ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Rybelsus 1.5 mg tablets
Rybelsus 4 mg tablets
Rybelsus 9 mg tablets
Rybelsus 25 mg tablets
Rybelsus 50 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Rybelsus 1.5 mg tablets

Each tablet contains 1.5 mg semaglutide*.

Rybelsus 4 mg tablets

Each tablet contains 4 mg semaglutide*.

Rybelsus 9 mg tablets

Each tablet contains 9 mg semaglutide*.

Rybelsus 25 mg tablets

Each tablet contains 25 mg semaglutide*.

Rybelsus 50 mg tablets

Each tablet contains 50 mg semaglutide*.

*human glucagon-like peptide-1 (GLP-1) analogue produced in *Saccharomyces cerevisiae* cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

Rybelsus 1.5 mg tablets

White to light yellow, round tablet (6.5 mm in diameter) debossed with ‘1.5’ on one side and ‘novo’ on the other side.

Rybelsus 4 mg tablets

White to light yellow, round tablet (6.5 mm in diameter) debossed with ‘4’ on one side and ‘novo’ on the other side.

Rybelsus 9 mg tablets

White to light yellow, round tablet (6.5 mm in diameter) debossed with ‘9’ on one side and ‘novo’ on the other side.

Rybelsus 25 mg tablets

White to light yellow, oval shaped tablet (6.8 mm x 12 mm), debossed with ‘25’ on one side and ‘novo’ on the other side.

Rybelsus 50 mg tablets

White to light yellow, oval shaped tablet (6.8 mm x 12 mm), debossed with ‘50’ on one side and ‘novo’ on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

- as monotherapy when metformin is considered inappropriate
- in combination with other medicinal products for the treatment of diabetes.

For study results with respect to combinations, effects on glycaemic control and cardiovascular events, and the populations studied, see sections 4.4, 4.5 and 5.1.

4.2 Posology and method of administration

Posology

The starting dose of semaglutide is 1.5 mg once daily for one month. After one month, the dose should be increased to a maintenance dose of 4 mg once daily. If needed, the dose can be escalated to the next higher dose after a minimum of one month on the current dose. The recommended single daily maintenance doses are 4 mg, 9 mg, 25 mg and 50 mg.

The maximum recommended single daily dose of semaglutide is 50 mg. Rybelsus should always be used as one tablet per day. Taking more than one tablet a day should not be done to achieve the effect of a higher dose.

Switching from subcutaneous to oral semaglutide
The effect of switching between oral and subcutaneous semaglutide cannot easily be predicted because oral semaglutide displays higher pharmacokinetic variability in absorption compared to subcutaneous semaglutide.

Patients treated with subcutaneous semaglutide 0.5 mg once weekly can be transitioned to oral semaglutide 4 mg or 9 mg once daily.
Patients treated with subcutaneous semaglutide 1 mg once weekly can be transitioned to oral semaglutide 9 mg or 25 mg once daily.
Patients treated with subcutaneous semaglutide 2 mg once weekly can be transitioned to oral semaglutide 25 mg or 50 mg once daily.
Patients can start oral semaglutide (Rybelsus) one week after their last dose of subcutaneous semaglutide.

When semaglutide 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 semaglutide is used in combination with a sulfonylurea or with insulin, a reduction in the dose of sulfonylurea or insulin may be considered to reduce the risk of hypoglycaemia (see sections 4.4 and 4.8).

Self-monitoring of blood glucose is not needed in order to adjust the dose of semaglutide. Blood glucose self-monitoring is necessary to adjust the dose of sulfonylurea and insulin, particularly when semaglutide is started and insulin is reduced. A stepwise approach to insulin reduction is recommended.

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

Elderly
No dose adjustment is required based on age.

Renal impairment
No dose adjustment is required for patients with mild, moderate or severe renal impairment. Experience with the use of semaglutide in patients with end-stage kidney disease is limited. Caution should be exercised when treating these patients with oral semaglutide (see section 5.2).

Hepatic impairment
No dose adjustment is required for patients with hepatic impairment. Experience with the use of semaglutide in patients with severe hepatic impairment is limited. Caution should be exercised when treating these patients with semaglutide (see section 5.2).

Paediatric population

The safety and efficacy of Rybelsus in children and adolescents below 18 years have not been established. No data are available.

Method of administration

Rybelsus is a tablet for once-daily oral use.

- This medicinal product should be taken on an empty stomach after a recommended fasting period of at least 8 hours (see section 5.2).
- It should be swallowed whole with a sip of water (up to half a glass of water equivalent to 120 mL). Tablets should not be split, crushed or chewed, as it is not known whether this impacts absorption of semaglutide.
- Patients should wait at least 30 minutes before eating, drinking or taking other oral medicinal products. Waiting less than 30 minutes decreases the absorption of semaglutide (see sections 4.5 and 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

General

Semaglutide 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 who had rapid discontinuation or dose reduction of insulin when treatment with a GLP-1 receptor agonist is started (see section 4.2).

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

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

Aspiration in association with general anaesthesia or deep sedation

Cases of pulmonary aspiration have been reported in patients receiving GLP-1 receptor agonists undergoing general anaesthesia or deep sedation. Therefore, the increased risk of residual gastric content due to delayed gastric emptying (see section 4.8) should be considered prior to performing procedures with general anaesthesia or deep sedation.

Gastrointestinal effects and dehydration

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 (see section 4.8). 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, semaglutide should be discontinued; if confirmed, semaglutide should not be restarted.

Hypoglycaemia

Patients treated with semaglutide in combination with a sulfonylurea or insulin may have an increased risk of hypoglycaemia (see section 4.8). The risk of hypoglycaemia can be lowered by reducing the dose of sulfonylurea or insulin when initiating treatment with semaglutide (see section 4.2).

Diabetic retinopathy

In patients with diabetic retinopathy treated with insulin and subcutaneous semaglutide, an increased risk of developing diabetic retinopathy complications has been observed, a risk that cannot be excluded for orally administered semaglutide (see section 4.8). Caution should be exercised when using semaglutide in patients with diabetic retinopathy. These patients should be monitored closely and treated according to clinical guidelines. Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy, but other mechanisms cannot be excluded. Long-term glycaemic control decreases the risk of diabetic retinopathy.

There is no experience with oral semaglutide 25 mg and 50 mg in patients with type 2 diabetes with uncontrolled or potentially unstable diabetic retinopathy.

Non-arteritic anterior ischaemic optic neuropathy (NAION)

Data from epidemiological studies indicates an increased risk for non-arteritic anterior ischaemic optic neuropathy (NAION) during treatment with semaglutide. There is no identified time interval for when NAION may develop following treatment start. A sudden loss of vision should lead to

ophthalmological examination and treatment with semaglutide should be discontinued if NAION is confirmed (see section 4.8).

Treatment response

Compliance with the dosing regimen is recommended for optimal effect of semaglutide. If the treatment response with semaglutide is lower than expected, the treating physician should be aware that the absorption of semaglutide is highly variable and may be minimal (2-4% of patients will not have any exposure), and that the absolute bioavailability of semaglutide is low.

Sodium content

1.5 mg, 4 mg and 9 mg tablets: This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

25 mg and 50 mg tablets: This medicinal product contains 23 mg sodium per tablet, equivalent to 1% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

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

Effects of semaglutide on other medicinal products

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

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.

Rosuvastatin
AUC of rosuvastatin was increased by 41% [90% CI: 24; 60] when co-administered with semaglutide. Based on the wide therapeutic index of rosuvastatin the magnitude of changes in the exposure is not considered clinically relevant.

Digoxin, oral contraceptives, metformin, furosemide
No clinically relevant change in AUC or C_{max} of digoxin, oral contraceptives (containing ethinylestradiol and levonorgestrel), metformin or furosemide was observed when concurrently administered with semaglutide.

Interactions with medicinal products with very low bioavailability (1%) have not been evaluated.

Effects of other medicinal products on semaglutide

Omeprazole
No clinically relevant change in AUC or C_{max} of semaglutide was observed when taken with omeprazole.

In a trial investigating the pharmacokinetics of semaglutide co-administered with five other tablets, the AUC of semaglutide decreased by 34% and C_{max} by 32%. This suggests that the presence of multiple tablets in the stomach influences the absorption of semaglutide if co-administered at the same time. After administering semaglutide, the patients should wait 30 minutes before taking other oral medicinal products (see section 4.2).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential have to use effective contraception during treatment with semaglutide.

Pregnancy

Studies in animals have shown reproductive toxicity (see section 5.3). There are limited data from the use of semaglutide in pregnant women. Therefore, semaglutide should not be used during pregnancy. If a patient wishes to become pregnant, or pregnancy occurs, semaglutide should be discontinued. Semaglutide should be discontinued at least 2 months before a planned pregnancy due to the long half-life (see section 5.2).

Breast-feeding

No measurable concentrations of semaglutide were found in breast milk of lactating women. Salcaprozate sodium was present in breast milk and some of its metabolites were excreted in breast milk 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 section 5.3).

4.7 Effects on ability to drive and use machines

Semaglutide has no or negligible influence on the ability to drive and use machines. However, dizziness can be experienced mainly during dose escalation. Driving or use of machines should be done cautiously if dizziness occurs.

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 section 4.4).

4.8 Undesirable effects

Summary of the safety profile

In 10 phase 3a trials, 5 707 patients were exposed to semaglutide 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 (very common), diarrhoea (very common) and vomiting (common).

Tabulated list of adverse reactions

Table 1 lists adverse reactions identified in phase 3 trials (further described in section 5.1) and post-marketing reports in patients with type 2 diabetes mellitus. The frequencies of the adverse reactions

(except diabetic retinopathy complications and dysaesthesia, see footnotes in Table 1) 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) and very rare: (< 1/10 000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1 Frequency of adverse reactions of oral semaglutide

MedDRA system organ class	**Very common**	**Common**	**Uncommon**	**Rare**	**Very Rare**	**Not known**
Immune system disorders			Hypersensitivity[c]	Anaphylactic reaction		
Metabolism and nutrition disorders	Hypoglycaemia when used with insulin or sulfonylurea[a]	Hypoglycaemia when used with other oral antidiabetic products[a] Decreased appetite				
Nervous system disorders		Dizziness Dysaesthesia[e] Headache	Dysgeusia			
Eye disorders		Diabetic retinopathy complications[b]			Non-arteritic anterior ischaemic optic neuropathy (NAION)	
Cardiac disorders			Increased heart rate			
Gastrointestinal disorders	Nausea Diarrhoea	Vomiting Abdominal pain Abdominal distension Constipation Dyspepsia Gastritis Gastro-oesophageal reflux disease Flatulence	Eructation Delayed gastric emptying	Acute pancreatitis		Intestinal obstruction[d,f]
Hepatobiliary disorders			Cholelithiasis			
General disorders and administration site conditions		Fatigue				

MedDRA system organ class	Very common	Common	Uncommon	Rare	Very Rare	Not known
Investigations		Increased lipase Increased amylase	Weight decreased			

[a)] Hypoglycaemia defined as blood glucose < 3.0 mmol/L or < 54 mg/dL.
[b)] Diabetic retinopathy complications are 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 subcutaneous semaglutide, but it cannot be excluded that the risk of diabetic retinopathy complications identified also applies to Rybelsus.
[c)] Grouped term covering also adverse events related to hypersensitivity such as rash and urticaria.
[d)] From post-marketing reports.
[e)] The frequency is based on the PIONEER PLUS trial results for 25 mg and 50 mg. Please refer to dysaesthesia subheading below for more information.
[f)] Grouped term covering PTs 'intestinal obstruction', 'ileus', 'small intestinal obstruction'.

Description of selected adverse reactions

Hypoglycaemia
Severe hypoglycaemia was primarily observed when semaglutide 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 semaglutide in combination with oral antidiabetics other than sulfonylurea.

Gastrointestinal adverse reactions
Nausea occurred in 15%, diarrhoea in 10%, and vomiting in 7% of patients when treated with semaglutide. 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 on treatment.

In PIONEER PLUS when treated with semaglutide 25 mg and 50 mg nausea occurred in 27% and 27%, diarrhoea in 13% and 14%, and vomiting in 17% and 18% of patients, respectively. These events led to treatment discontinuation in 6% and 8% of patients, respectively.

Most events were mild to moderate in severity and of short duration. The events were most frequently reported during dose escalation the first months on treatment.

Acute pancreatitis confirmed by adjudication has been reported in phase 3a trials, semaglutide (< 0.1%) and comparator (0.2%). In the cardiovascular outcomes trial PIONEER 6 the frequency of acute pancreatitis confirmed by adjudication was 0.1% for semaglutide and 0.2% for placebo (see section 4.4.). 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.

Diabetic retinopathy complications
A 2-year clinical trial with subcutaneous semaglutide investigated 3 297 patients with type 2 diabetes, with high cardiovascular risk, long duration of diabetes and poorly controlled blood glucose. In this trial, adjudicated events of diabetic retinopathy complications occurred in more patients treated with subcutaneous semaglutide (3.0%) compared to placebo (1.8%). This was observed in insulin-treated patients with known diabetic retinopathy. The treatment difference appeared early and persisted throughout the trial. Systematic evaluation of diabetic retinopathy complication was only performed in the cardiovascular outcomes trial with subcutaneous semaglutide. 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%).

Non-arteritic anterior ischaemic optic neuropathy (NAION)
Results from several large epidemiological studies suggest that exposure to semaglutide in adults with type 2 diabetes is associated with an approximately two-fold increase in the relative risk of developing NAION, corresponding to approximately one additional case per 10 000 person-years of treatment.

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 tested positive for anti-semaglutide antibodies at any time point after baseline was low (0.5%) and no subjects had neutralising anti-semaglutide antibodies or anti-semaglutide antibodies with neutralising effect on endogenous GLP-1 at end-of-trial.

Heart rate increase
Increased heart rate has been observed with GLP-1 receptor agonists. In the phase 3a trials, mean changes of 0 to 4 beats per minute (bpm) from a baseline of 69 to 76 were observed in patients treated with Rybelsus.

Dysaesthesia
Events related to a clinical picture of altered skin sensation such as paraesthesia, pain of skin, sensitive skin, dysaesthesia and burning skin sensation were reported in 2.1% and 5.2% of patients treated with oral semaglutide 25 mg and 50 mg, respectively. The events were mild to moderate in severity and most patients recovered while on continued treatment.

Reporting of suspected adverse reactions

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 suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 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. A prolonged period of observation and treatment of the symptoms may be necessary, taking into account the long half-life of semaglutide of approximately 1 week (see section 5.2). There is no specific antidote for overdose with semaglutide.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, Glucagon-like peptide-1 (GLP-1) analogues, ATC code: A10BJ06

Mechanism of action

Semaglutide is a GLP-1 analogue with 94% sequence homology to human GLP-1. Semaglutide acts as a GLP-1 receptor agonist that selectively binds to and activates the GLP-1 receptor, the target for native GLP-1.

GLP-1 is a physiological hormone that has multiple actions in glucose and appetite regulation, and in the cardiovascular system. The glucose and appetite effects are specifically mediated via GLP-1 receptors in the pancreas and the brain.

Semaglutide reduces blood glucose in a glucose-dependent manner by stimulating insulin secretion and lowering glucagon secretion when blood glucose is high. The mechanism of blood glucose lowering also involves a minor delay in gastric emptying in the early postprandial phase. During hypoglycaemia, semaglutide diminishes insulin secretion and does not impair glucagon secretion. The mechanism of semaglutide is independent of the route of administration.

Semaglutide reduces body weight and body fat mass through lowered energy intake, involving an overall reduced appetite. In addition, semaglutide reduces the preference for high fat foods.

