Summary of the risk management plan for Victoza (liraglutide in T2DM)

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

Victoza's Summary of Product Characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Victoza should be used.

This summary of the RMP for Victoza should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the EPAR.

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

I. The medicine and what it is used for

Victoza is authorised for the treatment of adults, adolescents and children above 10 years with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise (see SmPC for the full indication). It contains liraglutide as the active substance and it is injected subcutaneously.

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

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

Important risks of Victoza, together with measures to minimise such risks and the proposed studies for learning more about Victoza'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 public (e.g., with or without prescription) can help to minimises its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse events is collected continuously and regularly analysed, including periodic safety update report (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 Victoza is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Victoza 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 Victoza. 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	• Neoplasms (including melanoma) • Medullary thyroid cancer (C-cell carcinogenicity) • Pancreatic cancer
Missing information	• Off-label use, including abuse due to weight-lowering potential

II.B Summary of important risks

Important potential risk – Neoplasms (including melanoma)	
Evidence for linking the risk to the medicine	Completed therapeutic confirmatory trials (phase 3a and 3b trials) in which liraglutide was used as the investigational drug and market experience until the data lock point of this report are the evidence sources of this risk. In the T2DM clinical development programme, an imbalance in neoplasm reporting rates (liraglutide > comparator) was seen at the time of first marketing authorisation. The rate of malignant neoplasms was comparable between subjects treated with liraglutide and those not treated with liraglutide. In the trial EX2211-3748 (LEADER), similar proportions of subjects in the liraglutide group and in the placebo group had neoplasms confirmed by an expert group. In the trial EX2211-3748 (LEADER), the frequency of malignant melanoma confirmed by expert group was low, consistent with the rare occurrence of the disease. The numerical imbalance in the low number of patients with malignant melanoma of the skin was also reflected in a numerically higher rate of malignant melanoma observed for liraglutide (0.07 vs. 0.02 events per 100 PYO). Based on the above considerations, neoplasm (including melanoma) has been classified as an important potential risk for liraglutide in T2DM.
Risk factors and risk groups	There is no indication of a causal relationship between liraglutide and the overall neoplasm. Patient risk factors for neoplasm include T2DM, obesity, smoking, alcohol abuse, environmental factors, a history of neoplasm and genetic predisposition.
Risk minimisation measures	Routine risk minimisation measures *None proposed* Additional risk minimisation measures *None proposed*

Abbreviations: PYO = patient-years of observation; T2DM = type 2 diabetes mellitus.

Important potential risk – Medullary thyroid cancer (C-cell carcinogenicity)	
Evidence for linking the risk to the medicine	Thyroid C-cell tumours were observed in liraglutide carcinogenicity studies in mice and rats. Based on mechanistic data generated by Novo Nordisk and data from the literature, it has been shown that the C-cell tumours induced in mice and rats following dosing of liraglutide are caused by a non-genotoxic, specific GLP-1 receptor-mediated mechanism to which mice and rats are particularly sensitive, whereas monkeys and humans are not. The relevance for humans is likely to be low. Data from the intensive monitoring of calcitonin (a marker for MTC) in plasma in the liraglutide clinical development programme do not support a liraglutide effect on calcitonin in humans.
Risk factors and risk groups	There is no indication of a causal relationship between exposure to liraglutide and MTC. Patient risk factors for MTC include previous family history or personal medical history of MEN2.
Risk minimisation measures	Routine risk minimisation measures *Routine risk communication:* • *Nonclinical findings are described in Section 5.3 of the SmPC.* *Routine risk minimisation activities recommending specific clinical measures to address the risk:* • *A warning on thyroid disease is included in Section 4.4 of the SmPC and Section 2 of the PL* Additional risk minimisation measures: *None proposed*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *NN2211-3965: MTC registry (MTC- 22341)* See Section II.C of this summary for an overview of the post-authorisation development plan.

Abbreviations: EAC = Event Adjudication Committee; MEN2 = multiple endocrine neoplasia syndrome type 2; MTC = medullary thyroid cancer; PL = package leaflet; SmPC = Summary of Product Characteristics; SMQ = standardised MedDRA query; T2DM = type 2 diabetes mellitus.

Important potential risk – Pancreatic cancer	
Evidence for linking the risk to the medicine	Based on preclinical signals, an extensive review of all nonclinical and clinical trial data concerning pancreatic safety was performed by the FDA and the EMA, resulting in the publication of a joint commentary in 2014 stating that assertions concerning a causal association between incretin-based therapies and pancreatitis or pancreatic cancer were inconsistent with the available data. Patients with T2DM, as well as patients with overweight or obesity, have an increased risk of certain types of cancer such as pancreatic cancer. Currently, data from clinical trials do not support that GLP-1-based therapies increase the risk of pancreatic cancer. However, due to the questions surrounding a potential association between GLP-1-based therapies and pancreatic cancer, pancreatic cancer has been added as a separate potential risk in line with Article 5(3) of Regulation (EC) 726/ (EMEA/H/A-5(3)/1369).
Risk factors and risk groups	There is no indication of a causal relationship between liraglutide and pancreatic cancer. Patient risk factors for neoplasm include diabetes mellitus, chronic pancreatitis, obesity, physical inactivity, advanced age, smoking, alcohol abuse, environmental factors, history of neoplasm and family history of pancreatic cancer and other genetic predisposition.
Risk minimisation measures	Routine risk minimisation measures *None proposed* Additional risk minimisation measures *None proposed*

Abbreviations: EMA = European Medicines Agency; FDA = U.S. Food and Drug Administration; GLP-1 = glucagon-like peptide-1; T2DM = type 2 diabetes mellitus.

Missing information – Off-label use, including abuse due to weight-lowering potential	
Risk minimisation measures	Routine risk minimisation measures *Routine risk communication:* • *The approved indication is described in Section 4.1 of the SmPC and Section 1 of the PL*. *Routine risk minimisation activities recommending specific clinical measures to address the risk:* *None proposed* *Other risk minimisation measures beyond the Product Information:* • *By the legal status of the product; prescription only* Additional risk minimisation measures *None proposed*

Abbreviations: PL = package leaflet; SmPC = Summary of Product Characteristics.

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 authorisation or specific obligation of Victoza.

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

NN2211-3965: MTC registry (MTC-22341)

This active surveillance programme will monitor for any signal indicating a possible association between treatment with long-acting GLP-1 RAs and the development of MTC in the US population. The MTC registry is an FDA post-marketing requirement for long-acting GLP-1 RA products.

The objectives of this MTC Surveillance Study are:

- To systematically monitor the annual incidence of MTC in the US through North American Association of Central Cancer Registries (NAACCR) to identify any possible increase related to the introduction of long-acting GLP-1 RAs into the US market.
- To establish a registry of incident cases of MTC in adults in the US in order to characterise their medical histories and possible risk factors, including history of treatment with long acting GLP-1 RAs.