Summary of risk management plan for LYXUMIA (Lixisenatide)

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

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

This summary of the RMP for LYXUMIA 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 LYXUMIA's RMP.

1. THE MEDICINE AND WHAT IT IS USED FOR

LYXUMIA is authorized for the treatment of adults with type 2 diabetes mellitus to achieve glycemic control in combination with oral glucose-lowering medicinal products and/or basal insulin when these, together, with diet and exercise, do not provide adequate glycemic control (see SmPC for the full indication). It contains lixisenatide as the active substance and it is given by subcutaneous route (see SmPC for details).

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

https://www.ema.europa.eu/en/medicines/human/EPAR/lyxumia

2. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of LYXUMIA, together with measures to minimize such risks and the proposed studies for learning more about LYXUMIA's risks, are outlined in the next sections.

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 (eg, with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including periodic safety update report 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 LYXUMIA is not yet available, it is listed under 'missing information' outlined in the next section.

2.1. List of important risks and missing information

Important risks of LYXUMIA 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 LYXUMIA. 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 (eg, on the long-term use of the medicine);

Table 1 - List of important risks and missing information

Important identified risk	Pancreatitis
Important potential risks	Medullary thyroid cancer Pancreatic cancer Malignant neoplasm
Missing information	Use in patients with severe renal impairment (with and without low body weight)

2.2. Summary of important risks

Table 2 - Important risks and missing information with corresponding risk minimization activities and additional pharmacovigilance activities if any- Important identified risk: Pancreatitis

Important identified risk: Pancreatitis	
Evidence for linking the risk to the medicine	Clinical database, literature.
Risk factors and risk groups	The subgroup analysis for TEAEs potentially related to pancreatitis during the entire treatment period for all Phase 3 placebo-controlled studies by intrinsic factors did not reveal any specific trend.

Important identified risk: Pancreatitis	
	Subgroup analysis by anti-lixisenatide antibody status did not show any difference in the incidence of pancreatitis between antibody-positive or antibody-negative patients.
Risk minimization measures	Routine risk minimization measures: SmPC section 4.4. PL sections 2 and 4. Medicinal product subject to medical prescription. Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Pharmacoepidemiology study: Patient registry of lixisenatide use in adult type 2 diabetes.

PL: Package Leaflet; SmPC: Summary of Product Characteristics; TEAEs: Treatment Emergent Adverse Event.

Table 3 - Important risks and missing information with corresponding risk minimization activities and additional pharmacovigilance activities if any - Important potential risk: Medullary thyroid cancer

Important potential risk: Medullary thyroid cancer	
Evidence for linking the risk to the medicine	Non-clinical (mechanistic and carcinogenicity studies) and clinical data, literature, Liraglutide FDA Advisory Committee.[a]
Risk factors and risk groups	No risk factors identified.
Risk minimization measures	Routine risk minimization measures: SmPC section 5.3. Medicinal product subject to medical prescription. Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Pharmacoepidemiology study: Patient registry of lixisenatide use in adult type 2 diabetes.

FDA: Food and Drug Administration; SmPC: Summary of Product Characteristics.

a Liraglutide FDA Advisory Committee Minutes, 2009 Apr 02.

Table 4 - Important risks and missing information with corresponding risk minimization activities and additional pharmacovigilance activities if any - Important potential risk: Pancreatic cancer

Important potential risk: Pancreatic cancer	
Evidence for linking the risk to the medicine	Non-clinical and clinical data, literature.

Important potential risk: Pancreatic cancer	
Risk factors and risk groups	Patients with T2DM have an increased risk for pancreatic cancer. Additional known risk factors for pancreatic cancer includes smoking, chronic pancreatitis, obesity and family history of pancreatic cancer.
Risk minimization measures	Routine risk minimization measures: Medicinal product subject to medical prescription. Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Pharmacoepidemiology study: Patient registry of lixisenatide use in adult type 2 diabetes.

T2DM: Type 2 Diabetes Mellitus.

Table 5 - Important risks and missing information with corresponding risk minimization activities and additional pharmacovigilance activities if any - Important potential risk: Malignant neoplasm

Important potential risk: Malignant neoplasm	
Evidence for linking the risk to the medicine	Non-clinical and clinical data, literature.
Risk factors and risk groups	None could be identified.
Risk minimization measures	Routine risk minimization measures: SmPC section 5.3. Medicinal product subject to medical prescription. Additional risk minimization measures: None

SmPC: Summary of Product Characteristics.

Table 6 - Important risks and missing information with corresponding risk minimization activities and additional pharmacovigilance activities if any - Missing information: Use in patients with severe renal impairment (with and without low body weight)

Missing information: Use in patients with severe renal impairment (with and without low body weight)	
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.2, 4.4 and 5.2. PL section 2. Medicinal product subject to medical prescription. Additional risk minimization measures: None

PL: Package Leaflet; SmPC: Summary of Product Characteristics.

2.3. Post-authorization development plan

2.3.1. Studies which are conditions of the marketing authorization

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

2.3.2. Other studies in post-authorization development plan

Table 7 - Other studies in post-authorization development plan

Pharmacoepidemiology study (cat 3)
Purpose of the study:
A registry to monitor the occurrences of events of interest including acute pancreatitis, pancreatic cancer and thyroid cancer, especially medullary carcinoma of the thyroid, among adult type 2 diabetes patients treated with lixisenatide using the data from national registers and databases in Belgium.