Incruse Ellipta

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/2816	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.b - Introduction of, or change(s) to, the obligations and conditions of a marketing	13/03/2025	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).

	authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required				
SW/0042	Post Authorisation Safety Study results - EMEA/H/C/PSR/S/0048 – Variation	19/09/2024	14/11/2024	SmPC, Annex II and PL	This submission concerns the final results of the PASS study, which was a condition of the marketing authorisation(s) of medicinal products containing the active substance umeclidinium bromide, umeclidinium bromide/vilanterol. The primary objectives were to demonstrate non-inferiority of UMEC/VI combination and UMEC to tiotropium for risk of the composite endpoint of MI, stroke, heart failure or sudden cardiac death based on an analysis of time to first event for new users of UMEC/VI combination, UMEC or tiotropium and to quantify the incidence rate and frequency of the composite endpoint An increased risk of MI compared was observed in UMEC/VI cohort with respect to tiotropium: adjusted HR of 2.195 (1.053, 4.575). The risk of MI was lower between the UMEC and TIO (adjusted HR (95% CI) of 1.754 (0.748, 4.115)). The PRAC acknowledged that the study was powered to test for differences between cohorts for the primary composite endpoint only and not to test for non-inferiority in the secondary endpoints; however, such difference in the MI risk is to be noted. Nevertheless, the risk benefit balance was considered unchanged by PRAC. Cardiovascular disease is a common cause of death in patients with COPD, and is a key target for improving outcomes, and a higher risk of MI in COPD patients is expected, with respect to general population.

					Following the evaluation of PASS final report, the condition is now considered fulfilled and consequently an update of the Annex II conditions or restrictions with regard to the safe and effective use of the medicinal product is recommended to remove this condition. Consequently, this product is no anymore subject to additional monitoring and the black triangle should be removed from the PI.
IG/1716	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	04/04/2024	n/a		
IG/1709	B.II.e.3.a - Change in test procedure for the immediate packaging of the finished product - Minor changes to an approved test procedure	27/02/2024	n/a		
WS/2485	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	14/12/2023	14/11/2024	SmPC, Labelling and PL	
WS/2504/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.b.2.z - Change in test procedure for AS or	20/07/2023	n/a		

	starting material/reagent/intermediate - Other variation B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation				
IG/1633/G	This was an application for a group of variations. B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer B.I.a.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	18/07/2023	n/a		
PSUSA/10263 /202112	Periodic Safety Update EU Single assessment - umeclidinium	15/09/2022	09/11/2022	SmPC and PL	Please refer to EPAR: scientific conclusions and grounds recommending the variation to the terms of the marketing

					authorisation.
IB/0036	C.I.1.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a Union referral procedure - The product is not covered by the defined scope of the procedure but the change(s) implements the outcome of the procedure and no new additional data is required to be submitted by the MAH	24/08/2022	09/11/2022	SmPC, Annex II, Labelling and PL	
N/0034	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	11/08/2021	14/02/2022	PL	
IG/1340	A.7 - Administrative change - Deletion of manufacturing sites	16/02/2021	14/02/2022	Annex II and PL	
IG/1330	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	22/01/2021	n/a		
N/0031	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/12/2020	14/02/2022	PL	
WS/1589	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Submission of an updated RMP version 7.2 following completion of a category 3 study (WWE117397) "A Post-authorization safety Electronic Medical Records	29/10/2020	n/a		The MAH submitted with this variation an updated RMP version 7.2. following completion of a category 3 study (WWE117397) to reflect the utilization among new users (including possible off-label prescribing) of these medications in a real-world, post-approval setting. In addition, updates are also included relating to the Category 1 study 201038 and agreed in procedure PSA/S/0032.3

	database retrospective cohort study of new users of inhaled UMEC/VI or new users of inhaled UMEC in the primary care setting". In addition, updates are included relating to the Category 1 study 201038 "Post-authorisation Safety (PAS) Observational Cohort Study to Quantify the Incidence and Comparative Safety of Selected Cardiovascular and Cerebrovascular Events in COPD Patients Using Inhaled UMEC/VI Combination, or Inhaled UMEC versus Tiotropium (Study201038)." The RMP is also updated to align with the Guidance on the Good Pharmacovigilance Practice (GVP) Module V - Risk management systems Revision 2 guidelines. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required				which assessed substantial amendments to a non-interventional imposed PASS protocol in accordance with Article 107o of Directive 2001/83/EC. Those changes covered: Study title amended to align with the primary study objective, the primary and secondary objectives updated to include the composite endpoint and the sample size for the study. The reclassification of the safety concerns proposed by the MAH is acceptable.
WS/1863/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.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	24/09/2020	n/a		

