Forxiga

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/2299	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.	15/12/2022	03/02/2023	SmPC and PL	

[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).

	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
PSUSA/10029 /202110	Periodic Safety Update EU Single assessment - dapagliflozin	19/05/2022	15/07/2022	SmPC and PL	Please refer to EDISTRIDE, FORXIGA PSUSA-10029-202110 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation
WS/2284	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	23/06/2022	n/a		The PDCO has confirmed compliance with the agreed completed paediatric investigation plan as adopted November 2021. Therefore the statement indicating compliance with the agreed completed PIP has been confirmed.
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 variation	02/06/2022	n/a		
IG/1498/G	This was an application for a group of variations.	01/04/2022	15/07/2022	Annex II and	

	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			PL	
WS/1952	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Extension of indication for Forxiga / Edistride to include treatment of children aged 10 years and adolescents with T2DM based on the results from studies MB10209/D1690C000016 and MB102-138/D1690C00017; these are paediatric studies submitted according to Article 46 of the Paediatric Regulation. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 21 of the RMP has also been submitted. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	14/10/2021	15/11/2021	SmPC and PL	Please refer to Scientific Discussion dapagliflozin (Forxiga/ Edistride) 'Procedure No. EMEA/H/C/WS1952.
PSUSA/10029 /202104	Periodic Safety Update EU Single assessment - dapagliflozin	28/10/2021	n/a		PRAC Recommendation - maintenance
II/0071	Removal of the indication for 'the treatment of patients with Type 1 Diabetes Mellitus (T1DM) as an	16/09/2021	25/10/2021	SmPC, Annex II and PL	Removal of the Type 1 Diabetes Mellitus (T1DM) indication in adults in the product information for Forxiga 5mg based

	adjunct to insulin in patients with BMI ≥ 27 kg/m2 when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy' and related additional Risk Minimization Measures from Annex II for Forxiga 5 mg film-coated tablets. As a consequence, affected sections of the SmPC of the 5 mg tablets are updated. The Package Leaflet is updated in accordance. A combined SmPC/ Package Leaflet with the 10 mg tablets has been submitted. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				on the MAH's request. The RMP version 26.2 has been updated to remove the T1DM indication and all measures introduced as part of this indication, this includes the category 1 DKA PASS and all additional risk minimisation measures. Annex IID of the PI has been updated accordingly. A DHPC has been agreed to inform on the removal of the T1DM indication for Forxiga 5mg and its consequences.
WS/1941	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Extension of Indication to add the treatment of chronic kidney disease in adults. Sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated for Forxiga and Edistride based on the results from the renal outcomes study D169AC00001 (DAPA-CKD), and the Annex II.B and Package Leaflet of these products are updated accordingly. The DAPA-CKD study is a category 3, Post-Authorisation Safety Study (PASS) listed in the dapagliflozin RMP to evaluate the potential risk of lower limb amputation; it is a multicentre, event-driven, randomized, double-blind, parallel group, placebo-	24/06/2021	05/08/2021	SmPC, Annex II and PL	Please refer to Scientific Discussion Forxiga/ Edistride - EMEA/H/C/WS1941

	controlled study, evaluating the effect of dapagliflozin versus placebo, given once daily in addition to standard of care, to prevent the progression of chronic kidney disease (CKD) or cardiovascular (CV)/renal death. In addition, the Risk Management Plan for dapagliflozin (version 25s3) has been updated. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
WS/2069/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.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	10/06/2021	n/a		
IG/1401/G	This was an application for a group of variations. 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 manufacturing site for the FP - Primary packaging	04/06/2021	n/a		

	site				
PSUSA/10029 /202010	Periodic Safety Update EU Single assessment - dapagliflozin	06/05/2021	n/a		PRAC Recommendation - maintenance
IA/0068	B.II.e.4.a - Change in shape or dimensions of the container or closure (immediate packaging) - Non-sterile medicinal products	28/04/2021	05/08/2021	SmPC, Labelling and PL	
WS/2009/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.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	09/04/2021	n/a		
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/1335/G	This was an application for a group of variations.	12/02/2021	05/08/2021	Annex II and PL	

