Eklira Genuair

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/1394/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	31/05/2021		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.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release				
PSUSA/9005/ 202007	Periodic Safety Update EU Single assessment - aclidinium bromide	11/02/2021	n/a		PRAC Recommendation - maintenance
WS/1795	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 from study D6570R00002 listed as a category 3 study in the RMP. This is a descriptive, non-interventional, multinational European cohort study of new users of aclidinium, aclidinium/formoterol, and other selected COPD medications. The following safety concerns listed as missing information in the RMP: 'safety in patients with hepatic or severe renal impairment' and 'safety in patients with benign prostatic hyperplasia or urinary retention' are removed. The updated RMP version 8.0 is acceptable. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	29/10/2020	n/a		The MAH submitted the final study report for study D6570R00002 listed as a category 3 study in the RMP. This is a descriptive, non-interventional, multinational European cohort study of new users of aclidinium, aclidinium/formoterol, and other selected COPD medications. New users of aclidinium and aclidinium/formoterol were characterised as a population with high prevalence of chronic comorbidity, high use of co-medications and more severe chronic obstructive pulmonary disease (COPD) than users of other non-LAMA COPD medications. Off-label use of aclidinium and aclidinium/formoterol was observed to be low and the main reason was having a diagnosis of asthma in the absence of a recorded diagnosis of COPD. Discontinuation and switching for both drugs were important during follow-up period. The following safety concerns 'safety in patients with hepatic or severe renal impairment' and 'safety in patients with benign prostatic hyperplasia or urinary retention' are no longer considered as Missing Information and are thus removed from the RMP.
WS/1855/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No	24/09/2020	n/a		

	1234/2008. B.II.e.1.z - Change in immediate packaging of the finished product - Other variation B.II.e.2.z - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Other variation B.II.e.2.z - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Other variation B.II.e.2.z - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Other variation B.II.e.3.a - Change in test procedure for the immediate packaging of the finished product - Minor changes to an approved test procedure B.II.e.3.a - Change in test procedure for the immediate packaging of the finished product - Minor changes to an approved test procedure B.II.e.3.a - Change in test procedure for the immediate packaging of the finished product - Minor changes to an approved test procedure B.II.e.3.a - Change in test procedure for the immediate packaging of the finished product - Minor changes to an approved test procedure B.II.e.3.a - Change in test procedure for the immediate packaging of the finished product - Minor changes to an approved test procedure				
PSUSA/9005/ 201907	Periodic Safety Update EU Single assessment - aclidinium bromide	13/02/2020	n/a		PRAC Recommendation - maintenance

WS/1630	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.IV.1.a.3 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Spacer device for metered dose inhalers or other device which may have a significant impact on the delivery of the AS	16/01/2020	n/a		
WS/1542	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Updates of sections 4.4, 4.8 and 5.1 of the SmPC in order to add safety and efficacy information based on the ASCENT study, a phase IV double-blind, randomized, placebo-controlled, parallel-group outcome study to evaluate the effect of aclidinium on cardiovascular (CV) safety and COPD exacerbations in patients with moderate to very severe COPD, and prior history of CV events or CV risk factors. In addition, the Worksharing applicant (WSA) took the opportunity to update the list of local representatives in the Package Leaflet for Bretaris Genuair and to implement minor editorial changes in section 4.4, 4.6, 5.3 of the SmPC and section 2 of the PL for both Eklira Genuair and Bretaris Genuair. The worksharing procedure leads to amendments to	14/11/2019	20/11/2020	SmPC and PL	The procedure was initially submitted as a modification of indication in order to reflect the reduction of COPD exacerbations in the approved indication (section 4.1 of the SmPC). The evaluation of the data presented by the MAH led to an update of sections 4.4, 4.8 and 5.1 of the SmPC to describe information that may be relevant for the prescribers to take decisions in the step wise approach to COPD management. Results from the ASCENT study did not allow ascertaining the exact contribution of Eklira/Bretaris Genuair to the reduction in the rate of exacerbations therefore the revision of the indication was not accepted by the CHMP. However, the data were considered relevant from the clinical point of view taking into account the known correlation between exacerbations and morbidity/mortality. The following data are added to section 5.1 of the SmPC: Long Term Safety and Efficacy Trial up to 3 years The effect of aclidinium bromide on the occurrence of major adverse cardiovascular events (MACE) was assessed in a