GLP-1 receptors are expressed in the heart, vasculature, immune system and kidneys. Semaglutide has a beneficial effect on plasma lipids, lowers systolic blood pressure and reduces inflammation in clinical studies. In animal studies, semaglutide attenuates the development of atherosclerosis by preventing aortic plaque progression and reducing inflammation in the plaque.

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 reductions in hsCRP. The exact mechanism of cardiovascular risk reduction has not been established.

Pharmacodynamic effects

The pharmacodynamic evaluations described below were performed with orally administered semaglutide after 12 weeks of treatment.

Fasting and postprandial glucose
Semaglutide reduces fasting and postprandial glucose concentrations. In patients with type 2 diabetes, treatment with semaglutide resulted in a relative reduction compared to placebo of 22% [13; 30] for fasting glucose and 29% [19; 37] for postprandial glucose.

Glucagon secretion
Semaglutide lowers the postprandial glucagon concentrations. In patients with type 2 diabetes, semaglutide resulted in the following relative reductions in glucagon compared to placebo: postprandial glucagon response of 29% [15; 41].

Gastric emptying
Semaglutide causes a minor delay in early postprandial gastric emptying, with paracetamol exposure ($AUC_{0\text{-}1h}$) 31% [13; 46] lower in the first hour after the meal, thereby reducing the rate at which glucose appears in the circulation postprandially.

Fasting and postprandial lipids
Semaglutide compared to placebo lowered fasting triglyceride and very-low-density lipoproteins (VLDL) cholesterol concentrations by 19% [8; 28] and 20% [5; 33], respectively. The postprandial triglyceride and VLDL cholesterol response to a high fat meal was reduced by 24% [9; 36] and 21% [7; 32], respectively. ApoB48 was reduced both in fasting and postprandial state by 25% [2; 42] and 30% [15; 43], respectively.

Clinical efficacy and safety

The efficacy and safety of Rybelsus have been evaluated in eight global randomised controlled phase 3a trials. Phase 3a studies were conducted with tablets containing 3 mg, 7 mg and 14 mg semaglutide which are bioequivalent to 1.5 mg, 4 mg and 9 mg semaglutide, respectively. In seven trials, the

primary objective was the assessment of the glycaemic efficacy; in one trial (PIONEER 6), the primary objective was the assessment of cardiovascular outcomes.

The trials included 8 842 randomised patients with type 2 diabetes (5 169 treated with semaglutide), including 1 165 patients with moderate renal impairment. Patients had an average age of 61 years (range 18 to 92 years), with 40% of patients ≥ 65 years of age and 8% ≥ 75 years of age. The efficacy of semaglutide was compared with placebo or active controls (sitagliptin, empagliflozin and liraglutide).

The efficacy and safety of semaglutide 25 mg and 50 mg once daily was evaluated in a phase 3b trial (PIONEER PLUS) including 1 606 randomised patients.

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 semaglutide was not impacted by baseline age, gender, race, ethnicity, body weight, BMI, diabetes duration, upper gastrointestinal disease 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 semaglutide 3 mg, semaglutide 7 mg, semaglutide 14 mg or placebo once daily.

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

	Semaglutide 7 mg[2] (Bioequivalent to 4 mg)	**Semaglutide 14 mg[2] (Bioequivalent to 9 mg)**	**Placebo**
Full analysis set (N)	175	175	178
HbA_{1c} (%)			
Baseline	8.0	8.0	7.9
Change from baseline[1]	-1.2	-1.4	-0.3
Difference from placebo[1] [95% CI]	-0.9 [-1.1; -0.6]*	-1.1 [-1.3; -0.9]*	-
Patients (%) achieving HbA_{1c} < 7.0%	69[§]	77[§]	31
FPG (mmol/L)			
Baseline	9.0	8.8	8.9
Change from baseline[1]	-1.5	-1.8	-0.2
Difference from placebo[1] [95% CI]	-1.4 [-1.9; -0.8][§]	-1.6 [-2.1; -1.2][§]	-
Body weight (kg)			
Baseline	89.0	88.1	88.6
Change from baseline[1]	-2.3	-3.7	-1.4
Difference from placebo[1] [95% CI]	-0.9 [-1.9; 0.1]	-2.3 [-3.1; -1.5]*	-

[1] Irrespective of treatment discontinuation or initiation of rescue medication (pattern mixture model using multiple imputation). [*] p< 0.001 (unadjusted 2-sided) for superiority, controlled for multiplicity. [§] p< 0.05, not controlled for multiplicity; for 'Patients achieving HbA_{1c} < 7.0%', the p-value is for the odds ratio. [2] Bioequivalence has been confirmed between 4 mg and 7 mg doses, as well as, between 9 mg and 14 mg doses, see section 5.2 Pharmacokinetic properties.

PIONEER 2 – Semaglutide vs. empagliflozin, both in combination with metformin
In a 52-week open-label trial, 822 patients with type 2 diabetes were randomised to semaglutide 14 mg once daily or empagliflozin 25 mg once daily, both in combination with metformin.

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

	Semaglutide 14 mg[2] (Bioequivalent to 9 mg)	**Empagliflozin 25 mg**
Full analysis set (N)	411	410
Week 26		
HbA_{1c} (%)		
Baseline	8.1	8.1
Change from baseline[1]	-1.3	-0.9
Difference from empagliflozin[1] [95% CI]	-0.4 [-0.6; -0.3]*	-
Patients (%) achieving HbA_{1c} < 7.0%	67[§]	40
FPG (mmol/L)		
Baseline	9.5	9.7
Change from baseline[1]	-2.0	-2.0
Difference from empagliflozin[1] [95% CI]	0.0 [-0.2; 0.3]	-
Body weight (kg)		
Baseline	91.9	91.3
Change from baseline[1]	-3.8	-3.7
Difference from empagliflozin[1] [95% CI]	-0.1 [-0.7; 0.5]	-
Week 52		
HbA_{1c} (%)		
Change from baseline[1]	-1.3	-0.9
Difference from empagliflozin[1] [95% CI]	-0.4 [-0.5; -0.3][§]	-
Patients (%) achieving HbA_{1c} < 7.0%	66[§]	43
Body weight (kg)		
Change from baseline[1]	-3.8	-3.6
Difference from empagliflozin[1] [95% CI]	-0.2 [-0.9; 0.5]	-

[1] Irrespective of treatment discontinuation or initiation of rescue medication (pattern mixture model using multiple imputation). [*] p< 0.001 (unadjusted 2-sided) for superiority, controlled for multiplicity. [§] p< 0.05, not controlled for multiplicity; for 'Patients achieving HbA_{1c} < 7.0%', the p-value is for the odds ratio. [2] Bioequivalence has been confirmed between 9 mg and 14 mg doses, see section 5.2 Pharmacokinetic properties.

PIONEER 3 – Semaglutide 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 semaglutide 3 mg, semaglutide 7 mg, semaglutide 14 mg or sitagliptin 100 mg once daily, all in combination with metformin alone or metformin and sulfonylurea. Reductions in HbA_{1c} and body weight were sustained throughout the trial duration of 78 weeks.

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

	Semaglutide 7 mg[2] (Bioequivalent to 4 mg)	**Semaglutide 14 mg[2] (Bioequivalent to 9 mg)**	**Sitagliptin 100 mg**
Full analysis set (N)	465	465	467
Week 26			
HbA_{1c} (%)			
Baseline	8.4	8.3	8.3
Change from baseline[1]	-1.0	-1.3	-0.8
Difference from sitagliptin[1] [95% CI]	-0.3 [-0.4; -0.1][*]	-0.5 [-0.6; -0.4][*]	-
Patients (%) achieving HbA_{1c} < 7.0%	44[§]	56[§]	32
FPG (mmol/L)			
Baseline	9.4	9.3	9.5
Change from baseline[1]	-1.2	-1.7	-0.9
Difference from sitagliptin[1] [95% CI]	-0.3 [-0.6; 0.0][§]	-0.8 [-1.1; -0.5][§]	-

	Semaglutide 7 mg[2] (Bioequivalent to 4 mg)	Semaglutide 14 mg[2] (Bioequivalent to 9 mg)	Sitagliptin 100 mg
Body weight (kg)			
Baseline	91.3	91.2	90.9
Change from baseline[1]	-2.2	-3.1	-0.6
Difference from sitagliptin[1] [95% CI]	-1.6 [-2.0; -1.1][*]	-2.5 [-3.0; -2.0][*]	-
Week 78			
HbA_{1c} (%)			
Change from baseline[1]	-0.8	-1.1	-0.7
Difference from sitagliptin[1] [95% CI]	-0.1 [-0.3; 0.0]	-0.4 [-0.6; -0.3][§]	-
Patients (%) achieving HbA_{1c} < 7.0%	39[§]	45[§]	29
Body weight (kg)			
Change from baseline[1]	-2.7	-3.2	-1.0
Difference from sitagliptin[1] [95% CI]	-1.7 [-2.3; -1.0][§]	-2.1 [-2.8; -1.5][§]	-

[1] Irrespective of treatment discontinuation or initiation of rescue medication (pattern mixture model using multiple imputation). [*] p< 0.001 (unadjusted 2-sided) for superiority, controlled for multiplicity. [§] p< 0.05, not controlled for multiplicity; for 'Patients achieving HbA_{1c} < 7.0%', the p-value is for the odds ratio. [2] Bioequivalence has been confirmed between 4 mg and 7 mg doses, as well as, between 9 mg and 14 mg doses, see section 5.2 Pharmacokinetic properties.

PIONEER 4 – Semaglutide 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 semaglutide 14 mg, liraglutide 1.8 mg subcutaneous injection or placebo once daily, all in combination with metformin or metformin and an SGLT2 inhibitor.

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

	Semaglutide 14 mg[2] (Bioequivalent to 9 mg)	Liraglutide 1.8 mg	Placebo
Full analysis set (N)	285	284	142
Week 26			
HbA_{1c} (%)			
Baseline	8.0	8.0	7.9
Change from baseline[1]	-1.2	-1.1	-0.2
Difference from liraglutide[1] [95% CI]	-0.1 [-0.3; 0.0]	-	-
Difference from placebo[1] [95% CI]	-1.1 [-1.2; -0.9]*	-	-
Patients (%) achieving HbA_{1c} < 7.0%	68[§,a]	62	14
FPG (mmol/L)			
Baseline	9.3	9.3	9.2
Change from baseline[1]	-2.0	-1.9	-0.4
Difference from liraglutide[1] [95% CI]	-0.1 [-0.4; 0.1]	-	-
Difference from placebo[1] [95% CI]	-1.6 [-2.0; -1.3][§]	-	-
Body weight (kg)			
Baseline	92.9	95.5	93.2
Change from baseline[1]	-4.4	-3.1	-0.5
Difference from liraglutide[1] [95% CI]	-1.2 [-1.9; -0.6]*	-	-
Difference from placebo[1] [95% CI]	-3.8 [-4.7; -3.0]*	-	-
Week 52			
HbA_{1c} (%)			
Change from baseline[1]	-1.2	-0.9	-0.2
Difference from liraglutide[1] [95% CI]	-0.3 [-0.5; -0.1][§]	-	-
Difference from placebo[1] [95% CI]	-1.0 [-1.2; -0.8][§]	-	-
Patients (%) achieving HbA_{1c} < 7.0%	61[§,a]	55	15

	Semaglutide 14 mg[2] (Bioequivalent to 9 mg)	Liraglutide 1.8 mg	Placebo
Body weight (kg)			
Change from baseline[1]	-4.3	-3.0	-1.0
Difference from liraglutide[1] [95% CI]	-1.3 [-2.1; -0.5][§]	-	-
Difference from placebo[1] [95% CI]	-3.3 [-4.3; -2.4][§]	-	-

[1] Irrespective of treatment discontinuation or initiation of rescue medication (pattern mixture model using multiple imputation). [*] p< 0.001 (unadjusted 2-sided) for superiority, controlled for multiplicity. [§] p< 0.05, not controlled for multiplicity; for 'Patients achieving HbA_{1c} < 7.0%', the p-value is for the odds ratio. [a] vs placebo. [2] Bioequivalence has been confirmed between 9 mg and 14 mg doses, see section 5.2 Pharmacokinetic properties.

PIONEER 5 – Semaglutide 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) were randomised to semaglutide 14 mg or placebo once daily. Trial product was added to the patient's stable pre-trial antidiabetic regimen.

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

	Semaglutide 14 mg[2] (Bioequivalent to 9 mg)	Placebo
Full analysis set (N)	163	161
HbA_{1c} (%)		
Baseline	8.0	7.9
Change from baseline[1]	-1.0	-0.2
Difference from placebo[1] [95% CI]	-0.8 [-1.0; -0.6][*]	-
Patients (%) achieving HbA_{1c} < 7.0%	58[§]	23
FPG (mmol/L)		
Baseline	9.1	9.1
Change from baseline[1]	-1.5	-0.4
Difference from placebo[1] [95% CI]	-1.2 [-1.7; -0.6][§]	-
Body weight (kg)		
Baseline	91.3	90.4
Change from baseline[1]	-3.4	-0.9
Difference from placebo[1] [95% CI]	-2.5 [-3.2; -1.8][*]	-

[1] Irrespective of treatment discontinuation or initiation of rescue medication (pattern mixture model using multiple imputation). [*] p< 0.001 (unadjusted 2-sided) for superiority, controlled for multiplicity. [§] p< 0.05, not controlled for multiplicity; for 'Patients achieving HbA_{1c} < 7.0%', the p-value is for the odds ratio. [2] Bioequivalence has been confirmed between 9 mg and 14 mg doses, see section 5.2 Pharmacokinetic properties.

PIONEER 7 – Semaglutide vs. sitagliptin, both in combination with metformin, SGLT2 inhibitors, sulfonylurea or thiazolidinediones. Flexible-dose-adjustment trial
In a 52-week open-label trial, 504 patients with type 2 diabetes were randomised to semaglutide (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 semaglutide 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 semaglutide were evaluated at week 52.

At week 52, the proportion of patients on treatment with semaglutide 3 mg, 7 mg and 14 mg was approximately 10%, 30% and 60%, respectively.

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

	Semaglutide Flexible dose[2]	**Sitagliptin 100 mg**
Full analysis set (N)	253	251
HbA_{1c} (%)		
Baseline	8.3	8.3
Patients (%) achieving HbA_{1c} < 7.0%[1]	58*	25
Body weight (kg)		
Baseline	88.9	88.4
Change from baseline[1]	-2.6	-0.7
Difference from sitagliptin[1] [95% CI]	-1.9 [-2.6; -1.2]*	-

[1] Irrespective of treatment discontinuation (16.6% of the patients with semaglutide flexible dose and 9.2% with sitagliptin, where 8.7% and 4.0%, respectively, were due to AEs) or initiation of rescue medication (pattern mixture model using multiple imputation). * p< 0.001 (unadjusted 2-sided) for superiority, controlled for multiplicity (for 'Patients achieving HbA_{1c} < 7.0%', the p-value is for the odds ratio). [2]Bioequivalence has been confirmed between 1.5 mg and 3 mg, between 4 mg and 7 mg and between 9 mg and 14 mg doses, see section 5.2 Pharmacokinetic properties.

PIONEER 8 – Semaglutide 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 semaglutide 3 mg, semaglutide 7 mg, semaglutide 14 mg or placebo once daily.

