swissmedic

Date: 31 March 2026
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report
Extension of therapeutic indication

Rybelsus

International non-proprietary name:	semaglutide
Pharmaceutical form:	tablets
Dosage strength(s):	14 mg, 7 mg and 3 mg
Route(s) of administration:	oral
Marketing authorisation holder:	Novo Nordisk Pharma AG
Marketing authorisation no.:	67446
Decision and decision date:	extension of therapeutic indication approved on 03 February 2026

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
CKD	Chronic kidney disease
C_{max}	Maximum observed plasma/serum concentration of drug
CV	Cardiovascular
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MACE	Major adverse cardiovascular events
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
PY	patient-years
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
T2DM	Type 2 diabetes mellitus

2 Background information on the procedure

2.1 Applicant's request(s) and information regarding procedure

Extension(s) of the therapeutic indication(s)
The applicant requested the addition of a new therapeutic indication or modification of an approved one in accordance with Article 23 TPO.

2.2 Indication and dosage

2.2.1 Requested indication

Risk reduction of major cardiovascular events in adults with type 2 diabetes mellitus
Rybelsus is indicated to reduce the risk of major cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease and/or chronic kidney disease (see section "Clinical Efficacy").

2.2.2 Approved indication

Cardiovascular events reduction in adults with type 2 diabetes mellitus
Rybelsus is indicated to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease (including mild to moderate renal impairment). The treatment should be administered in addition to standard therapy for patients with established cardiovascular disease (see section "Clinical Efficacy").

2.2.3 Requested dosage

No change to the dosage recommendation was requested with the application for extension of indication.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	31 January 2025
Formal control completed	12 February 2025
List of Questions (LoQ)	25 June 2025
Response to LoQ	22 August 2025
Preliminary decision	30 October 2025
Response to preliminary decision	16 December 2025
Final decision	03 February 2026
Decision	approval

3 Medical context

The oral formulation of semaglutide (Rybelsus®) is authorised in Switzerland for the treatment of adult patients with type 2 diabetes mellitus (T2DM). A cardiovascular (CV) benefit has been shown for the subcutaneous semaglutide in patients with obesity or overweight and established CV disease. The SOUL study aimed to show such an effect for oral semaglutide in a target population of patients with T2DM at high risk of CV events.

4 Nonclinical aspects

The applicant did not submit new nonclinical studies to support the requested extension of the indication. This was considered acceptable since there are no changes with regard to posology and method of administration.
Based on the ERA, the extension of the indication will not be associated with a significant risk for the environment.
From the nonclinical point of view, there are no objections to approval of the proposed extension of indication.

5 Clinical aspects

5.1 Clinical pharmacology

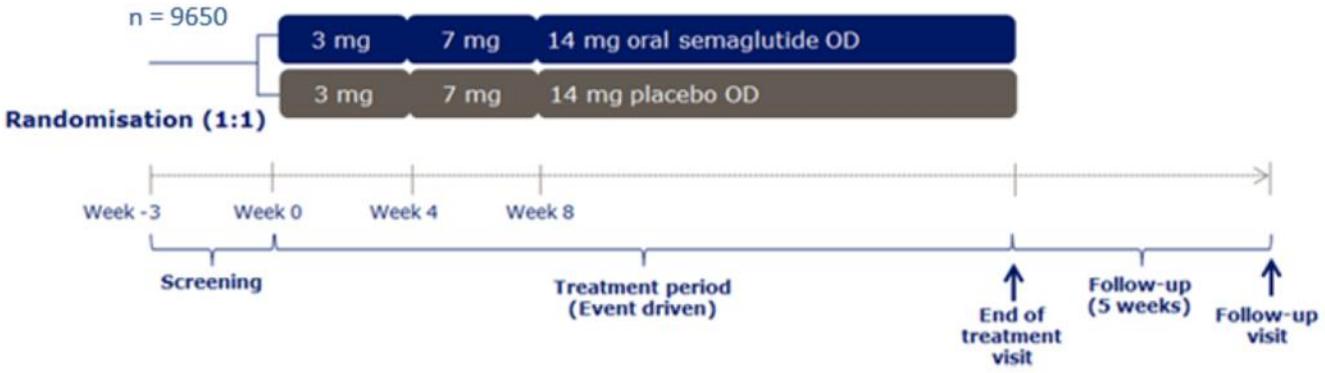
n/a

5.2 Dose finding and dose recommendation

The same dose regimen as recommended for the treatment T2DM was used.

5.3 Efficacy

The new indication is supported by data from the SOUL trial, a multi-national, multi-centre, randomised, double-blind, parallel-group, placebo-controlled trial comparing oral semaglutide versus placebo both added to standard of care in subjects with T2DM at high risk of CV events.



Treatment with oral semaglutide reduced the incidence/rate of major adverse CV events (MACE) (HR [95% CI] for the time to first event: 0.86 [0.77, 0.95]). Various sensitivity analyses support the robustness of this treatment effect (e.g., superiority confirmed after adjustment for group sequential design). The treatment effect was mainly driven by a reduction in non-fatal myocardial infarctions (1.0 vs. 1.4 events per 100 patient-years) and a slight reduction in CV mortality (1.4 vs. 1.5 events per 100 patient-years). Non-fatal strokes occurred at the same event rate in the two treatment arms (0.8 events per 100 PY). The same pattern was observed in the analysis of recurrent events.

This evidence was supported by data from PIONEER 6, a prior CV outcomes trial in a comparable study population of patients with T2DM ± established CV disease (>80%) ± diabetic nephropathy (>30%). Consistent with the results of SOUL, PIONEER 6 had shown a nominal or statistically significant decrease in MACE (HR [95% CI]: 0.79 [0.57, 1.11]), CV (HR [95% CI]: 0.49 [0.27, 0.92]) and all-cause mortality (HR [95% CI]: 0.44 [0.23, 0.82]).

5.4 Safety

The safety profile of semaglutide is well characterised, including in the population studied in SOUL. The safety data from SOUL confirmed the well-established safety profile of oral semaglutide. Small unfavourable imbalances observed in SOUL for specific malignancies are not consistent with the overall database for semaglutide. No new safety concerns emerged.

5.5 Final clinical benefit risk assessment

The benefit-risk ratio can be considered positive.
For further details concerning efficacy and safety, please see the Appendix of this report.

6 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

7 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Rybelsus was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

RYBELSUS®

Composition

Active substances

Semaglutide

Excipients

Salcaprozate sodium, equivalent to sodium 22.9 mg, Povidone K90,
Cellulose, microcrystalline, Magnesium stearate

Pharmaceutical form and active substance quantity per unit

Tablet for oral administration.
Each tablet contains 3 mg, 7 mg, or 14 mg semaglutide*, respectively.
The tablets are white to light yellow, oval shaped and debossed with "3", "7" or "14" on one side and "novo" on the other side.
* Genetically engineered by recombinant DNA technology in cells of *Saccharomyces cerevisiae*.

Indications/Uses

Type 2 diabetes mellitus
Rybelsus is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise:

- as monotherapy when metformin is considered inappropriate
- in combination with other glucose-lowering medications.

Cardiovascular events reduction in adults with type 2 diabetes mellitus
Rybelsus is indicated to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease (including mild to moderate renal impairment). The treatment should be administered in addition to standard therapy for patients with established cardiovascular disease (see section “Clinical Efficacy”).

Dosage/Administration

Usual dosage

The starting dose of Rybelsus is 3 mg once a day. After one month, the dose should be increased to 7 mg once daily (maintenance dose). If the glucose-lowering effect is insufficient after at least one month of treatment with the 7 mg dose, the maintenance dose can be increased to a maximum of 14 mg once daily.

Patients with established cardiovascular disease who participated in the SOUL study received a maintenance dose of 14 mg once daily (see “Clinical Efficacy”).

