Swiss Public Assessment Report

Rybelsus

International non-proprietary name: semaglutide

Pharmaceutical form: tablet

Dosage strength: 14 mg, 7 mg, 3 mg

Route(s) of administration: oral

Marketing Authorisation Holder: Novo Nordisk Pharma AG

Marketing Authorisation No.: 67446

Decision and Decision date: approved on 24 March 2020

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPAR

About Swissmedic

Swissmedic is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Swissmedic's activities are based on the Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (TPA, SR 812.21). The agency ensures that only high-quality, safe and effective drugs are available in Switzerland, thus making an important contribution to the protection of human health.

About Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a "final" document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

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1 Terms, Definitions, Abbreviations

AE	Adverse event
ADA	American Diabetes Association
ADME	Absorption, Distribution, Metabolism, Elimination
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC0-24h	Area under the plasma concentration-time curve for the 24-hour dosing interval
Cmax	Maximum observed plasma/serum concentration of drug
CV	Cardiovascular
CYP	Cytochrome P450
DPP-4	Dipeptidyl peptidase 4
ETD	Estimated treatment difference
ERA	Environmental Risk Assessment
EAC	Event Adjudication Committee
GI	Gastrointestinal
GLP	Good Laboratory Practice
GLP-1	Glucagon-like peptide-1
GLP-1RA	Glucagon-like peptide-1 receptor-agonist
Hb	Haemoglobin
ICH	International Council for Harmonisation
Ig	Immunoglobulin
IHSG	International Hypoglycaemia Study Group
INN	International Nonproprietary Name
LoQ	List of Questions
Max	Maximum
MAH	Marketing Authorisation Holder
Min	Minimum
N/A	Not applicable
NO(A)EL	No Observed (Adverse) Effect Level
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PLB	Placebo
Pop PK	Population PK
PPIs	Proton-pump inhibitors
PSP	Pediatric Study Plan (US-FDA)
PY	Patient Year
QW	once weekly dosage regimen
RMP	Risk Management Plan
SNAC	Salcaprozate sodium
SOC	System organ class
SwissPAR	Swiss Public Assessment Report
T2DM	Type 2 diabetes mellitus
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)
ULN	Upper limit of normal

2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance (INN) of the medicinal product mentioned above.

2.2 Indications and Dosage

2.2.1 Requested Indications

Rybelsus is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise.
Rybelsus is indicated to reduce the risk of serious undesirable cardiovascular events in adult patients with type 2 diabetes mellitus and established cardiovascular risk and/or chronic renal disease.

2.2.2 Approved Indications

Rybelsus is used in addition to diet and exercise to treat adults with inadequately controlled type 2 diabetes mellitus:
• as monotherapy in case of contraindication or intolerance of metformin (see section "Properties/Effects").
• in combination with other blood glucose-lowering medicines.
See section "Clinical efficacy" for results on the combinations examined in clinical studies and on cardiovascular safety.

2.2.3 Requested Dosage

The starting dose is 3 mg once daily in the morning. After 1 month, the dose should be increased to a maintenance dose of 7 mg once daily. If the blood glucose-decreasing effect is not sufficient after at least 1 month of treatment at a dose of 7 mg once daily, the maintenance dose can be increased to a maximum of 14 mg once daily.

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

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Application	15 May 2019
Formal control completed	16 May 2019
List of Questions (LoQ)	21 August 2019
Answers to LoQ	15 October 2019
Predecision	9 January 2020
Answers to Predecision	5 February 2020
Final Decision	24 March 2020
Decision	approval

2.4 Medical Context

Type 2 diabetes mellitus (T2DM) is a metabolic disease characterised by chronic hyperglycaemia that causes microvascular and macrovascular complications. Glucagon-like peptide 1 receptor-agonists (GLP-1RAs) represent a highly effective class of glucose-lowering agents. All GLP-1-RAs marketed so far are injectable peptide formulations. For some patients, the need for subcutaneous injection constitutes a substantial psychological barrier. Rybelsus is a new formulation of the analogue of human GLP-1 semaglutide applicable for oral administration.

3 Quality Aspects

3.1 Drug Substance

Semaglutide is a recombinant long-acting glucagon-like peptide-1 (GLP-1) receptor agonist. The GLP-1 analogue is acylated at lysine 26 with a fatty diacid moiety and has two amino acid substitutions (Ala^8 to Aib^8 (2-aminoisobutyric acid), Lys^{34} to Arg^{34}) compared to human GLP-1.
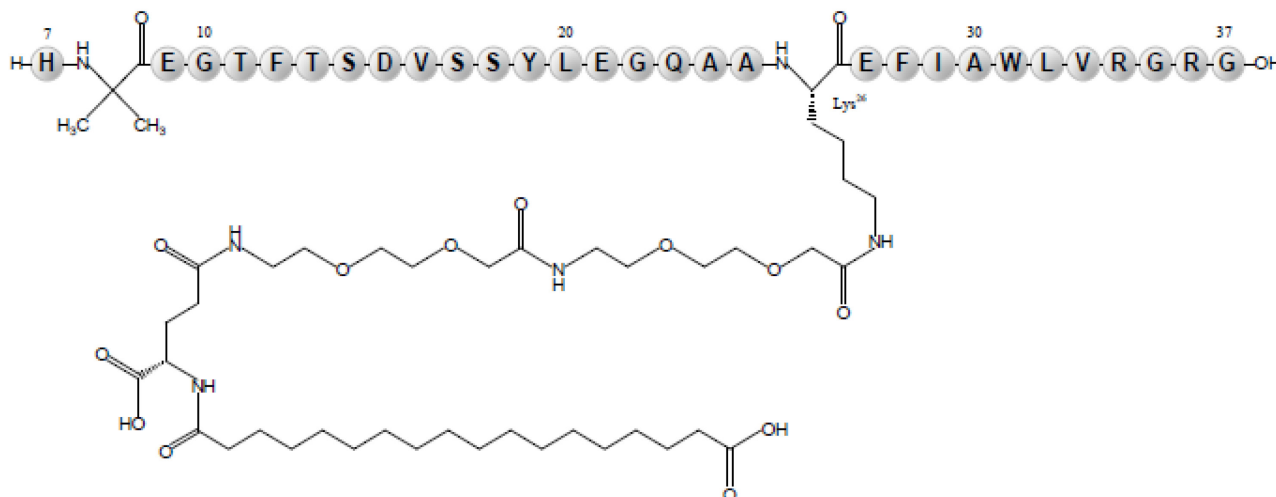
The extended half-life of the semaglutide molecule is obtained by high affinity binding to the fatty acid binding sites on albumin and protection from dipeptidyl peptidase 4 (DPP-4) degradation.

The drug substance semaglutide is produced in yeast (*Saccharomyces cerevisiae*) using recombinant DNA technology. The peptide is further chemically modified by acylation, and ligation with a dipeptide. The molecular weight for semaglutide is 4111.115 g/mol.

Semaglutide precursor is produced by yeast fermentation in a bioreactor.

Process performance qualification studies (in full production scale) were performed for process validation.

The physicochemical and biological properties of the drug substance and its impurities were characterised using state of the art methods.

The specifications include identity tests, impurity tests, assay and a cell-based potency assay.

Batch analysis data for non-clinical batches, clinical batches, and process performance qualification batches were provided. All the analytical methods are described and the non-compendial methods have been validated in accordance with international guidelines.

The drug substance is stored at – 20°C. No significant changes are observed within the proposed shelf life.

3.2 Drug Product

Rybelsus is an uncoated, immediate release, white to light yellow, oval shaped tablet (7.5 mm x 13.5°mm) and debossed, depending on the dose, with "3", "7" or "14", respectively. Rybelsus contains the excipient salcaprozate sodium (SNAC, a fatty acid derivative) which is used as an absorption enhancer to enhance the oral absorption of semaglutide.

The manufacturing process is appropriately described, including standard process parameters and suitable in-process controls. Satisfactory manufacturing process validation has been performed on three consecutive production-scale batches for each dose strength.