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

	Semaglutide 7 mg[2] (Bioequivalent to 4 mg)	**Semaglutide 14 mg[2] (Bioequivalent to 9 mg)**	**Placebo**
Full analysis set (N)	182	181	184
Week 26 (insulin dose capped to baseline level)			
HbA_{1c} (%)			
Baseline	8.2	8.2	8.2
Change from baseline[1]	-0.9	-1.3	-0.1
Difference from placebo[1] [95% CI]	-0.9 [-1.1; -0.7]*	-1.2 [-1.4; -1.0]*	-
Patients (%) achieving HbA_{1c} < 7.0%	43§	58§	7
FPG (mmol/L)			
Baseline	8.5	8.3	8.3
Change from baseline[1]	-1.1	-1.3	0.3
Difference from placebo[1] [95% CI]	-1.4 [-1.9; -0.8]§	-1.6 [-2.2; -1.1]§	-
Body weight (kg)			
Baseline	87.1	84.6	86.0
Change from baseline[1]	-2.4	-3.7	-0.4
Difference from placebo[1] [95% CI]	-2.0 [-3.0; -1.0]*	-3.3 [-4.2; -2.3]*	-
Week 52 (uncapped insulin dose)+			
HbA_{1c} (%)			
Change from baseline[1]	-0.8	-1.2	-0.2
Difference from placebo[1] [95% CI]	-0.6 [-0.8; -0.4]§	-0.9 [-1.1; -0.7]§	-
Patients (%) achieving HbA_{1c} < 7.0%	40§	54§	9
Body weight (kg)			
Change from baseline[1]	-2.0	-3.7	0.5
Difference from placebo[1] [95% CI]	-2.5 [-3.6; -1.4]§	-4.3 [-5.3; -3.2]§	-

[1] Irrespective of treatment discontinuation or initiation of rescue medication (pattern mixture model using multiple imputation). * p< 0.001 (unadjusted 2-sided) for superiority, controlled for multiplicity. § p< 0.05, not controlled for multiplicity; for 'Patients achieving HbA_{1c} < 7.0%', the p-value is for the odds ratio. + The total daily insulin dose was

statistically significantly lower with semaglutide than with placebo at week 52. [2] Bioequivalence has been confirmed between 4 mg and 7 mg doses, as well as, between 9 mg and 14 mg doses, see section 5.2 Pharmacokinetic properties.

PIONEER PLUS – Efficacy and safety of semaglutide 25 mg and 50 mg compared with semaglutide 14 mg once daily in subjects with type 2 diabetes
In a 68-week double-blinded clinical trial 1 606 patients with type 2 diabetes on stable doses of 1-3 oral anti-diabetic drugs (metformin, sulfonylureas, SGLT2 inhibitors or DPP-4 inhibitors*) were randomized to receive maintenance doses of either semaglutide 14 mg, semaglutide 25 mg or semaglutide 50 mg once daily.
*DPP-4 inhibitors were to be discontinued at randomisation.

Treatment with semaglutide 25 mg and 50 mg once daily was superior in reducing HbA_{1c} and body weight compared to semaglutide 14 mg (see Table 9). Week 68 data support a sustained effect of oral semaglutide 14 mg, 25 mg and 50 mg on HbA_{1c} and body weight (see Figure 1).

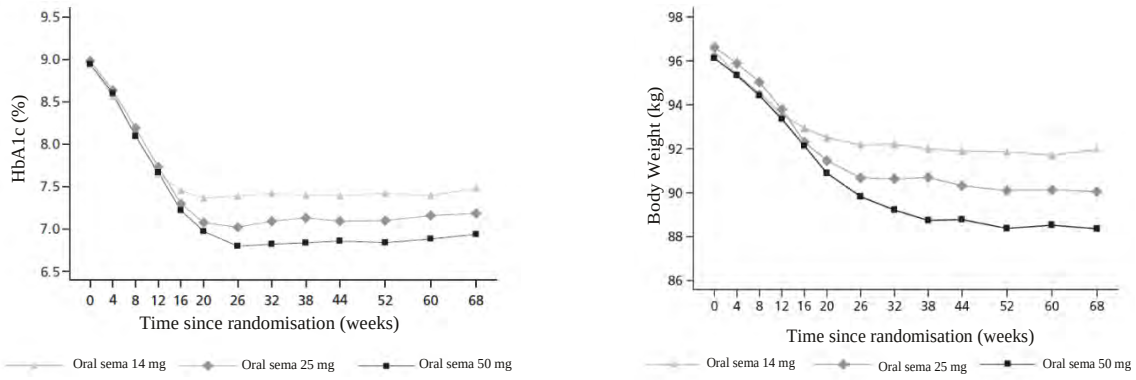


Figure 1 Mean HbA1c and mean body weight (kg) from baseline to week 68

Table 9 Results of a 52-week trial comparing semaglutide 25 mg and 50 mg with semaglutide 14 mg (PIONEER PLUS)

	Semaglutide 14 mg[2] (Bioequivalent to 9 mg)	**Semaglutide 25 mg**	**Semaglutide 50 mg**
Full analysis set (N)	536	535	535
Week 52			
HbA_{1c} (%)			
Baseline	8.9	9.0	8.9
Change from baseline[1]	-1.5	-1.8	-2.0
Difference from Rybelsus 14 mg [1] [95% CI]		-0.27 [-0.42; -0.12]*	-0.53 [-0.68: -0.38]*
Patients (%) achieving HbA_{1c} < 7.0%	39.0[§]	50.5[§]	63.0[§]
Patients (%) achieving HbA_{1c} ≤ 6.5%	25.8[§]	39.6[§]	51.2[§]
FPG (mmol/L)			
Baseline	10.8	11.0	10.8
Change from baseline[1]	-2.3	-2.8	-3.2
Difference from Rybelsus 14 mg [1] [95% CI]		-0.46 [-0.79; -0.13][§]	-0.82 [-1.15; -0.49][§]
Body weight (kg)			
Baseline	96.4	96.6	96.1
Change from baseline[1]	-4.4	-6.7	-8.0
Difference from Rybelsus 14 mg [1] [95% CI]		-2.32 [-3.11: -1.53]*	-3.63 [-4.42; -2.84]*

[1]Irrespective of treatment discontinuation or initiation of rescue medication (pattern mixture model using multiple imputation). [*] p< 0.001 (unadjusted 2-sided) for superiority, controlled for multiplicity. [§] p< 0.05, not controlled for multiplicity; for 'Patients achieving HbA_{1c} < 7.0%', the p-value is for the odds ratio. [2] Bioequivalence has been confirmed between 9 mg and 14 mg doses, see section 5.2 Pharmacokinetic properties.

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 (bioequivalent to semaglutide 9 mg) once-daily or placebo once daily added to standard of care.

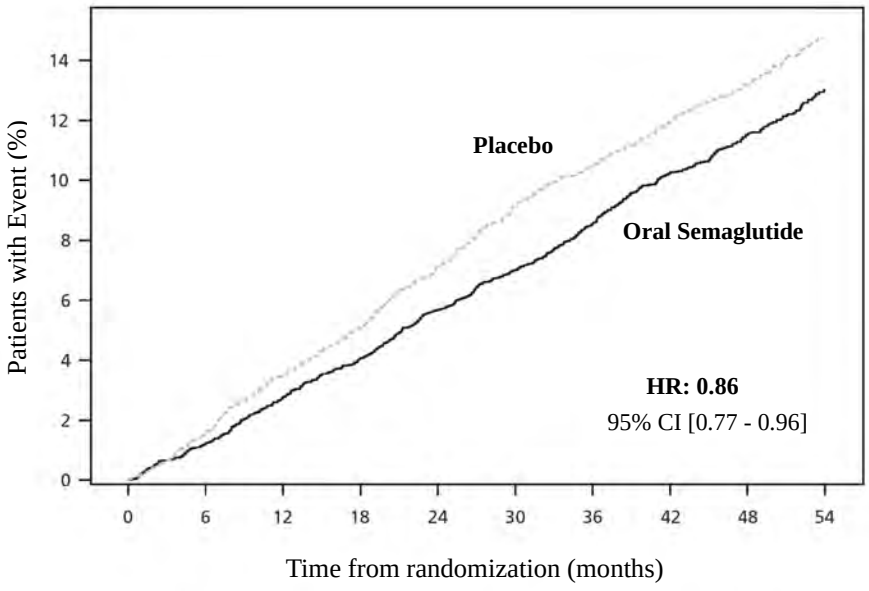
In total, 5 468 patients (56.7%) had established cardiovascular disease without chronic kidney disease, 1 241 (12.9%) had chronic kidney disease only and 2 620 (27.2%) had both cardiovascular disease and kidney disease. The mean age at baseline was 66.1 years, and 71.1% of the patients were men. The 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/1.73 m^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 Figure 2). The

reduction of MACE with semaglutide was consistent across subgroups of age, sex, race, ethnicity, BMI at baseline, or level of kidney function impairment.

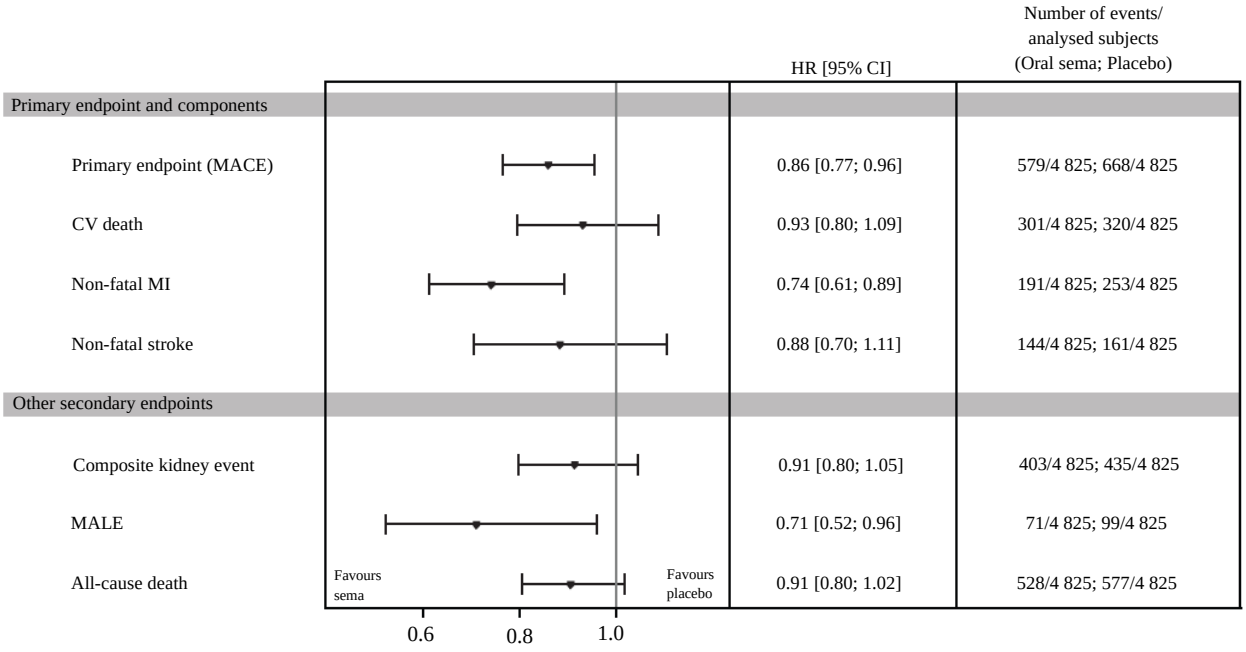
Analysis of the first composite kidney event (the first confirmatory secondary endpoint) resulted in a hazard ratio of 0.91 [0.80; 1.05] [95% CI].



Patients at risk										
Oral Semaglutide	4825	4743	4635	4542	4438	4346	4239	3831	2555	1346
Placebo	4825	4718	4583	4455	4322	4194	4101	3727	2517	1346

Data from the in-trial period and 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.
CV: cardiovascular, EAC: event adjudication committee, MACE: major adverse cardiovascular event.

Figure 2: Time from randomisation to first MACE Cumulative incidence function plot



Data from the in-trial period and 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.
Composite kidney event: endpoint consisting of cardiovascular death, kidney death, onset of persistent ≥ 50% reduction in estimated glomerular filtration rate (CKD-EPI) compared with baseline, onset of persistent eGFR (CKD-EPI) < 15 mL/min/1.73 m^2 or initiation of chronic kidney replacement therapy (dialysis or kidney transplantation).
MALE: major adverse limb events; composite endpoint consisting of acute or chronic limb ischemia hospitalisation.

Figure 3: Treatment effect for the primary endpoint, its components and other secondary endpoints (SOUL)

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

In a double-blind trial (PIONEER 6), 3 183 patients, 50 years of age or older with type 2 diabetes at high cardiovascular risk were randomised to semaglutide 14 mg (bioequivalent to semaglutide 9 mg) once daily or placebo in addition to standard-of-care. The median observation period was 16 months. PIONEER 6 was a pre−approval CVOT designed to establish CV safety.

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 total number of first MACE was 137: 61 (3.8%) with semaglutide and 76 (4.8%) with placebo. The analysis of time to first MACE resulted in a HR of 0.79 $[0.57; 1.11]_{95\% CI}$.

Body weight

By end-of-treatment, 27-65.7% of the patients had achieved a weight loss of ≥ 5% and 6-34.7% had achieved a weight loss of ≥ 10% with semaglutide, compared with 12-39% and 2-8%, respectively, with the active comparators.

In the cardiovascular outcomes trial SOUL, a reduction in body weight from baseline to week 104 was observed with semaglutide vs. placebo, in addition to standard-of-care (-4.22 kg vs. -1.27 kg).

Blood pressure

Treatment with semaglutide had reduced systolic blood pressure by 2-7 mmHg.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Rybelsus in one or more subsets of the paediatric population in type 2 diabetes (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Two formulations of the semaglutide tablets exist:
- 1.5 mg, 4 mg and 9 mg (round tablets)
- 3 mg, 7 mg and 14 mg (oval tablets)

Similar efficacy and safety can be expected for both formulations. Bioequivalent doses of the two formulations are outlined in the table below.

Table 10 Equal effect of the two oral formulations

Dose	**One round tablet**		**One oval tablet**
Starting dose	1.5 mg	Equal effect to	3 mg
Maintenance doses	4 mg	Equal effect to	7 mg
	9 mg	Equal effect to	14 mg

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.

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 approximately 1 hour post dose. Steady-state exposure was reached after 4-5 weeks of once-daily administration. In patients with type 2 diabetes, the average steady-state concentrations were approximately as listed below:
4 mg (bioequivalent to 7 mg): Average concentration was 7 nmol/L with 90% of subjects treated with semaglutide 7 mg having an average concentration between 2 and 22 nmol/L.
9 mg (bioequivalent to 14 mg): Average concentration was 15 nmol/L with 90% of subjects treated with semaglutide 14 mg having an average concentration between 4 and 45 nmol/L.
25 mg: Average concentration was 47 nmol/L with 90% of subjects treated with semaglutide 25 mg having an average concentration between 11 and 142 nmol/L.
50 mg: Average concentration was 92 nmol/L with 90% of subjects treated with semaglutide 50 mg having an average concentration between 23 and 279 nmol/L.

Systemic exposure of semaglutide increased in a dose-proportional manner.

Based on *in vitro* data, salcaprozate sodium facilitates absorption of semaglutide. The absorption of semaglutide predominantly occurs in the stomach.

The estimated bioavailability of semaglutide is approximately 1-2% following oral administration. The between-subject variability in absorption was high (coefficient of variation was approximately 100%). The estimation of the within-subject variability in bioavailability was not reliable.

Absorption of semaglutide is decreased if taken with food or large volumes of water. Different dosing schedules of semaglutide have been investigated. Studies show that longer pre- and post-dose fasting period results in higher absorption (see section 4.2).

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%).

Biotransformation

Semaglutide is metabolised through proteolytic cleavage of the peptide backbone and sequential beta-oxidation of the fatty acid sidechain. The enzyme neutral endopeptidase (NEP) is expected to be involved in the metabolism of semaglutide.

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.

Special populations

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

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, not Hispanic or Latino) had no clinically meaningful 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 40-212 kg evaluated in the clinical trials.

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 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 data from phase 3a studies.