Patients who are being treated with Rybelsus 14 mg once daily can be switched to a subcutaneous injection of 0.5 mg once a week (Ozempic). The patients can begin with Ozempic on the day after the last dose of Rybelsus. Patients who are being treated with a once weekly injection of Ozempic 0.5 mg s.c. can switch to Rybelsus 7 mg or 14 mg once daily. Patients can begin with Rybelsus up to 7 days after the last injection of Ozempic. For Ozempic 1 mg, there is no equivalent dose of Rybelsus.
When Rybelsus is used in combination with metformin and/or a sodium-glucose co-transporter-2 inhibitor (SGLT2i) or thiazolidinedione, the current dose of metformin and/or SGLT2i or thiazolidinedione can be continued.
When Rybelsus is used in combination with a sulfonylurea or with insulin, a reduction in the dose of sulfonylurea or insulin should be considered to reduce the risk of hypoglycaemia (see "Warnings and precautions").

Special patient groups

Elderly patients (≥65 years old)

A dose adjustment is not necessary for the elderly (see "Pharmacokinetics").

Patients with hepatic impairment

A dose adjustment is not necessary for patients with impaired liver function (see "Pharmacokinetics").

Patients with kidney impairment

A dose adjustment is not necessary for patients with impaired renal function (see "Pharmacokinetics").

Children and adolescents

The safety and efficacy of Rybelsus in children and adolescents under 18 years of age have not been investigated.
Rybelsus is a tablet for once-daily oral use.

Mode of administration

This medicinal product should be taken on an empty stomach. Rybelsus should be swallowed as a whole tablet with up to half a glass of water (120 ml). The tablet must not be crushed or chewed. Patients must wait at least 30 minutes before their first meal, first drink or taking other oral medicinal products. Waiting less than 30 minutes can decrease the absorption of semaglutide.
If a dose was forgotten, it should be skipped. The next dose should be taken on the following day.

Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Warnings and precautions

Rybelsus should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. Diabetic ketoacidosis has been reported in insulin-dependent patients due to discontinuation or overly rapid dose reduction of insulin when treatment with a GLP-1 receptor agonist is started.

Aspiration in association with general anaesthesia or deep sedation

Cases of pulmonary aspiration have been reported in patients receiving GLP-1 RAs undergoing general anaesthesia (GA) or deep sedation despite reported adherence to preoperative fasting recommendations. Therefore, the increased risk of residual gastric content because of delayed gastric emptying should be considered prior to performing procedures with GA or deep sedation.

Gastrointestinal effects and dehydration

Use of GLP-1 receptor agonists may be associated with gastrointestinal adverse reactions. This should be considered when treating patients with impaired renal function, as nausea, vomiting, and diarrhoea may cause dehydration, which in rare cases can lead to a deterioration of renal function (see “Undesirable effects”). Patients treated with semaglutide should be advised of the potential risk of dehydration in relation to gastrointestinal side effects and take precautions to avoid fluid depletion.

Acute pancreatitis

Acute pancreatitis has been observed with the use of GLP-1 receptor agonists. Patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, discontinue treatment with Rybelsus; if acute pancreatitis is confirmed, do not resume treatment with Rybelsus.
In the absence of other signs and symptoms of acute pancreatitis, elevations in pancreatic enzymes alone are not predictive of acute pancreatitis.

Hypoglycaemia

Patients treated with Rybelsus in combination with a sulfonylurea or insulin may have an increased risk of hypoglycaemia. The risk of hypoglycaemia can be lowered by reducing the dose of sulfonylurea or insulin when initiating treatment with Rybelsus.

Risk of thyroid C-cell tumours

Preclinical studies with GLP-1 receptor agonists on rodents suggest that GLP-1 receptor agonists may be associated with an increased risk of focal hyperplasia of thyroid C-cells and C-cell tumours (see "Preclinical data").
It is not known if there is an association between GLP-1 receptor agonists and thyroid C-cell tumours in humans, including medullary thyroid carcinoma (MTC). Patients with MTC and patients with multiple endocrine neoplasia syndrome, type 2 (MEN 2) in their medical history were not treated with

semaglutide in the clinical studies. Therefore, before treatment with Rybelsus, a careful risk-benefit assessment is required in this specific collective.
The clinical value of routine monitoring of the serum calcitonin level has not been demonstrated.

Diabetic retinopathy

Rapid improvement in glycaemic control has been associated with a temporary worsening of diabetic retinopathy. Long-term glycaemic control decreases the risk of diabetic retinopathy. Patients with a history of diabetic retinopathy should be monitored and treated according to clinical guidelines on site.

Cardiac failure

There is no therapeutic experience in patients with congestive heart failure NYHA (New York Heart Association) class IV and semaglutide is therefore not recommended in these patients.

Patients following bariatric surgery

There is no therapeutic experience with semaglutide in patients with bariatric surgery.

Gastrointestinal adverse reactions

Following the market introduction, there were reports of acute renal damage and a worsening of chronic kidney failure in patients who were treated with GLP-1 receptor agonists, which sometimes necessitated haemodialysis. Some of these events were reported in patients without known underlying kidney disorder. The majority of the reported events occurred in patients who were already suffering from nausea, vomiting, diarrhoea or dehydration. Kidney function should be monitored in patients who report severe adverse gastrointestinal reactions when treatment with Rybelsus is started or up-titrated.

Patients with gastroparesis

Semaglutide treated patients with gastroparesis may experience more serious or severe gastrointestinal adverse events. Semaglutide should be used with caution in these patients (see “Undesirable effects”).

This medicinal product contains 22.9 mg sodium per tablet, equivalent to 1% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Interactions

In-vitro studies have shown very low potential for semaglutide to inhibit or induce CYP-enzymes, and to inhibit drug transporters.
Semaglutide delays gastric emptying which may influence the absorption of other concomitantly administered oral medicinal products.
No clinically relevant drug interactions between semaglutide and the evaluated medicinal product were observed. Therefore, no dose adjustment is required for concomitant administration with Rybelsus.

It is essential that patients who are being treated concomitantly with Rybelsus and other orally administered medicinal products follow the dosage instructions in "Dosage".

Effects of Rybelsus on other medicinal products

Levothyroxine

Total exposure (AUC) of thyroxine (adjusted for endogenous levels) was increased by 33% following administration of a single dose of 600 µg levothyroxine. Maximum exposure (C_{max}) was unchanged. Monitoring of thyroid parameters should be considered when treating patients with Rybelsus at the same time as levothyroxine.

Rosuvastatin

Total exposure (AUC) of rosuvastatin was increased by 41% and the maximum exposure (C_{max}) by 10%. Based on the wide therapeutic index of rosuvastatin the magnitude of changes in the exposure is not considered clinically relevant.

Metformin

Total exposure (AUC) of metformin was increased by 32% and the maximum exposure (C_{max}) was unchanged. Based on the wide therapeutic index of metformin, the magnitude of changes in the exposure is not considered clinically relevant.

Furosemide

Total exposure (AUC) of furosemide was increased by 28% and the maximum exposure (C_{max}) was decreased by 34%. Based on the wide therapeutic index of furosemide, the magnitude of changes in the exposure is not considered clinically relevant.

Oral contraceptives

Semaglutide did not change the exposure (AUC or C_{max}) in combination with oral contraceptives (containing ethinylestradiol and levonorgestrel).

Warfarin and other coumarin derivatives

Semaglutide did not change the AUC or C_{max} of R- and S-warfarin following a single dose of warfarin, and the pharmacodynamic effects of warfarin as measured by the international normalised ratio (INR) were not affected in a clinically relevant manner. However, cases of decreased INR have been reported during concomitant use of acenocoumarol and semaglutide. Upon initiation of semaglutide treatment in patients on warfarin or other coumarin derivatives, frequent monitoring of INR is recommended.

Digoxin

Semaglutide did not alter the exposure (AUC or C_{max}) of digoxin.

Lisinopril

Semaglutide did not alter the exposure (AUC or C_{max}) of lisinopril.

Effects of other medicinal products on Rybelsus

Omeprazole

No clinically relevant change in AUC or C_{max} of semaglutide was observed (e.g. proton pump inhibitors that increase the gastric pH) when taken concomitantly with omeprazole.

