Summary of the risk management plan for Xoterna Breezhaler (Indacaterol maleate/glycopyrronium bromide)

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

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

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

I. The medicine and what it is used for

Xoterna 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 Xoterna Breezhaler inhaler.

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

(Link: https://www.ema.europa.eu/en/medicines/human/EPAR/xoterna-breezhaler)

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

Important risks of Xoterna Breezhaler, together with measures to minimize such risks and the proposed studies for learning more about Xoterna'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 Xoterna 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 Xoterna. 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
	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)
	QTc prolongation and Interaction with drugs prolonging QT interval
	Myocardial infarction
	Cardiac failure
	Cerebrovascular events
Missing information	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, 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 Cardiovascular and cerebrovascular (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
	Package leaflet (PL) Section 4
	Recommendation for stopping the treatment when clinically significant cardiovascular effects occur with Xoterna are included in SmPC Section 4.4; Package leaflet Section 2: patients with heart problems are advised to talk to the doctor, pharmacist or nurse before using Xoterna
	Legal Status: Restricted to medical prescription
	Additional risk minimisation measures: None

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, preclinical studies, clinical trial data and post-marketing reports, where causal relationship is established.
Risk factors and risk groups	Patients with preexisting Cardiovascular (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 Xoterna 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 Xoterna Legal Status: Restricted to medical prescription **Additional risk minimisation measures:** None

Table 4 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 Xoterna 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 Xoterna. Legal Status: Restricted to medical prescription **Additional risk minimisation measures:** None

Table 5 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 Xoterna 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 Xoterna. Legal Status: Restricted to medical prescription **Additional risk minimisation measures:** None

Table 5 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 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 Xoterna 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 6 Important potential Risk: QTc prolongation

Evidence for linking the risk to the medicine	Current evidence is based on literature, pre-clinical data, thorough QT/QTc 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 Xoterna 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 Xoterna. Legal Status: Restricted to medical prescription **Additional risk minimisation measures:** None

Table 7 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 Xoterna 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 Xoterna. Legal Status: Restricted to medical prescription **Additional risk minimisation measures:** None

Table 8 Important potential risk: Cardiac failure

Evidence for linking the risk to the medicine	Cardiac failure: Current evidence is based on 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 Xoterna 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 Xoterna. Legal Status: Restricted to medical prescription **Additional risk minimisation measures:** None

Table 9 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 Xoterna 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 Xoterna. Legal Status: Restricted to medical prescription **Additional risk minimisation measures:** None

Table 10 Missing Information: Use in pregnancy and lactation

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

II C: Post-authorization development planII.C.1 Studies which are conditions of the marketing authorization

There are no studies, which are conditions of the marketing authorization or specific obligation of Xoterna Breezhaler.

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

There are no studies required for Xoterna.