	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				randomised, double-blind, placebo-controlled, parallel-group study in 3630 adult patients between 40 and 91 years of age with moderate to very severe COPD, treated for up to 36 months. 58.7% were male and 90.7% were Caucasian, with a mean postbronchodilator FEV1 of 47.9% of predicted value and a mean CAT (COPD Assessment Test) of 20.7. All patients had a history of cardiovascular or cerebrovascular disease and/or significant cardiovascular risk factors. 59.8% of patients had at least one COPD exacerbation within the past 12 months from the screening visit. Approximately 48% of enrolled patients had a prior history of at least 1 documented previous cardiovascular event; cerebrovascular disease (13.1%), coronary artery disease (35.4%), peripheral vascular disease or history of claudication (13.6%). The study had an event-driven design and was terminated once sufficient MACE events for the primary safety analysis were observed. Patients discontinued treatment if they experienced a MACE event and entered into the post-treatment follow-up period during the study. 70.7% of patients completed the study per investigator assessment. The median time on-treatment in the Eklira Genuair and placebo groups was 1.1 and 1 year, respectively. The median time on-study in the Eklira Genuair and placebo groups was approximately 1.4 and 1.3 years, respectively. The primary safety endpoint was the time to first occurrence of MACE, defined as any of the following adjudicated events: cardiovascular death, non-fatal myocardial infarction (MI), or non-fatal ischemic stroke. The frequency of patients with at least one MACE was 3.85% vs. 4.23% patients in the aclidinium and placebo groups, respectively. Eklira Genuair did not increase the

					MACE risk in patients with COPD compared to placebo when added to current background therapy (hazard ratio (HR) 0.89; 95% CI: 0.64, 1.23). The upper bound of the confidence interval excluded a pre-defined risk margin of 1.8. The rate of moderate or severe COPD exacerbations per patient per year during the first year of treatment was evaluated as the primary efficacy endpoint in the study. Patients treated with Eklira Genuair showed a statistically significant reduction of 22% compared to placebo (rate ratio [RR] 0.78; 95% CI 0.68 to 0.89; p<0.001). In addition, Eklira Genuair showed a statistically significant reduction of 35% in the rate of hospitalisations due to COPD exacerbations while on-treatment during the first year compared with placebo (RR 0.65; 95% CI 0.48 to 0.89; p=0.006). The Eklira Genuair group showed a statistically significant delay in the time to first moderate or severe exacerbation while on-treatment compared to the placebo group. Patients in the aclidinium bromide group had a 18% relative reduction of the risk of an exacerbation (HR 0.82; 95% CI [0.73, 0.92], p<0.001).
PSUSA/9005/ 201807	Periodic Safety Update EU Single assessment - aclidinium bromide	14/02/2019	n/a		PRAC Recommendation - maintenance
WS/1402	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 in line with revision 2 of the RMP template including	29/11/2018	n/a		

	changes in the categorisation of safety concerns and missing information; furthermore, the RMP is updated also to include data from the first component of the Post Authorisation Safety Study (PASS) (D6560R00004) and from the completed ASCENT study (D6560C00002). 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				
N/0037	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	18/05/2018	20/11/2020	PL	
WS/1330	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 and 6.6 of the SmPC in order to optimize the Instructions for Use (IFU) for the products based on the results of a Human Factors (HF) study which assessed whether patients could understand and accurately follow the updated IFU to administer medication without serious use errors or problems. The Package Leaflet (PL) is updated accordingly. In addition, the applicant has taken the opportunity to make some minor editorial corrections in the labelling section (Annex III A) of the Product	22/02/2018	13/04/2018	SmPC, Labelling and PL	Patients should be instructed on how to administer the product correctly as the Genuair inhaler may work differently from inhalers the patients may have used previously. It is important to instruct the patients to carefully read the Instructions for Use in the Package Leaflet, which is packed together with each inhaler.

