Bronchitol

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
IAIN/0049/G	This was an application for a group of variations. 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	24/06/2022		Annex II 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).

	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) A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release				
IAIN/0048/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.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	03/02/2022	19/05/2022	Annex II and PL	
N/0047	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/07/2021	19/05/2022	PL	
IAIN/0046/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	26/03/2021	19/05/2022	Annex II and PL	

II/0042	Submission of an updated RMP based on the new RMP template (GVP module V, revision 2). In addition, the UK CF Registry study (cat 2, PASS) has been removed from the RMP following its completion; and clinical trial as well as post-marketing exposure and safety information have been updated to reflect the results of the DPM-CF-303 study (previously assessed in EMEA/H/C/001252/II/0034) and the information presented in the latest PSUR #9 (PSUSA/ 0009226/201904). 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	14/01/2021	n/a		Since the completion of the PASS on the UK registry, most safety concerns did not have additional pharmacovigilance activities ongoing or planned as well as additional minimisation measures and thus, could be removed from the list of the safety concerns in accordance with the GVP module V Rev 2. In light of this, PRAC agreed with the MAH's proposal to maintain 'Haemoptysis', 'Bronchospasm' and 'cough' as important identified risks and 'Increased risk of respiratory or systemic infection' as important potential risk. Furthermore, considering that the safety profile of Bronchitol may differ in patients with medical history of severe haemoptysis and patients with <30% predicted FEV1 and thus that these patients remain a population in need of further characterization; PRAC agreed to maintain those safety concerns as missing information in the RMP; PRAC also recommended to closely monitor 'Patients who have had significant haemoptysis in last 3 months' and 'Patients with <30% predicted FEV1' via routine pharmacovigilance and to report and discuss any new significant data within future PSURs.
IA/0045/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites 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 B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved	11/01/2021	n/a		

	manufacturer				
N/0044	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	07/01/2021	19/05/2022	PL	
N/0043	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	05/10/2020	19/05/2022	PL	
SW/0036	Post Authorisation Safety Study results - EMEA/H/C/PSR/S/0020	27/02/2020	04/05/2020	Annex II	The cystic fibrosis study PASS was a condition of the marketing authorisation of Bronchitol. Therefore, in view of the available data regarding the PASS final study report, the PRAC considered that changes to the conditions of the marketing authorisation were warranted. The PRAC recommends the deletion of the obligation to conduct post-authorisation measures in the section D of the Annex II.
N/0040	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/01/2020	04/05/2020	PL	
PSUSA/9226/ 201904	Periodic Safety Update EU Single assessment - mannitol (indicated in cystic fibrosis)	31/10/2019	n/a		PRAC Recommendation - maintenance
IA/0039/G	This was an application for a group of variations. B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting	23/10/2019	n/a		

	material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material)				
IA/0038/G	This was an application for a group of variations. 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	30/08/2019	n/a		

	manufacturer of a novel excipient B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer				
T/0035	Transfer of Marketing Authorisation	30/11/2018	23/01/2019	SmPC, Labelling and PL	
II/0034	Update of sections 4.8 and 5.1 of the SmPC in order to update the frequency of certain adverse events and to update the clinical safety and efficacy information based on the results of the clinical data from Study CF 303. This is a phase 3 safety and efficacy clinical trial in adult cystic fibrosis subjects. The package leaflet is updated accordingly. In addition, some clarifications and minor editorial changes were made in sections 4.2, 4.4 and 4.5 of the SmPC and in Annex A. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	17/01/2019	06/02/2020	SmPC and PL	The MAH submitted a variation to update section 4.8 and 5.1 of the Product Information to reflect the results from a completed phase 3 study CF 303 (supplementing the two pivotal trials submitted with the initial Marketing Authorisation application). The study was a double-blind, randomised, controlled, parallel group, multicentric trial in adult cystic fibrosis patients with age 18 years and above. The key aspects of the study design were consistent with the earlier pivotal studies. The study met the primary endpoint. Mannitol demonstrated a statistically significant improvement in absolute change in FEV1 over 26-week treatment period compared to the control arm (a sub-therapeutic dose of mannitol). However, the treatment effect of Bronchitol on FEV1 was less evident in the subgroup of patients who were receiving concomitant rhDNAse. In addition, Study 303 did not show a superior treatment effect of Bronchitol on FEV for female patients, in whom the underlying cystic fibrosis disease course may be worse than males for

