

# **Summary of risk management plan (RMP) for Rybelsus® (oral semaglutide)**

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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 Rybelsus® 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 / Informazione sul medicamento“, 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 Rybelsus® in Switzerland is the „Arzneimittelinformation / Information sur le médicament / Informazione sul medicamento“ (see [www.swissmedicinfo.ch](http://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 Rybelsus®.

## **Summary of risk management plan for Rybelsus (oral semaglutide)**

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

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

This summary of the RMP for Rybelsus 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 EPAR.

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

### **I. The medicine and what it is used for**

Rybelsus is authorised for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise (see SmPC for the full indication). It contains semaglutide as the active substance and it is given by oral route of administration.

Further information about the evaluation of Rybelsus' benefits can be found in Rybelsus' 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 Rybelsus, together with measures to minimise such risks and the proposed studies for learning more about Rybelsus' 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*.

### **II.A List of important risks and missing information**

Important risks of Rybelsus 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 Rybelsus. 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).

<b>List of important risks and missing information</b>	
Important identified risks	<ul style="list-style-type: none"> <li>• Diabetic retinopathy complications</li> </ul>
Important potential risks	<ul style="list-style-type: none"> <li>• Pancreatic cancer</li> <li>• Medullary thyroid cancer</li> <li>• Neoplasms (malignant and non-malignant)</li> </ul>
Missing information	<ul style="list-style-type: none"> <li>• Pregnancy and lactation</li> <li>• Patients with severe hepatic impairment</li> </ul>

## **II.B Summary of important risks**

<b>Diabetic retinopathy complications</b>	
Evidence for linking the risk to the medicine	The risk is included as an identified risk for oral semaglutide based on findings in the semaglutide s.c. clinical development programme. Based on the totality of data on diabetic retinopathy collected across the oral semaglutide phase 3a trials, there was no increased risk of diabetic retinopathy with oral semaglutide.
Risk factors and risk groups	Patient risk factors include increasing age, long duration of diabetes, poor glycaemic control, prior history of diabetic retinopathy and rapid decline in HbA <sub>1c</sub> .
Risk minimisation measures	<p><i>Routine risk minimisation measures:</i> SmPC Sections 4.4 and 4.8 and PL Sections 2 and 4.</p> <p><i>Additional risk minimisation measures:</i> None</p>
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Results from the study NN9535-4352 ( <i>Long-term effects of semaglutide on diabetic retinopathy in subjects with T2DM [FOCUS]</i> ) for semaglutide s.c. will also be relevant for the ongoing evaluation of the risk for oral semaglutide.

**Abbreviations:** CVOT = cardiovascular outcomes trial; MedDRA = Medical Dictionary for Regulatory Activities; PL = package leaflet; SmPC = Summary of Product Characteristics.

<b>Pancreatic cancer</b>	
Evidence for linking the risk to the medicine	Patients with T2DM, as well as patients being overweight or with obesity, have an increased risk of certain types of cancer such as pancreatic cancer. There is no evidence from clinical trials that GLP-1-based therapies increase the risk of pancreatic cancer. However, pancreatic cancer is included as an important potential risk, based on the EC regulation 726/2004 Article 5(3) referral procedure in 2013 (EMA/H/A-5(3)/1369).
Risk factors and risk groups	Patient risk factors for neoplasms include diabetes, chronic pancreatitis, obesity, physical inactivity, advanced age, smoking, alcohol abuse, environmental factors, history of neoplasms and family history of pancreatic cancer and other genetic predispositions.
Risk minimisation measures	No risk minimisation measures
Additional pharmacovigilance activities	<i>Additional pharmacovigilance activities:</i> <i>Study NN9535-4447 (Epidemiological assessment of the risk for pancreatic cancer associated with the use of Ozempic/Rybelsus (semaglutide s.c./oral semaglutide) in patients with T2DM)</i>

**Abbreviations:** GLP-1 = glucagon-like peptide-1; T2DM = type 2 diabetes mellitus.

<b>Medullary thyroid cancer</b>	
Evidence for linking the risk to the medicine	This potential class risk is based on findings in mice and rats for all currently approved long-acting GLP-1 RAs. Data from the monitoring of calcitonin (a marker for MTC) in plasma in the semaglutide s.c. and oral semaglutide clinical development programmes did not support a semaglutide effect on calcitonin in humans.
Risk factors and risk groups	Patient risk factors for MTC include previous family history or personal medical history of multiple endocrine neoplasia 2 (MEN2), a group of medical disorders associated with tumours of the endocrine system.
Risk minimisation measures	<i>Routine risk minimisation measures:</i> SmPC Section 5.3.  <i>Additional risk minimisation measures:</i> None
Additional pharmacovigilance activities	<i>Additional pharmacovigilance activities:</i> <i>Study MTC-22341 (Medullary Thyroid Carcinoma Surveillance Study: a Case-Series Registry)</i>  See Section II C of this summary for an overview of the post-authorisation development plan.

