Part VI: Summary of the risk management plan

Summary of risk management plan for Ulunar Breezhaler (Indacaterol/glycopyrronium)

This is a summary of the RMP for Ulunar Breezhaler. The RMP details important risks of Ulunar Breezhaler, how these risks can be minimized, and how more information will be obtained about Ulunar Breezhaler's risks and uncertainties (missing information).

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

This summary of the RMP for Ulunar Breezhaler 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 Ulunar Breezhaler's RMP.

I. The medicine and what it is used for

Ulunar Breezhaler is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD) (see SmPC for the full indication). It contains indacaterol and glycopyrronium as active substance and it is given by inhalation of the content of one capsule once-daily using Ulunar Breezhaler inhaler.

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

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Ulunar Breezhaler, together with measures to minimize such risks and the proposed studies for learning more about Ulunar's risks, are outlined below.

Measures to minimize 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 minimize its risks.

Together, these measures constitute routine risk minimization measures.

II.A List of important risks and missing information

Important risks of Ulunar are risks that need special risk management activities to further investigate or minimize 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 Ulunar. 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 1 List of important risks and missing information

Important identified risks	Ischemic heart disease
	Tachyarrhythmias
	Hyperglycemia
	Narrow-angle glaucoma
	Bladder obstruction/urinary retention
	Paradoxical bronchospasm
	Atrial fibrillation
Important potential risks	Cardiac arrhythmias (bradyarrhythmias, conduction abnormalities, ectopies, cardiac repolarization abnormalities, sudden death, non-specific cardiac arrhythmias)
	Intubation, hospitalization and death due to asthma related events in asthma population (off-label use)
	Medication errors
	QTc prolongation and Interaction with drugs prolonging QT interval
	Myocardial infarction
	Cardiac failure
	Cerebrovascular events
Missing information	Use in patients with prolonged QTc interval at baseline (>450 ms) or long QT-syndrome
	Use in pregnancy and lactation

II.B Summary of important risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

Table 2 Important identified risk: Ischemic heart disease

Evidence for linking the risk to the medicine	Current evidence is based on class effect information, literature (Salpeter 2004, Cazzola et al 2005), pre-clinical investigations, clinical studies and PMS data showing some evidence of causal relationship which is strengthened by mechanistic studies and MoA.
Risk factors and risk groups	Patients with preexisting CCV disease or other CCV risk factors. However, in the Core and in the Major Safety database, patients on

	indacaterol/glycopyrronium with ≥3 cardiovascular risk factors had no increased risk for ischemic heart disease RR 0.419 (95% CI 0.026, 6.706) and RR 0.811 (0.084, 7.799) compared to the placebo group.
Risk minimization measures	Routine risk minimisation measures: SmPC section 4.8 PL Section 4 Recommendation for stopping the treatment when clinically significant cardiovascular effects occur with Ulunar are included in SmPC section 4.4; PL Section 2: patients with heart problems are advised to talk to the doctor, pharmacist or nurse before using Ulunar Legal Status: Restricted to medical prescription Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: PASS: Multinational database cohort study in Europe (CQVA149A2402). See section II.C of this summary for an overview of the post-authorisation development plan.

Table 3 Important identified risk: Tachyarrhythmias

Evidence for linking the risk to the medicine	Strength of evidence: Current evidence is based on class effect information, literature (Sears 2002, Salpeter 2004, Kelly 2006, LaCroix et al 2008), preclinical studies, clinical trial data and post-marketing reports, where causal relationship is established.
Risk factors and risk groups	Patients with preexisting CV disease or other CV risk factors. In the Core Safety database, patients on indacaterol/glycopyrronium combination with ≥3 cardiovascular risk factors had no risk increase for cardiac arrhythmias in general (RR 1.68;95% CI 0.19, >9.99) compared to the placebo group. In the Major Safety database, patients on indacaterol/glycopyrronium combination with ≥3 cardiovascular risk factors had no risk increase for cardiac arrhythmias in general (RR 1.35 (0.16, >9.99) compared to the placebo group.
Risk minimization measures	Routine risk minimisation measures: SmPC Section 4.8 PL Section 4 Recommendation for stopping the treatment when clinically significant cardiovascular effects occur with Ulunar are included in SmPC section 4.4; PL Section 2: patients with heart problems are advised to talk to the doctor, pharmacist or nurse before using Ulunar Legal Status: Restricted to medical prescription Additional risk minimisation measures: None
Additional pharmacovigilance activities	PASS: Multinational database cohort study in Europe (CQVA149A2402). See section II.C of this summary for an overview of the post-authorisation development plan.

