Summary of Risk Management Plan (RMP)

for

Saxenda® (liraglutide)

Novo Nordisk Pharma AG

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The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine but also in connection with larger changes such as extension of the indication. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimize them.

The RMP summary of Saxenda® is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the „Arzneimittelinformation / Information sur le médicament“, approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Saxenda® in Switzerland is the „Arzneimittelinformation / Information sur le médicament“ (see www.swissmedicinfo.ch) approved and authorized by Swissmedic.

Novo Nordisk Pharma AG is fully responsible for the accuracy and correctness of the content of the here published summary RMP of Saxenda®.

Summary of the risk management plan for Saxenda (liraglutide in WM)

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

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

This summary of the RMP for Saxenda® 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 Saxenda's RMP.

1.0 The medicine and what it is used for

Saxenda is authorised for use as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adult and adolescent patients aged 12 years and above (see SmPC for the full indication). It contains liraglutide as the active substance and it is injected subcutaneously.

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

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

Important risks of Saxenda, together with measures to minimise such risks and the proposed studies for learning more about Saxenda'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 minimise 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 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 Saxenda is not yet available, it is listed under 'missing information' below.

2.1 List of important risks and missing information

Important risks of Saxenda 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 Saxenda. 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 2-1 List of important risks and missing information

Summary of safety concerns	
Important identified risks	• None
Important potential risks	• Neoplasms (including melanoma) • Medullary thyroid cancer (C-cell carcinogenicity) • Pancreatic cancer
Missing information	• Patients with a history of major depression or other severe psychiatric disorders • Concomitant use of other weight lowering products • Off-label use

Summary of important risks

Table 2-2 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 up 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). No causal relationship has been established. However, based on the above considerations, neoplasm (including melanoma) has been classified as an important potential risk for liraglutide in WM.
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; WM = weight management.

Table 2-3 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.* *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 3.2 of this summary for an overview of the post-authorisation development plan.

Abbreviations: GLP-1 = glucagon-like peptide-1; MEN2 = multiple endocrine neoplasia syndrome type 2; MTC = medullary thyroid cancer; PL = package leaflet; SmPC = Summary of Product Characteristics.

Table 2-4 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 then 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. There is currently no support from clinical trials 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.

Table 2-5 Missing information

Patients with a history of major depression or other severe psychiatric disorders	
Risk minimisation measures	Routine risk minimisation measures *None proposed* Additional risk minimisation measures *None proposed*
Concomitant use of other weight lowering products	
Risk minimisation measures	Routine risk minimisation measures *Routine risk communication:* • *The lack of data supporting co-administration with other products for weight management included in Section 4.4 of the SmPC* Additional risk minimisation measures *None proposed*
Off-label use	
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*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *PASS NN8022-4246* See Section 3.2 of this summary for an overview of the post-authorisation development plan.

Abbreviations: PASS = post authorisation safety study; PL = package leaflet; SmPC = Summary of Product Characteristics.

3.0 Post-authorisation development plan

3.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Saxenda.

3.2 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.

NN8022-4246: In-market utilisation of liraglutide used for weight management in the UK: a study in the CPRD primary care database

The aim of this study is to investigate usage of liraglutide for weight management in clinical practice using the Clinical Practice Research Datalink (CPRD) primary care database.

This is a descriptive drug utilisation study (DUS) to investigate in market utilisation of liraglutide used for weight management, more specifically:

Primary objective:

- Use of Saxenda according to approved indication

Secondary objectives:

- Use of Victoza for weight management
- Use of Saxenda according to approved posology

This summary was last updated in August 2021.