Adequate specifications at release and at shelf-life have been established. The specifications include relevant physicochemical characteristics, identification of the drug substance, assay, impurity tests, dissolution and microbial purity.

Rybelsus tablets are packaged in double-sided aluminium blisters.

Appropriate stability data have been generated for the packaging material for commercial use and according to the relevant international guidelines. Based on these studies, an appropriate shelf-life has been established. The storage recommendation is "Do not store above 30°C, store in the original container in order to protect the product from humidity".

3.3 Quality Conclusions

Satisfactory and consistent quality of drug substance and drug product has been demonstrated.

4 Nonclinical Aspects

Semaglutide is already approved in Switzerland for subcutaneous administration (Ozempic®) and, therefore, has adequately been characterised from a nonclinical perspective for the subcutaneous route of administration and the indication type 2 diabetes. To qualify semaglutide for oral administration to humans, the applicant conducted a series of additional (bridging) studies with oral semaglutide, which included pharmacokinetics and repeat-dose toxicity studies. To achieve acceptable oral bioavailability, semaglutide needs co-administration with an absorption enhancer, i.e. SNAC. This novel excipient was characterised in a full nonclinical programme.

Pharmacology

The applicant did not conduct any additional pharmacology studies with oral semaglutide. Studies conducted with the novel excipient SNAC demonstrated that, and elucidated how, SNAC enhances the absorption of semaglutide in the gastrointestinal tract. Studies in dogs suggested that the absorption of semaglutide co-formulated with SNAC in a tablet occurs in the stomach. As shown in rats and dogs, absorption is restricted to epithelial surfaces immediately under and around the tablet. The results of *in vitro* studies with simulated gastric fluid suggest that SNAC exerts buffering actions in the stomach, thereby decreasing the activity of gastric enzymes and protecting semaglutide from degradation. Dilution of both SNAC and semaglutide, either by food or liquid in the small intestine, weakens this effect. As stated in the product information, patients should take Rybelsus on an empty stomach and wait for at least 30 minutes before ingesting any food, drink or other drugs. Studies in human NCI-N87 cells (a model for gastric permeability studies) suggested that the absorption-enhancing effect of SNAC on the transport of semaglutide is mediated via the transcellular rather than the paracellular route. Immunostaining for semaglutide in the gastric mucosa of rats and dogs further confirmed this assumption.

Pharmacokinetics

Studies with oral semaglutide (plus SNAC) in the rat and monkey showed a low oral bioavailability (0.16% absolute and 2.4% relative bioavailability in the monkey) and a more variable systemic exposure after oral than after parenteral dosing. AUC_{0-24h} and C_{max} increased with the dose. Accumulation after repeated daily dosing was only observed in monkeys, which is in line with the longer half-life of semaglutide in this species (60 h) compared to rats (6.5 h). Plasma metabolite profiles in the rat and monkey were similar after oral and subcutaneous administration. After oral administration, there was a more rapid excretion of drug-related radioactivity via the faeces than after intravenous administration.

Toxicology

The applicant conducted additional repeat-dose toxicity studies with oral semaglutide (plus SNAC or another absorption enhancer) in the rat and monkey, the same species that were used in the programme for the subcutaneous product. Apart from mortality in two rats at 60 mg/kg/day, semaglutide was generally well tolerated after oral administration to rats and monkeys. The toxicity profile was similar to that of subcutaneous semaglutide. Findings were related to the pharmacology or were secondary to these (reduced food consumption and body weight/body weight gain, secondary changes in organ weight and clinical pathology, and changes in urinary parameters and hypertrophy of Brunner's glands of the duodenum). No local toxicity was noted in the gastrointestinal tract. The No Observed Adverse Effect Level (NOAEL) in the 26-week rat study was 20 mg/kg/day (plasma exposure 5.0 times human exposure), and the NOAEL in the 17-week monkey study was 20 mg/kg/day (plasma exposure 7.3 times human exposure). No antibodies against semaglutide were observed in animals dosed with oral semaglutide.

High doses of the enhancer SNAC were associated with mortality in all toxicology species. Based on mechanistic studies, the mortality is considered to be due to inhibition of cellular respiration at very high concentrations of free SNAC (≥100-fold the clinical C_{max}). In clinical trials with therapeutic and

supratherapeutic doses of SNAC, there were no effects on plasma lactate (a marker for inhibition of cellular respiration).

There are no concerns with regard to impurities.

The applicant provided a satisfactory ERA for semaglutide.

The nonclinical studies requested in the PIP were completed and the reports were included in this submission. The RMP addresses all relevant nonclinical safety findings.

Conclusion

The submitted nonclinical documentation is considered adequate to support the approval of Rybelsus (oral semaglutide) for the proposed indication. All safety-relevant nonclinical data are included in the information for healthcare professionals.

5 Clinical and Clinical Pharmacology Aspects

5.1 Clinical Pharmacology

Biopharmaceutical Development

Since orally administered semaglutide is subject to proteolytic degradation in the gastrointestinal tract, it is co-formulated with the absorption enhancer salcaprozate sodium (SNAC) to ensure adequate absorption. By buffering the local pH, SNAC reduces enzymatic degradation of semaglutide and transiently increases transcellular permeability of the gastric epithelium, which eventually facilitates absorption of the active ingredient.

The final to-be-marketed drug product is supplied in 3 mg, 7 mg, and 14 mg strengths as immediate-release tablets. Each strength is co-formulated with 300 mg SNAC.

During the biopharmaceutical development, it was shown that a longer fasting period following the administration of oral semaglutide, as well as a lower volume of water administered with it, resulted in higher exposures. Administration under fed conditions led to semaglutide plasma concentrations that were below the lower limit of quantitation. These findings are reflected in the proposed dosing conditions provided in the information for healthcare professionals, i.e. administration on an empty stomach with 120 mL water followed by 30 minutes post-fasting time.

ADME

The pharmacokinetic characterisation of oral semaglutide was primarily based on population PK analyses using the clinical pharmacology or phase 3 data. Based on the phase 3 population PK analysis, the average concentrations (C_{avg}) at steady-state following the administration of 3 mg, 7 mg, and 14 mg oral semaglutide were estimated at 2.7 nmol/L, 6.7 nmol/L, and 14.6 nmol/L, respectively. Based on the findings of Phase 1 studies, t_{max} following the recommended dosing conditions was approximately 1 h.

Overall, the bioavailability of oral semaglutide was less than 1% depending on the dosing conditions and the population.

The population PK analysis using the clinical pharmacology data estimated the steady-state accumulation ratio of semaglutide at 12.6 as expected considering the long half-life and the daily dosing. Within 26 days, 95% of the steady-state trough concentrations were reached.

Based on the phase 3 population PK analysis, the exposures were approximately dose-proportional in the proposed dose range. Between 7 mg and 14 mg, the exposures increased slightly more than dose-proportionally.

The population PK analysis based on the clinical pharmacology data demonstrated that a single missed dose or a single additional dose hardly affected the steady-state exposures. Furthermore, it was confirmed that shorter fasting times and increased water volumes resulted in lower exposures. However, these changes had to be continuous in order to have an impact on the steady-state exposures.

Although the mean exposures following subcutaneous administration appeared to be higher compared to those of the oral semaglutide, there was a considerable overlap suggesting adequate exposures.

In vitro and *in vivo* studies indicated a plasma protein binding of more than 99%.
Based on population PK analysis, the volume of distribution in T2D patients was estimated at 7.9 L.

Semaglutide was metabolised via proteolytic enzymes. Semaglutide and its metabolites were excreted via urine (53% of the absorbed dose) and via faeces (18.6%). Whereas unchanged semaglutide was the predominant entity in plasma, it was also identified in urine, accounting for 3.1% of the absorbed dose.
Based on population PK analysis, the clearance and half-life in T2D patients were estimated at 0.039 L/h and 145 h, respectively.

