Ebymect

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
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	26/06/2023	n/a		

[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).

	(excluding manufacturer for batch release)				
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	06/02/2023	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 variation	02/06/2022	n/a		
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	06/02/2023	Annex II and PL	
PSUSA/10294	Periodic Safety Update EU Single assessment -	02/09/2021	n/a		PRAC Recommendation - maintenance

/202101	dapagliflozin / metformin				
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 manufacturing site for the FP - Primary packaging site	17/06/2021	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/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	04/02/2022	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	03/09/2020	n/a		

	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 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
R/0046	Renewal of the marketing authorisation.	25/06/2020	25/08/2020	SmPC, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Ebymect in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
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 relevant Ph. Eur. Monograph - New certificate from a new manufacturer (replacement or addition)	23/07/2020	n/a		
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	25/08/2020	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. 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	16/01/2020	n/a		

IG/1171	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	11/12/2019	25/08/2020	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 (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	25/08/2020	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.

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 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) -	27/06/2019	01/08/2019	SmPC and PL	Please refer to the Scientific Disdcussion 'EMEA/H/C/xxxx/WS/1539'

	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	01/08/2019	SmPC and PL	
IB/0034	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	07/12/2018	11/01/2019	SmPC, Labelling 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 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	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 patients with GFR < 60 mL/min. The results of study D1690C00024 (DERIVE) have been reflected in section 5.1 of Edistride, Ebymect, Forxiga and

	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				Xigduo
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 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		
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	05/02/2018	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				
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	24/10/2017	n/a		

	the AS - Minor change in the manufacturing process of the AS				
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 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	14/09/2017	n/a		

	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.
A20/0013	Pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested on 15 April 2016 the PRAC to assess the impact on the benefit-risk balance of canagliflozin containing medicinal products of an increase in amputations, mostly affecting the toes, observed in an ongoing clinical trial (CANVAS) for canagliflozin and a numerical imbalance with regards to amputation events seen in an ongoing renal study CANVAS-R with a similar population as CANVAS. Considering that a class effect cannot be excluded, the European Commission extended on 6 July 2016 the scope of the procedure to include all SGLT2 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.	09/02/2017	04/05/2017	SmPC and PL	Please refer to the assessment report: SGLT2 inhibitors - EMEA/H/A-20/1442

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	
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 authorisation, including the RMP - Other variation	23/03/2017	n/a		
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	19/01/2017	04/05/2017	SmPC,	Based on literature data, information on interaction on the

	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			Labelling and PL	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.
A31/0007	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		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.	10/11/2016	n/a		

	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation				
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		
IAIN/0011	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	25/05/2016	12/12/2016	SmPC and PL	
WS/0894/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.	14/04/2016	n/a		

	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				
N/0009	Update of the package leaflet with revised contact details of local the representative for Spain. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	29/03/2016	12/12/2016	PL	
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		
IA/0003	A.7 - Administrative change - Deletion of	28/01/2016	n/a		

	manufacturing sites				
IG/0643	B.II.f.1.e - Stability of FP - Change to an approved stability protocol	12/01/2016	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		