I. SUMMARY OF THE RISK MANAGEMENT PLAN FOR DUAKLIR GENUAIR

This is a summary of the risk management plan (RMP) for Duaklir Genuair. The RMP details important risks of Duaklir Genuair, how these risks can be minimised, and how more information will be obtained about Duaklir Genuair risks and uncertainties (missing information).

Duaklir Genuair's Summary of Product Characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Duaklir Genuair should be used.

Important new concerns or changes to the current ones will be included in updates of Duaklir Genuair's RMP.

I.1 THE MEDICINE AND WHAT IT IS USED FOR

Duaklir Genuair is authorised for COPD (see SmPC for the full indication). It contains aclidinium/formoterol as the active substances and it is given by inhalation.

Further information about the evaluation of DUAKLIR GENUAIR benefits can be found in DUAKLIR GENUAIR's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/duaklir-genuair

I.2 RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of aclidinium/formoterol, together with measures to minimise such risks and the proposed studies for learning more about aclidinium/formoterol's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status - the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities.*

If important information that may affect the safe use of aclidinium/formoterol is not yet available, it is listed under 'missing information' below.

I.2.1 List of important risks and missing information

Important risks of aclidinium/formoterol are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of aclidinium/formoterol. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table I-1 List of important risks and missing information

Important identified risks	None
Important potential risks	Cardiac events (myocardial infarction, cardiac failure, cardiac arrhythmias) (aclidinium) Cerebrovascular events (stroke, transient ischaemic attack) (aclidinium) Mortality (aclidinium)
Missing Information	Safety in patients newly diagnosed or unstable arrhythmias, recent myocardial infarction, unstable angina or heart failure (NYHA Class III or IV) requiring recent hospitalisation (aclidinium)

I.2.2 Summary of important risks

Table I-2 Important potential risk: Cardiac events

Evidence for linking the risk to the medicine	Aclidinium increases the heart rate in some patients which might increase the risk of cardiac failure and myocardial infarction. Formoterol increases the heart rate, causes palpitations and can increase systolic blood pressure.
Risk factors and risk groups	Anticipated patient groups at risk of cardiac events include elderly and those with a history of cardiac disease, hypertension, dyslipidaemia, hyperglycaemia or diabetes mellitus, and body mass index >30 kg/m2.

Table I-2 Important potential risk: Cardiac events

Evidence for linking the risk to the medicine	Aclidinium increases the heart rate in some patients which might increase the risk of cardiac failure and myocardial infarction. Formoterol increases the heart rate, causes palpitations and can increase systolic blood pressure.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4, also presented in PIL
Additional pharmacovigilance activities	PASS Study D6560R00004

Table I-3 Important potential risk: Cerebrovascular events

Evidence for linking the risk to the medicine	If aclidinium increases the risk of myocardial infarction or atrial fibrillation, the risk of blood clots forming in the left atrium or left ventricle also increases, which in turn increases the risk of stroke. If one of the components in aclidinium/formoterol increases the risk of stroke, aclidinium/formoterol also increases the risk of stroke, although formoterol appears not to increase the risk of stroke.
Risk factors and risk groups	COPD patients have a moderate increase in the risk of strokes compared with non-COPD patients. Known risk factors include hypertension, dyslipidaemia, diabetes, atrial fibrillation, arterial stenosis, smoking, obesity, poor diet and physical inactivity.
Risk minimisation measures	Routine risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: PASS Study D6560R00004

Table I-4 Important potential risk: Mortality

Evidence for linking the risk to the medicine	There is currently no evidence of an increase in mortality with DUAKLIR GENUAIR
Risk factors and risk groups	Population-based studies have shown risk of mortality in patients with COPD to be greater in men and greatest in elderly adults aged 75 years and older.

Table I-4 Important potential risk: Mortality

Risk minimisation measures	Routine risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: PASS Study D6560R00004

Table I-5 Missing information: Patients with the following concomitant illnesses: newly diagnosed or unstable arrhythmias, recent myocardial infarction, unstable angina or heart failure

Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4, PIL section 2. Additional pharmacovigilance activities: D6560R00004/PASS (cardiac components),

I.2.3 Post-authorisation development plan

I.2.3.1 Studies which are conditions of the marketing authorisation

Study short name: Post-Authorisation Safety Study D6560R00004

Rationale and study objectives: To evaluate the cardiovascular safety concerns and all-cause mortality of aclidinium, aclidinium/formoterol and other bronchodilators used in patients with COPD.