Special Populations
Overall, no dose adjustments are required based on age, sex, body weight, race, ethnicity, upper gastrointestinal disease, renal function, or hepatic impairment.

Interactions
Semaglutide is a 4 kDa peptide and is not considered to be a substrate for cytochrome P450 (CYP) enzymes and drug transporters. Furthermore, semaglutide did not affect CYP enzyme activity levels. No clinically relevant drug-drug interactions related to inhibition and induction of CYP enzymes or drug transporters by semaglutide are anticipated. However, GLP-1 agonists have the potential to interact with co-administered compounds via delayed gastric emptying.
Whereas oral semaglutide did not have an impact on the exposures of lisinopril, warfarin, digoxin, ethylenestradiol/levonorgestrel, the AUCs of metformin (+32%), furosemide (+28%), rosuvastatin (+41%), and levothyroxine (+33%) were increased.
The co-administration of PPIs may have an impact on the semaglutide absorption because of the pH dependence of the solubility of SNAC as well as the increased gastric pH due to SNAC. Co-administration with omeprazole led to a minor semaglutide exposure increase (AUC +13%).

Pharmacodynamics
Semaglutide is a GLP-1 analogue. The effects of semaglutide on beta-cell function and glucose metabolism of patients suffering from T2DM were investigated in different settings. In summary, semaglutide treatment led to increased insulin and decreased glucagon secretion. During hypoglycaemia, treatment with semaglutide in subjects withT2DM did not compromise the increase in glucagon level and resulted in an overall comparable hormonal counter-regulation, as indicated by similar AUC_{GIR}, compared to placebo treatment. Treatment with semaglutide thus did not affect the ability to recover from hypoglycaemia compared with placebo treatment. The effect of semaglutide on energy intake and expenditure, appetite, body weight, and gastric emptying of obese subjects was investigated in a dedicated study. Generally, subjects receiving semaglutide had a lower energy intake and less appetite, exhibited a better food control and lost body weight. Semaglutide did not have an effect on overall gastric emptying; however, it did lead to a delay during the early postprandial phase.

A thorough QT/QTc study indicated no discernible potential for QT/QTc prolongation following the administration of semaglutide.

Across six phase 3 studies, only 0.5% of the subjects developed anti-semaglutide antibodies.

5.2   Dose Finding and Dose Recommendation

Dose selection was based on study 3790, a 26-week, 9-arm Phase 2 study comparing the glucose-lowering effect (primary endpoint: change in HbA_{1c}) of oral semaglutide for doses of 2.5 mg, 5 mg,

10 mg, 20 mg, and 40 mg with placebo (PLB) and semaglutide s.c. QW. Oral semaglutide was superior to PLB for all doses; efficacy increased with incremental doses. Non-inferiority to semaglutide s.c. QW was demonstrated for the doses of oral semaglutide ≥10 mg. Dose-dependent increases in adverse events (AEs) in study 3790 represented no prohibitive safety signal.

5.3 Efficacy

The glucose-lowering efficacy of oral semaglutide (3 mg, 7 mg, and 14 mg) has been well-documented in ten well-conducted randomised, double-blind, international, multicentre Phase 3 studies summarised in the table below.

Study	Treatment Duration [weeks]	Comparator / Status	Primary Efficacy Endpoint ETD [95% CI] in ΔHbA$_{1c}$ (%)		
PIONEER 1	26	Placebo	3 mg	-0.6 [-0.8; -0.4]	S
			7 mg	-0.9 [-1.1; -0.6]	S
			14 mg	-1.1 [-1.3; -0.9]	S
PIONEER 2	52	Empagliflozin	14 mg	-0.4 [-0.6; -0.3]	S
PIONEER 3	52	Sitagliptin	3 mg	0.2 [0.1; 0.3]	
			7 mg	-0.3 [-0.4; -0.1]	S
			14 mg	-0.5 [-0.6; -0.4]	S
PIONEER 4	52	Placebo and Liraglutide	14 mg	-1.1 [-1.2; -0.9]	S
				-0.1 [-0.3; -0.0]	N
PIONEER 5	26	Renal impairment	14 mg	-0.8 [-1.0; -0.6]	S
PIONEER 7	52	Sitagliptin (flexible dose adjustment for oral semaglutide [3-7-14 mg])	See text below		
PIONEER 8	52	Placebo (add-on to insulin)	3 mg	-0.5 [-0.7; -0.3]	S
			7 mg	-0.9 [-1.1; -0.7]	S
			14 mg	-1.2 [-1.4; -1.0]	S
PIONEER 9	52	Placebo	Combined Phase 2/3a dose-response and safety/efficacy trial in Japan		
PIONEER 10	52	Dulaglutide (add-on to 1 prior OAD)	Safety/efficacy trial in Japan		
PIONEER 6	Event-driven	Placebo (intensification according to standard of care)	**C**ardio**V**ascular **O**utcomes **T**rial (see Section 5.4)		

ETD, estimated treatment difference; CI, confidence interval; ΔHbA$_{1c}$, change in HbA$_{1c}$ from baseline; ΔBW, change in body weight from baseline; S, superiority of the treatment with oral semaglutide; N, non-inferiority of the treatment with oral semaglutide

The 52-week PIONEER 7 study examined the proportion of patients achieving HbA$_{1c}$<7% (responder rate) when using a flexible dose adjustment for oral semaglutide (starting with 3 mg with stepwise escalation to 7 mg and 14 mg at the discretion of the treating physician). At Week 52, the proportions of patients treated with 3 mg, 7 mg, and 14 mg amounted to 9%, 30.2%, and 59.4%, respectively. Oral semaglutide was superior to sitagliptin 100 mg for the responder rate (OR [95% CI]: 4.4 [2.89; 6.70]).

The robustness of the findings outlined above was supported by a variety of sensitivity analyses. Moreover, the findings for the secondary endpoints from the PIONEER programme were largely consistent with those for the primary endpoint (exception: oral semaglutide 3 mg and 7 mg failed superiority versus placebo for the change in body weight up to Week 26 in PIONEER 1).

5.4 Safety

The safety of the oral formulation of semaglutide can be partially based on the safety profile of injectable semaglutide, which is well established and dominated by gastrointestinal (GI) adverse events (AE) and additional concerns related to pancreatic function, thyroid cancer, and worsening of diabetic retinopathy.

Potential new safety issues for the oral formulation of semaglutide relate to the new route of administration and the additional excipient designed to boost gastrointestinal absorption of the semaglutide. The safety and tolerability evaluation was based on data from ten Phase 3 trials with substantial cumulative exposure.

SAS	Oral sema 3 mg		Oral sema 7 mg		Oral sema 14 mg		Oral sema[a]		Comparator[b]		Placebo	
	N	PYE	N	PYE	N	PYE	N	PYE	N	PYE	N	PYE
Phase 3a pool							4116	4379	2236	2335		
Placebo pool							1519	1197			665	523
Placebo dose pool	359	288	356	274	356	267					362	290

In the placebo pool, AEs were most frequently reported for the GI disorders SOC (particularly nausea, diarrhoea and vomiting), which also showed the largest treatment difference between oral semaglutide and placebo. The pattern of these AEs (e.g. dose-dependency and transient occurrence during initial dose escalation) resembled that previously described for other GLP-1RAs, including injectable semaglutide.

Total AEs – phase 3a pool and placebo pool – on-treatment

	Oral sema				Comparator or Placebo			
	N	(Adj.%)	E	Adj.R	N	(Adj.%)	E	Adj.R
Phase 3a pool								
Number of subjects	4116				2236			
Exposure time (years)	4379				2335			
AEs	3087	(74.9)	12459	302.2	1616	(73.0)	6004	259.0
Placebo pool								
Number of subjects	1519				665			
Exposure time (years)	1197				523			
AEs	1072	(71.3)	4055	356.7	438	(65.9)	1358	264.5

The cardiovascular (CV) safety was demonstrated in the PIONEER 6 study for a population with increased CV risk. Patients in the oral semaglutide arm experienced numerically fewer 3-point MACEs (CV death, non-fatal MI, non-fatal stroke) vs. placebo control (HR [95% CI]: 0.79 [0.57, 1.11]), confirming the non-inferiority hypothesis (superiority hypothesis failed). It is noteworthy that the treatment with oral semaglutide reduced CV mortality (HR [95% CI]: 0.49 [0.27, 0.92]) and all-cause mortality (HR [95% CI]: 0.44 [0.23, 0.82]).