Food interactions

Concomitant intake of food reduces the exposure of semaglutide (see "Dosage/Administration").

Pregnancy, lactation

Pregnancy

There are limited data on the use of semaglutide in pregnant women. Studies in animals have shown reproductive toxicity (see "Preclinical data").
Therefore, Rybelsus should not be used during pregnancy. Women of childbearing potential are recommended to use contraception when treated with Rybelsus. If a patient wishes to become pregnant or pregnancy occurs, treatment with Rybelsus should be discontinued. Treatment with Rybelsus should be discontinued at least 2 months before a planned pregnancy due to the long half-life.

Breast-feeding

No measurable concentrations of semaglutide were found in breastmilk of lactating women.
Salcaprozate sodium was present in breastmilk and some of its metabolites were excreted in breastmilk at low concentrations. As a risk to a breast-fed child cannot be excluded, Rybelsus should not be used during breast-feeding.

Fertility

The effect of semaglutide on fertility in humans is unknown. Semaglutide did not affect male fertility in rats. In female rats, an increase in oestrous length and a small reduction in number of ovulations were observed at doses associated with maternal body weight loss (see "Preclinical data").

Effects on the ability to drive and use machines

Dizziness can be experienced mainly initially during the dose escalation and may affect the ability to drive and using machines.
When it is used in combination with a sulfonylurea or insulin, patients should be advised to take precautions to avoid hypoglycaemia while driving and using machines (see "Warnings and precautions").

Undesirable effects

Summary of the safety profile:

In 10 phase 3a trials, 5 707 patients were exposed to Rybelsus alone or in combination with other glucose-lowering medicinal products. The duration of the treatment ranged from 26 weeks to 78 weeks.

The most frequently reported adverse reactions in clinical trials were gastrointestinal disorders, including nausea, diarrhoea and vomiting. In general, these reactions were mild or moderate in severity and of short duration.

In the cardiovascular outcomes trial (SOUL), including 9 650 adults with type 2 diabetes and established cardiovascular disease and/or chronic kidney disease, the safety profile was consistent with the safety profile of Rybelsus seen in the phase 3a trials.

Tabulated list of adverse reactions:

Table 1 lists adverse reactions identified in phase 3 trials (for further information, see "Properties/Effects") and post-marketing reports in patients with type 2 diabetes mellitus. The frequencies of the adverse reactions (except diabetic retinopathy complications, see footnote in Table 1) are based on a pool of the phase 3a trials excluding the cardiovascular outcomes trial.
The adverse reactions are listed below according to MedDRA system organ classes and the conventional frequencies as follows: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1 000, <1/100); rare (≥1/10 000, <1/1 000); very rare (<1/10 000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are present in order of decreasing seriousness.

Table 1: Frequency of adverse reactions of oral semaglutide

MedDRA system organ class	Very common	Common	Uncommon	Rare	Not known
Immune system disorders			Hypersensitivity [c]	Anaphylactic reaction	
Metabolism and nutrition disorders	Hypoglycaemia when used with insulin or SU (sulfonylurea)[a]	Hypoglycaemia when used with other oral			

		antidiabetic products (oral antidiabetics)[a] Decreased appetite			
Nervous system disorder		Dizziness, Headache	Dysgeusia		
Eye disorders		Diabetic retinopathy complications[b]			
Cardiac disorders			Increased heart rate		
Gastrointestinal disorders	Nausea Diarrhoea	Vomiting Abdominal pain Abdominal distension Constipation Dyspepsia Gastritis Gastrooesophageal reflux Flatulence	Eructation Delayed gastric emptying	Acute pancreatitis	Intestinal obstruction[d,e]
Hepatobiliary disorders		Increased lipase Increased amylase	Cholelithiasis Cholecystitis		
General disorders and administration site conditions		Fatigue			
Investigations			Weight decreased		

[a] Hypoglycaemia grade 2 (ADA 2018, <3.0 mmol/l or <54 mg/dl)

[b] Diabetic retinopathy complications is a composite of retinal photocoagulation, treatment with intravitreal agents, vitreous haemorrhage and diabetes-related blindness (uncommon). Frequency is based on the cardiovascular outcomes trial with s.c. semaglutide, but it cannot be excluded that the risk of diabetic retinopathy complications identified also applies to semaglutide per os.

[c] Grouped term covering also adverse events related to hypersensitivity such as skin rash and urticaria.

[d] From post-marketing reports

[e] Grouped term covering PTs Intestinal obstruction, Ileus, small intestinal obstruction

Description of specific adverse reactions and additional information

Hypoglycaemia

Very common – hypoglycaemia when used with insulin (24%) or SU (11%)

Common – hypoglycaemia when used with other oral antidiabetic products

Severe hypoglycaemia was primarily observed when Rybelsus was used with a sulfonylurea (<0.1% of subjects, <0.001 events/patient year) or insulin (1.1% of subjects, 0.013 events/patient year). Few episodes (0.1% of subjects, 0.001 events/patient year) were observed with Rybelsus in combination with oral antidiabetics other than sulfonylurea.

Gastrointestinal disorders

Patients with gastroparesis may experience more serious or severe gastrointestinal effects when treated with semaglutide.

Very common – nausea (15%), diarrhoea (10%)

Common – vomiting

Nausea occurred in 15%, diarrhoea in 10%, and vomiting in 7% of patients when treated with Rybelsus. Most events were mild to moderate in severity and of short duration. The events led to treatment withdrawal in 4% of subjects. The events were most frequently reported during the first months on treatment.

Rare – acute pancreatitis

Acute pancreatitis confirmed by adjudication has been reported in phase 3a trials, semaglutide (< 0.1%) and comparator (0.2%). In the cardiovascular outcomes trial the frequency of acute pancreatitis confirmed by adjudication was 0.1% for semaglutide and 0.2% for placebo. In phase 3b cardiovascular outcomes trial SOUL, the frequency of acute pancreatitis confirmed by adjudication was 0.4% for semaglutide and 0.4% for placebo (see "Warnings and precautions").

Treatment withdrawal due to an adverse reaction

The incidence of treatment withdrawals due to adverse reactions was 9% in patients who were treated with Rybelsus. The adverse reactions that most often led to withdrawal were gastrointestinal disorders.

Increased heart rate

In the phase 3 trials, a mean increase of 2 beats per minute with Rybelsus was observed.

Eye disorders

Common – diabetic retinopathy complications

In a 2-year clinical trial of s.c. semaglutide with 3 297 patients with type 2 diabetes mellitus and high cardiovascular risk, diabetic retinopathy complications were an endpoint. In this study, diabetic retinopathy complications occurred in more patients treated with s.c. semaglutide (3.0%) compared to placebo (1.8%). Over 80% of patients with a diabetic retinopathy complication had a documented case of diabetic retinopathy prior to the start of treatment. In patients who had no (documented) history of diabetic retinopathy, the number of events under semaglutide s.c. and placebo was similar.
In clinical trials with Rybelsus of up to 18 months duration involving 6 352 patients with type 2 diabetes mellitus, adverse events related to diabetic retinopathy were reported in similar proportions in subjects treated with semaglutide (4.2%) and comparators (3.8%).

Immunogenicity

Consistent with the potential immunogenic properties of medicinal products containing proteins or peptides, patients may develop antibodies following treatment with semaglutide. The proportion of subjects who tested positive for anti-semaglutide antibodies at any time point after the start of treatment was 14 (0.5%). Of these 14 patients, 7 patients (0.2% of the entire population) developed antibodies that cross-reacted with endogenous GLP-1. The neutralising activity of the antibody is currently still uncertain.

Post-marketing surveillance of undesirable effects

Renal and urinary disorders: Acute kidney injury (see "Warnings and precautions").
Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

In clinical studies, it was demonstrated that overdose with semaglutide may result in gastrointestinal disorders. In the event of overdose, appropriate supportive treatment must be initiated according to the patient's clinical signs and symptoms.