	site B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release/control, and secondary packaging, for biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes 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.z - Change in the manufacturing process of the finished or intermediate product - Other variation				
WS/1761	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Submission of the final report from study WWE117397 listed as a category 3 study in the RMP. This was a retrospective longitudinal non-interventional observational study of new users of inhaled umeclidinium/vilanterol (UMEC/VI) or new users of inhaled umeclidinium (UMEC) or new users or long-acting bronchodilators (LABD) in the primary care setting. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	09/07/2020	n/a		The primary objective of the study was to report the proportion of patients with a possible off-label use and characterize them in new users of UMEC/VI, UMEC, or other LABD. The second objective was to quantify incidence of major cardiovascular and cerebrovascular events, mortality and pneumonia, and rates of exacerbations of COPD during follow-up in new users of UMEC/VI or UMEC. The tertiary objective was in new users of UMEC/VI or UMEC with 12 or more months of follow-up following initiation, to describe treatment patterns and adherence. Despite the fact that several limitations were identified in data sources and did not allow to drawn sound conclusions for all the study objectives, the final report provides insight on UMEC and UMEC/VI utilisation patterns, including off-label prescribing rate of UMEC and UMEC/VI compared to other LABD in a primary care UK setting. Overall, the incidence of cardiovascular events and respiratory outcomes was as

					expected for these products classes, and no new safety signals were identified. Mortality rates reported in this study (using linked CPRD-HES-ONS) data are comparable to those reported using the same dataset for other LAMAs. The analysis of treatment patterns during the first 12 months after initiating treatment with UMEC or UMEC/VI showed a good level of continuity for the majority of new users. No major difference in treatment patterns of on-label or potential off-label use for both UMEC and UMEC/VI users was noted in all groups. It can also be concluded that in this setting the analysis reveals a moderate level of adherence to UMEC and UMEC/VI treatment. Overall, based on the data reviwed no change to the product information was deemed necessary.
PSUSA/10263 /201812	Periodic Safety Update EU Single assessment - umeclidinium	25/07/2019	23/09/2019	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10263/201812.
WS/1505	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 to add efficacy information based on the 52-week study CTT116855; a 52-week study designed to evaluate the efficacy of FF/UMEC/VI 100/62.5/25 compared with dual therapy of FF/VI 100/25 or UMEC/VI 62.5/25 in subjects with COPD. In addition, clarification on information related to the 24 week study submitted at time of initial authorisation is introduced in section 5.1. Update of section 4.8 of the SmPC to update the	19/09/2019	24/09/2020	SmPC and PL	The procedure started as a modification of indication in order to reflect prevention on COPD exacerbations in the approved indication. The evaluation of the presented data led to an update of section 5.1 to describe information that may be relevant for the prescribers to take decisions in the step wise approach to COPD management. Results from the IMPACT study do not allow ascertaining the exact contribution of Incruse/Rolufta Ellipta to the reduction in the rate of exacerbations. However the data are considered relevant from the clinical point of view taking into account the known correlation between exacerbations and morbidity/mortality. The following data added to section 5.1: In the randomised, double-blind, 52-week study (CTT116855, IMPACT) of 10,355 adult patients

	frequency of constipation from 'uncommon' to 'common'. The Package Leaflet is updated in accordance. The worksharing procedure leads to amendments to the Summary of Product Characteristics and Package Leaflet. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				with symptomatic COPD and a history of 1 or more moderate or severe exacerbations within the prior 12 months, treatment with fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI 99/55/22 micrograms) once daily as a single inhaler was compared with fluticasone furoate/vilanterol (FF/VI 99/22 micrograms) once daily as a single inhaler. The primary endpoint was annual rate of on-treatment moderate and severe exacerbations in subjects treated with FF/UMC/VI compared with FF/VI. The mean annual rate of exacerbations was 0.91 and 1.07 for FF/UMEC/VI and FF/VI respectively (Rate Ratio: 0.85; 95% CI: 0.80, 0.90; p<0.001). At Week 52, a statistically significant improvement in the least-squares (LS) mean change from baseline in trough FEV1 was observed for FF/UMEC/VI compared with FF/VI (mean change: +94 mL vs. -3 mL; treatment difference: 97 mL; 95% CI: 85, 109; p<0.001). In addition, clarification on information related to the 24 week study submitted at time of initial authorisation is introduced in section 5.1 , in particular information on the severity of disease in the trial population studied in the 24 week efficacy study, as well as information on the risk ratios and confidence intervals. Furthermore, based on the frequency reported in the IMPACT study, the frequency of constipation has been amended from 'uncommon' to 'common' in section 4.8 of the SmPC. The Package leaflet is amended accordingly.
N/0026	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/04/2019	19/07/2019	Labelling	

