety profile. The CHMP considers that the benefit/risk balance of Xigduo, in the approved indication of treatment of type 2 diabetes, remains positive.