					reasons that are not fully understood. The updated frequency of some Adverse Events following the extension of the safety dataset and post-marketing spontaneous reporting has also been reflected in the product information. The benefit-risk balance of Bronchitol remains positive.
PSUSA/9226/201804	Periodic Safety Update EU Single assessment - mannitol (indicated in cystic fibrosis)	31/10/2018	n/a		PRAC Recommendation - maintenance
IB/0032	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	08/08/2018	23/01/2019	Annex II	
II/0031	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	17/05/2018	n/a		
PSUSA/9226/201704	Periodic Safety Update EU Single assessment - mannitol (indicated in cystic fibrosis)	26/10/2017	n/a		PRAC Recommendation - maintenance
N/0029	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	02/06/2017	08/01/2018	PL	
R/0028	Renewal of the marketing authorisation.	10/11/2016	11/01/2017	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 Bronchitol in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
II/0027	C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing	15/12/2016	08/01/2018	Annex II	

	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				
PSUSA/9226/ 201604	Periodic Safety Update EU Single assessment - mannitol (indicated in cystic fibrosis)	27/10/2016	n/a		PRAC Recommendation - maintenance
IA/0025/G	This was an application for a group of variations. 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)	03/06/2016	n/a		
N/0024	Update of the package leaflet with revised contact details of the local representative for Poland and Spain. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	18/04/2016	11/01/2017	PL	
IB/0023	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	05/04/2016	n/a		

IB/0021	B.II.f.1.d - Stability of FP - Change in storage conditions of the finished product or the diluted/reconstituted product	29/03/2016	11/01/2017	SmPC, Labelling and PL	
IA/0022/G	This was an application for a group of variations. 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.5.a - Change to in-process tests or limits applied during the manufacture of the finished product - Tightening of in-process limits B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier	10/03/2016	n/a		
PSUSA/9226/ 201504	Periodic Safety Update EU Single assessment - mannitol (indicated in cystic fibrosis)	19/11/2015	14/01/2016	SmPC	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/9226/201504.
IA/0020	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	12/01/2016	n/a		
IAIN/0019	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	28/07/2015	n/a		

IAIN/0017/G	This was an application for a group of variations. A.1 - Administrative change - Change in the name and/or address of the MAH A.7 - Administrative change - Deletion of manufacturing sites	16/07/2015	14/01/2016	SmPC, Labelling and PL	
II/0016/G	This was an application for a group of variations. Update of the condition reported in annex II D of the product information in order to update the study protocol with regard to patient recruitment and consequentially to postpone the final study report due date. 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 C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	23/04/2015	14/01/2016	Annex II	
PSUV/0014	Periodic Safety Update	06/11/2014	n/a		PRAC Recommendation - maintenance
IAIN/0015	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 -	03/10/2014	n/a		

	Not including batch control/testing				
II/0011	Submission of further qualitative sputum microbiology data from study DPM-B-305 in relation to the safety concern of microbial infection via the inhaler device C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	25/09/2014	n/a		The Committee agreed that the presented safety results did not give rise to any significant safety concerns.
IAIN/0013	C.I.3.a - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Implementation of wording agreed by the competent authority	17/07/2014	11/12/2014	PL	
PSUV/0010	Periodic Safety Update	08/05/2014	n/a		PRAC Recommendation - maintenance
IA/0012	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	16/04/2014	n/a		
IAIN/0009	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	19/12/2013	11/12/2014	Annex II and PL	

N/0008	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	06/11/2013	18/12/2013	PL	Alignment of section 4 of the PIL with section 4.8 of the SmPC, to remove 'cold-sores', an uncommon side effect in the PIL which does not have a corresponding drug reaction term in the SmPC.
II/0007	Site specific increase to the batch size of the finished product. B.II.b.4.d - Change in the batch size (including batch size ranges) of the finished product - The change relates to all other pharmaceutical forms manufactured by complex manufacturing processes	27/06/2013	n/a		
IB/0006/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 site 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 batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold	08/05/2013	n/a		

	compared to the currently approved batch size				
IAIN/0005	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	17/12/2012	n/a		
IB/0004	B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	12/12/2012	18/12/2013	SmPC	
IA/0002	B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter	07/12/2012	n/a		
IAIN/0003/G	This was an application for a group of variations. C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV	03/12/2012	n/a		
IAIN/0001	B.II.b.2.b.1 - Change to batch release arrangements and quality control testing of the FP - Not including batch control/testing	08/06/2012	29/10/2012	Annex II and PL	