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 with 10 consecutive days of once-daily doses of semaglutide.

Upper GI tract disease
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.

Paediatric population

Semaglutide has not been studied in paediatric patients.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated 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. No other treatment-related tumours were observed. 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 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, this mechanism is considered unlikely to be 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.

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Salcaprozate sodium
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in the original blister package in order to protect from light and moisture.
This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

Alu/Alu blisters.
Pack sizes of: 10, 30, 60, 90 and 100 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark

8. MARKETING AUTHORISATION NUMBERS

EU/1/20/1430/016
EU/1/20/1430/017
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9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 03 April 2020
Date of latest renewal: 22 November 2024

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Rybelsus 3 mg tablets
Rybelsus 7 mg tablets
Rybelsus 14 mg tablets
Rybelsus 25 mg tablets
Rybelsus 50 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Rybelsus 3 mg tablets

Each tablet contains 3 mg semaglutide*.

Rybelsus 7 mg tablets

Each tablet contains 7 mg semaglutide*.

Rybelsus 14 mg tablets

Each tablet contains 14 mg semaglutide*.

Rybelsus 25 mg tablets

Each tablet contains 25 mg semaglutide*.

Rybelsus 50 mg tablets

Each tablet contains 50 mg semaglutide*.

*human glucagon-like peptide-1 (GLP-1) analogue produced in *Saccharomyces cerevisiae* cells by recombinant DNA technology.

Excipient with known effect

Each tablet, regardless of semaglutide strength, contains 23 mg sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

Rybelsus 3 mg tablets

White to light yellow, oval shaped tablet (7.5 mm x 13.5 mm) debossed with ‘3’ on one side and ‘novo’ on the other side.

Rybelsus 7 mg tablets

White to light yellow, oval shaped tablet (7.5 mm x 13.5 mm) debossed with ‘7’ on one side and ‘novo’ on the other side.

Rybelsus 14 mg tablets

White to light yellow, oval shaped tablet (7.5 mm x 13.5 mm) debossed with ‘14’ on one side and ‘novo’ on the other side.

Rybelsus 25 mg tablets

White to light yellow, oval shaped tablet (6.8 mm x 12 mm), debossed with ‘25’ on one side and ‘novo’ on the other side.

Rybelsus 50 mg tablets

White to light yellow, oval shaped tablet (6.8 mm x 12 mm), debossed with ‘50’ on one side and ‘novo’ on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

- as monotherapy when metformin is considered inappropriate
- in combination with other medicinal products for the treatment of diabetes.

For study results with respect to combinations, effects on glycaemic control and cardiovascular events, and the populations studied, see sections 4.4, 4.5 and 5.1.

4.2 Posology and method of administration

Posology

The starting dose of semaglutide is 3 mg once daily for one month. After one month, the dose should be increased to a maintenance dose of 7 mg once daily. If needed, the dose can be escalated to the next higher dose after a minimum of one month on the current dose. The recommended single daily maintenance doses are 7 mg, 14 mg, 25 mg and 50 mg.

The maximum recommended single daily dose of semaglutide is 50 mg. Rybelsus should always be used as one tablet per day. Taking more than one tablet a day should not be done to achieve the effect of a higher dose.

Switching from subcutaneous to oral semaglutide
The effect of switching between oral and subcutaneous semaglutide cannot easily be predicted because oral semaglutide displays higher pharmacokinetic variability in absorption compared to subcutaneous semaglutide.

Patients treated with subcutaneous semaglutide 0.5 mg once weekly can be transitioned to oral semaglutide 7 mg or 14 mg once daily.
Patients treated with subcutaneous semaglutide 1 mg once weekly can be transitioned to oral semaglutide 14 mg or 25 mg once daily.
Patients treated with subcutaneous semaglutide 2 mg once weekly can be transitioned to oral semaglutide 25 mg or 50 mg once daily.
Patients can start oral semaglutide (Rybelsus) one week after their last dose of subcutaneous semaglutide.

When semaglutide 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 semaglutide is used in combination with a sulfonylurea or with insulin, a reduction in the dose of sulfonylurea or insulin may be considered to reduce the risk of hypoglycaemia (see sections 4.4 and 4.8).

Self-monitoring of blood glucose is not needed in order to adjust the dose of semaglutide. Blood glucose self-monitoring is necessary to adjust the dose of sulfonylurea and insulin, particularly when semaglutide is started and insulin is reduced. A stepwise approach to insulin reduction is recommended.

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

Elderly
No dose adjustment is required based on age.

Renal impairment
No dose adjustment is required for patients with mild, moderate or severe renal impairment. Experience with the use of semaglutide in patients with end-stage kidney disease is limited. Caution should be exercised when treating these patients with oral semaglutide (see section 5.2).

Hepatic impairment
No dose adjustment is required for patients with hepatic impairment. Experience with the use of semaglutide in patients with severe hepatic impairment is limited. Caution should be exercised when treating these patients with semaglutide (see section 5.2).

Paediatric population

The safety and efficacy of Rybelsus in children and adolescents below 18 years have not been established. No data are available.

Method of administration

Rybelsus is a tablet for once-daily oral use.

- This medicinal product should be taken on an empty stomach after a recommended fasting period of at least 8 hours (see section 5.2).
- It should be swallowed whole with a sip of water (up to half a glass of water equivalent to 120 mL). Tablets should not be split, crushed or chewed, as it is not known whether this impacts absorption of semaglutide.
- Patients should wait at least 30 minutes before eating, drinking or taking other oral medicinal products. Waiting less than 30 minutes decreases the absorption of semaglutide (see sections 4.5 and 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

General

Semaglutide 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 who had rapid discontinuation or dose reduction of insulin when treatment with a GLP-1 receptor agonist is started (see section 4.2).

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

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

Aspiration in association with general anaesthesia or deep sedation

Cases of pulmonary aspiration have been reported in patients receiving GLP-1 receptor agonists undergoing general anaesthesia or deep sedation. Therefore, the increased risk of residual gastric content due to delayed gastric emptying (see section 4.8) should be considered prior to performing procedures with general anaesthesia or deep sedation.

Gastrointestinal effects and dehydration

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 (see section 4.8). 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, semaglutide should be discontinued; if confirmed, semaglutide should not be restarted.

Hypoglycaemia

Patients treated with semaglutide in combination with a sulfonylurea or insulin may have an increased risk of hypoglycaemia (see section 4.8). The risk of hypoglycaemia can be lowered by reducing the dose of sulfonylurea or insulin when initiating treatment with semaglutide (see section 4.2).

Diabetic retinopathy

In patients with diabetic retinopathy treated with insulin and subcutaneous semaglutide, an increased risk of developing diabetic retinopathy complications has been observed, a risk that cannot be excluded for orally administered semaglutide (see section 4.8). Caution should be exercised when using semaglutide in patients with diabetic retinopathy. These patients should be monitored closely and treated according to clinical guidelines. Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy, but other mechanisms cannot be excluded. Long-term glycaemic control decreases the risk of diabetic retinopathy.

There is no experience with oral semaglutide 25 mg and 50 mg in patients with type 2 diabetes with uncontrolled or potentially unstable diabetic retinopathy.

Non-arteritic anterior ischaemic optic neuropathy (NAION)

Data from epidemiological studies indicates an increased risk for non-arteritic anterior ischaemic optic neuropathy (NAION) during treatment with semaglutide. There is no identified time interval for when NAION may develop following treatment start. A sudden loss of vision should lead to ophthalmological examination and treatment with semaglutide should be discontinued if NAION is confirmed (see section 4.8).

Treatment response

Compliance with the dosing regimen is recommended for optimal effect of semaglutide. If the treatment response with semaglutide is lower than expected, the treating physician should be aware that the absorption of semaglutide is highly variable and may be minimal (2-4% of patients will not have any exposure), and that the absolute bioavailability of semaglutide is low.

Sodium content

This medicinal product contains 23 mg sodium per tablet, equivalent to 1% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

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

Effects of semaglutide on other medicinal products

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

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.

Rosuvastatin
AUC of rosuvastatin was increased by 41% [90% CI: 24;60] when co-administered with semaglutide. Based on the wide therapeutic index of rosuvastatin the magnitude of changes in the exposure is not considered clinically relevant.

Digoxin, oral contraceptives, metformin, furosemide
No clinically relevant change in AUC or C_{max} of digoxin, oral contraceptives (containing ethinylestradiol and levonorgestrel), metformin or furosemide was observed when concurrently administered with semaglutide.

Interactions with medicinal products with very low bioavailability (1%) have not been evaluated.

Effects of other medicinal products on semaglutide

Omeprazole
No clinically relevant change in AUC or C_{max} of semaglutide was observed when taken with omeprazole.

In a trial investigating the pharmacokinetics of semaglutide co-administered with five other tablets, the AUC of semaglutide decreased by 34% and C_{max} by 32%. This suggests that the presence of multiple tablets in the stomach influences the absorption of semaglutide if co-administered at the same time. After administering semaglutide, the patients should wait 30 minutes before taking other oral medicinal products (see section 4.2).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential have to use effective contraception during treatment with semaglutide.

Pregnancy

Studies in animals have shown reproductive toxicity (see section 5.3). There are limited data from the use of semaglutide in pregnant women. Therefore, semaglutide should not be used during pregnancy. If a patient wishes to become pregnant, or pregnancy occurs, semaglutide should be discontinued. Semaglutide should be discontinued at least 2 months before a planned pregnancy due to the long half-life (see section 5.2).

Breast-feeding

No measurable concentrations of semaglutide were found in breast milk of lactating women. Salcaprozate sodium was present in breast milk and some of its metabolites were excreted in breast milk 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 section 5.3).

4.7 Effects on ability to drive and use machines

Semaglutide has no or negligible influence on the ability to drive and use machines. However, dizziness can be experienced mainly during dose escalation. Driving or use of machines should be done cautiously if dizziness occurs.

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 section 4.4).

4.8 Undesirable effects

Summary of the safety profile

In 10 phase 3a trials, 5 707 patients were exposed to semaglutide 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 (very common), diarrhoea (very common) and vomiting (common).

Tabulated list of adverse reactions

Table 1 lists adverse reactions identified in phase 3 trials (further described in section 5.1) and post-marketing reports in patients with type 2 diabetes mellitus. The frequencies of the adverse reactions (except diabetic retinopathy complications and dysaesthesia, see footnotes in Table 1) 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) and very rare: (< 1/10 000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1 Frequency of adverse reactions of oral semaglutide

MedDRA system organ class	**Very common**	**Common**	**Uncommon**	**Rare**	**Very Rare**	**Not known**
Immune system disorders			Hypersensitivity[c]	Anaphylactic reaction		
Metabolism and nutrition disorders	Hypoglycaemia when used with insulin or sulfonylurea[a]	Hypoglycaemia when used with other oral antidiabetic products[a] Decreased appetite				
Nervous system disorders		Dizziness Dysaesthesia[e] Headache	Dysgeusia			
Eye disorders		Diabetic retinopathy complications[b]			Non-arteritic anterior ischaemic optic neuropathy (NAION)	
Cardiac disorders			Increased heart rate			
Gastrointestinal disorders	Nausea Diarrhoea	Vomiting Abdominal pain Abdominal distension Constipation Dyspepsia Gastritis Gastro-oesophageal reflux disease Flatulence	Eructation Delayed gastric emptying	Acute pancreatitis		Intestinal obstruction[d,f]
Hepatobiliary disorders			Cholelithiasis			
General disorders		Fatigue				

MedDRA system organ class	Very common	Common	Uncommon	Rare	Very Rare	Not known
and administration site conditions						
Investigations		Increased lipase Increased amylase	Weight decreased			

[a)] Hypoglycaemia defined as blood glucose < 3.0 mmol/L or < 54 mg/dL.
[b)] Diabetic retinopathy complications are 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 subcutaneous semaglutide, but it cannot be excluded that the risk of diabetic retinopathy complications identified also applies to Rybelsus.
[c)] Grouped term covering also adverse events related to hypersensitivity such as rash and urticaria.
[d)] From post-marketing reports.
[e)] The frequency is based on the PIONEER PLUS trial results for 25 mg and 50 mg. Please refer to dysaesthesia subheading below for more information.
[f)] Grouped term covering PTs 'intestinal obstruction', 'ileus', 'small intestinal obstruction'.

Description of selected adverse reactions

Hypoglycaemia
Severe hypoglycaemia was primarily observed when semaglutide 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 semaglutide in combination with oral antidiabetics other than sulfonylurea.

Gastrointestinal adverse reactions
Nausea occurred in 15%, diarrhoea in 10%, and vomiting in 7% of patients when treated with semaglutide. 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 on treatment.

In PIONEER PLUS when treated with semaglutide 25 mg and 50 mg nausea occurred in 27% and 27%, diarrhoea in 13% and 14%, and vomiting in 17% and 18% of patients, respectively. These events led to treatment discontinuation in 6% and 8% of patients, respectively.

Most events were mild to moderate in severity and of short duration. The events were most frequently reported during dose escalation the first months on treatment.

Acute pancreatitis confirmed by adjudication has been reported in phase 3a trials, semaglutide (< 0.1%) and comparator (0.2%). In the cardiovascular outcomes trial PIONEER 6 the frequency of acute pancreatitis confirmed by adjudication was 0.1% for semaglutide and 0.2% for placebo (see section 4.4.). 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.

Diabetic retinopathy complications
A 2-year clinical trial with subcutaneous semaglutide investigated 3 297 patients with type 2 diabetes, with high cardiovascular risk, long duration of diabetes and poorly controlled blood glucose. In this trial, adjudicated events of diabetic retinopathy complications occurred in more patients treated with subcutaneous semaglutide (3.0%) compared to placebo (1.8%). This was observed in insulin-treated patients with known diabetic retinopathy. The treatment difference appeared early and persisted throughout the trial. Systematic evaluation of diabetic retinopathy complication was only performed in the cardiovascular outcomes trial with subcutaneous semaglutide. 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%).

Non-arteritic anterior ischaemic optic neuropathy (NAION)
Results from several large epidemiological studies suggest that exposure to semaglutide in adults with type 2 diabetes is associated with an approximately two-fold increase in the relative risk of developing NAION, corresponding to approximately one additional case per 10 000 person-years of treatment.

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 tested positive for anti-semaglutide antibodies at any time point after baseline was low (0.5%) and no subjects had neutralising anti-semaglutide antibodies or anti-semaglutide antibodies with neutralising effect on endogenous GLP-1 at end-of-trial.

Heart rate increase
Increased heart rate has been observed with GLP-1 receptor agonists. In the phase 3a trials, mean changes of 0 to 4 beats per minute (bpm) from a baseline of 69 to 76 were observed in patients treated with Rybelsus.

Dysaesthesia
Events related to a clinical picture of altered skin sensation such as paraesthesia, pain of skin, sensitive skin, dysaesthesia and burning skin sensation were reported in 2.1% and 5.2% of patients treated with oral semaglutide 25 mg and 50 mg, respectively. The events were mild to moderate in severity and most patients recovered while on continued treatment.

Reporting of suspected adverse reactions

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 suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 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. A prolonged period of observation and treatment of the symptoms may be necessary, taking into account the long half-life of semaglutide of approximately 1 week (see section 5.2). There is no specific antidote for overdose with semaglutide.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, Glucagon-like peptide-1 (GLP-1) analogues, ATC code: A10BJ06

Mechanism of action

Semaglutide is a GLP-1 analogue with 94% sequence homology to human GLP-1. Semaglutide acts as a GLP-1 receptor agonist that selectively binds to and activates the GLP-1 receptor, the target for native GLP-1.

GLP-1 is a physiological hormone that has multiple actions in glucose and appetite regulation, and in the cardiovascular system. The glucose and appetite effects are specifically mediated via GLP-1 receptors in the pancreas and the brain.

