Anoro 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
PSUSA/10264 /202112	Periodic Safety Update EU Single assessment - umeclidinium bromide / vilanterol	15/09/2022	18/11/2022	SmPC and PL	Please refer to EPAR: scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation.
IG/1461/G	This was an application for a group of variations.	24/01/2022	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).

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	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.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				
IG/1443	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	13/09/2021	n/a		
N/0036	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	23/07/2021	02/06/2022	PL	
IG/1341/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	16/02/2021	02/06/2022	Annex II and PL	
IG/1339	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 -	27/01/2021	n/a		

	Not including batch control/testing				
WS/1968	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.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	14/01/2021	n/a		
N/0032	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/12/2020	02/06/2022	PL	
WS/1850	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	15/10/2020	n/a		
IG/1273	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	07/09/2020	n/a		
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.	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

	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				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.
WS/1586	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 8.0 following the renewal procedures (EMEA/H/C/4002751/R/0022	03/10/2019	n/a		As per PRAC recommendation for Anoro/Laventair Ellipta renewal procedures (EMEA/H/C/4002751/R/0022 and EMEA/H/C/003754/R/0025), the MAH updated the RMP in line with GVP revision 2, including the removal of the important identified risks of 'Hypersensitivity' and 'Paradoxical bronchospasm'. The product information of

	and EMEA/H/C/003754/R/0025) commitments to remove the important identified risks of 'hypersensitivity' and 'paradoxical bronchospasm' from the list of safety concerns and to update all relevant sections of the RMP in line with revision 2 of GVP module V on 'Risk management systems' and revision 2 of the guidance on the format of the RMP in the EU (template). In addition, the important potential risks of 'narrow angle glaucoma' and 'bladder outflow obstruction and urinary retention' are removed; as well as the missing information on 'safety in pregnancy and lactation', 'safety in long-term use' and 'safety in severe hepatic impairment'. 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				Anoro/Laventair has a warning to inform HCPs and patients on the risk of 'paradoxical bronchospasm' following administration of umeclidinium/vilanterol and section 4.8 of the SmPC list the adverse drug reaction (ADRs) with frequency 'rare'. Hypersensitivity reactions including: Rash, Anaphylaxis, angioedema, and urticaria are listed as ADRs in section 4.8 of the SmPC. The current risk minimisation measures are considered sufficient to minimise the risks.As per PRAC recommendations issued in July 2016 (EMEA/H/C/PSUSA/00010264/201512), the important potential risks of 'glaucoma' and 'bladder outflow obstruction/urinary retention' are removed from the RMP. 'Bladder outflow obstruction and urinary retention' and 'glaucoma' are ADRs listed in section 4.8 of SmPC of Anoro/Laventair with frequency 'rare'. The current risk minimisation measures are considered sufficient to minimise the risks. In preclinical studies, no evidence of a direct embryotoxic, fetotoxic, or teratogenic outcome was observed. The use of Anoro/Laventair during pregnancy is currently under routine PV monitoring and periodically reviewed in PSURs. Review of this data did not identify any new safety concern in this population. There are no cumulative reports of umeclidinium / vilanterol exposure during breast feeding. The product information of Anoro/Laventair in section 4.6 of the SmPC includes information addressing the safety in pregnancy and lactation. The current risk minimisation measures are considered sufficient to minimise the risk therefore 'safety in pregnancy and lactation' as missing information is removed from the RMP. Clinical pharmacology studies were performed in severe renal and moderate hepatic impaired subjects. Patients

					with moderate hepatic impairment showed no evidence of an increase in systemic exposure to either umeclidinium or vilanterol, and no evidence of altered protein binding between patients with moderate hepatic impairment and healthy volunteers. Conversely, no clinical pharmacology studies were performed in severe hepatic impaired patients. Umeclidinium is mainly metabolized by the hepatic CYP2D6 pathway; no difference in systemic exposure of umeclidinium has been shown in poor versus extensive metabolisers. Section 4.2 of the SmPC includes information on safety in sever hepatic impairment Based on the above, a change in benefit risk profile in patients with severe hepatic impairment is not expected. Therefore, 'Safety in severe hepatic impairment use' as missing information is removed from the RMP. From the last PSUSA (EMEA/H/C/PSUSA/00010264/201712) no specific pattern in reported AEs was seen in patients who had received Anoro/ Laventair Ellipta for longer than one year. There are no data suggesting that the safety of Anoro/ Laventair Ellipta in the long term may differ from the known safety profile. Safety in long-term use as missing information is therefore removed from the RMP.
PSUSA/10264 /201812	Periodic Safety Update EU Single assessment - umeclidinium bromide / vilanterol	25/07/2019	19/09/2019	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10264/201812.
WS/1501	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	19/09/2019	16/11/2020	SmPC	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