The rate of severe hypoglycaemic events according to the ADA 2013 classification with oral semaglutide was low and comparable to that with active-comparators, including the GLP-1RAs liraglutide and dulaglutide. The PIONEER 4 trial showed no increase in the risk of level 2 events (clinically significant hypoglycaemia) according to the ADA 2018/IHSG 2017 classification compared with liraglutide.

Immunogenicity-related AEs were less frequent in patients treated with oral semaglutide (phase 3a pool: 2.9% versus 4.6%; placebo pool: 1.8% versus 3.5%) and did not cluster for specific SOCs or types of event. The proportion of subjects positive for anti-semaglutide antibodies at any time point post-baseline was rather low (0.5% of subjects with antibody assessment in PIONEER 1–5 and 9).

Subjects with a history of pancreatitis were excluded from the PIONEER studies. The rate of EAC-adjudicated events of acute pancreatitis was low across treatment arms of the Phase 3a pool and not increased with oral semaglutide (events per 100 PY: <0.1 vs. 0.1) or in the placebo pool (events per 100 PY: 0 vs. 0.1).

Diabetic retinopathy may potentially worsen when starting treatment with potent glucose-lowering drugs, including GLP-1RAs. Based on the safety data presented, such an increased risk of retinopathy cannot be fully excluded for oral semaglutide.

Preclinical data with GLP-1RAs have raised the safety concern of neoplasms, including thyroid cancer. The safety analysis of the PIONEER programme revealed a minor excess of total malignant neoplasms in the Phase 3a pool and the placebo pool, the clinical relevance of which remains uncertain.

Renal disorders, including acute kidney disease, may occur as a consequence of the dehydration caused by GI adverse events (nausea, diarrhoea and vomiting). No increase in the risk of renal disorders with oral semaglutide was observed in the PIONEER 5 (patients with moderate renal impairment) or PIONEER 6 (population with increased CV risk) studies. This was confirmed by the results of a MedDRA-based analysis of renal disorder SOCs, and supported by the renal function parameters in the phase 3a pool (EAC-confirmed acute kidney injury: 0.4% versus 0.3%).

Several participants in the dose-finding study 3790 showed increased creatine kinase (CK) levels, including one subject in the oral semaglutide arm with rhabdomyolysis. A total of three SAEs of rhabdomyolysis were reported in three subjects (two taking oral semaglutide and one taking placebo) across all PIONEER studies. Increases in the CK level >10xULN were generally rare and less frequent in the oral semaglutide arm (Phase 3a pool: 0.2% versus 0.4%; placebo pool: 0.2% versus 0.3%).

5.5   Final Clinical and Clinical Pharmacology Benefit Risk Assessment

Due to their prominent glucose-lowering efficacy and the documentation of a CV-protective effect, the analogues of human GLP-1, such as liraglutide and dulaglutide, represent an important class of antihyperglycaemic drugs. All GLP-1 receptor agonists marketed to date in Switzerland need to be injected subcutaneously. Injection may represent a psychological barrier for patients. Long-acting substances requiring once-weekly injection have reduced this burden, but an oral formulation of a GLP-1RA could further advance the treatment of T2DM with respect to this issue.

The clinical pharmacology package was extensive and covered all the relevant aspects. Overall, the pharmacokinetic characteristics of the oral semaglutide are in line with those of semaglutide following SC administration. The pharmacokinetic profile of the absorption enhancer SNAC was comprehensively characterised in a battery of phase 1 studies. The population pharmacokinetic analysis revealed that no dose adjustment is necessary based on any of the evaluated covariates including age, sex, body weight, race, ethnicity, upper gastrointestinal disease, renal function, or hepatic impairment.

Oral semaglutide showed a glucose-lowering effect across all studies of the PIONEER programme. For the primary endpoint change in HbA1c, 3 mg, 7 mg, and 14 mg of oral semaglutide were superior to placebo (ETD [95% CI]: -0.6 [-0.8; -0.4], -0.9 [-1.1; -0.6], and -1.1 [-1.3; -0.9]), respectively. In addition, oral semaglutide 14 mg was superior to empagliflozin 25 mg (ETD [95% CI]: -0.4 [-0.6; -0.3]) and sitagliptin 100 mg (ETD [95% CI]: -0.5 [-0.6; -0.4]), and non-inferior to SC liraglutide 1.8 mg (ETD [95% CI]: -0.1 [-0.3; -0.0]). Patients who had moderate renal impairment shared the glucose-lowering effect. (ETD [95% CI] versus placebo for 14 mg: - 0.8 [-1.0; -0.6]). Moreover, oral semaglutide lowered plasma glucose in patients already treated with insulin (ETD [95% CI] versus placebo for 14 mg: -1.2 [-1.4; -1.0]). The glucose-lowering efficacy of oral semaglutide translated into a higher proportion of patients achieving glycaemic target (HbA$_{1c}$<7%). Finally, oral semaglutide reduced body weight.

The safety profile of the oral formulation of semaglutide is expected to largely resemble that of injectable semaglutide and its structural relative liraglutide. The safety profiles of injectable semaglutide and liraglutide are well established and clearly dominated by GI AEs. Other safety concerns relate to pancreatic function, diabetic retinopathy, and thyroid cancer. GI AEs were also prominent for oral semaglutide and accountable for the largest part of the overall increase in AEs. The rate of EAC-adjudicated events of acute pancreatitis was low across treatment arms of the Phase 3a pool and not increased with oral semaglutide (events per 100 PY: <0.1 vs. 0.1) or in the placebo pool (events per 100 PY: 0 vs. 0.1). There were marginal imbalances in the frequency of «Renal Disorder»

SOC events in the phase 3a pool reported for oral semaglutide vs. active comparator/PLB (MedDRA search: 0.8% vs. 0.5%; EAC-confirmed acute kidney injury: 0.4% vs 0.3%). However, treatment with oral semaglutide had no effect on eGFR, and the PIONEER 6 study in a more vulnerable population detected no safety signal with regard to renal function.

As described above, semaglutide is a potent antihyperglycaemic drug and, therefore, may cause hypoglycaemia; there was no meaningful increase in level 2 events (clinically relevant hypoglycaemia) in patients treated with oral semaglutide. However, level 3 events (severe) were more frequent in patients treated with oral semaglutide and, unsurprisingly, this difference was most prominent in the subgroup of patients additionally treated with insulin (adjusted rate per 100 PY: 1.3 vs. 0.6).

Diabetic retinopathy may worsen when starting treatment with potent glucose-lowering drugs such as GLP-1RAs. The safety data could not unequivocally exclude such a risk, and the Information for Professionals will include a warning equivalent to that for SC semaglutide.

Taken together, the benefit-risk ratio for oral semaglutide is considered positive.

5.6 Approved Indication and Dosage

See information for healthcare professionals in the Appendix.

6 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order 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. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. 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 occurring in populations or indications not included in the Swiss authorisations.

7 Appendix

7.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to 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 reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals approved and authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

▼ **This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.**

RYBELSUS®

Rybelsus® 3 mg tablets
Rybelsus® 7 mg tablets
Rybelsus® 14 mg tablets

Composition

Active substances

semaglutide

Excipients

salcaprozate sodium equivalent to 22.9 mg sodium, povidone K90, microcrystalline cellulose, magnesium stearate

Pharmaceutical form and active substance quantity per unit

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

Indications/Uses

Rybelsus is used in addition to diet and exercise to treat adults with inadequately controlled type 2 diabetes mellitus:

- as monotherapy in case of contraindication or intolerance of metformin (see section "Properties/Effects").
- in combination with other blood glucose-lowering medicines.