	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 A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites				
IB/0061	B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	11/11/2020	05/08/2021	SmPC, Labelling and PL	
WS/1737	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 for Edistride and Forxiga to add a new indication for the treatment of symptomatic heart failure with reduced ejection fraction in adults. The Package Leaflet and Labelling are updated in accordance. The RMP version 19.6 is agreed as part of this procedure. Furthermore, the PI is brought in line with the latest QRD template version 10.1, as well as editorial change (addition of SI unit for blood glucose).	15/10/2020	03/11/2020	SmPC, Labelling and PL	Please refer to Scientific Discussion 'Forxiga-H-C-002322-WS1737' and/or 'Edistride-H-C-04161/WS1737'

	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
PSUSA/10029 /202004	Periodic Safety Update EU Single assessment - dapagliflozin	29/10/2020	n/a		PRAC Recommendation - maintenance
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 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	03/09/2020	n/a		

	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				
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		
PSUSA/10029 /201910	Periodic Safety Update EU Single assessment - dapagliflozin	17/04/2020	n/a		PRAC Recommendation - maintenance
IG/1171	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	11/12/2019	15/10/2020	SmPC and PL	
WS/1692/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	14/11/2019	n/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.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				
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 (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	17/10/2019	15/10/2020	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.

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 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	27/06/2019	31/07/2019	SmPC and PL	Please refer to the Scientific Disdcussion 'EMEA/H/C/xxxx/WS/1539'

PSUSA/10029 /201810	Periodic Safety Update EU Single assessment - dapagliflozin	29/05/2019	25/07/2019	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10029/201810.
WS/1344	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	31/01/2019	20/03/2019	SmPC, Annex II, Labelling and PL	
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	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

	Moderate Renal Impairment (CKD 3A) Who Have 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				reviewed before considering initiation of metformin in 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
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		
PSUSA/10029 /201710	Periodic Safety Update EU Single assessment - dapagliflozin	12/04/2018	n/a		PRAC Recommendation - maintenance
IG/0892	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	28/02/2018	n/a		

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/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	12/10/2017	12/04/2018	SmPC and Labelling	

	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				
R/0035	Renewal of the marketing authorisation.	22/06/2017	28/08/2017	SmPC, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Forxiga in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
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	20/07/2017	12/04/2018	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

	new quality, preclinical, clinical or pharmacovigilance data				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.
PSUSA/10029 /201610	Periodic Safety Update EU Single assessment - dapagliflozin	18/05/2017	19/07/2017	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10029/201610.
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	19/07/2017	SmPC, Labelling and PL	
A20/0029	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	09/02/2017	20/04/2017	SmPC and PL	Please refer to the assessment report: SGLT2 inhibitors - EMEA/H/A-20/1442

	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 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	06/04/2017	n/a		

	starting material/reagent/intermediate for AS - Other variation				
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.
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		
A20/0021	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	25/02/2016	28/04/2016	SmPC and PL	Please refer to the assessment report: SGLT2 inhibitors - EMEA/H/A-20/1419

	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.				
PSUSA/10029 /201510	Periodic Safety Update EU Single assessment - dapagliflozin	14/04/2016	n/a		PRAC Recommendation - maintenance
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 intermediate used in the manufacture of the AS or manufacturer of a novel excipient	29/02/2016	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		
IG/0601	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)	09/09/2015	n/a		
PSUSA/10029 /201410	Periodic Safety Update EU Single assessment - dapagliflozin	07/05/2015	n/a		PRAC Recommendation - maintenance
IAIN/0020/G	This was an application for a group of variations.	01/04/2015	28/04/2016	Annex II and PL	

	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.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 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 B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the				

	dossier) - Replacement or addition of a supplier				
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		
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 manufacturer of a novel excipient	28/11/2014	n/a		