	Update of a section 5.1 of the SmPC in order 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. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				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 Anoro 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), 10,355 adult patients with symptomatic COPD and a history of 1 or more moderate/severe exacerbations in the prior 12 months were randomised (1:2:2) to receive umeclidinium/vilanterol (UMEC/VI 55/22 micrograms), fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI 92/55/22 micrograms), or fluticasone furoate/vilanterol (FF/VI 92/22 micrograms) administered once daily as a single inhaler. The primary endpoint was annual rate of on-treatment moderate and severe exacerbations in subjects treated with FF/UMEC/VI compared with FF/VI and UMEC/VI. The mean annual rate of exacerbations was 0.91, 1.07 and 1.21 for FF/UMEC/VI, FF/VI, and UMEC/VI respectively. The comparison of FF/UMEC/VI to FF/VI and UMEC/VI resulted in a statistically significant 14.8% reduction in risk of a moderate/severe exacerbation (based on analysis of time to first exacerbation) (Hazard Ratio 0.85; 95% CI: 0.80, 0.91; p<0.001) and 16.0% reduction in risk of a moderate/severe exacerbation respectively (based on analysis of time to first exacerbation) (Hazard Ratio 0.84; 95% CI: 0.78, 0.91; 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.
N/0027	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/04/2019	25/07/2019	Labelling	
IG/1016	B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing	16/01/2019	25/07/2019	Annex II and PL	
R/0022	Renewal of the marketing authorisation.	15/11/2018	15/01/2019	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 Anoro Ellipta in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
T/0023	Transfer of Marketing Authorisation	12/10/2018	06/12/2018	SmPC, Labelling 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	20/09/2018	n/a		

	- Qualitative and/or quantitative composition				
IG/0959	A.2.a - Administrative change - Change in the (invented) name of the medicinal product for CAPs	10/08/2018	26/11/2018	SmPC, Annex II, Labelling and PL	
PSUSA/10264 /201712	Periodic Safety Update EU Single assessment - umeclidinium bromide / vilanterol	12/07/2018	n/a		PRAC Recommendation - maintenance
IG/0940	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	28/06/2018	n/a		
WS/1189	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	13/07/2017	19/02/2018	SmPC and PL	
PSUSA/10264 /201612	Periodic Safety Update EU Single assessment - umeclidinium bromide / vilanterol	06/07/2017		SmPC and PL	PRAC Recommendation - maintenance
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	19/02/2018	SmPC, Labelling and PL	

WS/1031	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	26/01/2017	19/02/2018	SmPC, Labelling and PL	
PSUSA/10264 /201606	Periodic Safety Update EU Single assessment - umeclidinium bromide / vilanterol	12/01/2017	n/a		PRAC Recommendation - maintenance
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		
WS/0986	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	29/09/2016	n/a		
PSUSA/10264	Periodic Safety Update EU Single assessment -	21/07/2016	22/09/2016	SmPC and PL	Please refer to Anoro/Laventair

/201512	umeclidinium bromide / vilanterol				EMEA/H/C/PSUSA/00010264/201512 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation
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 the product information	26/07/2016	n/a		
PSUSA/10264 /201506	Periodic Safety Update EU Single assessment - umeclidinium bromide / vilanterol	28/01/2016	30/03/2016	SmPC and PL	Please refer to Anoro, Laventair PSUSA/00010264/201506 EPAR: Scientific conclusions and grounds for recommending the variation to the terms of the marketing authorisation
WS/0871/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 B.II.b.2.c.1 - Change to importer, batch release	14/01/2016	30/03/2016	Annex II and PL	

	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				
N/0008	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	21/12/2015	30/03/2016	PL	
WS/0823	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 4.8 of the SmPC to add the new ADRs 'rash', 'anaphylaxis, angioedema and urticaria', 'tremor', 'dysgeusia' and 'palpitations'. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to correct minor inaccuracies in sections 4.5 and 5.1 of the SmPC, to implement minor editorial changes in the SmPC and Package Leaflet and to align the SmPC with the latest QRD template. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	01/10/2015	30/03/2016	SmPC and PL	Anaphylaxis, angioedema and urticaria were added to the SmPC with an allocated frequency of 'rare'. Rash, tremor, dysgeusia and palpitations were added with a frequency category of 'uncommon'.
PSUSA/10264 /201412	Periodic Safety Update EU Single assessment - umeclidinium bromide / vilanterol	09/07/2015	n/a		PRAC Recommendation - maintenance
WS/0723/G	This was an application for a group of variations following a worksharing procedure according to	25/06/2015	n/a		

	Article 20 of Commission Regulation (EC) No 1234/2008. 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				
IB/0002	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	26/03/2015	30/03/2016	SmPC, Labelling and PL	
PSUV/0001	Periodic Safety Update	09/01/2015	n/a		PRAC Recommendation - maintenance