**Abbreviations:** MEN2 = multiple endocrine neoplasia 2; MTC = medullary thyroid cancer; SmPC = Summary of Product Characteristics.

<b>Neoplasms (malignant and non-malignant)</b>	
Evidence for linking the risk to the medicine	Patients with T2DM, as well as patients being overweight or with obesity, have an increased risk of certain types of cancer. There is no evidence from clinical trials that GLP-1-based therapies increase the risk of neoplasms. However, in the semaglutide s.c. as well as oral semaglutide phase 3a trials, the proportion of subjects with neoplasms (malignant and non-malignant) were slightly higher with semaglutide than with comparator. The number of subjects exposed to semaglutide s.c. or oral semaglutide for a longer period is considered insufficient for a thorough assessment of the risk of neoplasms, and therefore the risk is included in the RMP.
Risk factors and risk groups	Patient risk factors for neoplasm include T2DM, obesity, smoking, alcohol abuse, environmental factors, a history of neoplasm and genetic predisposition.
Risk minimisation measures	<i>Routine risk minimisation measures:</i> None.  <i>Additional risk minimisation measures:</i> None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Serious adverse event reporting pertaining to neoplasms from clinical trials ( $\geq 40$ weeks).

**Abbreviations:** GLP-1 = glucagon-like peptide-1; T2DM = type 2 diabetes mellitus.

<b>Pregnancy and lactation</b>	
Risk minimisation measures	<i>Routine risk minimisation measures:</i> SmPC Section 4.6 and PL Section 2.  <i>Additional risk minimisation measures:</i> None

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

<b>Patients with severe hepatic impairment</b>	
Risk minimisation measures	<i>Routine risk minimisation measures:</i> SmPC Sections 4.2 and 5.2.  <i>Additional risk minimisation measures:</i> None

**Abbreviations:** SmPC = Summary of Product Characteristics.

## ***II.C Post-authorisation development plan***

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

The following studies are conditions of the marketing authorisation:

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

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

#### **NN9535-4352 (FOCUS)**

Purpose of the study: The aim of this randomised clinical trial is to establish the long-term effects of semaglutide on diabetic retinopathy in subjects with type 2 diabetes mellitus (T2DM) using validated and standardised ophthalmic assessments.

#### **NN9535-4447**

Purpose of the study: The aim of this study is to evaluate whether exposure to Ozempic/Rybelsus increases the risk of pancreatic cancer in patients with T2DM.

#### **MTC-22341**

Purpose of the study: This active surveillance programme for MTC has been established to evaluate further a potential association between treatment with long-acting GLP-1 RAs and the occurrence of MTC in humans. The MTC registry is an FDA post-marketing requirement for long-acting GLP-1 RA products.

**The important potential risk Neoplasms (malignant and non-malignant) will be monitored through routine serious adverse events reporting in the following studies as per request from EMA:**

- NN9535-4321: FLOW – Effect of semaglutide versus placebo on the progression of renal impairment in subjects with type 2 diabetes and chronic kidney disease
- NN9535-4352: FOCUS – Long-term effects of semaglutide on diabetic retinopathy in subjects with type 2 diabetes
- NN9535-4386: SUSTAIN 11 – Effect of semaglutide once-weekly versus insulin aspart three times daily, both as add-on to metformin and optimised insulin glargine (U100) in subjects with type 2 diabetes

- NN9535-4430: A trial investigating the effect of semaglutide on atherosclerosis in patients with cardiovascular disease and type 2 diabetes
- NN9535-4506: Efficacy and safety of semaglutide 2.0 mg s.c. once-weekly compared to semaglutide 1.0 mg s.c. once-weekly in subjects with type 2 diabetes
- NN9535-4416: SePra – Long-term comparative effectiveness of once-weekly semaglutide versus standard of care in a real-world adult US population with type 2 diabetes – a randomised pragmatic clinical trial
- EX9924-4473: SOUL – Semaglutide cardiovascular outcomes trial in patients with type 2 diabetes

In addition, data will be collected from any future clinical trials ( $\geq 40$  weeks).