PSUV/0014	Periodic Safety Update	06/11/2014	n/a		PRAC Recommendation - maintenance
T/0015	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 with a sulphonylurea (SU; i.e, glipizide) as add-on to	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 dapagliflozin versus glipizide at 52 weeks and the primary

	metformin. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				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.
PSUV/0010	Periodic Safety Update	08/05/2014	n/a		PRAC Recommendation - maintenance
II/0008	Update of sections 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). The Package Leaflet was updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI is being brought in line with the latest QRD template version 9 except the black triangle wording which was subject to a separate Type IA(IN) variation. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	19/12/2013	05/03/2014	SmPC, Annex II and PL	The MAH proposed to include in the SmPC new information on the safety and efficacy of Dapagliflozin reflecting the results of study D1693C00005, which evaluated dapagliflozin in patients with Type 2 Diabetes who had inadequate glycaemic control on a background treatment combination of metformin and sulfonylurea. The CHMP considered that the results from study D1693C00005 showed convincing efficacy results. A statistical significant placebo-corrected reduction in HbA1c of -0.62 was observed after 24 weeks which was considered a clinically relevant effect size. It can therefore be concluded that dapagliflozin is effective as add on to standard therapy to control glucose levels in type 2 diabetes patients receiving metformin and a sulphonylurea in combination. An additional effect on body weight and blood pressure was shown as well. In addition no episodes of major hypoglycaemia were reported. No new safety concerns were identified by the CHMP. The CHMP considered that based on the submitted data it is appropriate to accept the proposed PI changes meant to reflect that the existing evidence supports the use of Forxiga in combination with metformin and a sulphonylurea

					taken concomitantly.
IAIN/0009	C.I.12 - Inclusion or deletion of black symbol and explanatory statements for medicinal products in the list of medicinal products that are subject to additional monitoring	25/10/2013	05/03/2014	SmPC and PL	
N/0007	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/09/2013	05/03/2014	PL	
IA/0006	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 currently approved batch size	24/06/2013	n/a		
II/0003	Update of sections 4.4, 4.8 and 5.1 of the SmPC in order to add information on the efficacy and safety of dapagliflozin as add-on to DPP-4 inhibitor (sitagliptin), with or without metformin. This variation is supported by data from Study D1690C00010. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	25/04/2013	05/03/2014	SmPC	The new clinical data are derived from a single clinical study (D1690C00010) that was stratified based on concomitant metformin use (sitagliptin monotherapy and sitagliptin + metformin). The primary efficacy evaluation was based on the first 24 weeks of treatment; maintenance of efficacy was also assessed as an exploratory objective at the 48-week time point. The placebo-corrected HbA1c reductions observed with dapagliflozin at Week 24 were maintained through Week 48 overall and within each stratum. Mean HbA1c levels gradually increased over time in the placebo group, whereas they remained relatively stable or increased to a lesser extent in the dapagliflozin group (Figure 1), resulting in numerical improvements in placebo-corrected estimates between Weeks 24 and 48 (-0.46% and -0.68%, respectively), excluding rescue, repeated measures analysis.

					Fasting plasma glucose (FPG) reductions observed during week 24 and week 48 showed that the effect of dapagliflozin compared to placebo on FPG were maintained until week 48 overall and in both strata; this is reflected in section 5.1 of the SmPC. Postprandial glucose levels showed a mean decrease from baseline in the absolute 2-hour post liquid meal glucose level compared to placebo at week 24 and was maintained until week 48; this point has also been refelcted in section 5.1 of the SmPC. Subjects with baseline seated systolic blood pressure (SBP) ≥130 mmHg and a measurement of seated SBP at week 8, week 24, and week 48 did not show a mean change from baseline in seated SBP at either time point in the dapagliflozin group compared to placebo (-0.86 mmHg versus placebo). The results suggest that dapagliflozin had no meaningful effect on seated SBP compared to placebo in subjects with baseline seated SBP ≥130 mmHg at week 8 and continued to show no effect on seated SBP until week 48. Overall, subjects in the dapagliflozin group showed a mean decrease from baseline in total body weight compared to placebo of 2.03 kg at week 24 and of 2.22 kg at week 48. Referring to strata, the placebo-corrected mean decrease from baseline in total body weight was 1.86 kg at week 24 and 2.23 kg at week 48 in stratum 1 as well as 2.04 kg at week 24 and 2.07 kg at week 48 in stratum 2. The results suggest that the effect of dapagliflozin compared to placebo on total body weight at week 24 was maintained until week 48 overall and in both strata; this is reflected in section 5.1 of the SmPC. The proportion of subjects achieving therapeutic glycaemic