Table 4 Important identified risk: Hyperglycemia

Evidence for linking the risk to the medicine	Strength of evidence: Current evidence is based on class effect information, literature (Rizza et al 1980, Decramer et al 2013), preclinical studies, clinical trial data a post-marketing reports, where causal relationship is established.
Risk factors and risk groups	Patients with history of diabetes mellitus/hyperglycemia at baseline. In the Major Safety database the relative risk vs placebo for abnormal glucose values (>9.99 mmol/l) was slightly increased for patients with history of diabetes (RR 1.71, CI 95% 0.65, 4.52) compared to patients without history of diabetes at baseline (RR 1.41, CI 95% 0.41, 4.88).

Risk minimization measures	Routine risk minimisation measures: SmPC section 4.8 PL Section 4 Recommendation for monitoring plasma glucose in diabetic patients during treatment are included in SmPC sections 4.4; PL Section 2: patients with diabetes are advised to talk to the doctor, pharmacist or nurse before using Ulunar Legal Status: Restricted to medical prescription Additional risk minimisation measures: None
Additional pharmacovigilance activities	PASS: Multinational database cohort study in Europe (CQVA149A2402). See section II.C of this summary for an overview of the post-authorisation development plan.

Table 5 Important identified risk: Narrow-angle glaucoma

Evidence for linking the risk to the medicine	Strength of evidence: Current evidence is based on class effect information, literature (Tripathi et al 2003), pre-clinical data, clinical studies and PMS reports, where causal relationship is established.
Risk factors and risk groups	Patients with preexisting ocular hypertension or narrow-angle glaucoma
Risk minimization measures	Routine risk minimisation measures: SmPC section 4.8 PL Section 4 Recommendations for monitoring the signs or symptoms of narrow-angle glaucoma and stop the treatment when signs or symptoms are observed are included in SmPC section 4.4 and PL section 2 Legal Status: Restricted to medical prescription Additional risk minimisation measures: None
Additional pharmacovigilance activities	PASS: Multinational database cohort study in Europe (CQVA149A2402). See section II.C of this summary for an overview of the post-authorisation development plan.

Table 6 Important identified risk: Bladder obstruction/urinary retention

Evidence for linking the risk to the medicine	Strength of evidence: Current evidence is based on class effect information, literature (Afonso et al 2010, Stephenson et al 2011), pre-clinical data, clinical studies and PMS reports, where causal relationship is established
Risk factors and risk groups	Patients with preexisting prostatic hyperplasia and bladder-neck obstruction.
Risk minimization measures	Routine risk minimisation measures: SmPC section 4.8 PL Section 4 Legal Status: Restricted to medical prescription Additional risk minimisation measures: None
Additional pharmacovigilance activities	PASS: Multinational database cohort study in Europe (CQVA149A2402). See section II.C of this summary for an overview of the post-authorisation development plan.

Table 7 Important identified risk: Paradoxical bronchospasm

Evidence for linking the risk to the medicine	Current evidence is based on class effect information, literature, clinical studies and PMS reports, where causal relationship is established

Risk factors and risk groups	Patients with hypersensitivity to indacaterol, glycopyrronium, lactose or any other excipient.
Risk minimization measures	Routine risk minimisation measures: SmPC section 4.8 PL Section 4 Recommendations for stopping of the treatment when adverse event are observed are included in SmPC section 4.4 and PL section 2 Legal Status: Restricted to medical prescription Additional risk minimisation measures: None
Additional pharmacovigilance activities	PASS: Multinational database cohort study in Europe (CQVA149A2402). See section II.C of this summary for an overview of the post-authorisation development plan.

