Summary of risk management plan for LAVENTAIR ELLIPTA

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

LAVENTAIR ELLIPTA 's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how LAVENTAIR ELLIPTA should be used.

This summary of the RMP for LAVENTAIR ELLIPTA should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

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

I. The medicine and what it is used for

LAVENTAIR ELLIPTA is authorised for maintenance bronchodilator treatment to relieve symptoms in adult patients with Chronic Obstructive Pulmonary Disease (COPD) (see SmPC for the full indication). It contains Umeclidinium bromide/Vilanterol as the active substance and it is given by inhalation route.

Further information about the evaluation of LAVENTAIR ELLIPTA's benefits can be found in LAVENTAIR ELLIPTA's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: link to product's EPAR summary landing page on the EMA webpage.

https://www.ema.europa.eu/en/medicines/human/EPAR/laventair-ellipta-previously-laventair

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of LAVENTAIR ELLIPTA, together with measures to minimise such risks and the proposed studies for learning more about LAVENTAIR ELLIPTA'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, including PSUR assessment 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 LAVENTAIR ELLIPTA is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of LAVENTAIR ELLIPTA 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 LAVENTAIR ELLIPTA. 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);

List of important risks and missing information	
Important identified risks	None
Important potential risks	Cardio- and Cerebrovascular Disorders Asthma-related intubation, hospitalisation and death
Missing information	Off-label use in Asthma (incl. paediatrics)

II.B Summary of important risks

Important potential risk: Cardio and cerebrovascular disorders	
Evidence for linking the risk to the medicine	Cardiovascular effects have been associated with use of muscarinic antagonists and β2-agonists in patients with COPD, however, no clear associations have been observed in the clinical development programme for UMEC/VI

Risk factors and risk groups	Patients with severe cardiovascular disease are at increased risk of future cardiovascular events. Older age, a history of previous cardiac disease and worse lung function were predictive of increased risk of cardiovascular events in the COPD population [Calverley, 2010].
Risk minimisation measures	**Routine risk minimisation measures**: Section 4.4 and section 4.8 of the SmPC (also Section 2 and 4 of Product Leaflet). **Additional risk minimisation measures**: None.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities**: Study 201038, Post-authorisation Safety (PAS) Observational Cohort Study to Quantify the Incidence and Comparative Safety of Selected Cardiovascular and Cerebrovascular Events in COPD Patients Using Inhaled UMEC/VI Combination or Inhaled UMEC versus Tiotropium. *See section II.C of this summary for an overview of the post-authorisation development plan.*
Important potential risk: Asthma-related intubation, hospitalization and death	
Evidence for linking the risk to the medicine	LABA-containing compounds carry a class risk. A FDA meta-analysis of LABA vs. no LABA (60,954 patients in 110 trials) by age group on a composite endpoint of asthma-related deaths, intubations, and hospitalisations (asthma composite index) showed a statistically significant difference among age groups. The composite event incidence difference for all ages was 6.3 events per 1000 PY with LABAs compared with no LABA use. Among the 15,192 patients with concurrent ICS use, the incidence difference was 0.4 events per 1000 PY. The authors noted a trend of greater excess risk with LABA among the younger age groups [McMahon, 2011]. However, based upon data from the recently completed ICS/LABA safety trials in asthma patients, the FDA have determined that revised labelling is necessary for LABA-containing products to incorporate changes based upon study results that showed that the risk of these events with an ICS/ LABA combination was similar to that identified with ICS monotherapy [Stempel, 2016a; Stempel, 2016b]. Therefore, as part of the prior approval supplement, currently under review for ANORO ELLIPTA, GSK proposed removal of the Boxed Warning for the risk of 'Asthma-Related Death' from the prescribing information to which FDA have agreed, as this event is not an event of concern for the COPD population and ANORO ELLIPTA is not