					response defined as decrease in HbA1c of at least 0.7% from baseline was larger by 20.9% in the dapagliflozin than in the placebo group at week 48. The CHMP agreed that no conclusion on the maintenance of therapeutic glycaemic response could be drawn because the criterion for therapeutic glycaemic response was not evaluated at week 24. At Week 48 when added to sitagliptin (with or without metformin), the adjusted mean change from baseline for dapagliflozin 10 mg and placebo was -0.30% and 0.38%, respectively. This has been reflected in section 5.1 of the SmPC. The results of the submitted data reflecting treatment with dapagliflozin as add-on therapy to DPP-4 Inhibitor sitagliptin, with or without metformin, over 48 weeks did not identify any new safety concerns. However, there were tendencies to higher incidences of hypovolemia and adverse events of renal impairment which emphasise the importance of the warnings and precautions included in the SmPC.
II/0005	Update of sections 4.8 and 5.1 of the SmPC in order to: • Change in frequency figures in Section 4.8, in the sub-section on "Vulvovaginitis, balanitis and related genital infections" to achieve consistency within this section, and also across this section and the sub-section on "Urinary tract infections" and to make the SmPC more clinically relevant for prescribers. • Correct the figures reported in Table 5, Section 5.1 (Pharmacodynamic properties, under heading "Combination therapy") due to a consistent programming error in late phase clinical studies with	21/03/2013	05/03/2014	SmPC	Based on the review of the submitted data and justifications which were generated by the MAH in order to correct the following: - two programming errors that affected only analyses of proportional efficacy endpoints - inconsistencies identified in the SmPC, Section 4.8 which affected the frequency figures mentioned for Vulvovaginitis, balanitis and related genital infections - an error associated with the omission of pioglitazone data from the SmPC affecting the figures mentioned in Section 5.1, sub-section "Fasting plasma glucose" (under headings "Glycaemic control" and "Combination therapy")

	dapagliflozin. • Correct the data in Section 5.1 (Pharmacodynamic properties), in the sub-section on "Fasting plasma glucose" (under heading "Glycaemic control") in order to remove the data related to pioglitazone. • Correct a rounding-off error in Section 5.1 of the SmPC, in the sub-section on "Patients with renal impairment" C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				- a correction of a rounding-off error which affected section 5.1 of the SmPC, subsection "Patients with renal impairment" the CHMP concluded that the updated figures are introducing numerically small changes and do not impact the evaluation and prior conclusions on the reported clinical efficacy and safety results. Moreover, the CHMP considers that the proposed SmPC changes reflect in an appropriate manner the updated clinical results.
II/0002/G	This was an application for a group of variations. Update of section 4.8 and 5.1 of the SmPC in order to update the safety and the pharmacology information based on the up to 2 years data presented in the clinical study reports of studies D1690C00004 and D1690C00006 and to correct an error in the SmPC section 5.1, in subsection 'Body weight'. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	21/03/2013	05/03/2014	SmPC	The up to 2 years safety and efficacy data has been reported in the clinical study reports of studies D1690C00004 and D1690C00006. Based on it the MAH has updated the SmPC sections 4.8 in order to report the frequency of the major and minor hypoglycaemic events and 5.1 in order to indicate that effect is maintained compared to placebo and dapagliflozin appeares to be at least as effective as glipizide during the 52 weeks up to 104 weeks study period following the initial 52 weeks study period reported previously. Concerning safety, in general, the identified risks were confirmed. Concerning potential risks, there were tendencies to higher incidences of hypovolaemia and AEs of renal impairment which are appropriately reflected through the already present SmPC warnings and precautions. In addition the reported figure for the body weight after short term treatment was corrected so that it does not include data after rescue treatment is given.

IB/0001	B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation	04/02/2013	n/a		
IG/0259	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	18/01/2013	n/a		