Duaklir 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
SW/0043	Post Authorisation Safety Study results - EMEA/H/C/PSR/S/0047 – Variation	12/12/2024	20/02/2025	SmPC, Annex II and PL	The results of the study show that aclidinium increases the risk of any cardiac arrhythmia and atrial fibrillation compared to LABAs and other LAMAs. In addition, the results also show that aclidinium/formoterol FDC increases the risk of any cardiac arrhythmia and atrial fibrillation compared to LABAs and other LAMA/LABA combinations.

[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).

					Therefore, in view of available data regarding the PASS final study report, the PRAC considered that changes to the product information are warranted.
WS/2720/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.z - Change in control of the AS - Other variation B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	31/10/2024	n/a		
IG/1698/G	This was an application for a group of variations. 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 A.7 - Administrative change - Deletion of manufacturing sites	02/02/2024	n/a		
WS/2546	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	12/10/2023	n/a		

	authorisation, including the RMP - Other variation				
IG/1614	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	12/06/2023	n/a		
PSUSA/10307 /202211	Periodic Safety Update EU Single assessment - aclidinium bromide / formoterol fumarate dihydrate	08/06/2023	n/a		PRAC Recommendation - maintenance
N/0037	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/01/2023	20/02/2025	PL	
T/0036	Transfer of Marketing Authorisation	03/11/2022	09/12/2022	SmPC, Labelling and PL	
IG/1552	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	05/09/2022	n/a		
PSUSA/10307 /202111	Periodic Safety Update EU Single assessment - aclidinium bromide / formoterol fumarate dihydrate	10/06/2022	n/a		PRAC Recommendation - maintenance
WS/2088/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.III.1.a.2 - Submission of a new/updated or	25/11/2021	n/a		

	deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer 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.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate 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				
PSUSA/10307 /202011	Periodic Safety Update EU Single assessment - aclidinium bromide / formoterol fumarate dihydrate	10/06/2021	n/a		PRAC Recommendation - maintenance
IG/1395/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.a - Administrative change - Change in the name	02/06/2021	24/06/2022	Annex II and PL	

	and/or address of a manufacturer/importer responsible for batch release				
WS/1794	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', 'safety in patients with benign prostatic hyperplasia or urinary retention' and 'use in pregnancy or lactation' are removed. The updated RMP version 5.0 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		Results from study D6570R00002 showed that 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', 'safety in patients with benign prostatic hyperplasia or urinary retention' and 'use in pregnancy or lactation' are no longer considered as Missing Information and are thus removed from the RMP.
WS/1856/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.e.1.z - Change in immediate packaging of the finished product - Other variation B.II.e.2.z - Change in the specification parameters	24/09/2020	n/a		

	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 B.II.e.2.z - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Other variation				
PSUSA/10307 /201911	Periodic Safety Update EU Single assessment - aclidinium bromide / formoterol fumarate dihydrate	11/06/2020	n/a		PRAC Recommendation - maintenance
WS/1632/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.	16/01/2020	n/a		

	B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure 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				
R/0026	Renewal of the marketing authorisation.	27/06/2019	23/08/2019	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 Duaklir Genuair in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
PSUSA/10307 /201811	Periodic Safety Update EU Single assessment - aclidinium bromide / formoterol fumarate dihydrate	27/06/2019	23/08/2019	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10307/201811.
IG/1021	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	06/12/2018	n/a		
WS/1403	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	29/11/2018	n/a		

	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				
PSUSA/10307 /201711	Periodic Safety Update EU Single assessment - aclidinium bromide / formoterol fumarate dihydrate	14/06/2018	n/a		PRAC Recommendation - maintenance
N/0022	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	18/05/2018	03/08/2018	PL	
IB/0021/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites 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.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.III.1.a.3 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - New certificate from a new manufacturer (replacement or addition) 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	15/03/2018	n/a		

	batch control/testing takes place				
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 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	22/02/2018	03/08/2018	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.
PSUSA/10307 /201705	Periodic Safety Update EU Single assessment - aclidinium bromide / formoterol fumarate dihydrate	30/11/2017	n/a		PRAC Recommendation - maintenance
WS/1219	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 5.2 of the SmPC in order to include information based on results from study KRP-AB1102F-302 [KRP-AB1102F Phase II Clinical	16/11/2017	03/08/2018	SmPC and Annex II	Following inhalation of Duaklir Genuair 340/12 micrograms, with plasma sampling up to 24 hours post-dose, the terminal elimination half-life observed for aclidinium bromide ranged from 11-33 hours and for formoterol from 12-18 hours. Mean effective half-lives (half-life consistent with product accumulation based on a known dose regimen) observed