Semaglutide reduces blood glucose in a glucose-dependent manner by stimulating insulin secretion and lowering glucagon secretion when blood glucose is high. The mechanism of blood glucose lowering also involves a minor delay in gastric emptying in the early postprandial phase. During hypoglycaemia, semaglutide diminishes insulin secretion and does not impair glucagon secretion. The mechanism of semaglutide is independent of the route of administration.

Semaglutide reduces body weight and body fat mass through lowered energy intake, involving an overall reduced appetite. In addition, semaglutide reduces the preference for high fat foods.

GLP-1 receptors are expressed in the heart, vasculature, immune system and kidneys. Semaglutide has a beneficial effect on plasma lipids, lowers systolic blood pressure and reduces inflammation in clinical studies. In animal studies, semaglutide attenuates the development of atherosclerosis by preventing aortic plaque progression and reducing inflammation in the plaque.

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 reductions in hsCRP. The exact mechanism of cardiovascular risk reduction has not been established.

Pharmacodynamic effects

The pharmacodynamic evaluations described below were performed with orally administered semaglutide after 12 weeks of treatment.

Fasting and postprandial glucose
Semaglutide reduces fasting and postprandial glucose concentrations. In patients with type 2 diabetes, treatment with semaglutide resulted in a relative reduction compared to placebo of 22% [13; 30] for fasting glucose and 29% [19; 37] for postprandial glucose.

Glucagon secretion
Semaglutide lowers the postprandial glucagon concentrations. In patients with type 2 diabetes, semaglutide resulted in the following relative reductions in glucagon compared to placebo: postprandial glucagon response of 29% [15; 41].

Gastric emptying
Semaglutide causes a minor delay in early postprandial gastric emptying, with paracetamol exposure ($AUC_{0\text{-}1h}$) 31% [13; 46] lower in the first hour after the meal, thereby reducing the rate at which glucose appears in the circulation postprandially.

Fasting and postprandial lipids
Semaglutide compared to placebo lowered fasting triglyceride and very-low-density lipoproteins (VLDL) cholesterol concentrations by 19% [8; 28] and 20% [5; 33], respectively. The postprandial triglyceride and VLDL cholesterol response to a high fat meal was reduced by 24% [9; 36] and 21% [7; 32], respectively. ApoB48 was reduced both in fasting and postprandial state by 25% [2; 42] and 30% [15; 43], respectively.

Clinical efficacy and safety

The efficacy and safety of Rybelsus have been evaluated in eight global randomised controlled phase 3a trials. Phase 3a studies were conducted with tablets containing 3 mg, 7 mg and 14 mg semaglutide which are bioequivalent to 1.5 mg, 4 mg and 9 mg semaglutide, respectively. In seven trials, the

primary objective was the assessment of the glycaemic efficacy; in one trial (PIONEER 6), the primary objective was the assessment of cardiovascular outcomes.

The trials included 8 842 randomised patients with type 2 diabetes (5 169 treated with semaglutide), including 1 165 patients with moderate renal impairment. Patients had an average age of 61 years (range 18 to 92 years), with 40% of patients ≥ 65 years of age and 8% ≥ 75 years of age. The efficacy of semaglutide was compared with placebo or active controls (sitagliptin, empagliflozin and liraglutide).

The efficacy and safety of semaglutide 25 mg and 50 mg once daily was evaluated in a phase 3b trial (PIONEER PLUS) including 1 606 randomised patients.

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 semaglutide was not impacted by baseline age, gender, race, ethnicity, body weight, BMI, diabetes duration, upper gastrointestinal disease 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 semaglutide 3 mg, semaglutide 7 mg, semaglutide 14 mg or placebo once daily.

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

	Semaglutide 7 mg	**Semaglutide 14 mg**	**Placebo**
Full analysis set (N)	175	175	178
HbA_{1c} (%)			
Baseline	8.0	8.0	7.9
Change from baseline[1]	-1.2	-1.4	-0.3
Difference from placebo[1] [95% CI]	-0.9 [-1.1; -0.6]*	-1.1 [-1.3; -0.9]*	-
Patients (%) achieving HbA_{1c} < 7.0%	69[§]	77[§]	31
FPG (mmol/L)			
Baseline	9.0	8.8	8.9
Change from baseline[1]	-1.5	-1.8	-0.2
Difference from placebo[1] [95% CI]	-1.4 [-1.9; -0.8][§]	-1.6 [-2.1; -1.2][§]	-
Body weight (kg)			
Baseline	89.0	88.1	88.6
Change from baseline[1]	-2.3	-3.7	-1.4
Difference from placebo[1] [95% CI]	-0.9 [-1.9; 0.1]	-2.3 [-3.1; -1.5]*	-

[1] Irrespective of treatment discontinuation or initiation of rescue medication (pattern mixture model using multiple imputation). * p< 0.001 (unadjusted 2-sided) for superiority, controlled for multiplicity. § p< 0.05, not controlled for multiplicity; for 'Patients achieving HbA_{1c} < 7.0%', the p-value is for the odds ratio.

PIONEER 2 – Semaglutide vs. empagliflozin, both in combination with metformin
In a 52-week open-label trial, 822 patients with type 2 diabetes were randomised to semaglutide 14 mg once daily or empagliflozin 25 mg once daily, both in combination with metformin.

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

	Semaglutide 14 mg	**Empagliflozin 25 mg**
Full analysis set (N)	411	410
Week 26		
HbA_{1c} (%)		
Baseline	8.1	8.1
Change from baseline[1]	-1.3	-0.9
Difference from empagliflozin[1] [95% CI]	-0.4 [-0.6; -0.3]*	-
Patients (%) achieving HbA_{1c} < 7.0%	67§	40
FPG (mmol/L)		
Baseline	9.5	9.7
Change from baseline[1]	-2.0	-2.0
Difference from empagliflozin[1] [95% CI]	0.0 [-0.2; 0.3]	-
Body weight (kg)		
Baseline	91.9	91.3
Change from baseline[1]	-3.8	-3.7
Difference from empagliflozin[1] [95% CI]	-0.1 [-0.7; 0.5]	-
Week 52		
HbA_{1c} (%)		
Change from baseline[1]	-1.3	-0.9
Difference from empagliflozin[1] [95% CI]	-0.4 [-0.5; -0.3]§	-
Patients (%) achieving HbA_{1c} < 7.0%	66§	43
Body weight (kg)		
Change from baseline[1]	-3.8	-3.6
Difference from empagliflozin[1] [95% CI]	-0.2 [-0.9; 0.5]	-

[1] Irrespective of treatment discontinuation or initiaton of rescue medicaton (pattern mixture model using multiple imputation). * p< 0.001 (unadjusted 2-sided) for superiority, controlled for multiplicity. § p< 0.05, not controlled for multiplicity; for 'Patients achieving HbA_{1c} < 7.0%', the p-value is for the odds ratio.

PIONEER 3 – Semaglutide 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 semaglutide 3 mg, semaglutide 7 mg, semaglutide 14 mg or sitagliptin 100 mg once daily, all in combination with metformin alone or metformin and sulfonylurea. Reductions in HbA_{1c} and body weight were sustained throughout the trial duration of 78 weeks.

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

	Semaglutide 7 mg	**Semaglutide 14 mg**	**Sitagliptin 100 mg**
Full analysis set (N)	465	465	467
Week 26			
HbA_{1c} (%)			
Baseline	8.4	8.3	8.3
Change from baseline[1]	-1.0	-1.3	-0.8
Difference from sitagliptin[1] [95% CI]	-0.3 [-0.4; -0.1]*	-0.5 [-0.6; -0.4]*	-
Patients (%) achieving HbA_{1c} < 7.0%	44§	56§	32
FPG (mmol/L)			
Baseline	9.4	9.3	9.5
Change from baseline[1]	-1.2	-1.7	-0.9
Difference from sitagliptin[1] [95% CI]	-0.3 [-0.6; 0.0]§	-0.8 [-1.1; -0.5]§	-

	Semaglutide 7 mg	Semaglutide 14 mg	Sitagliptin 100 mg
Body weight (kg)			
Baseline	91.3	91.2	90.9
Change from baseline[1]	-2.2	-3.1	-0.6
Difference from sitagliptin[1] [95% CI]	-1.6 [-2.0; -1.1][*]	-2.5 [-3.0; -2.0][*]	-
Week 78			
HbA_{1c} (%)			
Change from baseline[1]	-0.8	-1.1	-0.7
Difference from sitagliptin[1] [95% CI]	-0.1 [-0.3; 0.0]	-0.4 [-0.6; -0.3][§]	-
Patients (%) achieving HbA_{1c} < 7.0%	39[§]	45[§]	29
Body weight (kg)			
Change from baseline[1]	-2.7	-3.2	-1.0
Difference from sitagliptin[1] [95% CI]	-1.7 [-2.3; -1.0][§]	-2.1 [-2.8; -1.5][§]	-

[1] Irrespective of treatment discontinuation or initiation of rescue medication (pattern mixture model using multiple imputation). [*] p< 0.001 (unadjusted 2-sided) for superiority, controlled for multiplicity. [§] p< 0.05, not controlled for multiplicity; for 'Patients achieving HbA_{1c} < 7.0%', the p-value is for the odds ratio.

PIONEER 4 – Semaglutide 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 semaglutide 14 mg, liraglutide 1.8 mg subcutaneous injection or placebo once daily, all in combination with metformin or metformin and an SGLT2 inhibitor.

Table 5 Results of a 52-week trial comparing semaglutide with liraglutide and placebo (PIONEER4)

	Semaglutide 14 mg	Liraglutide 1.8 mg	Placebo
Full analysis set (N)	285	284	142
Week 26			
HbA_{1c} (%)			
Baseline	8.0	8.0	7.9
Change from baseline[1]	-1.2	-1.1	-0.2
Difference from liraglutide[1] [95% CI]	-0.1 [-0.3; 0.0]	-	-
Difference from placebo[1] [95% CI]	-1.1 [-1.2; -0.9]*	-	-
Patients (%) achieving HbA_{1c} < 7.0%	68[§,a]	62	14
FPG (mmol/L)			
Baseline	9.3	9.3	9.2
Change from baseline[1]	-2.0	-1.9	-0.4
Difference from liraglutide[1] [95% CI]	-0.1 [-0.4; 0.1]	-	-
Difference from placebo[1] [95% CI]	-1.6 [-2.0; -1.3][§]	-	-
Body weight (kg)			
Baseline	92.9	95.5	93.2
Change from baseline[1]	-4.4	-3.1	-0.5
Difference from liraglutide[1] [95% CI]	-1.2 [-1.9; -0.6]*	-	-
Difference from placebo[1] [95% CI]	-3.8 [-4.7; -3.0]*	-	-
Week 52			
HbA_{1c} (%)			
Change from baseline[1]	-1.2	-0.9	-0.2
Difference from liraglutide[1] [95% CI]	-0.3 [-0.5; -0.1][§]	-	-
Difference from placebo[1] [95% CI]	-1.0 [-1.2; -0.8][§]	-	-
Patients (%) achieving HbA_{1c} < 7.0%	61[§,a]	55	15
Body weight (kg)			
Change from baseline[1]	-4.3	-3.0	-1.0

	Semaglutide 14 mg	Liraglutide 1.8 mg	Placebo
Difference from liraglutide[1] [95% CI]	-1.3 [-2.1; -0.5][§]	-	-
Difference from placebo[1] [95% CI]	-3.3 [-4.3; -2.4][§]	-	-

[1] Irrespective of treatment discontinuation or initiation of rescue medication (pattern mixture model using multiple imputation). [*] p< 0.001 (unadjusted 2-sided) for superiority, controlled for multiplicity. [§] p< 0.05, not controlled for multiplicity; for 'Patients achieving HbA_{1c} < 7.0%', the p-value is for the odds ratio. [a] vs placebo.

PIONEER 5 – Semaglutide 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) were randomised to semaglutide 14 mg or placebo once daily. Trial product was added to the patient's stable pre-trial antidiabetic regimen.

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

	Semaglutide 14 mg	Placebo
Full analysis set (N)	163	161
HbA_{1c} (%)		
Baseline	8.0	7.9
Change from baseline[1]	-1.0	-0.2
Difference from placebo[1] [95% CI]	-0.8 [-1.0; -0.6][*]	-
Patients (%) achieving HbA_{1c} < 7.0%	58[§]	23
FPG (mmol/L)		
Baseline	9.1	9.1
Change from baseline[1]	-1.5	-0.4
Difference from placebo[1] [95% CI]	-1.2 [-1.7; -0.6][§]	-
Body weight (kg)		
Baseline	91.3	90.4
Change from baseline[1]	-3.4	-0.9
Difference from placebo[1] [95% CI]	-2.5 [-3.2; -1.8][*]	-

[1] Irrespective of treatment discontinuation or initiation of rescue medication (pattern mixture model using multiple imputation). [*] p< 0.001 (unadjusted 2-sided) for superiority, controlled for multiplicity. [§] p< 0.05, not controlled for multiplicity; for 'Patients achieving HbA_{1c} < 7.0%', the p-value is for the odds ratio.

PIONEER 7 – Semaglutide vs. sitagliptin, both in combination with metformin, SGLT2 inhibitors, sulfonylurea or thiazolidinediones. Flexible-dose-adjustment trial
In a 52-week open-label trial, 504 patients with type 2 diabetes were randomised to semaglutide (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 semaglutide 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 semaglutide were evaluated at week 52.

At week 52, the proportion of patients on treatment with semaglutide 3 mg, 7 mg and 14 mg was approximately 10%, 30% and 60%, respectively.

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

	Semaglutide Flexible dose	**Sitagliptin 100 mg**
Full analysis set (N)	253	251
HbA_{1c} (%)		
Baseline	8.3	8.3
Patients (%) achieving HbA_{1c} < 7.0%[1]	58*	25
Body weight (kg)		
Baseline	88.9	88.4
Change from baseline[1]	-2.6	-0.7
Difference from sitagliptin[1] [95% CI]	-1.9 [-2.6; -1.2]*	-

[1] Irrespective of treatment discontinuation (16.6% of the patients with semaglutide flexible dose and 9.2% with sitagliptin, where 8.7% and 4.0%, respectively, were due to AEs) or initiation of rescue medication (pattern mixture model using multiple imputation). * p< 0.001 (unadjusted 2-sided) for superiority, controlled for multiplicity (for 'Patients achieving HbA_{1c} < 7.0%', the p-value is for the odds ratio).

PIONEER 8 – Semaglutide 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 semaglutide 3 mg, semaglutide 7 mg, semaglutide 14 mg or placebo once daily.

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

	Semaglutide 7 mg	**Semaglutide 14 mg**	**Placebo**
Full analysis set (N)	182	181	184
Week 26 (insulin dose capped to baseline level)			
HbA_{1c} (%)			
Baseline	8.2	8.2	8.2
Change from baseline[1]	-0.9	-1.3	-0.1
Difference from placebo[1] [95% CI]	-0.9 [-1.1; -0.7]*	-1.2 [-1.4; -1.0]*	-
Patients (%) achieving HbA_{1c} < 7.0%	43§	58§	7
FPG (mmol/L)			
Baseline	8.5	8.3	8.3
Change from baseline[1]	-1.1	-1.3	0.3
Difference from placebo[1] [95% CI]	-1.4 [-1.9; -0.8]§	-1.6 [-2.2; -1.1]§	-
Body weight (kg)			
Baseline	87.1	84.6	86.0
Change from baseline[1]	-2.4	-3.7	-0.4
Difference from placebo[1] [95% CI]	-2.0 [-3.0; -1.0]*	-3.3 [-4.2; -2.3]*	-
Week 52 (uncapped insulin dose)+			
HbA_{1c} (%)			
Change from baseline[1]	-0.8	-1.2	-0.2
Difference from placebo[1] [95% CI]	-0.6 [-0.8; -0.4]§	-0.9 [-1.1; -0.7]§	-
Patients (%) achieving HbA_{1c} < 7.0%	40§	54§	9
Body weight (kg)			
Change from baseline[1]	-2.0	-3.7	0.5
Difference from placebo[1] [95% CI]	-2.5 [-3.6; -1.4]§	-4.3 [-5.3; -3.2]§	-

[1] Irrespective of treatment discontinuation or initiation of rescue medication (pattern mixture model using multiple imputation). * p< 0.001 (unadjusted 2-sided) for superiority, controlled for multiplicity. § p< 0.05, not controlled for multiplicity; for 'Patients achieving HbA_{1c} < 7.0%', the p-value is for the odds ratio. + The total daily insulin dose was statistically significantly lower with semaglutide than with placebo at week 52.