Table 8 Important identified risk: Atrial fibrillation

Evidence for linking the risk to the medicine	Current evidence is based on class effect information, literature, clinical studies and PMS reports, where causal relationship is established
Risk factors and risk groups	Patients with pre-existing cardiac disorders especially history of intermittent atrial fibrillation.
Risk minimization measures	Routine risk minimisation measures: SmPC section 4.8 PL Section 4 Recommendation for stopping the treatment when clinically significant cardiovascular effects occur with Ulunar are included in SmPC section 4.4; PL Section 2: patients with heart problems are advised to talk to the doctor, pharmacist or nurse before using Ulunar. Legal Status: Restricted to medical prescription Additional risk minimisation measures: None
Additional pharmacovigilance activities	PASS: Multinational database cohort study in Europe (CQVA149A2402). See section II.C of this summary for an overview of the post-authorisation development plan.

Table 9 Important potential risk: Cardiac arrhythmias (bradyarrhythmias, conduction abnormalities, ectopies, cardiac repolarization abnormalities, sudden death and non-specific cardiac arrhythmias)

Evidence for linking the risk to the medicine	Current evidence is based on literature, pre-clinical data, clinical studies and PMS reports. Causal relationship was not established.
Risk factors and risk groups	Patients with preexisting CV disease or other CV risk factors.
Risk minimization measures	Routine risk minimisation measures: Recommendation for stopping the treatment when clinically significant cardiovascular effects occur with Ulunar are included in SmPC section 4.4; PL Section 2: patients with heart problems are advised to talk to the doctor, pharmacist or nurse before using Ulunar. Legal Status: Restricted to medical prescription Additional risk minimisation measures: None
Additional pharmacovigilance activities	PASS: Multinational database cohort study in Europe (CQVA149A2402). See section II.C of this summary for an overview of the post-authorisation development plan.

Table 10 Important potential risk: Intubation, hospitalisation and death due to asthma related events in asthma population (off-label use) (Other details)

Evidence for linking the risk to the medicine	Strength of evidence: Current evidence is based on literature (McFadden and Warren 1997, Nelson et al 2006), pre-clinical data, clinical studies and PMS reports. Causal relationship was not established.
Risk factors and risk groups	Patients with asthma or mixed disease asthma/COPD, which are not receiving ICS concomitantly.
Risk minimization measures	Routine risk minimisation measures: Recommendation for prohibiting the use of Ulunar for the treatment of asthma are included in SmPC section 4.4 and PL section 2 Legal Status: Restricted to medical prescription Additional risk minimisation measures: None

Table 11 Important potential risk: Medication errors

Evidence for linking the risk to the medicine	Current evidence is based on literature, pre-clinical data, clinical studies and PMS reports. Causal relationship was not established.
Risk factors and risk groups	Patients, who are not trained appropriately and patients with mental or physical disabilities limiting a correct use of the product.
Risk minimization measures	Routine risk minimisation measures: Instructions for method administration of the product are provided in SmPC section 4.2 and PL section 6.6 Labelling outer packaging (in Red and surrounded by a box) Legal Status: Restricted to medical prescription Additional risk minimisation measures: None

Table 12 Important potential risk: QTc prolongation

Evidence for linking the risk to the medicine	Current evidence is based on literature, pre-clinical data, thorough QT7TC studies, clinical trials and PMS reports. Causal relationship was not established.
Risk factors and risk groups	Pre-existing long QT interval, hypokalemia, drugs associated with low serum potassium (non-potassium sparing diuretics). Concomitant intake of drugs with potential to prolong QTc interval, e.g. cardiac anti-arrhythmics Class Ia & III, terfenadine, astemizole, mizolastin, tricyclic antidepressants.
Risk minimization measures	Routine risk minimisation measures: Recommendation for stopping the treatment when clinically significant cardiovascular effects occur with Ulunar are included in SmPC section 4.4; PL Section 2: patients with heart problems are advised to talk to the doctor, pharmacist or nurse before using Ulunar. Legal Status: Restricted to medical prescription Additional risk minimisation measures: None
Additional pharmacovigilance activities	PASS: Multinational database cohort study in Europe (CQVA149A2402). See section II.C of this summary for an overview of the post-authorisation development plan.

