Part VI: Summary of the risk management plan

Summary of risk management plan for Enurev Breezhaler (glycopyrronium bromide)

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

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

This summary of the RMP for Enurev 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 Enurev Breezhaler RMP.

I. The medicine and what it is used for

Enurev Breezhaler is authorized for maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (see SmPC for the full indication). It contains glycopyrronium bromide as the active substance and it is given by Inhalation powder hard capsules.

Further information about the evaluation of Enurev Breezhaler's benefits can be found in the EPAR, including in its plain-language summary, available on the European Medicines Agency (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 Enurev Breezhaler, together with measures to minimize such risks and the proposed studies for learning more about Enurev Breezhaler'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.

If important information that may affect the safe use of Enurev Breezhaler is not yet available, it is listed under "missing information" below.

II.A List of important risks and missing information

Important risks of Enurev Breezhaler are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. 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 Enurev Breezhaler. 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	Hypersensitivity including angioedema
	Atrial fibrillation
Important potential risks	Cerebrovascular events
	Cardiovascular event/Myocardial infarction
	Cardiovascular event/Heart failure
	Cardiovascular event/Cardiac arrhythmia
	Medication errors
Missing information	Use in unstable ischemic heart disease, arrhythmia and long QT-syndrome
	Use in pregnancy and lactation

II.B Summary of important risks

Table 2 Important identified risk: Hypersensitivity including angioedema

Evidence for linking the risk to the medicine	Causal association was based on post-marketing data supported by data from class effect, clinical trial, and published literature (Guglielmi et al 2006).
Risk factors and risk groups	Patients with pre-existing hypersensitivity to drugs are in higher risk for developing new reaction. Women are shown to have a higher incidence of ADRs than men. On-going diseases may favor drug hypersensitivity reactions. For instance, patients affected with asthma or nasal polyposis are more frequently hypersensitive to nonsteroidal anti-inflammatory drugs. Drug allergy in HIV infected patients occurs at a 10-100 time increased rate when compared to HIV-negative subjects. The herpes infection is also a risk factor for ADRs. Atopy in general is not a risk factor, but atopic patients may suffer from more severe reactions (Guglielmi et al 2006). Patients with pre-existing hypersensitivity to drugs are in higher risk for developing new reactions including angioedema. In addition, patients with hereditary angioedema are in a much higher risk.
Risk minimization measures	Routine risk minimization measures SmPC Section 4.8 and PL Section 4 SmPC Section 4.3 where advice is given on contraindication SmPC Section 4.4 where advice is given on monitoring signs and stopping the treatment when signs suggesting allergic reaction are observed.

	Additional risk minimization measures None

Table 3 Important identified risk: Atrial fibrillation

Evidence for linking the risk to the medicine	Current evidence is based on clinical trial data, post-marketing data, published literature, pre-clinical data and class effects.
Risk factors and risk groups	Patient with pre-existing cardiac disorders especially history of intermittent atrial fibrillation
Risk minimization measures	Routine risk minimization measures SmPC Section 4.8 and PL Section 4 SmPC Section 4.4 where advice is given on use of Enurev with caution in patients with a history of cardiovascular disease. Additional risk minimization measures None

Table 4 Important potential risk - Cerebrovascular events

Evidence for linking the risk to the medicine	It is a potential class effect, causal relationship not established (Singh et al 2008).
Risk factors and risk groups	Patients with pre-existing CV disease or other CV risk factors. However, in patients with CV comorbidity or other CV risk factors glycopyrronium exposure was not associated with a higher risk for CV events than the control group on placebo.
Risk minimization measures	Routine risk minimization measures SmPC Section 4.4 where advice is given on use of Enurev with caution in patients with a history of cardiovascular disease. Additional risk minimization measures None

Table 5 Important potential risk - Cardiovascular event/Myocardial infarction

Evidence for linking the risk to the medicine	It is a potential class effect, causal relationship not established (Singh et al 2008).
Risk factors and risk groups	Patients with pre-existing CV disease or other CV risk factors. However, in patients with CV comorbidity or other CV risk factors glycopyrronium exposure was not associated with a higher risk for CV events than the control group on placebo.
Risk minimization measures	Routine risk minimization measures SmPC Section 4.4 where advice is given on use of Enurev with caution in patients with a history of cardiovascular disease. Additional risk minimization measures None

Table 6 Important potential risk - Cardiovascular event/Heart failure

Evidence for linking the risk to the medicine	It is a potential class effect, causal relationship not well established.
Risk factors and risk groups	Patients with pre-existing CV disease or other CV risk factors. However, in patients with CV comorbidity or other CV risk factors glycopyrronium exposure was not associated with a higher risk for CV events than the control group on placebo.
Risk minimization measures	Routine risk minimization measures SmPC Section 4.4 where advice is given on use of Enurev with caution in patients with a history of cardiovascular disease. Additional risk minimization measures None

Table 7 Important potential risk - Cardiovascular event/Cardiac arrhythmia

Evidence for linking the risk to the medicine	It is a potential class effect, causal relationship not established (Singh et al 2008).
Risk factors and risk groups	Patients with preexisting CV disease or other CV risk factors. However, in patients with CV comorbidity or other CV risk factors glycopyrronium exposure was not associated with a higher risk for CV events than the control group on placebo.
Risk minimization measures	Routine risk minimization measures SmPC Section 4.4 where advice is given on use of Enurev with caution in patients with a history of cardiovascular disease. Additional risk minimization measures None

Table 8 Important potential risk - Medication errors

Evidence for linking the risk to the medicine	Current evidence is based on post-marketing reports. The most frequent medication error was swallowing/ingestion of the capsule instead of placing the capsule in the device for inhalation, which may lead to decreased effect of the medication.
Risk factors and risk groups	None. Elderly patients are at higher risk due to difficulties to follow medication guide appropriately.
Risk minimization measures	Routine risk minimization measures SmPC Sections 4.2 and 6.6 where advice is given on Instructions for use of Enurev. Additional risk minimization measures None.

Table 9 Missing information - Use in unstable ischemic heart disease, arrhythmia and long QT-syndrome

Risk minimization measures	Routine risk minimization measures SmPC Section 4.4 where advice is given on use of Enurev with caution in patients with a history of cardiovascular disease. Additional risk minimization measures None

Table 10 Missing information - Use in pregnancy and lactation

Risk minimization measures	Routine risk minimization measures SmPC Section 4.6 where advice is given on use of Enurev during pregnancy. Additional risk minimization measures: None.

II.C Post-authorisation development plan

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

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