In view of the long half-life of semaglutide of approximately 1 week (see "Pharmacokinetics"), a prolonged period of observation and treatment of the symptoms may be necessary. There is no specific antidote for overdose with semaglutide.

Properties/Effects

ATC code:

A10BJ06

Mechanism of action

Semaglutide is a GLP-1 analogue of the human peptide GLP-1 involved in the regulation of glucose homeostasis. Due to its pronounced albumin binding, the renal clearance of semaglutide is delayed. In addition, due to its modified structure compared to native GLP-1, semaglutide is not susceptible to degradation by DPP-4.
Semaglutide acts as a GLP-1 receptor agonist for native GLP-1. GLP-1 receptors are expressed in the pancreas, brain, heart, vasculature, immune system and kidneys. Depending on the blood glucose level, the stimulation of GLP-1 receptors by semaglutide leads to stimulation of the insulin reaction and inhibition of glucagon secretion. A delay in gastric emptying in the early postprandial phase also occurs. Semaglutide reduces body weight and body fat mass through lowered energy intake. The mechanism comprises an overall reduced appetite, which includes an increased feeling of fullness and a reduced feeling of hunger. Insulin resistance is reduced. Presumably, this ensues due to the reduction of body weight.

The mechanism of action of semaglutide for cardiovascular risk reduction is likely multifactorial, in part driven by reduction in HbA_{1c} and effects on known cardio-kidney-metabolic risk factors including reduction in blood pressure, and body weight, improvements in lipid profile, and kidney function, and anti-inflammatory effects as demonstrated by reduction in hsCRP. The exact mechanism of cardiovascular risk reduction has not been established.

Pharmacodynamics

Rybelsus reduces fasting blood glucose and self-measured blood glucose level. The effect sets in early; in patients with type 2 diabetes mellitus, a reduction in FBG (fasting blood glucose) occurs in the first week.
All pharmacodynamic investigations were performed once weekly in steady state with 1 mg semaglutide injections after 12 treatment weeks (including dose escalation).

Fasting blood glucose and postprandial increases

Semaglutide reduces fasting blood glucose and postprandial blood glucose. In patients with type 2 diabetes mellitus, treatment with semaglutide led to a reduction of the blood glucose level, both with regard to absolute change compared to baseline and also relative reduction compared to placebo with respect to fasting blood glucose (1.6 mmol/l/29 mg/dl; 22%), postprandial blood glucose at 2 hours (4.1 mmol/l/74 mg/dl; 37%), mean 24-hour blood glucose level (1.7 mmol/l/30 mg/dl; reduction of 22%) and postprandial blood glucose excursions over 3 meals (0.6–1.1 mmol/l/11–20 mg/dl) compared to placebo.

Beta cell function and insulin secretion

Semaglutide improves beta cell function. Compared to placebo, semaglutide improved first and second phase insulin response by threefold or twofold and increased the maximum secretory capacity of beta cells according to an arginine stimulation test in patients with type 2 diabetes mellitus. Moreover, treatment with semaglutide increased fasting insulin concentrations compared to placebo.

Glucagon secretion

Semaglutide lowers the fasting and postprandial glucagon concentrations. In patients with type 2 diabetes mellitus, semaglutide resulted in the following relative reductions in glucagon compared to placebo: Fasting glucagon (8–21%), postprandial glucagon response (14–15%) and mean 24-hour glucagon level (12%).

Glucose-dependent insulin and glucagon secretion

Semaglutide lowered high blood glucose levels by glucose-dependent stimulation of insulin secretion and inhibition of glucagon secretion. With semaglutide, the insulin secretion rate in patients with type 2 diabetes mellitus was comparable to that of healthy patients.
While an induced hypoglycaemia altered semaglutide compared to placebo, the counter-regulatory reactions on the increased glucagon level did not reduce the lowering of C-peptide in patients with type 2 diabetes mellitus.

Gastric emptying

Semaglutide caused a minor delay in early postprandial gastric emptying, and by doing so reduced the glucose rate that was attained in the postprandial circulation.

Body weight and composition

Rybelsus achieved a greater weight reduction than that of the comparable preparations (placebo, sitagliptin, empagliflozin and liraglutide). The weight loss was primarily attributable to the loss of fatty tissue, with a loss of visceral fat mass that was three times as large as the loss of muscle mass.

Appetite, energy intake and selection of food

Compared to placebo, semaglutide reduced the energy supply from 3 successive *ad libitum* meals by 18–35%. This was achieved by a suppression of appetite induced by semaglutide in a fasting state, as well as by a postprandial improved control of the meal, less hunger and a relatively low preference for fatty foods.

Fasting blood lipids and postprandial blood lipids

Compared to placebo, semaglutide lowered the fasting triglyceride and VLDL (very low density lipoprotein) cholesterol concentration by 12% and 21%, respectively. The postprandial triglyceride and VLDL cholesterol response after a very fatty meal were reduced by >40%.

Cardiac electrophysiology (QTc)

The effect of semaglutide on cardiac repolarisation was investigated in a comprehensive QTc study. At an average level of exposure that was four times greater than the maximum recommended dose of Rybelsus, semaglutide did not prolong the QTc interval to any clinically relevant extent.

Clinical efficacy

The efficacy and safety of Rybelsus have been evaluated in eight global randomised controlled phase 3a trials. In seven trials, the primary objective was the assessment of the glycaemic efficacy, while in another trial, the primary objective was the assessment of cardiovascular safety.
The phase 3a trials included 8 842 randomised patients with type 2 diabetes mellitus (5 169 treated with Rybelsus), including 1 162 patients with moderate renal impairment. The efficacy of Rybelsus was compared with placebo, empagliflozin, sitagliptin, liraglutide and dulaglutide. In all studies, treatment with Rybelsus led to a clinically significant improvement of HbA_{1c}, fasting blood glucose (FBG) and body weight. These effects were maintained for up to a study duration of 78 weeks.

A phase 3b cardiovascular outcomes trial (SOUL) including 9 650 patients was conducted to demonstrate that oral semaglutide lowers the risk of major adverse cardiovascular events (MACE) compared to placebo in addition to standard of care, in patients with type 2 diabetes and established cardiovascular disease and/or chronic kidney disease.

The efficacy of Rybelsus was not impacted by baseline age, gender, race, ethnicity, body weight, BMI, diabetes duration, upper gastrointestinal disorder and level of renal function.

PIONEER 1 – Monotherapy

In a 26-week double-blind trial, 703 patients with type 2 diabetes inadequately controlled with diet and exercise were randomised to Rybelsus 3 mg, Rybelsus 7 mg, Rybelsus 14 mg or placebo once daily.

Table 2: Results of a 26-week monotherapy trial (PIONEER 1) comparing Rybelsus with placebo

	Rybelsus 7 mg	Rybelsus 14 mg	Placebo
Population (N)[1]	175	175	178
HbA_{1c} (%)			
Baseline[2]	8.0	8.0	7.9
Change from baseline in Week 26[3]	-1.3	-1.5	-0.1
Difference from placebo[3] [95% CI]	-1.2 [-1.5; -1.0][§]	-1.4 [-1.7; -1.2][§]	-
Patients (%) achieving an HbA_{1c} <7.0%[2]	72[#]	80[#]	34
Body weight (kg)			
Baseline[2]	89.0	88.1	88.6
Change from baseline in Week 26[3]	-2.5	-4.1	-1.5
Difference from placebo[3] [95% CI]	-1.0 [-1.8; -0.2][§]	-2.6 [-3.4; -1.8][§]	-

[1] Full Analysis Set: All randomised patients

[2] Observed mean/proportion

[3] Estimated with a mixed model for repeated measurements, adjusted to base value, background medication and region. Data recorded after discontinuation of the investigational product or the start of rescue medication are excluded.