Table 13 Important potential risk: Myocardial infarction

Evidence for linking the risk to the medicine	Current evidence is based on literature, pre-clinical data, clinical studies and PMS reports. Causal relationship was not established.
Risk factors and risk groups	Patients with pre-existing CV disease or other CV risk factors.
Risk minimization measures	Routine risk minimisation measures: Recommendation for stopping the treatment when clinically significant

	cardiovascular effects occur with Ulunar are included in SmPC section 4.4; PL Section 2: patients with heart problems are advised to talk to the doctor, pharmacist or nurse before using Ulunar. Legal Status: Restricted to medical prescription Additional risk minimisation measures: None
Additional pharmacovigilance activities	PASS: Multinational database cohort study in Europe (CQVA149A2402). See section II.C of this summary for an overview of the post-authorisation development plan.

Table 14 Important potential risk: Cardiac failure

Evidence for linking the risk to the medicine	Cardiac failure: Current evidence is based on literature (Parati and Esler 2012), pre-clinical data, clinical studies and PMS reports. Causal relationship was not established.
Risk factors and risk groups	Patients with preexisting CV disease or other CV risk factors.
Risk minimization measures	Routine risk minimisation measures: Recommendation for stopping the treatment when clinically significant cardiovascular effects occur with Ulunar are included in SmPC section 4.4; PL Section 2: patients with heart problems are advised to talk to the doctor, pharmacist or nurse before using Ulunar. Legal Status: Restricted to medical prescription Additional risk minimisation measures: None
Additional pharmacovigilance activities	PASS: Multinational database cohort study in Europe (CQVA149A2402). See section II.C of this summary for an overview of the post-authorisation development plan.

Table 15 Important potential risk: Cerebrovascular events

Evidence for linking the risk to the medicine	Current evidence is based on literature, pre-clinical data, clinical studies and PMS reports. Causal relationship was not established.
Risk factors and risk groups	Patients with preexisting CCV disease or other CCV risk factors. However, in the Core Safety database for ischemic cerebrovascular events, patients on indacaterol/glycopyrronium combination with 2 cardiovascular risk factors had no increased risk RR 0.53 (95% CI 0.03, 8.39) compared to the placebo group. In the Major safety database for ischemic cerebrovascular events the risk for patients with ≥3 CCV risk factors was similar to patients on placebo (RR 0.60; 95% CI 0.11, 3.29).
Risk minimization measures	Routine risk minimisation measures: Recommendation for stopping the treatment when clinically significant cardiovascular effects occur with Ulunar are included in SmPC section 4.4; PL Section 2: patients with heart problems are advised to talk to the doctor, pharmacist or nurse before using Ulunar. Legal Status: Restricted to medical prescription Additional risk minimisation measures: None
Additional pharmacovigilance activities	PASS: Multinational database cohort study in Europe (CQVA149A2402). See section II.C of this summary for an overview of the post-authorisation development plan.

Table 16 Missing information: Use in patients with prolonged QTc interval at baseline (>450 ms) or long QT-syndrome

Risk minimization measures	Routine risk minimisation measures: Recommendation for stopping the treatment when clinically significant cardiovascular effects occur with Ulunar are included in SmPC section 4.4; PL Section 2: patients with heart problems are advised to talk to the doctor, pharmacist or nurse before using Ulunar.

	Legal Status: Restricted to medical prescription Additional risk minimisation measures: None

Table 17 Missing information: Use in pregnancy and lactation

Risk minimization measures	Routine risk minimisation measures: Recommendation for use of Ulunar during pregnancy are included in SmPC section 4.6 Legal Status: Restricted to medical prescription Additional risk minimisation measures: None

II.C Post-authorisation development plan

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

Table 18 Studies which are conditions of the marketing authorization

Study short name	Purpose of the study:
PASS of indacaterol/glycopyrronium in Europe - study CQVA149A2402	The purpose of this PASS is to assess the risk of various RMP-specified endpoints in a broader, real-world COPD population. Objectives: To assess the incidence rates and relative risks (expressed as Hazard Ratios) of various adverse events among patients with a diagnosis of COPD initiating inhaled QVA149 compared to patients with a diagnosis of COPD initiating comparator medications (single constituent LABA, single constituent LAMA, free combination of LAMA/LABA, LABA/inhaled corticosteroids [ICS], or LAMA/LABA/ICS or fixed dose combination of LABA+ICS with or without LAMA or fixed combination of LAMA/LABA (other than QVA149)) with COPD.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Ulunar.