	approved for the treatment of asthma. Additionally, GSK propose to communicate the risk of asthma-related death via the Warnings and Precautions section of the USPI. The current sNDA is under review. LABA monotherapy without opposing ICS, for the treatment of asthma may be associated with increased risk of serious asthma-related events (including hospitalisation, intubation and death [GINA, 2017;Lazarus, 2001]. The SMART (Salmeterol Multi-centre Asthma Research Trial) study showed an increase in asthma-related deaths in patients receiving salmeterol, as compared with placebo, when added to usual care [Nelson, 2006]. Post-hoc analyses observed that asthma-related death occurred at a higher rate in Caucasian patients treated with salmeterol than in patients treated with placebo. In African-Americans asthma-related death also occurred at a higher rate in patients treated with salmeterol than those treated with placebo. Although the relative risks of asthma-related death were similar in Caucasians and African-Americans, the estimate of excess deaths in patients treated with salmeterol was greater in African-Americans because there was a higher overall rate of asthma-related death in the latter [Nelson, 2006].
Risk factors and risk groups	Asthma-related deaths are rare and are in part related to poor asthma control. In asthma studies conducted with the combination of an inhaled corticosteroid (fluticasone furoate; FF) and VI, there were no reported asthma-related intubations or deaths. It is plausible that asthma patients who are at an increased risk for asthma exacerbations are also at risk of serious respiratory events. Risk factors for exacerbations include poorly controlled asthma, viral or respiratory infections and exposure to asthma triggers (e.g. pet ownership, smoking). Moreover, asthma disease severity, classified by either frequency and/or dose of medications used, hospitalisation for exacerbations or lung function measurements, has been repeatedly correlated to the risk of asthma-related death [DiSantostefano, 2008].
Risk minimisation measures	**Routine risk minimisation measures**: Section 4.4 of the SmPC (also Section 2, 3 and 4 of Product Leaflet). **Additional risk minimisation measures**: None.
Additional pharmacovigilance activities	None.

Missing information: Off label use in asthma (incl.paediatrics)	
Evidence for linking the risk to the medicine	Use of UMEC/VI in an asthma population (including paediatrics) is not indicated. Long-acting beta2-agonists are not recommended as monotherapy in asthma, as they do not influence airway inflammation and are potentially associated with a risk of asthma-related deaths [Bateman, 2008; Sears, 2009; Nelson, 2006]. Additionally, the benefits of LAMAs in asthma management have not been established.
Risk factors and risk groups	It is plausible that asthma patients who are at an increased risk for asthma exacerbations are also at risk of serious respiratory events. Risk factors for exacerbations include poorly controlled asthma, viral or respiratory infections and exposure to asthma triggers (e.g. pet ownership, smoking). Moreover, asthma disease severity, classified by either frequency and/or dose of medications used, hospitalisation for exacerbations or lung function measurements, has been repeatedly correlated to the risk of asthma-related death [DiSantostefano, 2008].
Risk minimisation measures	**Routine risk minimisation measures**: Section 4.4 of the SmPC (also Section 1 and 2 of Product Leaflet). **Additional risk minimisation measures**: None.
Additional pharmacovigilance activities	None *See section II.C of this summary for an overview of the post-authorisation development plan.*

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

The following study is a condition of the marketing authorisation:

Study Short Name: Post-Authorisation Safety (PAS) Observational Cohort to quantify the Incidence and Comparative Safety of Selected Cardiovascular and Cerebrovascular Events in COPD patients using Inhaled UMEC/VI Combination or Inhaled UMEC versus Tiotropium (Study 201038)

Purpose of the Study: The purpose of this study is to expand understanding of the potential cardiovascular (CV) and cerebrovascular risks of myocardial infarction (MI), stroke and new onset or acute worsening/decompensation heart failure of UMEC/VI and UMEC as compared to tiotropium. Tiotropium is a LAMA with a well-established safety and efficacy profile.

The primary objectives of the study are:

1. To demonstrate non-inferiority of UMEC/VI combination and UMEC to tiotropium for risk of the composite endpoint of MI, stroke, heart failure or sudden cardiac death based on an analysis of time to first event for new users of UMEC/VI combination, UMEC or Tiotropium.
2. To quantify the incidence rate and frequency of the composite endpoint of MI, stroke heart failure or sudden cardiac death for new users of UMEC/VI combination, UMEC, or tiotropium.