See section "Clinical efficacy" for results on the combinations examined in clinical studies and on cardiovascular safety.

Dosage/Administration

Dose

The starting dose of Rybelsus is 3 mg once daily. After 1 month, the dose should be increased to a maintenance dose of 7 mg once daily. If the blood glucose decreasing effect is not sufficient after at least 1 month of treatment at a dose of 7 mg once daily, the maintenance dose can be increased to a maximum of 14 mg once daily.

Patients treated with Rybelsus 14 mg once daily can be transitioned to subcutaneous injection of 0.5 mg once weekly (Ozempic). Patients can start Ozempic the day after their last dose of Rybelsus.

Patients treated with once-weekly Ozempic 0.5 mg by subcutaneous injection can be transitioned to Rybelsus 7 mg or 14 mg once daily. Patients can start Rybelsus up to 7 days after their last injection of Ozempic. There is no equivalent dose of Rybelsus for Ozempic 1 mg.

When Rybelsus is used in combination with metformin and/or a sodium-glucose cotransporter 2 inhibitor (SGLT2i) or a glitazone, the current dose of metformin and/or SGLT2i/glitazone can be continued.

When Rybelsus is used in combination with a sulfonylurea or insulin, a reduction in the dose of the sulfonylurea or insulin may be considered to reduce the risk of hypoglycaemia (see section "Special warnings and precautions for use").

Special dosage instructions

Elderly patients (≥65)

No dose adjustment is required based on age.

Patients with impaired renal function

Dose adjustment is not required in patients with renal impairment.

Patients with impaired hepatic function

Dose adjustment is not required in patients with hepatic impairment.

Children and adolescents

The safety and efficacy of Rybelsus in children and adolescents below 18 years have not been established.

Rybelsus is a tablet for once-daily oral use.

Mode of administration

Rybelsus 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). Do not crush or chew the tablet. Wait at least 30 minutes before the first meal or drink of the day or taking other oral medicinal products. Waiting less than 30 minutes may decrease the absorption of semaglutide.

If a dose is missed, the missed dose should be skipped. The next dose should be taken the following day.

Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in the section "Qualitative and quantitative composition".

Warnings and precautions

Rybelsus should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

Gastrointestinal adverse effects

Use of GLP-1 receptor agonists may be associated with gastrointestinal adverse reactions that can cause dehydration, which in rare cases can lead to a deterioration of renal function.

Acute pancreatitis

Acute pancreatitis has been observed with the use of GLP-1 receptor agonists. Patients must be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, Rybelsus should be discontinued; if confirmed, Rybelsus should not be restarted. Caution should be exercised in patients with a history of pancreatitis.

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 thyroidal C-cell tumours

Preclinical studies with GLP-1 receptor agonists in rodents suggest that GLP-1 receptor agonists may be associated with an increased risk of focal hyperplasia of the thyroid C-cells and C-cell tumours (see section "Preclinical safety data").

It is not known if there is a connection in humans between GLP-1 receptor agonists and thyroid C-cell tumours, including medullary thyroid carcinoma (MTC). Patients with MTC or multiple endocrine neoplasia type 2 (MEN 2) syndrome in their medical history were not treated with semaglutide in the clinical studies. Therefore, a careful benefit-risk assessment is necessary before treatment with Rybelsus in this specific population.

The clinical value of routine monitoring of the serum calcitonin level has not been documented

Diabetic retinopathy

Rapid improvement in glucose 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.

Cardiac insufficiency

There is no therapeutic experience in patients with congestive heart failure New York Heart Association (NYHA) class IV.

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

Interactions

In-vitro studies have indicated very low potential of semaglutide for inhibition or induction of CYP enzymes and for inhibition of active substance transporters.

Semaglutide delays gastric emptying, which may influence the absorption of other oral medicinal products.

No clinically relevant drug-drug interaction with semaglutide was observed based on the evaluated medicinal products. Therefore, no dose adjustment is required for medicinal products when taken with Rybelsus.

It is important that patients treated with other orally administered drugs at the same time strictly follow the dosing instructions under section "Posology and method of administration".

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 levothyroxine 600 µg co-administered with semaglutide. Maximum exposure (C_{max}) was unchanged. Based on the narrow therapeutic index of levothyroxine, monitoring of thyroid parameters should be considered when treating patients with semaglutide at the same time as levothyroxine.

Rosuvastatin:

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

Oral contraceptives:

Semaglutide did not change the exposures (AUC or C_{max}) of combined oral contraceptives (containing ethinylestradiol and levonorgestrel).

Warfarin:

Semaglutide did not change the exposures (AUC or C_{max}) of warfarin (both R- and S-forms).

Digoxin:

Semaglutide did not change the exposures (AUC or C_{max}) of digoxin.

Lisinopril:

Semaglutide did not change the exposures (AUC or C_{max}) of lisinopril.

Effects of other medicinal products on Rybelsus

Omeprazole:

No clinically relevant change in the exposures (AUC or C_{max}) of semaglutide was observed when co-administered with omeprazole (i.e. a proton pump inhibitor that increases gastric pH).

Interactions with food

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

Pregnancy, lactation

Pregnancy

Studies in animals have shown reproductive toxicity (see section "Preclinical data"). There are limited data on the use of semaglutide in pregnant women.

Therefore, Rybelsus should not be used during pregnancy. Women of childbearing age are recommended to use effective contraception methods during treatment with Rybelsus. If a patient wishes to become pregnant, or pregnancy occurs, Rybelsus should be discontinued. Rybelsus should be discontinued at least 2 months before a planned pregnancy due to the long half-life.

Breastfeeding

In lactating rats, semaglutide and SNAC (salcaprozate sodium) were excreted in milk. As a risk to a breastfed child cannot be excluded, Rybelsus should not be used during breastfeeding.

Fertility

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

Effects on ability to drive and use machines

Rybelsus has no or negligible influence on the ability to drive or use machines. When it is used in combination with sulfonylurea or insulin, patients should be advised to take precautions to avoid hypoglycaemia (see section "Warnings and precautions").

Undesirable effects

Summary of 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.

Tabulated list of adverse reactions:

Table 1 lists adverse reactions reported in all phase 3a trials in patients with type 2 diabetes mellitus (further described in the section "Pharmacodynamic properties/effects"). The frequencies of the adverse reactions are based on a pool of the phase 3a trials excluding the cardiovascular outcomes trial.

The reactions are listed below by system organ class and absolute frequency. Frequencies are defined as: very common: (≥1/10); common: (≥1/100 to <1/10); uncommon: (≥1/1,000 to <1/100); rare: (≥1/10,000 to <1/1,000), very rare: (<1/10,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1   Adverse reactions from the controlled phase 3a trials

MedDRA system organ class	Very common	Common	Uncommon	Rare
Immune system disorders				Anaphylactic reaction
Metabolism and nutrition disorders	Hypoglycaemia when used with insulin or SU[a]	Hypoglycaemia when used with other OADs[a] Decreased appetite		
Eye disorders		Complications of diabetic retinopathy[b]		
Cardiac disorders			Increased heart rate	
Gastrointestinal disorders	Nausea Diarrhoea	Vomiting Abdominal pain Abdominal distension Constipation Dyspepsia Gastritis Gastroesophageal reflux disease	Eructation	

		Flatulence		
Hepatobiliary disorders		Increased lipase Increased amylase	Cholelithiasis	
General disorders and administration site conditions		Fatigue		
Investigations			Weight loss	

a Level 2 hypoglycaemia (ADA 2018, < 3.0 mmol/L or <54 mg/dL)

b Complications of diabetic retinopathy is a composite of: retinal photocoagulation, treatment with intravitreal agents, vitreous haemorrhage, diabetes-related blindness (uncommon). Frequency is based on the cardiovascular outcomes trial with s.c. semaglutide.