	Information for Duaklir Genuair and Brimica Genuair C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
PSUSA/9005/ 201707	Periodic Safety Update EU Single assessment - aclidinium bromide	08/02/2018	n/a		PRAC Recommendation - maintenance
WS/1207	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 D6560R00005, (Aclidinium Bromide Drug Utilisation Post-Authorisation Safety Studies (DUS 1) in the United Kingdom, Denmark, and Germany) listed as a category 3 study in the RMP (MEA002). The updated RMP version 6.0 has also been submitted. 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/1070	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 4.3 of the SmPC in order to modify the contraindication section deleting reference to hypersensitivity to atropine or its derivative	21/04/2017	13/04/2018	SmPC and PL	

	providing justification for the claim that the chemical structure of aclidinium is unrelated to that of atropine or its derivatives. Moreover, a minor change is introduced in section 4.2 of the SmPC. 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				
R/0031	Renewal of the marketing authorisation.	23/02/2017	20/04/2017	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 Eklira Genuair in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
IG/0785/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.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	16/03/2017	n/a		
PSUSA/9005/201607	Periodic Safety Update EU Single assessment - aclidinium bromide	09/02/2017	n/a		PRAC Recommendation - maintenance
PSUSA/9005/201601	Periodic Safety Update EU Single assessment - aclidinium bromide	15/09/2016	14/11/2016	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/9005/201601.

IG/0735	A.7 - Administrative change - Deletion of manufacturing sites	20/10/2016	n/a		
WS/0974	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 5.2 and 5.3 of the SmPC in order to reflect new pharmacokinetic data from a clinical study of aclidinium bromide BID conducted in Japanese patients with COPD (KRP-AB1102-D202). In addition, the Worksharing applicant (WSA) took the opportunity to update the list of local representatives for Poland and Portugal in the Package Leaflet for Eklira Genuair and for Bulgaria in the Package leaflet for Bretaris Genuair. Moreover the MAH has taken this occasion to bring the PI in line with the latest QRD template version 10.0. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	15/09/2016	14/11/2016	SmPC, Annex II, Labelling and PL	The terminal elimination half-life and effective half-life of aclidinium bromide are approximately 14 hours and 10 hours, respectively, following inhalation of twice daily 400 µg doses in COPD patients. Following repeated inhalations, the systemic exposure of aclidinium bromide has been observed to be similar in Japanese and Caucasian patients. The safety margins for human systemic exposure with 400 µg twice daily over the no observed adverse effect levels in animal studies ranged from 7- to 73-fold.
IG/0689	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	09/06/2016	n/a		
PSUSA/9005/ 201507	Periodic Safety Update EU Single assessment - aclidinium bromide	11/02/2016	n/a		PRAC Recommendation - maintenance

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		
IA/0024	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)	06/11/2015	n/a		
PSUSA/9005/201501	Periodic Safety Update EU Single assessment - aclidinium bromide	10/09/2015	n/a		PRAC Recommendation - maintenance
PSUSA/9005/201407	Periodic Safety Update EU Single assessment - aclidinium bromide	26/02/2015	24/04/2015	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/9005/201407.
T/0021	Transfer of Marketing Authorisation	02/02/2015	05/03/2015	SmPC, Labelling and PL	
IB/0019/G	This was an application for a group of variations. B.I.a.1.i - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a new site of micronisation B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold	01/12/2014	n/a		

	increase compared to the originally approved batch size 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.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.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 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.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				