[§] Statistically significant ($p<0.05$)

[#] The likelihood of achieving the goal was statistically significantly greater with Rybelsus than with placebo ($p<0.05$)

PIONEER 2 – Rybelsus vs. Empagliflozin, both in combination with metformin:

In a 52-week open-label trial, 822 patients with type 2 diabetes mellitus were randomised to Rybelsus 14 mg once daily or empagliflozin 25 mg once daily, both in combination with metformin.
Treatment with Rybelsus 14 mg once daily reduced HbA_{1c} by -1.4% points at Week 26. The reduction was statistically significantly greater than with empagliflozin, with an estimated treatment difference of -0.5% points [-0.7; -0.4] $_{95\% CI}$.

Table 3: Results of a 52-week trial comparing Rybelsus with empagliflozin (PIONEER 2)

	Rybelsus 14 mg	Empagliflozin 25 mg
Population (N)[1]	411	410
HbA_{1c} (%)		
Baseline[2]	8.1	8.1
Change from baseline in Week 52[3]	-1.3	-0.8
Difference from empagliflozin[3] [95% CI]	-0.5 [-0.7; -0.4][§]	-
Patients (%) achieving an HbA_{1c} <7.0%[2]	72[#]	48
Body weight (kg)		
Baseline[2]	91.9	91.3
Change from baseline in Week 52[3]	-4.7	-3.8
Difference from empagliflozin[3] [95% CI]	-0.9 [-1.6; -0.2][§]	-

[1] Full Analysis Set: All randomised patients

[2] Observed mean/proportion

[3] Estimated with a mixed model for repeated measurements, adjusted to base value, background medication and region. Data recorded after discontinuation of the investigational product or after the start of treatment with rescue medication are excluded.

[§] Statistically significant ($p<0.05$)

[#] The likelihood of achieving the goal was statistically significantly greater with Rybelsus than with empagliflozin ($p<0.05$)

PIONEER 3 – Rybelsus vs. sitagliptin, both in combination with metformin or metformin with a sulfonylurea

In a 78-week, double-blind, double-dummy trial, 1 864 patients with type 2 diabetes were randomised to Rybelsus 3 mg, Rybelsus 7 mg, Rybelsus 14 mg or sitagliptin 100 mg once daily, all in combination with metformin alone or metformin and sulfonylurea.

Treatment with Rybelsus 7 mg and 14 mg once daily reduced HbA_{1c} by -1.1% points or -1.4% points at Week 26; the reduction was statistically significantly greater than with sitagliptin, with an estimated treatment difference of -0.3% points [-0.4; -0.2] $_{95\% CI}$ and -0.6% points [-0.7; -0.5] $_{95\% CI}$.

The reductions in HbA_{1c} and body weight were sustained throughout the trial duration of 78 weeks (Table 4).

Table 4: Results of a 78-week trial comparing Rybelsus with sitagliptin (PIONEER 3)

	Rybelsus 7 mg	Rybelsus 14 mg	Sitagliptin 100 mg
Population (N)[1]	465	465	467
HbA_{1c} (%)			
Baseline[2]	8.4	8.3	8.3
Change from baseline in Week 78[3]	-0.7	-1.1	-0.4
Difference from sitagliptin[3] [95% CI]	-0.3 [-1.6; -0.2][§]	-0.7 [-0.8; -0.5][§]	-
Patients (%) achieving an HbA_{1c} <7.0%[2]	50[#]	52[#]	39
Body weight (kg)			
Baseline[2]	91.3	91.2	90.9
Change from baseline in Week 78[3]	-2.7	-3.5	-1.1
Difference from sitagliptin[3] [95% CI]	-1.6 [-2.2; -0.9][§]	-2.4 [-3.0; -1.7][§]	-

[1] Full Analysis Set: All randomised patients

[2] Observed mean/proportion

[3] Estimated with a mixed model for repeated measurements, adjusted to base value, background medication and region. Data recorded after discontinuation of the investigational product or after the start of treatment with rescue medication are excluded.

[§] Statistically significant ($p<0.05$)

[#] The likelihood of achieving the goal was statistically significantly greater with Rybelsus than with sitagliptin ($p<0.05$)

PIONEER 4 – Rybelsus vs. liraglutide and placebo, each time in combination with metformin or metformin and an SGLT2 inhibitor

In a 52-week, double-blind, double-dummy trial, 711 patients with type 2 diabetes were randomised to Rybelsus 14 mg, liraglutide 1.8 mg s.c. or placebo once daily, each time in combination with metformin or metformin and an SGLT2 inhibitor.

Treatment with Rybelsus 14 mg once daily reduced HbA_{1c} by -1.3% points at Week 26; the reduction was statistically significantly greater than with placebo and liraglutide, with an estimated treatment difference of -1.2% points [-1.4; -1.0] $_{95\% CI}$ and -0.2% points [-0.3; -0.1] $_{95\% CI}$.

Table 5: Results of a 52-week trial comparing Rybelsus with liraglutide and placebo (PIONEER 4)

	Rybelsus 14 mg	Liraglutide 1.8 mg	Placebo
Population (N)[1]	285	284	142
HbA_{1c} (%)			
Baseline[2]	8.0	8.0	7.9
Change from baseline in Week 52[3]	-1.2	-0.9	0.2
Difference from liraglutide[3] [95% CI]	-0.3 [-0.4; -0.1][§]	-	-
Difference from placebo[3] [95% CI]	-1.4 [-1.6; -1.2][§]	-	-
Patients (%) achieving an HbA_{1c} <7.0%[2]	69[*]	63	18
Body weight (kg)			
Baseline[2]	92.9	95.5	93.2
Change from baseline in Week 52[3]	-5.0	-3.1	-1.2
Difference from liraglutide[3] [95% CI]	-1.8 [-2.6; -1.0][§]	-	-
Difference from placebo[3] [95% CI]	-3.8 [-4.8; -2.7][§]	-	-

[1] Full Analysis Set: All randomised patients

[2] Observed mean/proportion

[3] Estimated with a mixed model for repeated measurements, adjusted to base value, background medication and region. Data recorded after discontinuation of the investigational product or after the start of treatment with rescue medication are excluded.

[§] Statistically significant ($p<0.05$)

[#] The likelihood of achieving the goal was statistically significantly greater with Rybelsus than with liraglutide ($p<0.05$)

PIONEER 5 – Rybelsus vs. placebo, both in combination with basal insulin alone, metformin and basal insulin or metformin and/or sulfonylurea, in patients with moderate renal function disorder

In a 26-week double-blind trial, 324 patients with type 2 diabetes and moderate renal impairment (eGFR 30-59 ml/min/1.73 m^2), who were on stable antidiabetic therapy, were also randomised to Rybelsus 14 mg or placebo once daily.

The efficacy and safety profile of Rybelsus in patients with type 2 diabetes and moderate renal function corresponded to the profile generally described for GLP-1 receptor agonists.

Table 6: Results of a 26-week trial comparing Rybelsus in patients with type 2 diabetes and moderate renal function disorder with placebo (PIONEER 5)

	Rybelsus 14 mg	Placebo
Population (N)[1]	163	161
HbA_{1c} (%)		
Baseline[2]	8.0	7.9
Change from baseline in Week 26[3]	-1.1	-0.1
Difference from placebo[3] [95% CI]	-1.0 [-1.2; -0.8][§]	-
Patients (%) achieving an HbA_{1c} <7.0%[2]	64[#]	21
Body weight (kg)		
Baseline[2]	91.3	90.4
Change from baseline in Week 26[3]	-3.7	-1.1
Difference from placebo[3] [95% CI]	-2.7 [-3.5; -1.9][§]	-

[1] Full Analysis Set: All randomised patients

[2] Observed mean/proportion

[3] Estimated with a mixed model for repeated measurements, adjusted to base value, background medication and region. Data recorded after discontinuation of the investigational product or after the start of treatment with rescue medication are excluded.

[§] Statistically significant ($p<0.05$)

[#] The likelihood of achieving the goal was statistically significantly greater with Rybelsus than with placebo ($p<0.05$)

PIONEER 7 – Rybelsus vs. sitagliptin, each time in combination with metformin, SGLT2 inhibitors, a sulfonylurea or thiazolidinedione (flexible dose adjustment study)

In a 52-week open-label trial, 504 patients with type 2 diabetes were randomised to Rybelsus (flexible dose adjustment of 3 mg, 7 mg, and 14 mg once daily) or sitagliptin 100 mg once daily, all in combination with 1-2 oral glucose-lowering medicinal products (metformin, SGLT2 inhibitors, sulfonylurea or thiazolidinediones). The dose of Rybelsus was adjusted every 8 weeks based on patient's glycaemic response and tolerability. The sitagliptin 100 mg dose was fixed. The efficacy and safety of Rybelsus were evaluated at Week 52.
At week 52, the percentage of patients on treatment with Rybelsus 3 mg, 7 mg and 14 mg was 9%, 30% and 60%, respectively.

Table 7: Results of a 52-week flexible-dose-adjustment trial of Rybelsus compared to sitagliptin (PIONEER 7)

	Rybelsus Flexible dose	Sitagliptin 100 mg
Population (N)[1]	253	251
HbA_{1c} (%)		
Baseline[2]	8.3	8.3
Change from baseline in Week 52[3]	-1.4	-0.7
Difference from sitagliptin[3] [95% CI]	-0.7 [-0.9; -0.5][§]	-
Patients (%) achieving an HbA_{1c} <7.0%[2]	63[#]	28
Body weight (kg)	88.9	88.4
Baseline[2]	-2.9	-0.8
Change from baseline in Week 52[3]	-2.2 [-2.9; -1.5][§]	-
Difference from sitagliptin[3] [95% CI]	28[#]	13

[1] Full Analysis Set: All randomised patients

[2] Observed mean/proportion

[3] Estimated with a mixed model for repeated measurements, adjusted to base value, background medication and region. Estimated with a mixed model for repeated measurements, adjusted to base value, background medication and region.

[§] Statistically significant (p<0.05)

[#] The likelihood of achieving the goal was statistically significantly greater with Rybelsus than with sitagliptin (p<0.05)

PIONEER 8 – Rybelsus vs. placebo, both in combination with insulin with or without metformin

In a 52-week double-blind trial, 731 patients with type 2 diabetes inadequately controlled on insulin (basal, basal/bolus or premixed) with or without metformin were randomised to Rybelsus 3 mg, Rybelsus 7 mg, Rybelsus 14 mg or placebo once daily.

Treatment with Rybelsus 7 mg and 14 mg once daily reduced HbA_{1c} at Week 26 by -1.0% points and -1.4% points, respectively; the reduction was statistically significantly greater than with placebo, with an estimated treatment difference of -1.0% points [-1.2; -0.8], 95% CI and -1.4% points [-1.6; -1.2], respectively 95% CI.

Table 8: Results of a 52-week trial comparing Rybelsus in combination with insulin with placebo (PIONEER 8)

	Rybelsus 7 mg	Rybelsus 14 mg	Placebo
Population (N)[1]	182	181	184
HbA_{1c} (%)			
Baseline[2]	8.2	8.2	8.2
Change from baseline in Week 52[3]	-0.8	-1.2	0.0
Difference from placebo[3] [95% CI]	-0.9 [-1.1; -0.6][§]	-1.3 [-1.5; -1.0][§]	-
Patients (%) achieving an HbA_{1c} <7.0%[2]	47[#]	64[#]	10
Body weight (kg)			
Baseline[2]	87.1	84.6	86.0
Change from baseline in Week 52[3]	-2.9	-4.3	0.6

	Rybelsus 7 mg	Rybelsus 14 mg	Placebo
Difference from placebo[3] [95% CI]	-3.5 [-4.5; -2.6][§]	-4.9 [-5.9; -3.9][§]	-

[1] Full Analysis Set: All randomised patients

[2] Observed mean/proportion

[3] Estimated with a mixed model for repeated measurements, adjusted to base value, background medication and region. Estimated with a mixed model for repeated measurements, adjusted to base value, background medication and region.

[§] Statistically significant ($p<0.05$)

[#] The likelihood of achieving the goal was statistically significantly greater with Rybelsus than with placebo ($p<0.05$)

Cardiovascular outcomes

SOUL - Cardiovascular outcomes trial in patients with type 2 diabetes

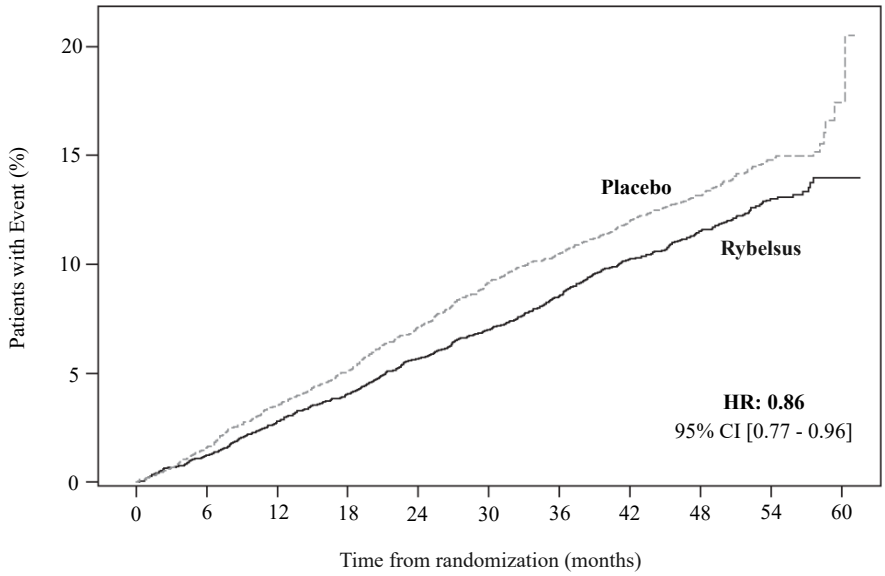
In a double-blind, placebo-controlled, event driven trial, 9 650 patients, 50 years of age or older with type 2 diabetes at high cardiovascular risk, defined as having established cardiovascular disease and/or chronic kidney disease, were randomised to either semaglutide 14 mg once-daily or placebo once-daily added to standard of care.

In total, 5 468 patients (56.7 %) had established cardiovascular disease without chronic kidney disease, 1 241 (12.9 %) had chronic kidney disease only and 2 620 (27.2 %) had both cardiovascular disease and kidney disease. The mean age at baseline was 66.1 years, and 71.1% of the patients were men. The mean duration of diabetes was 15.4 years, the mean HbA_{1c} was 8.0%, the mean BMI was 31.1 kg/m^2, and the mean eGFR was 73.8 $mL/min/1.73m^2$. Medical history included stroke (15.4 %), myocardial infarction (40.0 %), and peripheral artery disease (15.7 %). At baseline, 26.9% of the patients were treated with sodium-glucose cotransporter2 (SGLT2) inhibitors.

The primary endpoint was time from randomisation to first occurrence of a major adverse cardiovascular event (MACE): cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke. The primary endpoint, time to first MACE, occurred in 1 247 of the 9 650 included patients, 579 first MACE (12.0%) were recorded among the 4 825 patients treated with semaglutide, compared to 668 first MACE (13.8%) among the 4 825 patients treated with placebo.

Superiority of semaglutide versus placebo for MACE was confirmed with a hazard ratio of 0.86 [0.77; 0.96] [95% CI], corresponding to a relative risk reduction in MACE of 14 % (see Figures 1 &

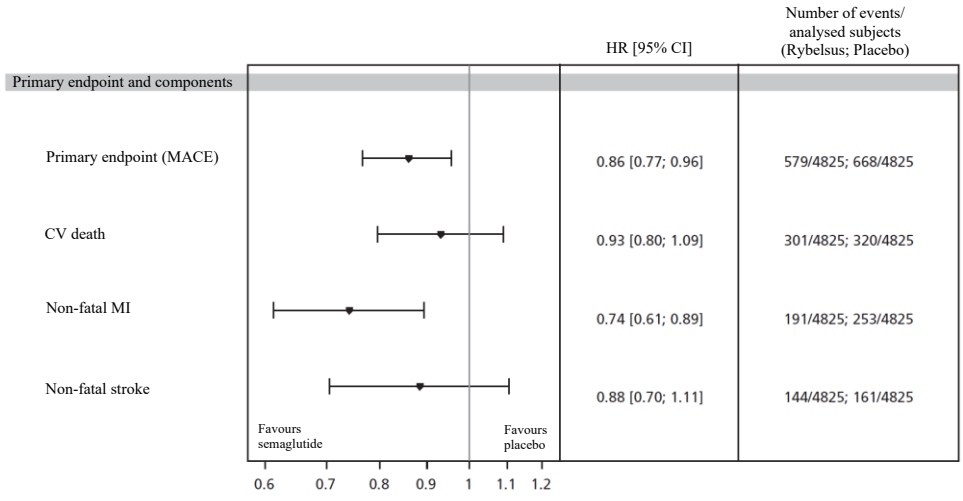
2). The reduction of MACE with semaglutide was consistent across subgroups of age, sex, race, ethnicity, BMI at baseline, and level of kidney function impairment.
Analysis of the first composite kidney event (the first confirmatory secondary endpoint) resulted in a hazard ratio of 0.91 [0.80; 1.05] [95% CI].



Patients at risk											
Semaglutide	4 825	4 743	4 635	4 542	4 438	4 346	4 239	3 831	2 555	1 346	47
Placebo	4 825	4 718	4 583	4 455	4 322	4 194	4 101	3 727	2 517	1 346	38

Data from the in-trial period based on full analysis set. Cumulative incidence estimates are based on time from randomisation to first EAC-confirmed MACE with non-CV death modelled as competing risk using the Aalen-Johansen estimator. Subjects without events of interest were censored at the end of their in-trial observation period. Time from randomisation to first MACE was analysed using a Cox proportional hazards model with treatment as categorical fixed factor. The hazard ratio and confidence interval are adjusted for the group sequential design using the likelihood ratio ordering.
HR: Hazard Ration, CI: Confidence Interval, CV: cardiovascular, EAC: event adjudication committee, MACE: major adverse cardiovascular event.

Figure 1: Time from randomisation to first MACE Cumulative incidence function plot



Data from the in-trial period based on full analysis set. Time from randomisation to each endpoint was analysed using a Cox proportional hazards model with treatment as categorical fixed factor. Subjects without events of interest were censored at the end of their in-trial period. For the primary endpoint the HR and CI were adjusted for the group sequential design using likelihood ratio ordering. CV death includes both cardiovascular death and undetermined cause of death.
HR: hazard ratio CI: Confidence interval, CV: cardiovascular, MI: myocardial infarction.

Figure 2: Treatment effect for the primary endpoint and its components (SOUL)

PIONEER 6 - Cardiovascular outcomes trial in patients with type 2 diabetes

In this double-blind trial, 3 183 patients with type 2 diabetes at high cardiovascular risk (2 695 [85%] patients with previous cardiovascular disease as well as 488 [15%] patients with cardiovascular risk factors without previous cardiovascular disease) in addition to prior anti-hyperglycemic therapy were randomised to Rybelsus 14 mg once daily or treated with placebo (mean treatment duration 16 months). The treatment could be intensified in both arms according to the applicable therapy guidelines. PIONEER 6 was a pre-approval CVOT designed to establish CV safety.

The primary analysis was time from randomisation to first occurrence of a severe cardiovascular event (MACE: cardiovascular death, nonfatal myocardial infarction or nonfatal stroke). The cardiovascular risk was numerically reduced in the patients treated with semaglutide.

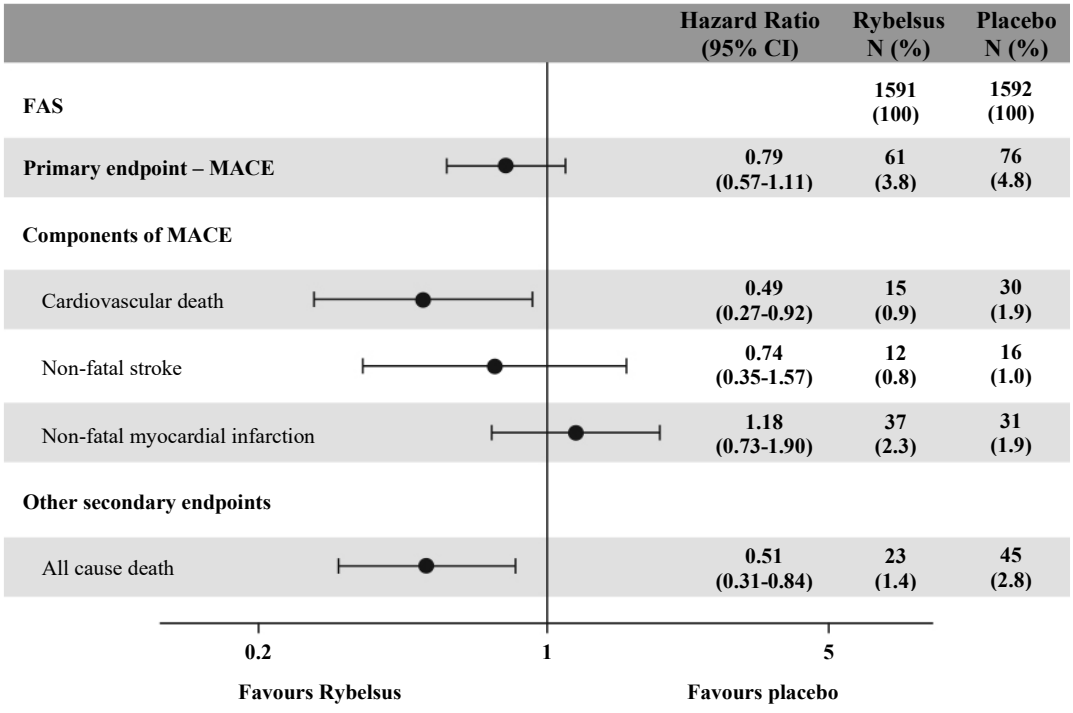


Figure 3: Forest Plot: Treatment effect for the primary composite endpoint MACE, its components and all cause death (PIONEER 6)

This effect is primarily based on a decrease in cardiovascular death.

SUSTAIN 6 – Cadiovascular outcomes trial with subcutaneously injected semaglutide in patients with type 2 diabetes

In this 104-week double-blind trial, 3 297 patients with type 2 diabetes at high cardiovascular risk (2 735 [83%] patients with previous cardiovascular disease as well as 562 [27%] patients with cardiovascular risk factors without previous cardiovascular disease) in addition to prior anti-hyperglycemic therapy were randomised to semaglutide 0.5 mg s.c., semaglutide 1 mg s.c. or treated with placebo (mean treatment duration 2 years).
The primary analysis was time from randomisation to first occurrence of a severe cardiovascular event (MACE: cardiovascular death, nonfatal myocardial infarction or nonfatal stroke). The cardiovascular risk was on average reduced over 2 years in the patients treated with semaglutide.