Description of selected adverse reactions

Hypoglycaemia

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

Common – Hypoglycaemia when used with other OADs

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

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 discontinuation in 4% of subjects. The events were most frequently reported during the first months of treatment.

Discontinuation due to an adverse event

The incidence of discontinuation of treatment due to adverse events was 9% for patients treated with Rybelsus. The most frequent adverse events leading to discontinuation were gastrointestinal disorders.

Increased heart rate

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

Eye disorders

Common – Complications of diabetic retinopathy

Complications of diabetic retinopathy were an endpoint in a 2-year clinical trial with s.c. semaglutide involving 3,297 patients with type 2 diabetes mellitus and high cardiovascular risk. In this trial, complications of diabetic retinopathy occurred more frequently in patients who were treated with s.c. semaglutide (3.0%) than with placebo (1.8%). Over 80% of patients with a complication of diabetic retinopathy had documented diabetic retinopathy before the start of treatment. In patients who had no (documented) diabetic retinopathy in their medical history, the number of events with s.c. semaglutide and placebo was similar.

In clinical trials with Rybelsus of up to 18 months duration involving 6,352 patients with type 2 diabetes, 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 number of subjects who tested positive for anti-semaglutide antibodies at any time point after baseline was 14 (0.5%). Of these 14 patients, 7 patients (0.2% of the overall population) developed antibodies which cross-reacted with native GLP-1. The neutralising activity of the antibodies is uncertain at this time.

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any new or severe adverse reactions using the online portal ElViS (Electronic Vigilance System). For more information, see www.swissmedic.ch.

Overdose

Effects of overdose with semaglutide in clinical studies may be associated with gastrointestinal disorders. In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

Properties/Effects

ATC code

A10BJ06

Mechanism of action

Semaglutide is a GLP-1 analogue of the human peptide GLP-1, which is involved in the regulation of glucose homeostasis. Due to its pronounced albumin binding, the renal clearance of semaglutide is delayed. Furthermore, due to its modified structure compared to native GLP-1, semaglutide is insensitive to degradation by DPP-4.

Semaglutide acts as an agonist at the target receptor for native GLP-1. GLP-1 receptors are expressed in the pancreas, brain, heart, vascular system, immune system and kidneys. The stimulation of GLP-1 receptors by semaglutides leads to the stimulation of insulin secretion and the

inhibition of glucagon secretion, depending on the blood sugar level. In addition, gastric emptying is delayed in the early postprandial phase.

Semaglutide reduces body weight and body fat mass by means of a reduced energy intake. The mechanism includes a generally reduced appetite, which includes increased satiety and decreased hunger. Insulin resistance is reduced. This is presumably achieved by reducing body weight.

Pharmacodynamics

Rybelsus lowers fasting glucose and self-measured plasma glucose. The effect starts early on, with a lowering of fasting glucose within the first week of treatment.

All pharmacodynamic evaluations described below were performed after 12 weeks of treatment (including dose escalation) at steady state, with 1 mg semaglutide injections once weekly.

Fasting and postprandial glucose

Semaglutide reduces fasting and postprandial glucose concentrations. In patients with type 2 diabetes, treatment with semaglutide resulted in reductions in glucose in terms of absolute change from baseline and relative reduction compared to placebo for fasting glucose (1.6 mmol/L / 29 mg/dl; 22% reduction), 2-hour postprandial glucose (4.1 mmol/L / 74 mg/dl; 37% reduction), mean 24-hour glucose concentration (1.7 mmol/L / 30 mg/dl; 22% reduction) and postprandial glucose excursions over 3 meals (0.6–1.1 mmol/L / 11-20 mg/dl).

Beta cell function and insulin secretion

Semaglutide improves beta cell function. Compared to placebo, semaglutide improved both first- and second-phase insulin response, with a 3- and 2-fold increase, respectively, and increased maximum beta cell secretory capacity after an arginine stimulation test in patients with type 2 diabetes. In addition, semaglutide treatment increased fasting insulin concentrations compared to placebo.

Glucagon secretion

Semaglutide lowers fasting and postprandial glucagon concentrations. In patients with type 2 diabetes, 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 concentration (12%).

Glucose-dependent insulin and glucagon secretion

Semaglutide lowers high blood glucose concentrations by stimulating insulin secretion and inhibiting glucagon secretion in a glucose-dependent manner. With semaglutide, the insulin secretion rate in patients with type 2 diabetes was comparable to that in healthy subjects.

During induced hypoglycaemia, semaglutide did not alter the counter-regulatory responses of increased glucagon and did not impair the decrease of C-peptide in patients with type 2 diabetes compared to placebo.

Gastric emptying

Semaglutide causes a minor delay in early postprandial gastric emptying, thereby reducing the rate at which glucose appears in the circulation postprandially.

Body weight and composition

Greater weight reduction was achieved with Rybelsus than with the comparator drugs (placebo, sitagliptin, empagliflozin and liraglutide). The weight loss was mainly attributable to the loss of fat tissue, with a loss of fat mass three times that of the loss of muscle mass.

Appetite, energy intake and food choices

Compared to placebo, semaglutide lowered the energy intake of 3 consecutive *ad libitum* meals by 18–35%. This was supported by a semaglutide-induced suppression of appetite in the fasting state as well as postprandially, improved control of eating, fewer food cravings and a relative lower preference for high-fat food.

Fasting blood lipids and postprandial blood lipids

Compared to placebo, semaglutide lowered fasting triglyceride and very-low-density lipoprotein (VLDL) cholesterol concentrations by 12% and 21%, respectively. The postprandial triglyceride and VLDL cholesterol response to a high-fat meal was reduced by >40%.

Cardiac electrophysiology (QTc)

The effect of semaglutide on cardiac repolarisation was tested in a thorough QTc trial. At an average exposure level 4-fold higher than that of the maximum recommended dose of Rybelsus, semaglutide did not prolong QTc intervals to any clinically relevant extent.

Clinical efficacy

The efficacy and safety of Rybelsus have been evaluated in 8 global randomised controlled phase 3a trials. In 7 trials, the primary objective was the assessment of the glycaemic efficacy; in 1 trial, the primary objective was the assessment of cardiovascular safety.

The phase 3a trials included 8,842 randomised patients with type 2 diabetes (5,169 treated with Rybelsus), including 1,164 patients with moderate renal impairment. The efficacy of Rybelsus was compared with placebo, empagliflozin, sitagliptin, liraglutide and dulaglutide.

In all trials, treatment with Rybelsus showed clinically significant improvements in HbA$_{1c}$, fasting plasma glucose (FPG) and body weight. These effects were maintained up to a trial duration of 78 weeks.

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

<u>PIONEER 1 – Monotherapy</u>

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 monotherapy trial (PIONEER 1) comparing Rybelsus with placebo at week 26

	Rybelsus 7 mg	Rybelsus 14 mg	Placebo
Population (N)[1]	175	175	178
HbA$_{1c}$ (%)			
Baseline[2]	8.0	8.0	7.9
Change compared to 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 (%) who achieved an HbA$_{1c}$ <7.0%[2]	72#	80#	34
Body weight (kg)			
Baseline[2]	89.0	88.1	88.6
Change compared to 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 using a mixed model for repeated measurements adjusted for baseline value, background medication and region. Data collected after premature discontinuation of the investigational product or initiation of rescue medication are excluded.

§ Statistically significant (p<0.05)

Odds were statistically significantly greater with Rybelsus than with placebo of achieving the target (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 were randomised to Rybelsus 14 mg once daily or empagliflozin 25 mg once daily, both in combination with metformin.

At week 26, treatment with Rybelsus 14 mg once daily reduced the HbA$_{1c}$ by -1.4 percentage points; the reduction was statistically significantly greater than with empagliflozin, with an estimated treatment difference of -0.5 percentage points [-0.7; -0.4]$_{95\% CI}$.