N/0020	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	27/11/2014	05/03/2015	PL	
PSUV/0015	Periodic Safety Update	25/09/2014	19/11/2014	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUV/0015.
II/0012	Submission of an updated RMP (version 4.3), upon request by the CHMP, in order to implement changes raised by the PRAC following the assessment of the previous RMP version. The requested variation proposed no amendments to the PI. 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	25/09/2014	n/a		N/A
IA/0017	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	30/07/2014	n/a		
IAIN/0016	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	22/05/2014	19/11/2014	Annex II and PL	
PSUV/0008	Periodic Safety Update	20/02/2014	23/04/2014	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for

					PSUV/0008.
IAIN/0014/G	This was an application for a group of variations. B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test B.II.e.6.a - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that affects the product information	13/02/2014	23/04/2014	SmPC and PL	
II/0009	Update of the instructions for use of the inhaler in section 4.2 of the SmPC and section 7 of the Package Leaflet to improve clarity and avoid misuse and complaints with the use of Genuair device. In addition the MAH introduced the general classification for supply ("Medicinal product subject to medical prescription") in the Labelling. Furthermore, the list of local representatives in the Package Leaflet has been revised to amend contact details for the representatives of SK and CZ. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	23/01/2014	23/04/2014	SmPC, Labelling and PL	The MAH proposed changes to section 4.2 of the SmPC to include an advice to healthcare professionals that patients should be instructed on how to administer the product correctly (i.e. to push the green button all the way down and then release it) as it may be overlooked by patients. The Package Leaflet has been updated accordingly. The CHMP is in agreement with the changes proposed by the MAH.
IB/0011/G	This was an application for a group of variations. 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	17/12/2013	n/a		

	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS				
IA/0010	B.II.e.2.a - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Tightening of specification limits	28/11/2013	n/a		
PSUV/0007	Periodic Safety Update	19/09/2013	15/11/2013	SmPC and PL	Please refer to Eklira Genuair-H-C-2211-PSU-004 EPAR Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation. In addition the MAH has taken the opportunity to correct a typo in the contact details of the German local representative.
II/0004	Amendment of section 5.1 of the SmPC to include a description of the principal results of the exercise tolerance study M/34273/40. Additionally, a better description of the potential taste has been included in the Instructions for use in section 4.2 of the SmPC and in the package leaflet. The product information has been amended with minor linguistic changes and to include the statement on additional monitoring in accordance with the latest QRD template. The list of local representatives has been updated. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	30/05/2013	15/11/2013	SmPC and PL	Study M/34273/40 was a 3-week crossover, randomised, placebo-controlled clinical study to assess the effect of aclidinium bromide 400 µg BID on exercise endurance in patients with moderate to severe, stable chronic obstructive pulmonary disease) in which aclidinium bromide was associated with a statistically significant improvement in exercise endurance time in comparison to placebo of 58 seconds (95% CI=9-108; p=0.021; pre-treatment value: 486 seconds). Aclidinium bromide statistically significantly reduced lung hyperinflation at rest (functional residual capacity [FRC]=0.197 L [95% CI=0.321, 0.072; p=0.002]; residual volume [RV]=0.238 L [95% CI=0.396, 0.079; p=0.004]) and also improved trough inspiratory capacity (by 0.078 L;

					95% CI=0.01, 0.145; p=0.025) and reduced dyspnoea during exercise (Borg scale) (by 0.63 Borg units; 95% CI=1.11, 0.14; p=0.012). The CHMP concluded that the improvement in exercise endurance time demonstrated in study M/34273/40 in conjunction with the improvements seen in other lung parameters can be considered to be clinically relevant in the studied patient population.
IB/0006/G	This was an application for a group of variations. B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - 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 currently approved batch size B.I.c.2.c - Change in the specification parameters and/or limits of the immediate packaging of the AS - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.c.2.c - Change in the specification parameters and/or limits of the immediate packaging of the AS - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	11/03/2013	n/a		
IB/0005	B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale	22/02/2013	15/11/2013	SmPC	

	(supported by real time data)				
IB/0003/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	09/01/2013	n/a		
IA/0001	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	13/12/2012	n/a		
N/0002	"Update of the local representative's contact details for the Netherlands." Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	03/12/2012	15/11/2013	PL	

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