PIONEER PLUS – Efficacy and safety of semaglutide 25 mg and 50 mg compared with semaglutide 14 mg once daily in subjects with type 2 diabetes
In a 68-week double-blinded clinical trial 1 606 patients with type 2 diabetes on stable doses of 1-3 oral anti-diabetic drugs (metformin, sulfonylureas, SGLT2 inhibitors or DPP-4 inhibitors*) were randomized to receive maintenance doses of either semaglutide 14 mg, semaglutide 25 mg or semaglutide 50 mg once daily.
*DPP-4 inhibitors were to be discontinued at randomisation.

Treatment with semaglutide 25 mg and 50 mg once daily was superior in reducing HbA_{1c} and body weight compared to semaglutide 14 mg (see Table 9). Week 68 data support a sustained effect of oral semaglutide 14 mg, 25 mg and 50 mg on HbA_{1c} and body weight (see Figure 1).

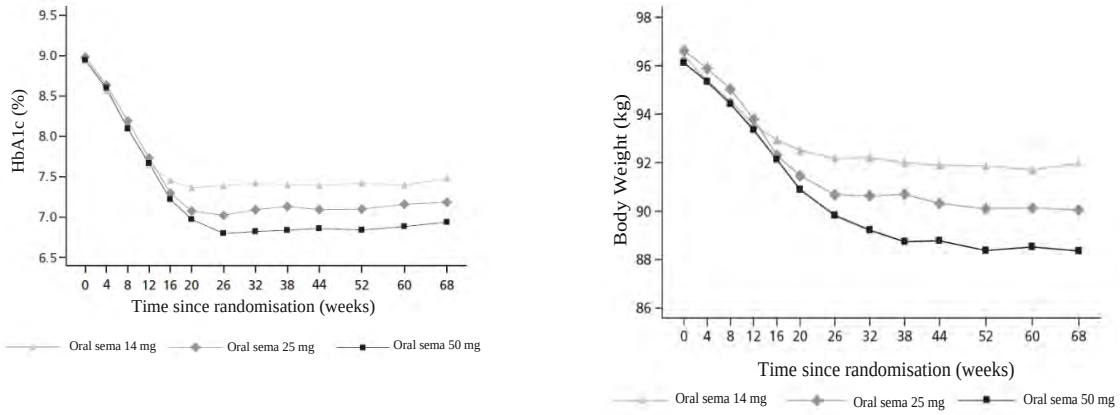


Figure 1 Mean HbA1c and mean body weight (kg) from baseline to week 68

Table 9 Results of a 52-week trial comparing semaglutide 25 mg and 50 mg with semaglutide 14 mg (PIONEER PLUS)

	Semaglutide 14 mg[2] (Bioequivalent to 9 mg)	**Semaglutide 25 mg**	**Semaglutide 50 mg**
Full analysis set (N)	536	535	535
Week 52			
HbA_{1c} (%)			
Baseline	8.9	9.0	8.9
Change from baseline[1]	-1.5	-1.8	-2.0
Difference from Rybelsus 14 mg[1] [95% CI]		-0.27 [-0.42; -0.12]*	-0.53 [-0.68: -0.38]*
Patients (%) achieving HbA_{1c} < 7.0%	39.0§	50.5§	63.0§
Patients (%) achieving $HbA_{1c} \leq 6.5\%$	25.8§	39.6§	51.2§
FPG (mmol/L)			
Baseline	10.8	11.0	10.8
Change from baseline[1]	-2.3	-2.8	-3.2
Difference from Rybelsus 14 mg[1] [95% CI]		-0.46 [-0.79; -0.13]§	-0.82 [-1.15; -0.49]§
Body weight (kg)			
Baseline	96.4	96.6	96.1
Change from baseline[1]	-4.4	-6.7	-8.0
Difference from Rybelsus 14 mg[1] [95% CI]		-2.32 [-3.11: -1.53]*	-3.63 [-4.42; -2.84]*

[1]Irrespective of treatment discontinuation or initiation of rescue medication (pattern mixture model using multiple imputation). * p< 0.001 (unadjusted 2-sided) for superiority, controlled for multiplicity. § p< 0.05, not controlled for

multiplicity; for 'Patients achieving HbA_{1c} < 7.0%', the p-value is for the odds ratio. [2] Bioequivalence has been confirmed between 9 mg and 14 mg doses, see section 5.2 Pharmacokinetic properties.

Cardiovascular outcomes

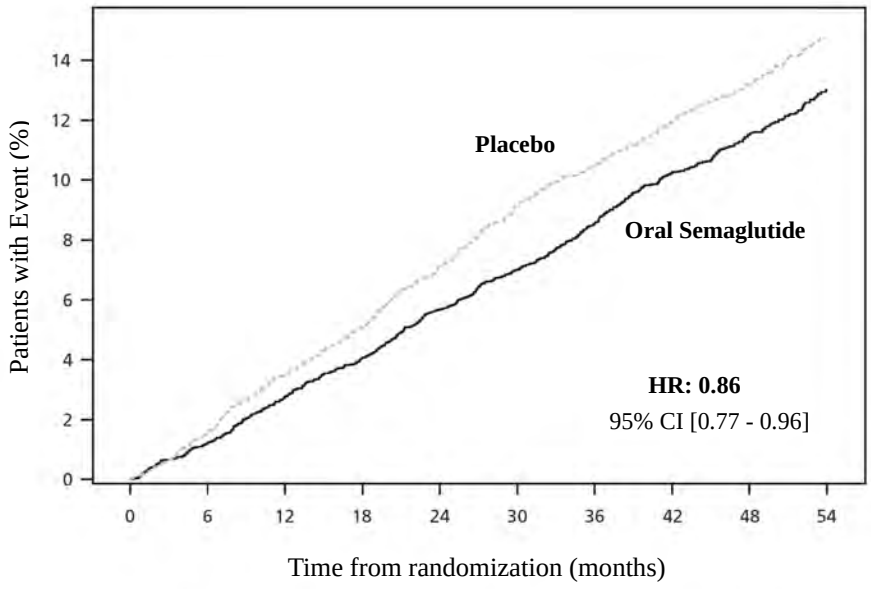
SOUL: Cardiovascular outcomes trial in patients with type 2 diabetes
In a double-blind, placebo-controlled, event driven trial, 9 650 patients, 50 years of age or older with type 2 diabetes at high cardiovascular risk, defined as having established cardiovascular disease and/or chronic kidney disease, 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 HbA1c was 8.0%, the mean BMI was 31.1 kg/m^2, and the mean eGFR was 73.8 ml/min/1.73 m^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 Figure 2). The reduction of MACE with semaglutide was consistent across subgroups of age, sex, race, ethnicity, BMI at baseline, or 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].

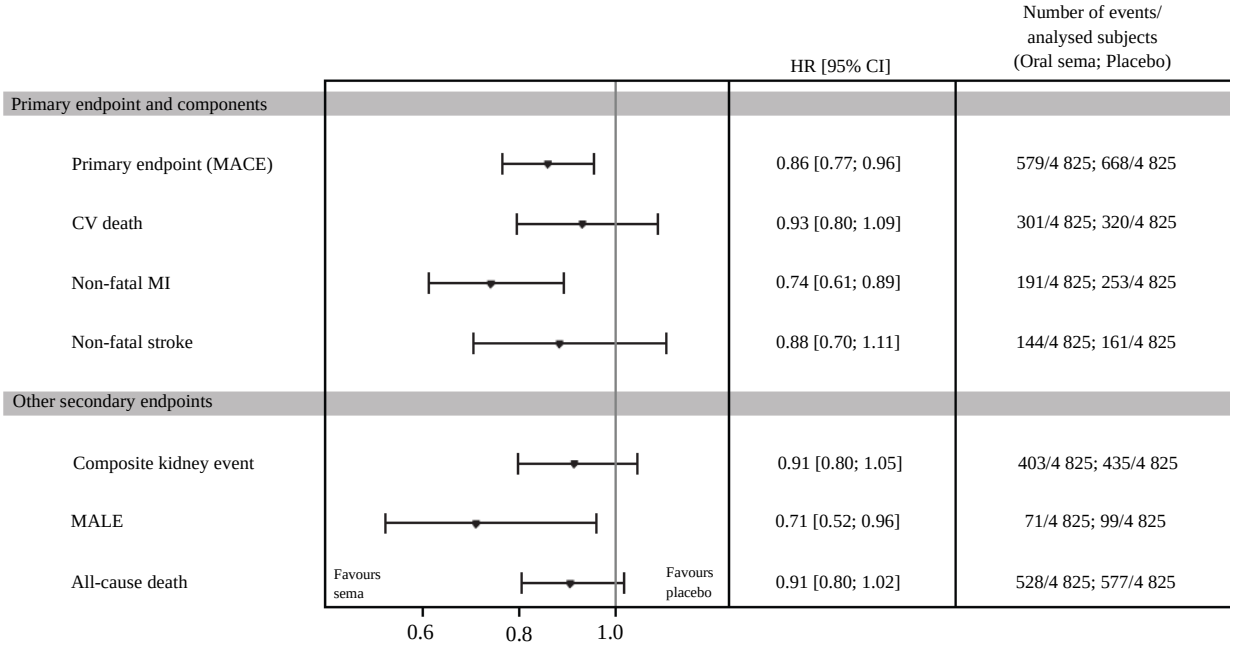


Patients at risk										
Oral Semaglutide	4825	4743	4635	4542	4438	4346	4239	3831	2555	1346
Placebo	4825	4718	4583	4455	4322	4194	4101	3727	2517	1346

Data from the in-trial period and 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.
CV: cardiovascular, EAC: event adjudication committee, MACE: major adverse cardiovascular event.

Figure 2: Time from randomisation to first MACE Cumulative incidence function plot



Data from the in-trial period and 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.
Composite kidney event: endpoint consisting of cardiovascular death, kidney death, onset of persistent ≥ 50% reduction in estimated glomerular filtration rate (CKD-EPI) compared with baseline, onset of persistent eGFR (CKD-EPI) < 15 mL/min/1.73 m^2 or initiation of chronic kidney replacement therapy (dialysis or kidney transplantation).
MALE: major adverse limb events; composite endpoint consisting of acute or chronic limb ischemia hospitalisation.

Figure 3: Treatment effect for the primary endpoint, its components and other secondary endpoints (SOUL)

PIONEER 6: Cardiovascular outcomes trial in patients with type 2 diabetes
In a double-blind trial (PIONEER 6), 3 183 patients, 50 years of age or older with type 2 diabetes at high cardiovascular risk were randomised to semaglutide 14 mg once daily or placebo in addition to standard-of-care. The median observation period was 16 months. PIONEER 6 was a pre-approval CVOT designed to establish CV safety.

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 total number of first MACE was 137: 61 (3.8%) with semaglutide and 76 (4.8%) with placebo. The analysis of time to first MACE resulted in a HR of 0.79 $[0.57; 1.11]_{95\% CI}$.

Body weight

By end-of-treatment, 27-65.7% of the patients had achieved a weight loss of ≥ 5% and 6-34.7% had achieved a weight loss of ≥ 10% with semaglutide, compared with 12-39% and 2-8%, respectively, with the active comparators.

In the cardiovascular outcome trial SOUL, a reduction in body weight from baseline to week 104 was observed with semaglutide vs. placebo, in addition to standard-of-care (-4.22 kg vs. -1.27 kg).

Blood pressure

Treatment with semaglutide had reduced systolic blood pressure by 2-7 mmHg.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Rybelsus in one or more subsets of the paediatric population in type 2 diabetes (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Two formulations of the semaglutide tablets exist:
- 1.5 mg, 4 mg and 9 mg (round tablets)
- 3 mg, 7 mg and 14 mg (oval tablets).

Similar efficacy and safety can be expected for both formulations. Bioequivalent doses of the two formulations are outlined in the table below.

Table 10 Equal effect of the two oral formulations

Dose	**One round tablet**		**One oval tablet**
Starting dose	1.5 mg	Equal effect to	3 mg
Maintenance doses	4 mg	Equal effect to	7 mg
	9 mg	Equal effect to	14 mg

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.

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 approximately 1 hour post dose. Steady-state exposure was reached after 4-5 weeks of once-daily administration. In patients with type 2 diabetes, the average steady-state concentrations were approximately as listed below:
7 mg: Average concentration was 7 nmol/L with 90% of subjects treated with semaglutide 7 mg having an average concentration between 2 and 22 nmol/L.
14 mg: Average concentration was 15 nmol/L with 90% of subjects treated with semaglutide 14 mg having an average concentration between 4 and 45 nmol/L.
25 mg: Average concentration was 47 nmol/L with 90% of subjects treated with semaglutide 25 mg having an average concentration between 11 and 142 nmol/L.
50 mg: Average concentration was 92 nmol/L with 90% of subjects treated with semaglutide 50 mg having an average concentration between 23 and 279 nmol/L.

Systemic exposure of semaglutide increased in a dose-proportional manner within formulations (i.e. between 7 mg and 14 mg, and between 25 mg and 50 mg)**,** with higher bioavailability for the 25 and 50 mg strengths.

Based on *in vitro* data, salcaprozate sodium facilitates absorption of semaglutide. The absorption of semaglutide predominantly occurs in the stomach.

The estimated bioavailability of semaglutide is approximately 1% for the 3 mg, 7 mg and 14 mg strengths and up to 2% for the 25 mg and 50 mg strengths following oral administration. The between-

subject variability in absorption was high (coefficient of variation was approximately 100%). The estimation of the within-subject variability in bioavailability was not reliable.

Absorption of semaglutide is decreased if taken with food or large volumes of water. Different dosing schedules of semaglutide have been investigated. Studies show that longer pre- and post-dose fasting period results in higher absorption (see section 4.2).

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%).

Biotransformation

Semaglutide is metabolised through proteolytic cleavage of the peptide backbone and sequential beta-oxidation of the fatty acid sidechain. The enzyme neutral endopeptidase (NEP) is expected to be involved in the metabolism of semaglutide.

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.

Special populations

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

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, not Hispanic or Latino) had no clinically meaningful 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 40-212 kg evaluated in the clinical trials.

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 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 data from phase 3a studies.

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 with 10 consecutive days of once-daily doses of semaglutide.

Upper GI tract disease
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.

Paediatric population

Semaglutide has not been studied in paediatric patients.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated 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. No other treatment-related tumours were observed. 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 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, this mechanism is considered unlikely to be 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.

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

3 mg, 7 mg and 14 mg:
Salcaprozate sodium
Povidone K90
Cellulose, microcrystalline
Magnesium stearate

25 mg and 50 mg:
Salcaprozate sodium
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 mg: 2 years.
7 mg: 30 months.
14 mg: 30 months.
25 mg: 3 years.
50 mg: 3 years.