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

	Rybelsus 14 mg	Empagliflozin 25 mg

Population (N)[1]	411	410
HbA$_{1c}$ (%)		
Baseline[2]	8.1	8.1
Change from baseline at week 52[3]	-1.3	-0.8
Difference from empagliflozin[3] [95% CI]	-0.5 [-0.7; -0.4]§	-
Patients (%) who achieved an HbA$_{1c}$ <7.0%[2]	72#	48
Body weight (kg)		
Baseline[2]	91.9	91.3
Change from baseline at 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 using a mixed model for repeated measurements adjusted for baseline value, background medication and region. Data collected after premature discontinuation of the investigational product or initiation of rescue medication are excluded

§ Statistically significant (p<0.05)

Odds were statistically significantly greater with Rybelsus than with empagliflozin of achieving the target (p<0.05)

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

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

Reductions in HbA$_{1c}$ and body weight were sustained throughout the trial duration of 78 weeks (Table 4).

Table 4   Results of a trial comparing Rybelsus with sitagliptin at week 78 (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 at 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 (%) who achieved an HbA$_{1c}$ <7.0%[2]	50[#]	52[#]	39
Body weight (kg)			
Baseline[2]	91.3	91.2	90.9
Change from baseline at 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 using a mixed model for repeated measurements adjusted for baseline value, background medication and region. Data collected after premature discontinuation of the investigational product or initiation of rescue medication are excluded

[§] Statistically significant (p<0.05)

[#] Odds were statistically significantly greater with Rybelsus than with sitagliptin of achieving the target (p<0.05)

PIONEER 4 – Rybelsus vs. liraglutide and placebo, all in combination with metformin or metformin with 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. injection or placebo once daily, all in combination with metformin or metformin and an SGLT2 inhibitor.

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

Table 5   Results of a trial comparing Rybelsus with liraglutide and placebo at week 52 (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 at 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 (%) who achieved an HbA$_{1c}$ <7.0%[2]	69*	63	18
Body weight (kg)			
Baseline[2]	92.9	95.5	93.2
Change from baseline at 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 using a mixed model for repeated measurements adjusted for baseline value, background medication and region. Data collected after premature discontinuation of the investigational product or initiation of rescue medication are excluded

§ Statistically significant (p<0.05)

$^#$ Odds were statistically significantly greater with Rybelsus than with liraglutide of achieving the target (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 impairment

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 a stable antidiabetic regimen were 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 impairment corresponded with that generally described for GLP-1 receptor agonists.

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

	Rybelsus 14 mg	Placebo
Population (N)[1]	163	161
HbA$_{1c}$ (%)		
Baseline[2]	8.0	7.9
Change compared to baseline in week 26[3]	-1.1	-0.1
Difference from placebo[3] [95% CI]	-1.0 [-1.2; -0.8]§	-
Patients (%) who achieved an HbA$_{1c}$ <7.0%[2]	64$^#$	21
Body weight (kg)		
Baseline[2]	91.3	90.4
Change compared to 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 using a mixed model for repeated measurements adjusted for baseline value, background medication and region. Data collected after premature discontinuation of the investigational product or initiation of rescue medication are excluded.

§ Statistically significant (p<0.05)

$^#$ Odds were statistically significantly greater with Rybelsus than with placebo of achieving the target (p<0.05)

PIONEER 7 – Rybelsus vs. sitagliptin, both in combination with metformin, SGLT2 inhibitors, sulfonylurea or glitazone (flexible dose adjustment trial)

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 glitazone). The dose of Rybelsus was adjusted every 8 weeks based on the 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 proportion of patients on treatment with Rybelsus 3 mg, 7 mg and 14 mg was 9%, 30% and 60%, respectively.

Table 7   Results of a flexible dose adjustment trial comparing Rybelsus with sitagliptin at week 52 (PIONEER 7)

	Rybelsus Flexible dose	Sitagliptin 100 mg
Population (N)[1]	253	251
HbA$_{1c}$ (%)		
Baseline[2]	8.3	8.3
Change from baseline at week 52[3]	-1.4	-0.7
Difference from sitagliptin[3] [95% CI]	-0.7 [-0.9; -0.5]§	-
Patients (%) who achieved an HbA$_{1c}$ <7.0%[2]	63#	28
Body weight (kg)	88.9	88.4
Baseline[2]	-2.9	-0.8
Change from baseline at 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 using a mixed model for repeated measurements adjusted for baseline value, background medication and region.

§ Statistically significant (p<0.05)

Odds were statistically significantly greater with Rybelsus than with sitagliptin of achieving the target (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 inadequately controlled type 2 diabetes on insulin (basal, basal/bolus or premixed insulin) with or without metformin were randomised to Rybelsus 3 mg, Rybelsus 7 mg, Rybelsus 14 mg or placebo once daily.

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

Table 8   Results of a trial comparing Rybelsus with placebo in combination with insulin at week 52 (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 at 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 (%) who achieved an HbA_{1c} <7.0%[2]	47[#]	64[#]	10
Body weight (kg)			
Baseline[2]	87.1	84.6	86.0
Change from baseline at week 52[3]	-2.9	-4.3	0.6
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 using a mixed model for repeated measurements adjusted for baseline value, background medication and region. [§] Statistically significant (p<0.05)

[#] Odds were statistically significantly greater with Rybelsus than with placebo of achieving the target (p<0.05)

Cardiovascular safety

The cardiovascular effects of oral semaglutide were investigated in the PIONEER 6 cardiovascular outcome study. Additional data on the cardiovascular safety of subcutaneously injected semaglutide was collected in the SUSTAIN 6 cardiovascular outcome study.

PIONEER 6

In this double-blind study, 3,183 patients with type 2 diabetes and high cardiovascular risk (2,695 [85%] patients with pre-existing cardiovascular disease and 488 [15%] patients with cardiovascular risk factors without pre-existing cardiovascular disease) were randomised to Rybelsus 14 mg once daily or placebo (mean duration of treatment 16 months) in addition to pre-existing anti-hyperglycaemic therapy. The treatment was intensified in both arms according to the applicable therapy guidelines.

The primary endpoint was the time from randomisation to the occurrence of the first major adverse cardiovascular event (MACE: cardiovascular death, non-fatal heart attack or non-fatal stroke). The cardiovascular risk was numerically reduced in the patients treated with semaglutide.
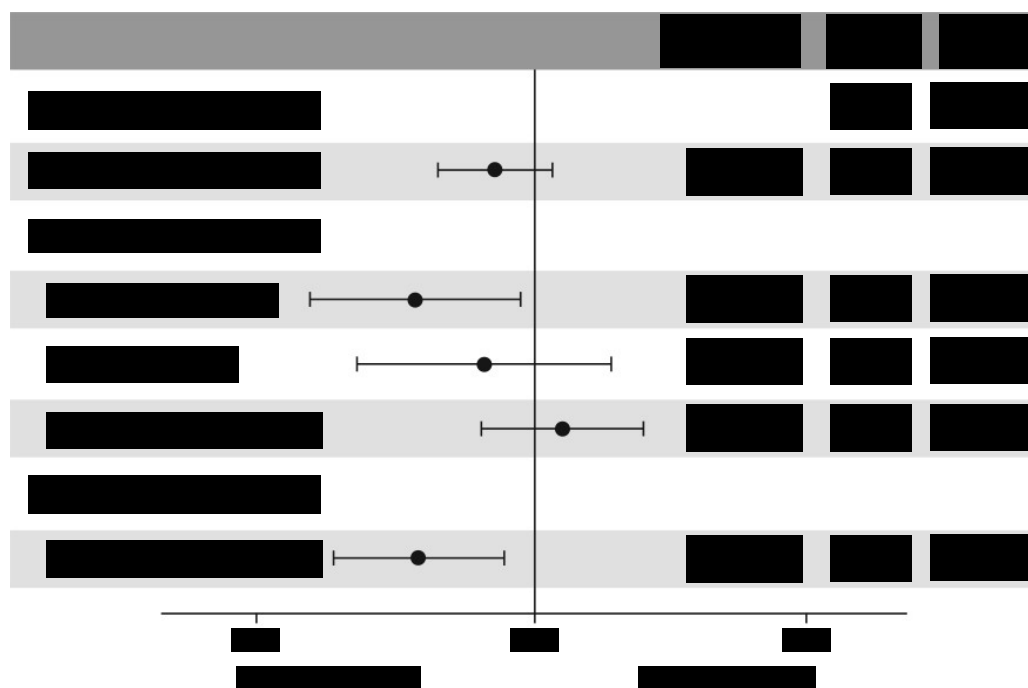

Figure 7   Forest plot: Treatment effect for the primary composite endpoint MACE, its components and all causes of death (PIONEER 6)

This effect was primarily based on a decrease in cardiovascular mortality

SUSTAIN 6

In this 104-week double-blind study, 3,297 patients with type 2 diabetes and high cardiovascular risk (2,735 [83%] patients with pre-existing cardiovascular disease and 562 [27%] patients with

cardiovascular risk factors without pre-existing cardiovascular disease) were randomised to semaglutide 0.5 mg s.c., semaglutide 1 mg s.c. or to placebo in addition to pre-existing anti-hyperglycaemic therapy.

The primary endpoint was the time from randomisation to the occurrence of the first major adverse cardiovascular event (MACE: cardiovascular death, non-fatal heart attack or non-fatal stroke). The cardiovascular risk was reduced in the patients treated with semaglutide on average over 2 years.

		Hazard Ratio (95% CI)	S.c. semaglutide N (%)	Placebo N (%)
FAS			1648 (100)	1649 (100)
Primary endpoint – MACE		0.74 (0.58- 0.95)	108 (6.6)	146 (8.9)
Components of MACE				
Cardiovascular death		0.98 (0.65-1.48)	44 (2.7)	46 (2.8)
Non-fatal stroke		0.61 (0.38-0.99)	27 (1.6)	44 (2.7)
Non-fatal myocardial infarction		0.74 (0.51-1.08)	47 (2.9)	64 (3.9)
Other secondary endpoints				
All cause death		1.05 (0.74-1.50)	62 (3.8)	60 (3.6)

0.2   1   5

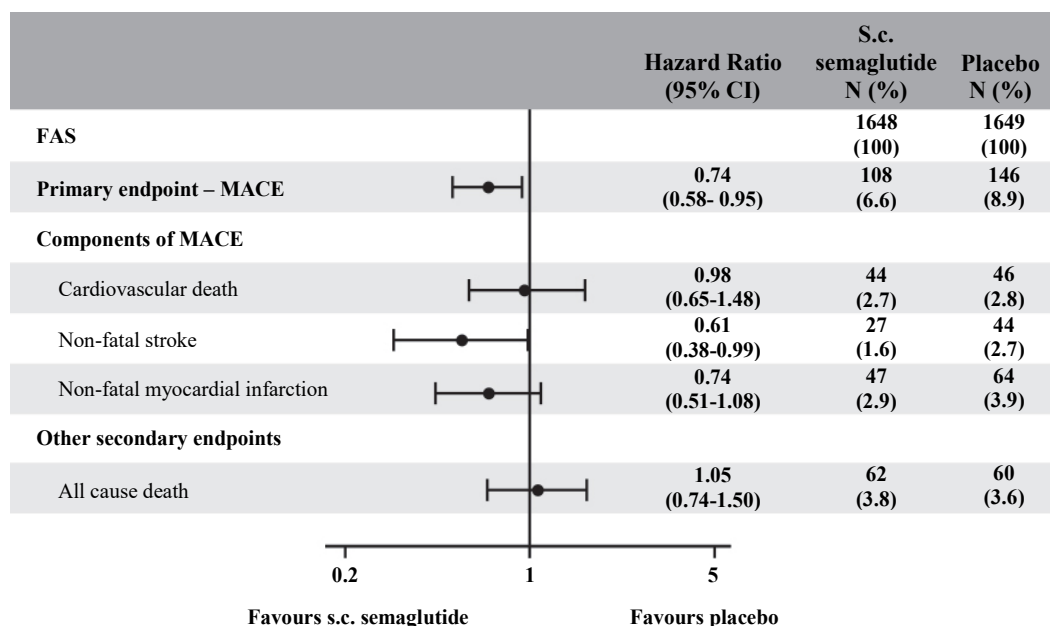**Favours s.c. semaglutide**   **Favours placebo**

Figure 8   Forest plot: Treatment effect for the primary composite endpoint, its components and all-cause death (SUSTAIN 6)

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

Pharmacokinetics

Absorption

Semaglutide is co-formulated with salcaprozate sodium, which facilitates the absorption of semaglutide after oral administration. The absorption of semaglutide predominantly occurs in the stomach.

The pharmacokinetics of semaglutide have been extensively characterised in healthy subjects and 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 population pharmacokinetic analyses using data from patients with type 2 diabetes mellitus, the average steady-state concentrations were approximately 6.7 nmol/L and

14.6 nmol/L with Rybelsus 7 mg and 14 mg, respectively. Systemic exposure of semaglutide increased in a dose-proportional manner.

Absorption of semaglutide is decreased if taken with food.

The estimated absolute bioavailability of semaglutide is less than 1% following oral administration.

Distribution

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

Metabolism

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

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 about 5 weeks after the last dose. The clearance of semaglutide in patients with type 2 diabetes is approximately 0.04 L/h.

Average exposure levels for semaglutide for oral and subcutaneous administration

Based on population pharmacokinetic analysis, the average exposure associated with s.c. semaglutide 0.5 mg will be approximately 90% of that for Rybelsus 14 mg. Average exposures associated with Rybelsus 7 mg or 14 mg will be approximately 60% and 110%, respectively, of that for s.c. semaglutide 0.5 mg.

Kinetics in specific patient groups

Hepatic impairment

Hepatic impairment 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 hepatic impairment compared with subjects with normal hepatic function in a study involving 10 consecutive days of once-daily doses of semaglutide.

Renal impairment

Renal impairment 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 renal disease on dialysis compared with subjects with normal renal function in a study involving 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 using data from the phase 3a studies.

Elderly patients

Age had no effect on the pharmacokinetics of semaglutide based on data from clinical trials, which studied patients up to 92 years of age.

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. Semaglutide provided adequate systemic exposure over the body weight range of 40–188 kg evaluated in the clinical trials.

Upper GI tract disorders

Upper GI tract disease (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 GI tract disease, dosed for 10 consecutive days with once-daily doses of semaglutide.

This was also shown for subjects with type 2 diabetes and upper GI tract disease based on data from phase 3a studies.

Preclinical data

Preclinical data reveal no special hazards for humans based on conventional studies of safety pharmacology, repeat-dose toxicity or genotoxicity.

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, semaglutide caused thyroid C-cell tumours at clinically relevant exposures. The rodent C-cell tumours are caused by a non-genotoxic, specific GLP-1 receptor mediated mechanism to which rodents are particularly sensitive. The relevance for humans is considered to be low, but cannot be completely excluded.

In fertility studies in rats, semaglutide did not affect mating performance or male fertility. In female rats, an increase in oestrous 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, this mechanism is considered unlikely to be of relevance to humans.

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.

Post-natal growth and development were evaluated in cynomolgus monkeys. Infants were slightly smaller at delivery, but recovered during the lactation period.

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 container.

Special precautions for storage

Store out of sight and reach of children.

Do not store above 30°C.

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

Authorisation number

67446 (Swissmedic)

Packs

Tablets of 3 mg, 7 mg or 14 mg in blister packaging.

3 mg: pack size of 30 tablets

7 mg: pack sizes of 30 and 90 tablets

14 mg: pack sizes of 30 and 90 tablets.

Marketing authorisation holder

Novo Nordisk Pharma AG, Zurich

Manufacturer

Novo Nordisk A/S, DK-2880 Bagsvaerd

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