IAIN/0027	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	25/03/2019	n/a		
R/0021	Renewal of the marketing authorisation.	15/11/2018	11/01/2019	SmPC, Annex II, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Incruse Ellipta in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
T/0022	Transfer of Marketing Authorisation	12/10/2018	20/11/2018	SmPC, Labelling and PL	
IAIN/0024	B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing	19/11/2018	19/07/2019	Annex II and PL	
WS/1437/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.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 B.I.c.1.a - Change in immediate packaging of the AS - Qualitative and/or quantitative composition	20/09/2018	n/a		

PSUSA/10263 /201712	Periodic Safety Update EU Single assessment - umeclidinium	06/09/2018	n/a		PRAC Recommendation - maintenance
IG/0959	A.2.a - Administrative change - Change in the (invented) name of the medicinal product for CAPs	10/08/2018	14/11/2018	SmPC, Annex II, Labelling and PL	
WS/1276/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.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.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release/control, and secondary packaging, for biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes	22/03/2018	n/a		
WS/1191	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	13/07/2017	12/06/2018	SmPC and PL	

	data				
PSUSA/10263 /201610	Periodic Safety Update EU Single assessment - umeclidinium	18/05/2017	13/07/2017	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10263/201610.
WS/1030	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	21/04/2017	13/07/2017	SmPC, Labelling and PL	
II/0013	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	21/04/2017	13/07/2017	SmPC and PL	
PSUSA/10263 /201604	Periodic Safety Update EU Single assessment - umeclidinium	10/11/2016	04/01/2017	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10263/201604.
WS/0979	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	13/10/2016	n/a		
IG/0715	B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect	26/07/2016	n/a		

	the product information				
PSUSA/10263 /201510	Periodic Safety Update EU Single assessment - umeclidinium	13/05/2016	n/a		PRAC Recommendation - maintenance
IB/0009	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	03/05/2016	11/11/2016	Labelling	
II/0007	Update of section 4.8 of the SmPC in order to add Dysgeusia as an Adverse Drug Reaction (ADR) with an uncommon frequency. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives for Iceland in the Package Leaflet and to implement the QRD version 9.1 in the Product Information. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	12/11/2015	11/11/2016	SmPC, Annex II and PL	
PSUSA/10263 /201504	Periodic Safety Update EU Single assessment - umeclidinium	06/11/2015	n/a		PRAC Recommendation - maintenance
IB/0006	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	30/09/2015	14/12/2015	SmPC, Labelling and PL	
WS/0723/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.	25/06/2015	n/a		

	Submission of two non-clinical studies (2014N214514 and 2014N214870) regarding in-vitro investigations to determine the potential for drug-drug interactions in fulfilment of MEA003 for Anoro and Laventair and MEA002 for Incruse; the RMP is updated accordingly (final versions adopted are: Anoro v6.0, Laventair v6.0 and incruse v6.0). In addition the MAH takes the occasion to include minor routine updates in the RMP and to include in the MA for Anoro and Laventair report 2012N156532 on results of physiologically based PK modelling and simulation already assessed during the Incruse MAA. 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				
PSUSA/10263 /201410	Periodic Safety Update EU Single assessment - umeclidinium	07/05/2015	n/a		PRAC Recommendation - maintenance
II/0002	Update of sections 5.1 of the SmPC in order to update pharmacokinetic information on the use of umeclidinium bromide in association with other COPD treatments. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/04/2015	14/12/2015	SmPC	In two 12-week, placebo controlled studies (200109 and 200110), the addition of Incruse to fluticasone furoate/vilanterol (FF/VI) (100/25 micrograms) once daily in adult patients with a clinical diagnosis of COPD, resulted in statistically significant and clinically meaningful improvements in the primary endpoint of trough FEV1 at Day 85 compared to placebo plus FF/VI (124 mL (95% CI 93, 154, p<0.001) and 122 mL (95%CI 91, 152, p<0.001)).

					Improvements in lung function were supported with reductions in use of salbutamol over Weeks 1-12 (-0.4 puffs per day (95% CI -0.7, -0.2, p<0.001) and -0.3 puffs per day (95% CI -0.5, -0.1, p=0.003)) compared to placebo plus FF/VI but improvements in SGRQ at week 12 were not statistically significant (200109) or clinically relevant (200109 and 200110). The short duration of the studies and limited number of exacerbation events, preclude any conclusion regarding additional effect of Incruse on COPD exacerbation rate. No new adverse drug reactions were identified with the addition of Incruse to FF/VI in these studies.
II/0001	Update of section 4.8 of the SmPC in order to add the adverse reactions constipation and dry mouth with a frequency uncommon. The frequency of other adverse reactions is also corrected. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity add the date of first marketing authorisation in the SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	18/12/2014	14/12/2015	SmPC and PL	