Enurev Breezhaler

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/2176	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	28/10/2021		SmPC, Annex II, Labelling and PL	
IG/1459/G	This was an application for a group of variations.	27/10/2021	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).

	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 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)				
WS/2103	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	30/09/2021	n/a		
IG/1391	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	22/04/2021		SmPC, Annex II and PL	
IG/1376/G	This was an application for a group of variations. A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the	14/04/2021	n/a		

	finished product, including quality control sites (excluding manufacturer for batch release)				
IG/1347/G	This was an application for a group of variations. B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier	22/02/2021	n/a		
WS/1977	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	04/02/2021	n/a		
IG/1320/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name	16/12/2020	n/a		

	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 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)				
PSUSA/10047 /201909	Periodic Safety Update EU Single assessment - glycopyrronium bromide (for centrally authorised product indicated for chronic obstructive pulmonary disease)	14/05/2020	n/a		PRAC Recommendation - maintenance
IG/1197/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites 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	28/01/2020	20/11/2020	Annex II and PL	
WS/1706	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	12/12/2019	20/11/2020	SmPC, Labelling and PL	

WS/1561	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	14/03/2019	n/a		
IG/1028/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	05/12/2018	n/a		
T/0027	Transfer of Marketing Authorisation	13/06/2018	02/07/2018	SmPC, Labelling and PL	
IB/0026/G	This was an application for a group of variations. 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.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	16/05/2018	n/a		

WS/1299	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 study report of the Category 1 Post-Authorisation Safety Study (PASS) on cardio- and cerebrovascular outcomes (Multinational, multidatabase cohort study to assess adverse cardiovascular and cerebrovascular outcomes and mortality in association with inhaled NVA237 in Europe / CNVA237A2402T) with subsequent update of Annex II. Consequently, the deletion from the list of additional monitoring led to the update of Annex I and IIIB. The MAH also took this opportunity to update the local representatives. The RMP version 8 was submitted. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	12/04/2018	02/07/2018	SmPC, Annex II and PL	Changes in the SmPC, PL and Annex II relate only to the deletion of the PASS commitment and consequent removal from the list of additional monitoring.
WS/1298	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	12/04/2018	n/a		
WS/1247/G	This was an application for a group of variations following a worksharing procedure according to	28/09/2017	n/a		

	Article 20 of Commission Regulation (EC) No 1234/2008. B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition) B.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State				
IG/0837	B.II.e.4.a - Change in shape or dimensions of the container or closure (immediate packaging) - Non-sterile medicinal products	21/09/2017	n/a		
R/0020	Renewal of the marketing authorisation.	18/05/2017	13/07/2017	SmPC, Labelling and PL	
IG/0816	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)	19/06/2017	n/a		
PSUSA/10047 /201609	Periodic Safety Update EU Single assessment - glycopyrronium bromide (for centrally authorised product indicated for chronic obstructive pulmonary disease)	06/04/2017	n/a		PRAC Recommendation - maintenance
IG/0750	B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier	02/12/2016	n/a		

WS/1002	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 Study Report of DUS (CNVA237A2401T) and RMP update (version 6.0). C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	15/09/2016	n/a		
WS/1001	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Revision of section 4.8 of SmPC to include a new ADR, Dysphonia. The PL is updated accordingly. The MAHs took the opportunity to update to the latest QRD template v10. The MAH also took the opportunity to update in Annex II the wording of the PASS study milestones, following the assessment of ANX01 commitment to date. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	15/09/2016	13/07/2017	SmPC, Annex II, Labelling and PL	Update to the product information to include the ADR Dysphonia with the frequency 'uncommon'. The wording of the latest QRD wording (version 10) was implemented.
PSUSA/10047 /201509	Periodic Safety Update EU Single assessment - glycopyrronium bromide (for centrally authorised	14/04/2016	n/a		PRAC Recommendation - maintenance

	product indicated for chronic obstructive pulmonary disease)				
IG/0630/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	05/11/2015	n/a		
WS/0782	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 4.5 of the SmPC in order to add class labelling text regarding the concomitant use with some commonly used medicines. 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	30/07/2015	12/05/2016	SmPC and PL	Although no formal drug interaction studies have been performed, Seebri Breezhaler has been used concomitantly with other medicinal products commonly used in the treatment of COPD without clinical evidence of drug interactions. These include sympathomimetic bronchodilators, methylxanthines, and oral and inhaled steroids.
WS/0781	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 in order to add pruritus with frequency uncommon and paradoxical bronchospasm with frequency not known as new ADRs based on post marketing reports already	30/07/2015	12/05/2016	SmPC and PL	

	submitted in the PSUR 4 (EMEA/H/C/PSUSA/00010047/201409). The Package Leaflet is updated accordingly. The MAH took the opportunity to make minor editorial changes in the SmPC and Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IG/0568	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	27/05/2015	n/a		
IB/0010/G	This was an application for a group of variations. B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.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	19/05/2015	12/05/2016	SmPC, Labelling and PL	

	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 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 A.1 - Administrative change - Change in the name and/or address of the MAH				
PSUSA/10047 /201409	Periodic Safety Update EU Single assessment - glycopyrronium bromide (for centrally authorised product indicated for chronic obstructive pulmonary disease)	10/04/2015	n/a		PRAC Recommendation - maintenance
PSUV/0006	Periodic Safety Update	09/10/2014	n/a		PRAC Recommendation - maintenance
IG/0443	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)	20/08/2014	n/a		
PSUV/0004	Periodic Safety Update	25/04/2014	19/06/2014	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUV/0004.
IB/0005	B.II.e.7.z. - Change in supplier of packaging components or devices (when mentioned in the dossier) - Other variation	30/01/2014	n/a		

WS/0456	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 accurately reflect the percentage of cases of dry mouth and section 5.1 to revise the p-values of trough FEV1 and the information on the reduction of COPD exacerbations in the pivotal studies A2304 and A2303. Furthermore, the MAH took this opportunity to bring the PI in line with the latest QRD template, to make minor editorial changes and to include the black triangle to reflect that the product is under additional monitoring. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	18/12/2013	19/06/2014	SmPC, Annex II and PL	The clinical phase III development program for glycopyrronium bromide included two pivotal studies: a 6-month placebo-controlled study (CNVA237A2304) and a 12-month placebo and active-controlled (open label tiotropium 18 micrograms once daily) study (CNVA237A2303), both in patients with clinical diagnosis of moderate to severe COPD. The SmPC reflects the primary endpoint trough FEV1 for glycopyrronium bromide compared to placebo at the 6-month time-point (108mL) for study A2304 and at the 12-month time-point (97mL) for study A2303. In order to more precisely reflect the study results, the p-values for both studies are being changed from $p<0.05$ to $p<0.001$ in section 5.1 of the SmPC. In addition, the information related to the reduction of COPD exacerbations is being revised in section 5.1 of the SmPC to improve clarity and accuracy. The percentage of cases of “dry mouth” reported for glycopyrronium bromide compared to placebo is 2.4% versus 1.1% for the MedDRA Preferred Term “dry throat”. This was changed in order to reflect the actual number of patients with the MedDRA Preferred Term (PT) “dry mouth” in the 6-month database i.e. 2.2% versus 1.1% in accordance with the EPAR.
N/0002	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	30/07/2013	19/06/2014	PL	Update of the local representative's contact details for Spain and inclusion of an additional

					local representative of the MAH for the new Member State, Croatia.
IG/0248	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	17/12/2012	n/a		