	Pharmacology Study - An Investigation into the Pharmacokinetics upon Repeated Administration of KRP-AB1102F to COPD Patients as Subjects]. In addition, the Worksharing applicant (WSA) took the opportunity to update footnotes of the table in section 4.8 as requested during PSUR procedure EMEA/H/C/PSUSA/00010307/201511 and to amend annex II following request from procedure EMEA/H/C/PSA/S/0017. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				for both aclidinium and formoterol (based on the accumulation ratio) are approximately 10 hours. Following repeated inhalations of Duaklir Genuair 340/12 micrograms, the systemic exposure of aclidinium and formoterol, as measured by AUC, is similar in Japanese and Caucasian patients.
WS/1221	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	26/10/2017	n/a		
WS/1218	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 in order to update information following results from study M-40464-33 (A Multiple Dose, Randomised, Double-Blind, Placebo Controlled, Parallel Clinical Trial to Assess the Effect of Aclidinium Bromide/Formoterol Fumarate Fixed-Dose Combination on Lung Hyperinflation, Exercise	14/09/2017	03/08/2018	SmPC	The effect of the aclidinium bromide/ formoterol fumarate dihydrate fixed dose combination on lung volumes, exercise endurance and physical activity was investigated in an 8-week parallel, randomised, placebo-controlled clinical study in COPD patients with hyperinflation (functional residual capacity [FRC] >120%). After 4 weeks of treatment Brimica Genuair implied improvement versus placebo in change from baseline in morning pre-dose (trough) FRC, the primary endpoint, but the difference was not statistically significant. Brimica Genuair showed

	Capacity and Physical Activity in Patients with Moderate to Severe Chronic Obstructive Pulmonary Disease (COPD)) C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				improvements compared to placebo in lung volumes at 2-3h post dose. Brimica Genuair also showed improvements in exercise endurance time compared to placebo after 8 weeks of treatment. After 4 weeks of treatment, Brimica Genuair improved the number of steps per day compared to placebo and reduced the percentage of inactive patients. Improvements in the PROactive total score were observed in patients treated with Brimica Genuair compared with placebo. A behavioural intervention program was added to both treatment groups for an additional 4 weeks. The number of steps/day in the Brimica Genuair treatment group was maintained resulting in a treatment effect compared to placebo of 510 steps/day and a reduction versus placebo in the percentage of inactive patients (<6000 steps per day).
PSUSA/10307 /201611	Periodic Safety Update EU Single assessment - aclidinium bromide / formoterol fumarate dihydrate	09/06/2017	n/a		PRAC Recommendation - maintenance
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/10307 /201605	Periodic Safety Update EU Single assessment - aclidinium bromide / formoterol fumarate dihydrate	15/12/2016	16/02/2017	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10307/201605.

PSUSA/10307 /201511	Periodic Safety Update EU Single assessment - aclidinium bromide / formoterol fumarate dihydrate	23/06/2016	22/08/2016	SmPC, Labelling and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10307/201511.
IG/0690/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.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites	07/07/2016	n/a		
IB/0009	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	19/05/2016	22/08/2016	SmPC, Labelling and PL	
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		
PSUSA/10307 /201505	Periodic Safety Update EU Single assessment - aclidinium bromide / formoterol fumarate dihydrate	03/12/2015	n/a		PRAC Recommendation - maintenance
IA/0006/G	This was an application for a group of variations. A.5.b - Administrative change - Change in the name	06/11/2015	n/a		

	and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release) A.7 - Administrative change - Deletion of manufacturing sites				
IAIN/0004	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	08/05/2015	26/05/2016	SmPC, Labelling and PL	
T/0003	Transfer of Marketing Authorisation	02/02/2015	26/02/2015	SmPC, Labelling and PL	
IB/0002/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 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	07/01/2015	n/a		

	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				
N/0001	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/12/2014	26/02/2015	PL	