6.4 Special precautions for storage

Store in the original blister package in order to protect from light and moisture. This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

Alu/Alu blisters.
Pack sizes of: 10, 30, 60, 90 and 100 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark

8. MARKETING AUTHORISATION NUMBERS

EU/1/20/1430/001
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EU/1/20/1430/036
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9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 03 April 2020
Date of latest renewal: 22 November 2024

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu

ANNEX II

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Novo Nordisk A/S
Hallas Allé
DK-4400 Kalundborg
Denmark

Hovione FarmaCiencia S.A.
Quinta Sao Pedro, Sete Casas
PT-2674-506 Loures
Portugal

Novo Nordisk Pharmaceutical Industries Inc.
3612 Powhatan Road
Clayton
North Carolina 27527-9217
United States

Name and address of the manufacturer responsible for batch release

Novo Nordisk A/S
Novo Allé
DK-2800 Bagsværd
Denmark

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Rybelsus 1.5 mg tablets
semaglutide

2. STATEMENT OF ACTIVE SUBSTANCE

Each tablet contains 1.5 mg of semaglutide.

3. LIST OF EXCIPIENTS

Contains sodium.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

10 tablets
30 tablets
60 tablets
90 tablets
100 tablets

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.
Oral use.
How to take Rybelsus.
Take on an empty stomach, after a recommended fasting of at least 8 hours.
Take the tablet whole with a sip of water (up to 120 mL). Do not split, crush or chew.
Wait at least 30 minutes before eating, drinking or taking any other oral medicines.

Push down and push back.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNINGS, IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark

12. MARKETING AUTHORISATION NUMBERS

EU/1/20/1430/016 10 tablets
EU/1/20/1430/017 30 tablets
EU/1/20/1430/018 60 tablets
EU/1/20/1430/019 90 tablets
EU/1/20/1430/020 100 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

rybelsus 1.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Rybelsus 1.5 mg tablets
semaglutide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Rybelsus 3 mg tablets
semaglutide

2. STATEMENT OF ACTIVE SUBSTANCE

Each tablet contains 3 mg of semaglutide.

3. LIST OF EXCIPIENTS

Contains sodium.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

10 tablets
30 tablets
60 tablets
90 tablets
100 tablets

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.
Oral use.
How to take Rybelsus.
Take on an empty stomach, after a recommended fasting of at least 8 hours.
Take the tablet whole with a sip of water (up to 120 mL). Do not split, crush or chew.
Wait at least 30 minutes before eating, drinking or taking any other oral medicines.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNINGS, IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark

12. MARKETING AUTHORISATION NUMBERS

EU/1/20/1430/001 10 tablets
EU/1/20/1430/002 30 tablets
EU/1/20/1430/003 60 tablets
EU/1/20/1430/004 90 tablets
EU/1/20/1430/011 100 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

rybelsus 3 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Rybelsus 3 mg tablets
semaglutide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Rybelsus 4 mg tablets
semaglutide

2. STATEMENT OF ACTIVE SUBSTANCE

Each tablet contains 4 mg of semaglutide.

3. LIST OF EXCIPIENTS

Contains sodium.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

10 tablets
30 tablets
60 tablets
90 tablets
100 tablets

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.
Oral use.
How to take Rybelsus.
Take on an empty stomach, after a recommended fasting of at least 8 hours.
Take the tablet whole with a sip of water (up to 120 mL). Do not split, crush or chew.
Wait at least 30 minutes before eating, drinking or taking any other oral medicines.

Push down and push back.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNINGS, IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark

12. MARKETING AUTHORISATION NUMBERS

EU/1/20/1430/021 10 tablets
EU/1/20/1430/022 30 tablets
EU/1/20/1430/023 60 tablets
EU/1/20/1430/024 90 tablets
EU/1/20/1430/025 100 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

rybelsus 4 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Rybelsus 4 mg tablets
semaglutide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Rybelsus 7 mg tablets
semaglutide

2. STATEMENT OF ACTIVE SUBSTANCE

Each tablet contains 7 mg of semaglutide.

3. LIST OF EXCIPIENTS

Contains sodium.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

10 tablets
30 tablets
60 tablets
90 tablets
100 tablets

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.
Oral use.
How to take Rybelsus.
Take on an empty stomach, after a recommended fasting of at least 8 hours.
Take the tablet whole with a sip of water (up to 120 mL). Do not split, crush or chew.
Wait at least 30 minutes before eating, drinking or taking any other oral medicines.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNINGS, IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark

12. MARKETING AUTHORISATION NUMBERS

EU/1/20/1430/014 10 tablets
EU/1/20/1430/005 30 tablets
EU/1/20/1430/006 60 tablets
EU/1/20/1430/007 90 tablets
EU/1/20/1430/012 100 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

rybelsus 7 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Rybelsus 7 mg tablets
semaglutide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Rybelsus 9 mg tablets
semaglutide

2. STATEMENT OF ACTIVE SUBSTANCE

Each tablet contains 9 mg of semaglutide.

3. LIST OF EXCIPIENTS

Contains sodium.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

10 tablets
30 tablets
60 tablets
90 tablets
100 tablets

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.
Oral use.
How to take Rybelsus.
Take on an empty stomach, after a recommended fasting of at least 8 hours.
Take the tablet whole with a sip of water (up to 120 mL). Do not split, crush or chew.
Wait at least 30 minutes before eating, drinking or taking any other oral medicines.

Push down and push back.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNINGS, IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark

12. MARKETING AUTHORISATION NUMBERS

EU/1/20/1430/026 10 tablets
EU/1/20/1430/027 30 tablets
EU/1/20/1430/028 60 tablets
EU/1/20/1430/029 90 tablets
EU/1/20/1430/030 100 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

rybelsus 9 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Rybelsus 9 mg tablets
semaglutide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Rybelsus 14 mg tablets
semaglutide

2. STATEMENT OF ACTIVE SUBSTANCE

Each tablet contains 14 mg of semaglutide.

3. LIST OF EXCIPIENTS

Contains sodium.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

10 tablets
30 tablets
60 tablets
90 tablets
100 tablets

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.
Oral use.
How to take Rybelsus.
Take on an empty stomach, after a recommended fasting of at least 8 hours.
Take the tablet whole with a sip of water (up to 120 mL). Do not split, crush or chew.
Wait at least 30 minutes before eating, drinking or taking any other oral medicines.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNINGS, IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark

12. MARKETING AUTHORISATION NUMBERS

EU/1/20/1430/015 10 tablets
EU/1/20/1430/008 30 tablets
EU/1/20/1430/009 60 tablets
EU/1/20/1430/010 90 tablets
EU/1/20/1430/013 100 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

rybelsus 14 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Rybelsus 14 mg tablets
semaglutide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Rybelsus 25 mg tablets
semaglutide

2. STATEMENT OF ACTIVE SUBSTANCE

Each tablet contains 25 mg of semaglutide.

3. LIST OF EXCIPIENTS

Contains sodium.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

10 tablets
30 tablets
60 tablets
90 tablets
100 tablets

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.
Oral use.
How to take Rybelsus.
Take on an empty stomach, after a recommended fasting of at least 8 hours.
Take the tablet whole with a sip of water (up to 120 mL). Do not split, crush or chew.
Wait at least 30 minutes before eating, drinking or taking any other oral medicines.

Push down and push back.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNINGS, IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark

12. MARKETING AUTHORISATION NUMBERS

EU/1/20/1430/031 10 tablets
EU/1/20/1430/032 30 tablets
EU/1/20/1430/033 60 tablets
EU/1/20/1430/034 90 tablets
EU/1/20/1430/035 100 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

rybelsus 25 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Rybelsus 25 mg tablets
semaglutide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Rybelsus 50 mg tablets
semaglutide

2. STATEMENT OF ACTIVE SUBSTANCE

Each tablet contains 50 mg of semaglutide.

3. LIST OF EXCIPIENTS

Contains sodium.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

10 tablets
30 tablets
60 tablets
90 tablets
100 tablets

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.
Oral use.
How to take Rybelsus.
Take on an empty stomach, after a recommended fasting of at least 8 hours.
Take the tablet whole with a sip of water (up to 120 mL). Do not split, crush or chew.
Wait at least 30 minutes before eating, drinking or taking any other oral medicines.

Push down and push back.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNINGS, IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark

12. MARKETING AUTHORISATION NUMBERS

EU/1/20/1430/036 10 tablets
EU/1/20/1430/037 30 tablets
EU/1/20/1430/038 60 tablets
EU/1/20/1430/039 90 tablets
EU/1/20/1430/040 100 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

rybelsus 50 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Rybelsus 50 mg tablets
semaglutide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Rybelsus 1.5 mg tablets
Rybelsus 4 mg tablets
Rybelsus 9 mg tablets
Rybelsus 25 mg tablets
Rybelsus 50 mg tablets
semaglutide

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
– Keep this leaflet. You may need to read it again.
– If you have any further questions, ask your doctor, pharmacist or nurse.
– This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
– If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Rybelsus is and what it is used for

Rybelsus contains the active substance semaglutide. It is a medicine that is used to lower blood sugar levels.

Rybelsus is used to treat adults (aged 18 years and older) with type 2 diabetes when diet and exercise is not enough:
- on its own - when you cannot use metformin (another diabetes medicine) or
- with other medicines for diabetes - when the other medicines are not enough to control your blood sugar levels. These may be medicines you take by mouth or inject such as insulin.

It is important that you continue with your diet and exercise plan as agreed with your doctor, pharmacist or nurse.

What is type 2 diabetes?
Type 2 diabetes is a condition in which your body does not make enough insulin, and the insulin that your body makes does not lower your blood sugar the way it should. In some cases, your body can produce too much blood sugar. If your blood sugar increases and remains high over a long period of time, this can lead to harmful effects such as heart problems, kidney disease, eye disorders and poor circulation in your limbs. That is why it is important to keep your blood sugar levels within a normal range.

2. What you need to know before you take Rybelsus

Do not take Rybelsus
- if you are allergic to semaglutide or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor, pharmacist or nurse before taking Rybelsus.

Traceability
In order to improve the traceability of biological medicinal products, record the name and the lot number (included on the outer cartons and blister) of the medicine you are taking and provide this information when reporting any side effects.

General
This medicine is not the same as insulin and you should not use it if:
- you have type 1 diabetes (your body does not produce any insulin)
- you develop diabetic ketoacidosis. This is a complication of diabetes with high blood sugar, breathing difficulty, confusion, excessive thirst, a sweet smell to the breath or a sweet or metallic taste in the mouth.

If you know that you are due to have surgery where you will be under anaesthesia (sleeping), please tell your doctor that you are taking Rybelsus.

Stomach and gut problems and dehydration
During treatment with this medicine, you may feel sick (nausea) or be sick (vomiting), or have diarrhoea. These side effects can cause dehydration (loss of fluids). It is important that you drink enough fluids to prevent dehydration. This is especially important if you have kidney problems. Talk to your doctor if you have any questions or concerns.

Severe and on-going stomach pain which could be due to an inflamed pancreas
If you have severe and on-going pain in the stomach area - see a doctor straight away as this could be a sign of inflamed pancreas (acute pancreatitis).

Low blood sugar (hypoglycaemia)
Taking a sulfonylurea medicine or insulin with Rybelsus might increase the risk of getting low blood sugar (hypoglycaemia). See section 4 for the warning signs of low blood sugar levels.

Your doctor may ask you to test your blood sugar levels. This will help to decide if the dose of the sulfonylurea or insulin needs to be changed to reduce the risk of low blood sugar.

Diabetic eye disease (retinopathy)
Fast improvements in blood sugar control may lead to a temporary worsening of diabetic eye disease. If you have diabetic eye disease and get eye problems while taking this medicine, talk to your doctor.

Treatment response
If the treatment response with semaglutide is lower than expected, this may be due to low absorption caused by variability in absorption and low absolute bioavailability. You should follow the instructions given in section 3 for optimal effect of semaglutide.

Sudden changes to your eyesight
If you notice a sudden loss of vision or rapidly worsening eyesight during treatment with this medicine, immediately contact your doctor for advice. This may be caused by a very rare side effect called non- arteritic anterior ischaemic optic neuropathy (NAION) (See section 4: Serious side effects). Your doctor may refer you for an eye examination and you may have to stop treatment with this medicine.

Children and adolescents
This medicine is not recommended in children and adolescents aged under 18 years as the safety and efficacy in this age group have not been established.

Other medicines and Rybelsus
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

In particular, tell your doctor, pharmacist or nurse if you are using medicines containing any of the following:

- levothyroxine which is used for thyroid disease. This is because your doctor may need to check your thyroid levels if you are taking Rybelsus together with levothyroxine.
- warfarin or similar medicines taken by mouth to reduce blood clotting (oral anti-coagulants). You may need frequent blood tests to check how quickly your blood clots.
- If you are using insulin, your doctor will tell you how to reduce the dose of insulin and will recommend you monitor your blood sugar more frequently, in order to avoid hyperglycaemia (high blood sugar) and diabetic ketoacidosis (a complication of diabetes that occurs when the body is unable to breakdown glucose because there is not enough insulin).

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

This medicine should not be used during pregnancy, as it is not known if it affects your unborn baby. Therefore, you have to use contraception while taking this medicine. If you wish to become pregnant, discuss how to change your treatment with your doctor as you should stop using this medicine at least 2 months in advance. If you become pregnant while using this medicine, talk to your doctor straight away, as your treatment will need to be changed.

Do not use this medicine if you are breast-feeding. The medicine passes into breast milk, and it is not known how it affects your baby.

Driving and using machines
Rybelsus is unlikely to affect your ability to drive and use machines.

Some patients may feel dizzy when taking Rybelsus. If you feel dizzy, be extra careful while driving or using machines. Talk to your doctor for the further information.

If you use this medicine in combination with a sulfonylurea or insulin, low blood sugar (hypoglycaemia) may occur which may reduce your ability to concentrate. Do not drive or use machines if you get any signs of low blood sugar. See section 2, ‘Warning and precautions’ for information on increased risk of low blood sugar and section 4 for the warning signs of low blood sugar. Talk to your doctor for further information.

Rybelsus contains sodium
Rybelsus 1.5 mg, 4 mg and 9 mg tablets: This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

Rybelsus 25 mg and 50 mg tablets: This medicine contains 23 mg sodium (main component of cooking/table salt) in each tablet. This is equivalent to 1% of the recommended maximum daily dietary intake of sodium for an adult.

3. How to take Rybelsus

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

How much to take

- The starting dose is one 1.5 mg tablet once a day for one month.
- After one month, your doctor will increase your dose to one 4 mg tablet once a day.
- Your doctor will instruct you to stay on a dose for minimum one month before increasing to a higher dose.
- Your doctor may step-wise increase your dose to one 9 mg, 25 mg or 50 mg tablet once a day if needed.
- Your doctor will prescribe the strength that is right for you. Do not change your dose unless your doctor has told you so.
- Rybelsus should always be taken as one tablet per day. You should not take two tablets to get the effect of a higher dose.

Taking this medicine

- Take your Rybelsus tablet on an empty stomach after a recommended fasting period of at least 8 hours.
- Swallow your Rybelsus tablet whole with a sip of water (up to 120 mL). Do not split, crush or chew the tablet, as it is not known if it affects absorption of semaglutide.
- After taking your Rybelsus tablet wait at least 30 minutes before eating, drinking or taking other oral medicines. Waiting less than 30 minutes lowers the absorption of semaglutide.

If you take more Rybelsus than you should

If you take more Rybelsus than you should, talk to your doctor straight away. You may get side effects such as feeling sick (nausea).

If you forget to take Rybelsus

If you forget to take a dose, skip the missed dose and just take your normal dose the next day.

If you stop taking Rybelsus

Do not stop using this medicine without talking to your doctor. If you stop using it, your blood sugar levels may increase.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects

Common (may affect up to 1 in 10 people)

- complications of diabetic eye disease (retinopathy). You should tell your doctor if you get eye problems, such as changes in vision, during treatment with this medicine.