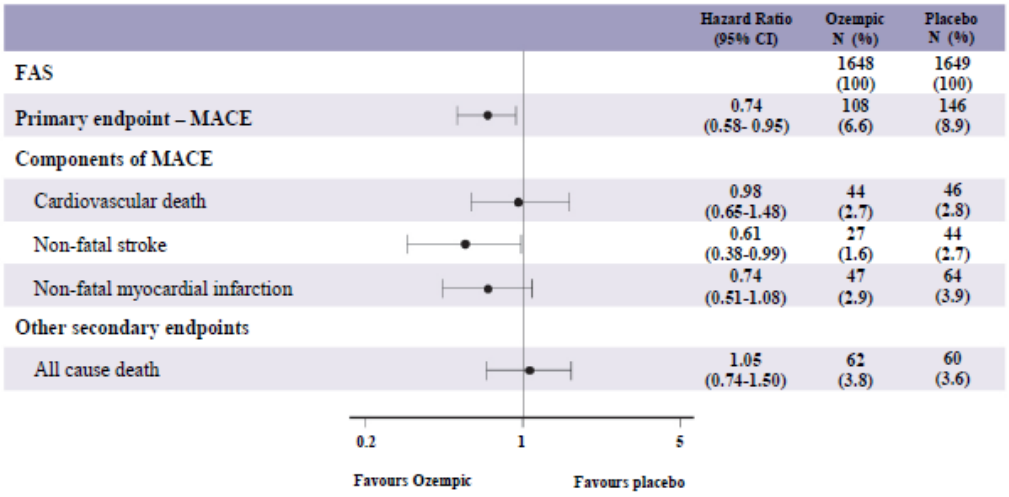


Figure 4: Forest Plot: Treatment effect on the primary composite endpoint MACE, its components and all causes of death (SUSTAIN 6)

The reduction of cardiovascular risk is primarily based on a reduction in the number of non-fatal strokes. In contrast to the results of the PIONEER 6 study for oral semaglutide, no positive effect on cardiovascular mortality was observed for treatment with subcutaneously applied semaglutide.

Pharmacokinetics

Absorption

Orally administered semaglutide has a low absolute bioavailability and a variable absorption. Daily administration according to the recommended posology in combination with a long half-life reduces day-to-day fluctuation of the exposure.

Semaglutide is co-formulated with salcaprozate sodium, whereby the absorption of semaglutide is facilitated following oral administration. Semaglutide is primarily absorbed in the stomach.

The pharmacokinetics of semaglutide have been extensively characterised in healthy subjects and in patients with type 2 diabetes. Following oral administration, maximum plasma concentration of semaglutide occurred 1 hour post dose. Steady-state exposure was reached after 4–5 weeks of once-daily administration. Based on the population pharmacokinetic analyses of data from patients with type 2 diabetes mellitus, the average steady-state concentrations of Rybelsus 7 and 14 mg were approximately 6.7 nmol/l and 14.6 nmol/l, respectively. The systemic exposure by semaglutide increased proportionally to the dose.
Absorption of semaglutide is decreased if taken with food or large volumes of water. A longer post-dose fasting period results in higher absorption.
The estimated absolute bioavailability of semaglutide after oral administration is less than 1%.

Distribution

The estimated absolute volume of distribution in patients with type 2 diabetes is approximately 8 l. Semaglutide is strongly bound to plasma proteins (>99%).

Metabolism

Semaglutide is metabolised through proteolytic cleavage of the peptide backbone and sequential beta-oxidation of the fatty acid sidechain.

Elimination

The primary excretion routes of semaglutide-related material are via the urine and faeces.
Approximately 3% of the absorbed dose is excreted as intact semaglutide via the urine.
With an elimination half-life of approximately 1 week, semaglutide will be present in the circulation for up to 5 weeks after the last dose. The clearance of semaglutide in patients with type 2 diabetes is approximately 0.04 l/h.

Average exposure level for semaglutide with oral and subcutaneous administration

Based on the population pharmacokinetic analyses, the average exposure of semaglutide 0.5 mg s.c. corresponds to about 90% of that of Rybelsus 14 mg. The average exposure of Rybelsus 7 or 14 mg corresponds to about 60% or 110% of that of semaglutide 0.5 mg s.c.

Kinetics in specific patient groups

Hepatic impairment

Impaired hepatic function did not impact the pharmacokinetics of semaglutide in a clinically relevant manner. The pharmacokinetics of semaglutide were evaluated in patients with mild, moderate or severe renal impairment and compared with subjects with normal renal function in a study with 10 consecutive days of once-daily doses of semaglutide.

Renal impairment

Impaired kidney function did not impact the pharmacokinetics of semaglutide in a clinically relevant manner. The pharmacokinetics of semaglutide were evaluated in patients with mild, moderate or severe renal impairment and patients with end-stage kidney disorder on dialysis compared with subjects with normal renal function in a study with 10 consecutive days of once-daily doses of semaglutide. This was also shown for subjects with type 2 diabetes and renal impairment based on population pharmacokinetic analyses of data from phase 3a studies.

Elderly patients

Based on data from clinical trials that studied patients up to age 92,
age had no effect on the pharmacokinetics of semaglutide.

Children and adolescents

Semaglutide has not been studied in paediatric patients.

Gender

Gender had no clinically meaningful effects on the pharmacokinetics of semaglutide.

Race and ethnicity

Race (White, Black or African-American, Asian) and ethnicity (Hispanic or Latino) had no effect on the pharmacokinetics of semaglutide.

Body weight

Body weight had an effect on the exposure of semaglutide. Higher body weight was associated with lower exposure. However, Rybelsus provided adequate systemic exposure over the body weight range of 40-188 kg evaluated in the clinical trials.

Upper gastrointestinal disorders

Upper gastrointestinal tract disorder (chronic gastritis and/or gastroesophageal reflux disease) did not impact the pharmacokinetics of semaglutide in a clinically relevant manner. The pharmacokinetics were evaluated in patients with type 2 diabetes with or without upper gastrointestinal tract disorder dosed for 10 consecutive days with once-daily doses of semaglutide.
This was also shown for patients with type 2 diabetes mellitus and upper gastrointestinal tract disorder based on data from phase 3a studies.

Preclinical data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity or genotoxicity.

Carcinogenicity

Non-lethal thyroid C-cell tumours observed in rodents are a class effect for GLP-1 receptor agonists. In 2-year carcinogenicity studies in rats and mice, thyroid C-cell tumours occurred at clinically relevant exposures. The C-cell tumours in rodents are caused by a non-genotoxic mechanism specifically mediated by the GLP-1 receptor, to which rodents are particularly predisposed. The relevance for humans is probably low but cannot be completely ruled out.

Reproductive toxicity

In fertility studies in rats, semaglutide did not negatively affect mating performance or male fertility. In female rats, an increase in oestrous cycle length and a small reduction in corpora lutea (ovulations) were observed at doses associated with maternal body weight loss.
In embryo-foetal development studies in rats, semaglutide caused embryotoxicity below clinically relevant exposures. Semaglutide caused marked reductions in maternal body weight and reductions in embryonic survival and growth. In foetuses, major skeletal and visceral malformations were observed, including effects on long bones, ribs, vertebrae, tail, blood vessels and brain ventricles. Mechanistic evaluations indicated that the embryotoxicity involved a GLP-1 receptor mediated impairment of the nutrient supply to the embryo across the rat yolk sac. Due to species differences in yolk sac anatomy and function, and due to the lack of GLP-1 receptor expression in the yolk sac of non-human primates, it is considered unlikely that the GLP-1 receptor-mediated mechanism observed in rats is of relevance to humans. However, a direct effect of semaglutide on the foetus cannot be excluded.
In developmental toxicity studies in rabbits and cynomolgus monkeys, increased pregnancy loss and slightly increased incidence of foetal abnormalities were observed at clinically relevant exposures. The findings coincided with marked maternal body weight loss of up to 16%. Whether these effects are related to the decreased maternal food consumption as a direct GLP-1 effect is unknown.
Postnatal growth and development were evaluated in cynomolgus monkeys. Infants were slightly smaller at delivery, but recovered during the lactation period.

Toxicity tests with juvenile animals

In juvenile rats, semaglutide caused delayed sexual maturation in both males and females. These delays had no impact upon fertility and reproductive capacity of either sex, or on the ability of the females to maintain pregnancy.

Other information

Incompatibilities

Not applicable.

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.

Special precautions for storage

Do not store above 30 °C.

Store in the original blister package in order to protect the content from light and moisture.

Keep out of the reach of children.

Authorisation number

67446 (Swissmedic)

Packs

3 mg, 7 mg, or 14 mg tablets in blister package.

3 mg: Packages with 30 tablets [B]

7 mg: Packages with 30 and 90 tablets [B]

14 mg: Packages with 30 and 90 tablets [B]

Marketing authorisation holder

Novo Nordisk Pharma AG, Kloten

Domicile: Zurich

Date of revision of the text

October 2025