Rare (may affect up to 1 in 1 000 people)

- serious allergic reactions (anaphylactic reactions). You must get immediate medical help and inform your doctor straight away if you get symptoms such as breathing problems, swelling of face and throat, wheezing, fast heartbeat, pale and cold skin, feeling dizzy or weak.
- inflamed pancreas (acute pancreatitis) which could cause severe pain in the stomach and back which does not go away. You should see a doctor immediately if you experience such symptoms.

Very Rare (may affect up to 1 in 10 000 people)
- A medical condition of the eye called non-arteritic anterior ischaemic optic neuropathy (NAION), which may cause loss of vision to one of your eyes without any pain. You should immediately contact your doctor if you notice sudden or gradually worsening eyesight (see section 2: “Sudden changes to your eyesight”)

Not known (frequency cannot be estimated from the available data)
- bowel obstruction. A severe form of constipation with additional symptoms such as stomach ache, bloating, vomiting etc.

Other side effects

Very common (may affect more than 1 in 10 people)
- low blood sugar (hypoglycaemia) when this medicine is used with medicines that contain a sulfonylurea or insulin. Your doctor may reduce your dose of these medicines before you start using this medicine.
- feeling sick (nausea) - this usually goes away over time
- diarrhoea - this usually goes away over time.

The warning signs of low blood sugar may come on suddenly. They can include: cold sweat, cool pale skin, headache, fast heartbeat, feeling sick (nausea) or very hungry, changes in vision, feeling sleepy or weak, feeling nervous, anxious or confused, difficulty concentrating or shaking.
Your doctor will tell you how to treat low blood sugar and what to do if you notice these warning signs.

Common (may affect up to 1 in 10 people)
- low blood sugar (hypoglycaemia) when this medicine is used with oral diabetes medicine other than sulfonylurea or insulin
- less appetite
- feeling dizzy
- being sick (vomiting) - this usually goes away over time and may happen more often when increasing your dose to 25 mg and 50 mg
- stomach pain
- bloating of the stomach
- constipation
- upset stomach or indigestion
- inflamed stomach (‘gastritis’) - the signs include stomach ache, feeling sick (nausea) or being sick (vomiting)
- reflux or heartburn - also called ‘gastro-esophageal reflux disease’
- gas (flatulence)
- tiredness
- increase of pancreatic enzymes (such as lipase and amylase) shown in blood tests
- changed skin sensation - this usually goes away over time and may happen with 25 mg and 50 mg
- Headache.

Uncommon (may affect up to 1 in 100 people)
- allergic reactions like rash, itching or hives
- change in the way food or drink tastes
- fast pulse
- burping
- a delay in the emptying of the stomach
- gallstones
- weight loss.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Rybelsus

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the blister and carton after 'EXP'. The expiry date refers to the last day of that month.

Store in the original package in order to protect from light and moisture.
This medicine does not require any special temperature storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Rybelsus contains
- The active substance is semaglutide. Each tablet contains 1.5, 4, 9, 25 or 50 mg semaglutide.
- The other ingredients are salcaprozate sodium, magnesium stearate. See also section 2, 'Rybelsus contains sodium'.

What Rybelsus looks like and contents of the pack

Rybelsus 1.5 mg tablets are white to light yellow and round (6.5 mm in diameter). They have '1.5' on one side and 'novo' on the other side.
Rybelsus 4 mg tablets are white to light yellow and round (6.5 mm in diameter). They have '4' on one side and 'novo' on the other side.
Rybelsus 9 mg tablets are white to light yellow and round (6.5 mm in diameter). They have '9' on one side and 'novo' on the other side.
Rybelsus 25 mg tablets are white to light yellow and oval shaped (6.8 mm × 12 mm). They have '25' on one side and 'novo' on the other side.
Rybelsus 50 mg tablets are white to light yellow and oval shaped (6.8 mm × 12 mm). They have '50' on one side and 'novo' on the other side.

The 1.5 mg, 4 mg, 9 mg, 25 mg and 50 mg tablets are available in alu/alu blister cards in pack sizes of 10, 30, 60, 90 and 100 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark

This leaflet was last revised in

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site:
https://www.ema.europa.eu/

Package leaflet: Information for the patient

Rybelsus 3 mg tablets
Rybelsus 7 mg tablets
Rybelsus 14 mg tablets
Rybelsus 25 mg tablets
Rybelsus 50 mg tablets
semaglutide

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
– Keep this leaflet. You may need to read it again.
– If you have any further questions, ask your doctor, pharmacist or nurse.
– This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
– If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Rybelsus is and what it is used for

Rybelsus contains the active substance semaglutide. It is a medicine that is used to lower blood sugar levels.

Rybelsus is used to treat adults (aged 18 years and older) with type 2 diabetes when diet and exercise is not enough:
- on its own - when you cannot use metformin (another diabetes medicine) or
- with other medicines for diabetes - when the other medicines are not enough to control your blood sugar levels. These may be medicines you take by mouth or inject such as insulin.

It is important that you continue with your diet and exercise plan as agreed with your doctor, pharmacist or nurse.

What is type 2 diabetes?
Type 2 diabetes is a condition in which your body does not make enough insulin, and the insulin that your body makes does not lower your blood sugar the way it should. In some cases, your body can produce too much blood sugar. If your blood sugar increases and remains high over a long period of time, this can lead to harmful effects such as heart problems, kidney disease, eye disorders and poor circulation in your limbs. That is why it is important to keep your blood sugar levels within a normal range.

2. What you need to know before you take Rybelsus

Do not take Rybelsus
- if you are allergic to semaglutide or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor, pharmacist or nurse before taking Rybelsus.

Traceability
In order to improve the traceability of biological medicinal products, record the name and the lot number (included on the outer cartons and blister) of the medicine you are taking and provide this information when reporting any side effects.

General
This medicine is not the same as insulin and you should not use it if:
- you have type 1 diabetes (your body does not produce any insulin)
- you develop diabetic ketoacidosis. This is a complication of diabetes with high blood sugar, breathing difficulty, confusion, excessive thirst, a sweet smell to the breath or a sweet or metallic taste in the mouth.

If you know that you are due to have surgery where you will be under anaesthesia (sleeping), please tell your doctor that you are taking Rybelsus.

Stomach and gut problems and dehydration
During treatment with this medicine, you may feel sick (nausea) or be sick (vomiting), or have diarrhoea. These side effects can cause dehydration (loss of fluids). It is important that you drink enough fluids to prevent dehydration. This is especially important if you have kidney problems. Talk to your doctor if you have any questions or concerns.

Severe and on-going stomach pain which could be due to an inflamed pancreas
If you have severe and on-going pain in the stomach area - see a doctor straight away as this could be a sign of inflamed pancreas (acute pancreatitis).

Low blood sugar (hypoglycaemia)
Taking a sulfonylurea medicine or insulin with Rybelsus might increase the risk of getting low blood sugar (hypoglycaemia). See section 4 for the warning signs of low blood sugar levels.

Your doctor may ask you to test your blood sugar levels. This will help to decide if the dose of the sulfonylurea or insulin needs to be changed to reduce the risk of low blood sugar.

Diabetic eye disease (retinopathy)
Fast improvements in blood sugar control may lead to a temporary worsening of diabetic eye disease. If you have diabetic eye disease and get eye problems while taking this medicine, talk to your doctor.

Treatment response
If the treatment response with semaglutide is lower than expected, this may be due to low absorption caused by variability in absorption and low absolute bioavailability. You should follow the instructions given in section 3 for optimal effect of semaglutide.

Sudden changes to your eyesight
If you notice a sudden loss of vision or rapidly worsening eyesight during treatment with this medicine, immediately contact your doctor for advice. This may be caused by a very rare side effect called non- arteritic anterior ischaemic optic neuropathy (NAION) (See section 4: Serious side effects). Your doctor may refer you for an eye examination and you may have to stop treatment with this medicine.

Children and adolescents
This medicine is not recommended in children and adolescents aged under 18 years as the safety and efficacy in this age group have not been established.

Other medicines and Rybelsus
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

In particular, tell your doctor, pharmacist or nurse if you are using medicines containing any of the following:

- levothyroxine which is used for thyroid disease. This is because your doctor may need to check your thyroid levels if you are taking Rybelsus together with levothyroxine.
- warfarin or similar medicines taken by mouth to reduce blood clotting (oral anti-coagulants). You may need frequent blood tests to check how quickly your blood clots.
- If you are using insulin, your doctor will tell you how to reduce the dose of insulin and will recommend you monitor your blood sugar more frequently, in order to avoid hyperglycaemia (high blood sugar) and diabetic ketoacidosis (a complication of diabetes that occurs when the body is unable to breakdown glucose because there is not enough insulin).

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

This medicine should not be used during pregnancy, as it is not known if it affects your unborn baby. Therefore, you have to use contraception while taking this medicine. If you wish to become pregnant, discuss how to change your treatment with your doctor as you should stop using this medicine at least 2 months in advance. If you become pregnant while using this medicine, talk to your doctor straight away, as your treatment will need to be changed.

Do not use this medicine if you are breast-feeding. The medicine passes into breast milk, and it is not known how it affects your baby.

Driving and using machines
Rybelsus is unlikely to affect your ability to drive and use machines.

Some patients may feel dizzy when taking Rybelsus. If you feel dizzy, be extra careful while driving or using machines. Talk to your doctor for the further information.

If you use this medicine in combination with a sulfonylurea or insulin, low blood sugar (hypoglycaemia) may occur which may reduce your ability to concentrate. Do not drive or use machines if you get any signs of low blood sugar. See section 2, ‘Warning and precautions’ for information on increased risk of low blood sugar and section 4 for the warning signs of low blood sugar. Talk to your doctor for further information.

Rybelsus contains sodium
This medicine contains 23 mg sodium (main component of cooking/table salt) in each tablet. This is equivalent to 1% of the recommended maximum daily dietary intake of sodium for an adult.

3. How to take Rybelsus

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

How much to take

- The starting dose is one 3 mg tablet once a day for one month.
- After one month, your doctor will increase your dose to one 7 mg tablet once a day.
- Your doctor will instruct you to stay on a dose for minimum one month before increasing to a higher dose.
- Your doctor may step-wise increase your dose to one 14 mg, 25 mg or 50 mg tablet once a day if needed.

- Your doctor will prescribe the strength that is right for you. Do not change your dose unless your doctor has told you so.
- Rybelsus should always be taken as one tablet per day. You should not take two tablets to get the effect of a higher dose.

Taking this medicine
- Take your Rybelsus tablet on an empty stomach after a recommended fasting period of at least 8 hours.
- Swallow your Rybelsus tablet whole with a sip of water (up to 120 mL). Do not split, crush or chew the tablet, as it is not known if it affects absorption of semaglutide.
- After taking your Rybelsus tablet wait at least 30 minutes before eating, drinking or taking other oral medicines. Waiting less than 30 minutes lowers the absorption of semaglutide.

If you take more Rybelsus than you should
If you take more Rybelsus than you should, talk to your doctor straight away. You may get side effects such as feeling sick (nausea).

If you forget to take Rybelsus
If you forget to take a dose, skip the missed dose and just take your normal dose the next day.

If you stop taking Rybelsus
Do not stop using this medicine without talking to your doctor. If you stop using it, your blood sugar levels may increase.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects

Common (may affect up to 1 in 10 people)
- complications of diabetic eye disease (retinopathy). You should tell your doctor if you get eye problems, such as changes in vision, during treatment with this medicine.

Rare (may affect up to 1 in 1 000 people)
- serious allergic reactions (anaphylactic reactions). You must get immediate medical help and inform your doctor straight away if you get symptoms such as breathing problems, swelling of face and throat, wheezing, fast heartbeat, pale and cold skin, feeling dizzy or weak.
- inflamed pancreas (acute pancreatitis) which could cause severe pain in the stomach and back which does not go away. You should see a doctor immediately if you experience such symptoms.

Very Rare (may affect up to 1 in 10 000 people)
- A medical condition of the eye called non-arteritic anterior ischaemic optic neuropathy (NAION), which may cause loss of vision to one of your eyes without any pain. You should immediately contact your doctor if you notice sudden or gradually worsening eyesight (see section 2: “Sudden changes to your eyesight”)

Not known (frequency cannot be estimated from the available data)
- bowel obstruction. A severe form of constipation with additional symptoms such as stomach ache, bloating, vomiting etc.

Other side effects

Very common (may affect more than 1 in 10 people)
- low blood sugar (hypoglycaemia) when this medicine is used with medicines that contain a sulfonylurea or insulin. Your doctor may reduce your dose of these medicines before you start using this medicine.
- feeling sick (nausea) - this usually goes away over time
- diarrhoea - this usually goes away over time.

The warning signs of low blood sugar may come on suddenly. They can include: cold sweat, cool pale skin, headache, fast heartbeat, feeling sick (nausea) or very hungry, changes in vision, feeling sleepy or weak, feeling nervous, anxious or confused, difficulty concentrating or shaking.
Your doctor will tell you how to treat low blood sugar and what to do if you notice these warning signs.

Common (may affect up to 1 in 10 people)
- low blood sugar (hypoglycaemia) when this medicine is used with oral diabetes medicine other than sulfonylurea or insulin
- less appetite
- feeling dizzy
- being sick (vomiting) - this usually goes away over time and may happen more often when increasing your dose to 25 mg and 50 mg
- stomach pain
- bloating of the stomach
- constipation
- upset stomach or indigestion
- inflamed stomach (‘gastritis’) - the signs include stomach ache, feeling sick (nausea) or being sick (vomiting)
- reflux or heartburn - also called ‘gastro-esophageal reflux disease’
- gas (flatulence)
- tiredness
- increase of pancreatic enzymes (such as lipase and amylase) shown in blood tests
- changed skin sensation - this usually goes away over time and may happen with 25 mg and 50 mg
- Headache.

Uncommon (may affect up to 1 in 100 people)
- allergic reactions like rash, itching or hives
- change in the way food or drink tastes
- fast pulse
- burping
- a delay in the emptying of the stomach
- gallstones
- weight loss.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Rybelsus

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the blister and carton after 'EXP'. The expiry date refers to the last day of that month.

Store in the original package in order to protect from light and moisture.
This medicine does not require any special temperature storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Rybelsus contains

- The active substance is semaglutide. Each tablet contains 3, 7, 14, 25 or 50 mg semaglutide.
- The other ingredients in the 3 mg, 7 mg and 14 mg tablets are salcaprozate sodium, povidone K90, cellulose microcrystalline, magnesium stearate. See also section 2, 'Rybelsus contains sodium'.
- The other ingredients in the 25 mg and 50 mg tablets are salcaprozate sodium and magnesium stearate. See also section 2, 'Rybelsus contains sodium'.

What Rybelsus looks like and contents of the pack

Rybelsus 3 mg tablets are white to light yellow and oval shaped (7.5 mm x 13.5 mm). They have '3' on one side and 'novo' on the other side.
Rybelsus 7 mg tablets are white to light yellow and oval shaped (7.5 mm x 13.5 mm). They have '7' on one side and 'novo' on the other side.
Rybelsus 14 mg tablets are white to light yellow and oval shaped (7.5 mm x 13.5 mm). They have '14' on one side and 'novo' on the other side.
Rybelsus 25 mg tablets are white to light yellow and oval shaped (6.8 mm × 12 mm). They have '25' on one side and 'novo' on the other side.
Rybelsus 50 mg tablets are white to light yellow and oval shaped (6.8 mm × 12 mm). They have '50' on one side and 'novo' on the other side.

The 3 mg, 7 mg, 14 mg, 25 mg and 50 mg tablets are available in alu/alu blister cards in pack sizes of 10, 30, 60, 90 and 100 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu/