For the use only of registered medical practitioner or a hospital or a laboratory

℞

1. Generic Name

Semaglutide Tablets
Rybelsus® 3 mg tablets
Rybelsus® 7 mg tablets
Rybelsus®14 mg tablets

Tablet for once daily oral use

Semaglutide is a human glucagon-like peptide-1 (GLP-1) receptor agonist produced in *Saccharomyces cerevisiae* by recombinant DNA technology followed by protein purification

2. Qualitative and quantitative composition

Rybelsus® 3 mg tablets*
Each tablet contains semaglutide 3 mg.

Rybelsus® 7 mg tablets*
Each tablet contains semaglutide 7 mg.

Rybelsus® 14 mg tablets*
Each tablet contains semaglutide 14 mg.

**Excipient with known effect*
Each tablet contains salcaprozate sodium equivalent to 23 mg sodium.
For the full list of excipients, see Section 8 Pharmaceutical Particulars

3. Dosage form and Strength

Rybelsus® 3 mg tablets
White to light yellow, oval shaped tablet debossed with '3' on one side and 'novo' on the other side.

Rybelsus® 7 mg tablets
White to light yellow, oval shaped tablet debossed with '7' on one side and 'novo' on the other side.

Rybelsus® 14 mg tablets
White to light yellow, oval shaped tablet debossed with '14' on one side and 'novo' on the other side.

4. Clinical particulars

4.1 Therapeutic indication

RYBELSUS® is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Limitations of Use

- RYBELSUS® has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis [see section 4.4 special warnings and precautions for use].
- RYBELSUS® is not indicated for use in patients with type 1 diabetes mellitus.

4.2 Posology and method of administration

Posology

The starting dose of Rybelsus® 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. After at least one month on with a dose of 7 mg once daily, the dose can be increased to a maintenance dose of 14 mg once daily to further improve glycaemic control.

The maximum recommended single daily dose of Rybelsus® is 14 mg. Taking two 7 mg tablets to achieve the effect of a 14 mg dose has not been studied and is therefore not recommended.

Rybelsus® can be used as monotherapy or in combination with one or more glucose-lowering medicinal products (See Clinical efficacy and safety under section 5.2 Pharmacodynamics properties).

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

When Rybelsus® is used in combination with a sulfonylurea or insulin, a reduction in the dose of sulfonylurea or insulin should be considered to reduce the risk of hypoglycaemia (See section 4.4 Special warnings and precautions for use).

Self-monitoring of blood glucose is not needed in order to adjust the dose of Rybelsus®. Blood glucose self-monitoring is necessary to adjust the dose of sulfonylurea and insulin, particularly when Rybelsus® 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.

Special Population:

Elderly (≥65 years old)
No dose adjustment is required based on age. Therapeutic experience in patients ≥75 years

Table 1 Adverse reactions from controlled phase 3a trials

MedDRA system organ class	Very common	Common	Uncommon	Rare
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		
Eye disorders		Diabetic retinopathy complications[b]		
Cardiac disorders			Increased heart rate	
Gastrointestinal disorders	Nausea Diarrhoea	Vomiting Abdominal pain Abdominal distension Constipation Dyspepsia Gastritis Gastro-oesophageal reflux disease Flatulence	Eructation	Acute Pancreatitis
Hepatobiliary disorders			Cholelithiasis	
General disorders and administration site conditions		Fatigue		
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 is a composite of retinal photocoagulation, treatment with intravitreal agents, vitreous haemorrhage and diabetes-related blindness (uncommon). Frequency is based on the cardiovascular outcomes trial with s.c semaglutide, but it cannot be excluded that the risk of diabetic retinopathy complications identified also applies to Rybelsus®.
[c] Grouped term covering also adverse events related to hypersensitivity such as rash and urticaria

Description of selected adverse reactions

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

Gastrointestinal adverse reactions
Nausea occurred in 15%, diarrhoea in 10%, vomiting in 7% of patients when treated with Rybelsus®. Most events were mild to moderate in severity and of short duration. The events led to treatment discontinuation in 4% of subjects. The events were most frequently reported during the first months 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 the frequency of acute pancreatitis confirmed by adjudication was 0.1% for semaglutide and 0.2% for placebo.

Diabetic retinopathy complications
A 2-year clinical trial with s.c 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 s.c 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 s.c 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%).

Discontinuation due to an adverse event
Discontinuation of treatment due to adverse events was 9% for patients treated with Rybelsus®. The most frequent adverse events leading to discontinuation were gastrointestinal.

Immunogenicity
Consistent with the potential immunogenic properties of medicinal products containing

4. Clinical particulars

4.1 Therapeutic indication

RYBELSUS® is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

Limitations of Use

- RYBELSUS® has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis [see section 4.4 special warnings and precautions for use].
- RYBELSUS® is not indicated for use in patients with type 1 diabetes mellitus

4.2 Posology and method of administration

Posology

The starting dose of Rybelsus® 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. After at least one month on with a dose of 7 mg once daily, the dose can be increased to a maintenance dose of 14 mg once daily to further improve glycaemic control.

The maximum recommended single daily dose of Rybelsus® is 14 mg. Taking two 7 mg tablets to achieve the effect of a 14 mg dose has not been studied and is therefore not recommended.

Rybelsus® can be used as monotherapy or in combination with one or more glucose-lowering medicinal products (See Clinical efficacy and safety under section 5.2 Pharmacodynamics properties).

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

When Rybelsus® is used in combination with a sulfonylurea or insulin, a reduction in the dose of sulfonylurea or insulin should be considered to reduce the risk of hypoglycaemia (See section 4.4 Special warnings and precautions for use).

Self-monitoring of blood glucose is not needed in order to adjust the dose of Rybelsus®. Blood glucose self-monitoring is necessary to adjust the dose of sulfonylurea and insulin, particularly when Rybelsus® 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.

Special Population:

Elderly (≥65 years old)

No dose adjustment is required based on age. Therapeutic experience in patients ≥75 years of age is limited (see section 5.3 Pharmacokinetic properties).

Gender

No dose adjustment is required based on gender.

Race and ethnicity

No dose adjustment is required based on race and ethnicity.

Patients with 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 Clinical efficacy and safety under section 5.2 Pharmacodynamics properties and see section 5.3 Pharmacokinetic properties).

Patients with 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 severe renal impairment is limited. Semaglutide is not recommended in patients with end stage renal disease (See Clinical efficacy and safety under section 5.2 Pharmacodynamics properties and see section 5.3 Pharmacokinetic properties).

Children and adolescents

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.

Rybelsus® should be taken on an empty stomach. Rybelsus® should be swallowed whole with up to half a glass of water equivalent to 120 ml. Do not split, crush or chew the tablet. Wait at least 30 minutes before the first meal or drink of the day or taking other oral medicinal products. Waiting less than 30 minutes may decrease the absorption of semaglutide.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 8. Pharmaceutical Particulars

4.4 Special warnings and precautions for use

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

There is no therapeutic experience with Rybelsus® in patients with bariatric surgery.

Gastrointestinal effects and dehydration

[illegible] be associated with gastrointestinal adverse reactions

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

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

Description of selected adverse reactions

Hypoglycaemia

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

Gastrointestinal adverse reactions

Nausea occurred in 15%, diarrhoea in 10%, vomiting in 7% of patients when treated with Rybelsus®. Most events were mild to moderate in severity and of short duration. The events led to treatment discontinuation in 4% of subjects. The events were most frequently reported during the first months 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 the frequency of acute pancreatitis confirmed by adjudication was 0.1% for semaglutide and 0.2% for placebo.

Diabetic retinopathy complications

A 2-year clinical trial with s.c.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 s.c.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 s.c.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%).

Discontinuation due to an adverse event

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

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.

Increased heart rate

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.

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. There is no specific antidote for overdose with semaglutide.

5 Pharmacological properties

5.1 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 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 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.

5.2 Pharmacodynamics properties

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

Pharmacodynamic effects

Rybelsus® lowers fasting [illegible] glucose. The onset happens

that can cause dehydration, which in rare cases can lead to a deterioration of renal function. 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, Rybelsus® should be discontinued; if confirmed, Rybelsus® should not be restarted. Caution should be exercised in patients with a history of pancreatitis.

In the absence of other signs and symptoms of acute pancreatitis, elevations in pancreatic enzymes alone are not predictive of acute pancreatitis.

Hypoglycaemia

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

Diabetic retinopathy

Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy but other mechanism cannot be excluded. Long-term glycaemic control decreases the risk of diabetic retinopathy. Patients with a history of diabetic retinopathy should be monitored for worsening and treated according to clinical guidelines.

Heart failure

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.

4.5 Drugs interactions

In vitro studies have shown very low potential for semaglutide to inhibit or induce CYP enzymes, and to inhibit drug transporters.

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

Effects of Rybelsus® on other medicinal products

Thyroxine

Total exposure (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

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, 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 in 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 (F: 1%) have not been evaluated.

Effects of other medicinal products on semaglutide

Omeprazole

No clinically relevant change in AUC or Cmax 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.

Interaction with food

Concomitant intake of food reduces the exposure of semaglutide (see section 4.2 Posology and method of administration).

4.6 Use in special populations (Fertility, pregnancy and lactation)

Women of childbearing potential

Women of childbearing potential are recommended to use contraception when treated with Rybelsus®.

Pregnancy

Studies in animals have shown reproductive toxicity (see section 6. Nonclinical properties). There are limited data from the use of semaglutide in pregnant women. Therefore, Rybelsus® should not be used during pregnancy. Women of childbearing potential are recommended to use contraception when treated with Rybelsus®. If a patient wishes to become pregnant, or pregnancy occurs, Rybelsus® should be discontinued. Rybelsus® should be discontinued at least 2 months before a planned pregnancy due to the long half-life.

Breast-feeding

In lactating rats, semaglutide, sodium and/or its metabolites were excreted in

early with a lowering of fasting glucose within the first week of treatment.

All pharmacodynamic evaluations described below were performed 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.

Beta-cell function and insulin secretion

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

Glucagon secretion

Semaglutide lowers the fasting and 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].

Glucose-dependent insulin and glucagon secretion

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.

Gastric emptying

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

Body weight and body composition

A greater reduction in body weight was observed with Rybelsus® compared to studied comparators (placebo, sitagliptin, empagliflozin and liraglutide). The body weight loss with semaglutide was predominantly from fat tissue with loss of fat mass being 3-fold larger than loss of lean mass.

Appetite, energy intake and food choice

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

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.

Cardiac electrophysiology (QTc)

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

Clinical efficacy and safety

The efficacy and safety of Rybelsus® have been evaluated in eight global randomised controlled phase 3a trials. In seven trials, the primary objective was the assessment of the glycaemic efficacy; in one trial, the primary objective was the assessment of cardiovascular outcomes. Additionally, two phase 3a trials were conducted with Rybelsus® in Japanese patients.

The trials included 9,543 randomised patients with type 2 diabetes (5,707 treated with Rybelsus®), including 1,170 patients with moderate renal impairment. The efficacy of Rybelsus® was compared with placebo or active controls (sitagliptin, empagliflozin and liraglutide).

In all trials, treatment with Rybelsus® resulted in clinically meaningful improvements in HbA1c, fasting plasma glucose (FPG) and body weight. These effects were maintained up to a trial duration of 78 weeks.

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

Clinical efficacy – presentation of PIONEER trials

PIONEER 1 – Monotherapy

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

The mean age of the study population was 55 years, and the mean duration of type 2 diabetes was 3.5 years. Overall, 75% were White, 5% were Black or African American and 17% were Asian. Hispanic or Latino patients compromised 26% (n=180) of the population. The mean body weight at baseline was 88 kg.

Monotherapy with Rybelsus® 7 mg and 14 mg once daily was superior at week 26 in reducing HbA_{1c} compared with placebo. Rybelsus® 14 mg was superior in reducing body weight compared with placebo (**Table 2**).

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

International normalised ratio (INR) were not affected in a clinically relevant manner. However, 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 in 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 (F: 1%) have not been evaluated.

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Interaction with food
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4.6 Use in special populations (Fertility, pregnancy and lactation)

Women of childbearing potential
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Pregnancy
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Breast-feeding
In lactating rats, semaglutide, salcaprozate sodium and/or its metabolites were excreted in milk. 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.

4.7 Effects on ability to drive and use machines
Rybelsus® has no or negligible influence on the ability to drive or use machines. When it is used in combination with a sulfonylurea or insulin, patients should be advised to take precautions to avoid hypoglycaemia while driving and using machines.

4.8 Undesirable Effects

Summary of safety profile
In 10 phase 3a trials, 5,707 patients were exposed to Rybelsus® alone or in combination with other glucose-lowering medicinal products. The duration of the treatment ranged from 26 weeks to 78 weeks. The most frequently reported adverse reactions in clinical trials were gastrointestinal disorders, including nausea, diarrhoea and vomiting. In general, these reactions were mild or moderate in severity and of short duration.

Tabulated list of adverse reactions
Table 1 lists adverse reactions identified in all phase 3a trials in patients with type 2 diabetes mellitus (further described in section 5.2 Pharmacodynamics properties). The frequencies of the adverse reactions are based on a pool of the phase 3a trials excluding the cardiovascular outcomes trial.

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

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.

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

Clinical efficacy – presentation of PIONEER trials

PIONEER 1 – Monotherapy

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Monotherapy with Rybelsus® 7 mg and 14 mg once daily was superior at week 26 in reducing HbA_{1c} compared with placebo. Rybelsus® 14 mg was superior in reducing body weight compared with placebo (**Table 2**).

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

	Rybelsus® 7 mg	Rybelsus® 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 (mean)	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 vs placebo.

PIONEER 2 – Rybelsus® vs. empagliflozin, both in combination with metformin
In a 52-week open-label trial (26-week primary endpoint), 822 patients with type 2 diabetes were randomised to Rybelsus® 14 mg once daily or empagliflozin 25 mg once daily, both in combination with metformin.

The mean age of the trial population was 58 years, and the mean duration of type 2 diabetes was 7.4 years. Overall, 86% were White, 7% were Black or African American and 6% were Asian. Hispanic or Latino patients comprised 24% (n=199) of the population. The mean body weight at baseline was 92 kg.

Treatment with Rybelsus® 14 mg once daily was superior at week 26 in reducing HbA_{1c} compared to empagliflozin 25 mg once daily (**Table 3**).

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

	Rybelsus® 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 vs empagliflozin 25 mg.

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

In a 78-week, double-blind, double-dummy trial (26-week primary endpoint), 1,864 patients with type 2 diabetes were randomised to Rybelsus® 3 mg, Rybelsus® 7 mg, Rybelsus® 14 mg or sitagliptin 100 mg once daily, all in combination with metformin alone or metformin and sulfonylurea.

The mean age of the trial population was 58 years, and the mean duration of type 2 diabetes was 8.6 years. Overall, 71% were White, 9% were Black or African American and 13% were Asian. Hispanic or Latino patients comprised 17% (n=321) of the population. The mean body weight at baseline was 91 kg.

Treatment with Rybelsus® 7 mg and 14 mg once daily was superior at week 26 in reducing HbA_{1c} and body weight compared to sitagliptin 100 mg once daily (**Table 4**).

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

	Rybelsus® 7 mg	Rybelsus® 14 mg	Sitagliptin 100 mg
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][§]	-
Body weight (kg)			
Baseline	91.3	91.2	90.9

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

	Rybelsus® 14 mg	Placebo
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 vs placebo.

PIONEER 7 – Rybelsus® 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 Rybelsus® (flexible dose adjustment of 3 mg, 7 mg, and 14 mg once daily) or sitagliptin 100 mg once daily, all in combination with 1-2 oral glucose-lowering medications (metformin, SGLT2 inhibitors, sulfonylurea or thiazolidinediones). The dose of Rybelsus® was adjusted every 8 weeks based on patient's glycaemic response and tolerability. The sitagliptin 100 mg dose was fixed. The efficacy and safety of Rybelsus® were evaluated at week 52. At the end of 52 weeks, the percentage of patients on-treatment with Rybelsus® 7 mg were 30.2% and Rybelsus® 14 mg were 59.4%.

The mean age of the trial population was 57 years, and the mean duration of type 2 diabetes was 8.8 years. Overall, 76% were White, 9% were Black or African American and 14% were Asian. Hispanic or Latino patients comprised 21% (n=105) of the population. The mean body weight at baseline was 89 kg.

After 52 weeks of treatment, 58.3% of the patients achieved the target of HbA_{1c} <7.0% with adjustable dosing of Rybelsus® compared to 25.2% of patients treated with sitagliptin 100 mg. Rybelsus® was superior to sitagliptin at week 52 in enabling patients to achieve HbA_{1c} <7.0% and in reducing body weight (**Table 7**)

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

	Rybelsus® 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 vs sitagliptin 100 mg)

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

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

All patients reduced their insulin dose by 20% at randomization to reduce the risk of hypoglycemia. For the first 26 weeks, patients were allowed to increase the insulin dose only up to the starting insulin dose prior to randomization. After the 26 weeks, patients were allowed to adjust the insulin dose as needed. At randomization, the total daily insulin dose were 55 U, 63 U, and 53 U for placebo, Rybelsus® 7 mg and Rybelsus® 14 mg, respectively.

[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 vs empagliflozin 25 mg

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

In a 78-week, double-blind, double-dummy trial (26-week primary endpoint), 1,864 patients with type 2 diabetes were randomised to Rybelsus® 3 mg, Rybelsus® 7 mg, Rybelsus® 14 mg or sitagliptin 100 mg once daily, all in combination with metformin alone or metformin and sulfonylurea.

The mean age of the trial population was 58 years, and the mean duration of type 2 diabetes was 8.6 years. Overall, 71% were White, 9% were Black or African American and 13% were Asian. Hispanic or Latino patients comprised 17% (n=321) of the population. The mean body weight at baseline was 91 kg.

Treatment with Rybelsus® 7 mg and 14 mg once daily was superior at week 26 in reducing HbA_{1c} and body weight compared to sitagliptin 100 mg once daily (**Table 4**).

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

	Rybelsus® 7 mg	Rybelsus® 14 mg	Sitagliptin 100 mg
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][§]	-
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 HbA1c <7.0%', the p-value is for the odds ratio vs sitagliptin 100 mg.

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

In a 52-week double-blind, double-dummy trial (26-week primary endpoint), 711 patients with type 2 diabetes were randomised to Rybelsus® 14 mg, liraglutide 1.8 mg s.c. injection or placebo once daily, all in combination with metformin or metformin and an SGLT2 inhibitor.

The mean age of the trial population was 56 years, and the mean duration of type 2 diabetes was 7.6 years. Overall, 73% were White, 4% were Black or African American and 13% were Asian. Hispanic or Latino patients comprised 6% (n=40) of the population. The mean body weight at baseline was 94 kg.

Treatment with Rybelsus® 14 mg once daily was superior at week 26 in reducing HbA_{1c} and body weight compared with placebo. Treatment with Rybelsus® 14 mg was non-inferior in reducing HbA_{1c} and superior in reducing body weight at week 26 compared with liraglutide 1.8 mg (**Table 5**).

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

	Rybelsus® 14 mg	Liraglutide 1.8 mg	Placebo
	[illegible]	[illegible]	[illegible]

was 8.8 years. Overall, 76% were White, 9% were Black or African American and 14% were Asian. Hispanic or Latino patients comprised 21% (n=105) of the population. The mean body weight at baseline was 89 kg.

After 52 weeks of treatment, 58.3% of the patients achieved the target of HbA_{1c} <7.0% with adjustable dosing of Rybelsus® compared to 25.2% of patients treated with sitagliptin 100 mg. Rybelsus® was superior to sitagliptin at week 52 in enabling patients to achieve HbA_{1c} <7.0% and in reducing body weight (**Table 7**)

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

	Rybelsus® 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 vs sitagliptin 100 mg)

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

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

All patients reduced their insulin dose by 20% at randomization to reduce the risk of hypoglycemia. For the first 26 weeks, patients were allowed to increase the insulin dose only up to the starting insulin dose prior to randomization. After the 26 weeks, patients were allowed to adjust the insulin dose as needed. At randomization, the total daily insulin dose were 55 U, 63 U, and 53 U for placebo, Rybelsus® 7 mg and Rybelsus® 14 mg, respectively.

The mean age of the trial population was 61 years, and the mean duration of type 2 diabetes was 15.0 years. Overall, 51% were White, 7% were Black or African American and 36% were Asian. Hispanic or Latino patients comprised 13% (n=97) of the population. The mean body weight at baseline was 86 kg.

Treatment with Rybelsus® 7 mg and 14 mg once daily was superior in reducing HbA_{1c} and body weight compared with placebo (**Table 8**)

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

	Rybelsus® 7 mg	Rybelsus® 14 mg	Placebo
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]	-0.6 [-0.8; -0.4][§]	-0.9 [-1.1; -0.7][§]	-

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[§]	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[§]	55	15
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 vs placebo.

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

In a 26-week double-blind trial, 324 patients with type 2 diabetes and moderate renal impairment (eGFR 30-59 ml/min/1.73 m²) were randomised to Rybelsus® 14 mg or placebo once daily. Trial product was added to the patient's stable pre-trial antidiabetic regimen.

The mean age of the trial population was 70 years, and the mean duration of type 2 diabetes was 14.0 years. Overall, 96% were White, 4% were Black or African American and less than 1% were Asian. Hispanic or Latino patients comprised 6% (n=21) of the population. The mean body weight at baseline was 91 kg.

Treatment with Rybelsus® 14 mg once daily was superior at week 26 in reducing HbA_{1c} and body weight compared with placebo.

[95% CI]			
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 vs placebo. * The total daily insulin dose was statistically significantly lower with semaglutide than with placebo at week 52.

The mean changes from baseline in total daily insulin dose at week 26 were –1 U, –8 U and –9 U for placebo, Rybelsus® 7 mg and Rybelsus® 14 mg, respectively. The difference from placebo for Rybelsus® 7 mg and Rybelsus® 14 mg was –8 [–12; –3]$_{95\%\ CI}$ and –8 [–13; –3]$_{95\%\ CI}$, respectively. The mean changes from baseline in daily insulin dose at week 52 were 10 U, –6 U and –7 U for placebo, Rybelsus® 7 mg and Rybelsus® 14 mg, respectively. The difference from placebo for Rybelsus® 7 mg and Rybelsus® 14 mg was –16 [–25; –8]$_{95\%\ CI}$ and –17[–25; –9]$_{95\%\ CI}$, respectively.

Prevention of cardiovascular events

Two cardiovascular outcomes trials examining the effects of semaglutide versus placebo on risk of cardiovascular events have been conducted; SUSTAIN 6 with semaglutide injection and PIONEER 6 with semaglutide in a tablet formulation (Rybelsus®).

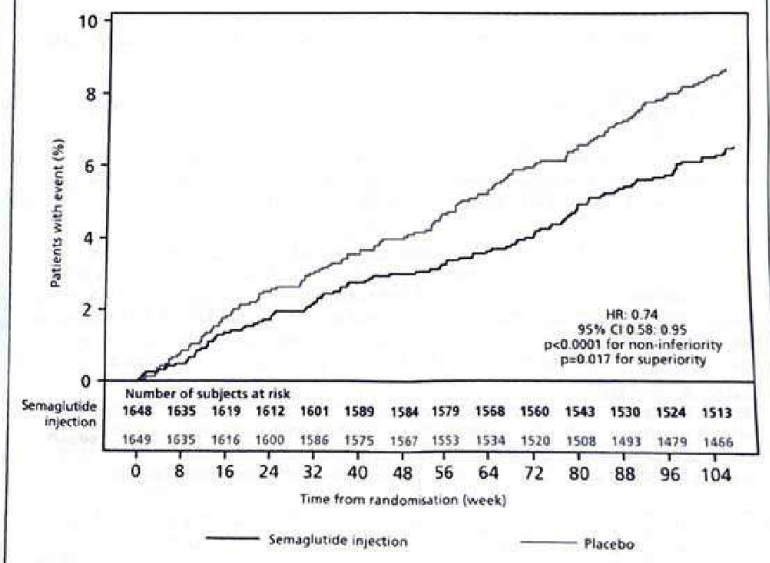
SUSTAIN 6

In a 104-week double-blind trial, 3,297 patients with type 2 diabetes mellitus at high cardiovascular risk were randomised to either semaglutide injection 0.5 mg once weekly, semaglutide injection 1 mg once weekly or placebo in addition to standard-of-care hereafter followed for 2 years.

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.

Patients eligible to enter the trial were: 50 years of age or older and with established cardiovascular disease and/or chronic kidney disease, or 60 years of age or older and with cardiovascular risk factors only. In total, 1,940 patients (58.8%) had established cardiovascular disease without chronic kidney disease, 353 (10.7%) had chronic kidney disease only and 442 (13.4%) had both cardiovascular disease and kidney disease. 562 patients (17.0%) had cardiovascular risk factors only. The mean age at baseline was 65 years, and 61% of the patients were men. The mean duration of diabetes was 13.9 years and the mean BMI was 33 kg/m². Medical history included stroke (12.2%), myocardial infarction (32.5%) and peripheral artery disease (13.7%).

The total number of first MACE was 254: 108 (6.6%) with semaglutide and 146 (8.9%) with placebo. Treatment with semaglutide resulted in a 26% reduction in the risk of MACE comprising cardiovascular death, non-fatal myocardial infarction or non-fatal stroke (HR: 0.74 [0.58; 0.95]$_{95\%\ CI}$).



Kaplan-Meier plot of primary outcome (a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke).
Abbreviations: CI: Confidence interval, HR: Hazard ratio

Figure 1 Cumulative incidence of time to first occurrence of MACE in SUSTAIN 6

The treatment effect for the primary composite endpoint and its components in the

Change from baseline[1]	-4.3	-3.0	-1.0
Difference from liraglutide[1] [95% CI]	-1.3 [-2.1; -0.5][5]	-	-
Difference from placebo[1] [95% CI]	-3.3 [-4.3; -2.4][5]	-	-

[1] Irrespective of treatment discontinuation or initiation of rescue medication (pattern mixture model using multiple imputation). [4] p<0.001 (unadjusted 2-sided) for superiority, controlled for multiplicity. [5] p<0.05, not controlled for multiplicity; for 'Patients achieving HbA_{1c} <7.0%', the p-value is for the odds ratio vs placebo.

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

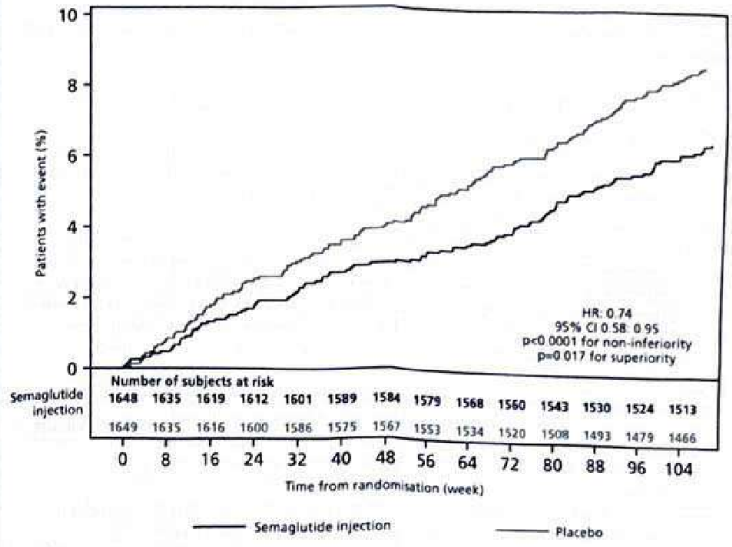
In a 26-week double-blind trial, 324 patients with type 2 diabetes and moderate renal impairment (eGFR 30-59 ml/min/1.73 m²) were randomised to Rybelsus® 14 mg or placebo once daily. Trial product was added to the patient's stable pre-trial antidiabetic regimen.

The mean age of the trial population was 70 years, and the mean duration of type 2 diabetes was 14.0 years. Overall, 96% were White, 4% were Black or African American and less than 1% were Asian. Hispanic or Latino patients comprised 6% (n=21) of the population. The mean body weight at baseline was 91 kg.

Treatment with Rybelsus® 14 mg once daily was superior at week 26 in reducing HbA_{1c} and body weight compared with placebo.

65 years, and 61% of the patients were men. The mean duration of diabetes was 13.9 years and the mean BMI was 33 kg/m². Medical history included stroke (12.2%), myocardial infarction (32.5%) and peripheral artery disease (13.7%).

The total number of first MACE was 254: 108 (6.6%) with semaglutide and 146 (8.9%) with placebo. Treatment with semaglutide resulted in a 26% reduction in the risk of MACE comprising cardiovascular death, non-fatal myocardial infarction or non-fatal stroke (HR: 0.74 [0.58, 0.95]$_{95\% CI}$).



Kaplan-Meier plot of primary outcome (a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke).
Abbreviations: CI: Confidence interval, HR: Hazard ratio

Figure 1 Cumulative incidence of time to first occurrence of MACE in SUSTAIN 6

The treatment effect for the primary composite endpoint and its components in the SUSTAIN 6 trial is shown in Figure 2.

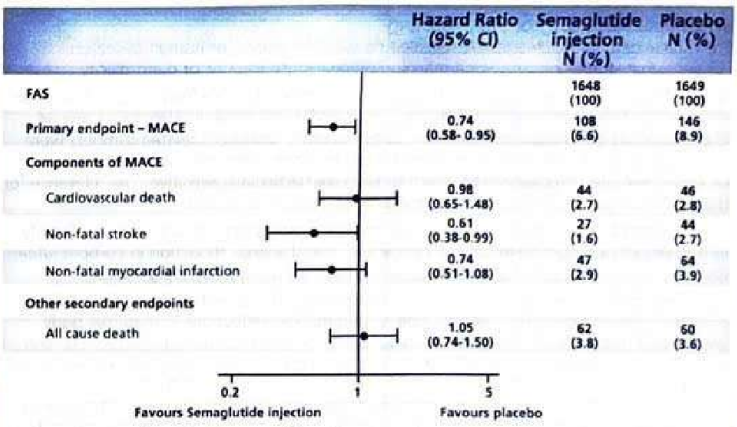


Figure 2 Forest plot: Treatment effect for the primary composite endpoint, its components and all cause death (SUSTAIN 6)

PIONEER 6

In a double-blind trial, 3,183 patients with type 2 diabetes at high cardiovascular risk were randomised to Rybelsus® 14 mg once daily or placebo in addition to standard-of-care. The median observation period was 16 months.

The primary endpoint was time from randomisation to first occurrence of a MACE event: cardiovascular death, non-fatal myocardial infarction or non-fatal stroke.

Patients eligible to enter the trial were: 50 years of age or older and with established cardiovascular disease and/or chronic kidney disease, or 60 years of age or older and with cardiovascular risk factors only. In total, 1,797 patients (56.5%) had established cardiovascular disease without chronic kidney disease, 354 (11.1%) had chronic kidney disease only and 544 (17.1%) had both cardiovascular disease and kidney disease. 488 patients (15.3%) had cardiovascular risk factors only. The mean age at baseline was 66 years, and 68% of the patients were men. The mean duration of diabetes was 14.9 years and the mean BMI was 32.2 kg/m². Medical history included stroke (11.7%) and myocardial infarction (36.1%).

10. Details of Manufacturer

Manufactured by:
Novo Nordisk A/S,
Novo Alle,
DK-2880 Bagsvaerd, Denmark

Imported by:
Novo Nordisk India Private Limited,
Plot No.32, 47 - 50, EPIP Area,
Whitefield, Bangalore - 560 066 India
www.novonordisk.co.in

Rybelsus® is a trademark owned by Novo Nordisk A/S, Denmark.

11. Details of permission or licence number with date

- F. No. BIO/IMP/23/000116 dated 19 Jan 2024

12. Date of revision
15 Mar 2024

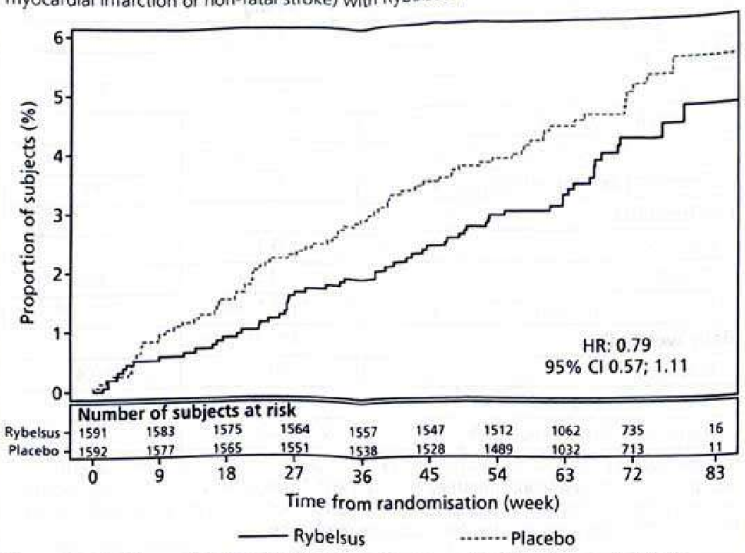
novo nordisk®

8-0503-26-001-3

Semaglutide Tablets
Rybelsus®

novo nordisk®

The total number of first MACE endpoint was 137: 61 (3.8%) with Rybelsus® and 76 (4.8%) with placebo. The analysis of time to first MACE resulted in a HR of 0.79 [0.57; 1.11]$_{95\%\ CI}$ indicating a 21% reduction in the risk of MACE (cardiovascular death, non-fatal myocardial infarction or non-fatal stroke) with Rybelsus®.



Cumulative incidence plot of primary outcome (a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) with non-cardiovascular death as competing risk.
Abbreviations: CI: Confidence interval, HR: Hazard ratio

Figure 3 Cumulative incidence of time to first occurrence of MACE in PIONEER 6

The treatment effect for the primary composite endpoint and its components in the PIONEER 6 trial is shown in **Figure 4**.

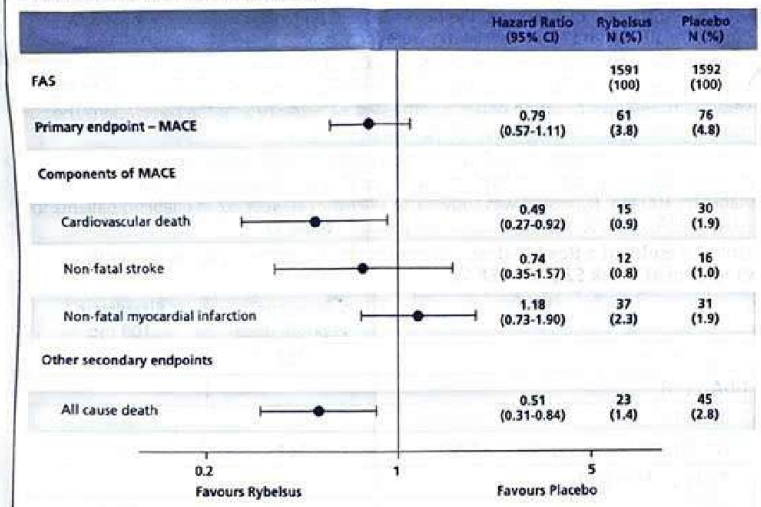


Figure 4 Forest plot: Treatment effect for the primary composite endpoint, its components and all cause death (PIONEER 6)

Combined analysis of SUSTAIN 6 and PIONEER 6

Consistent cardiovascular risk reduction was shown in SUSTAIN 6 and PIONEER 6, supported by an analysis including data from both trials. In this analysis, patients treated with semaglutide had a statistically significant lower risk of the first occurrence of MACE compared to placebo. The estimated HR was 0.76 [0.62; 0.92]$_{95\%\ CI}$.

Proportion of patients achieving HbA_{1c} targets

Up to 80% of the patients achieved HbA_{1c} <7.0%. The odds of achieving HbA1c <7.0% were statistically significantly greater with Rybelsus® than with sitagliptin, empagliflozin and placebo. Up to 68% of the patients achieved HbA_{1c} ≤6.5%. The odds of achieving HbA_{1c} ≤6.5% were statistically significantly greater with Rybelsus® than with sitagliptin, empagliflozin, liraglutide and placebo.

Up to 73% of the patients achieved HbA_{1c} <7.0% without severe or blood glucose confirmed symptomatic hypoglycaemia and without weight gain. The odds of achieving the target were statistically significantly greater with Rybelsus® than with placebo, sitagliptin, empagliflozin and liraglutide.

Body weight

7.Description

The semaglutide drug products are white to light yellow oval shaped tablets. The primary packaging is a blister card composed of coloured forming foil and non-coloured lid foil. The colour of the forming foil is unique for each tablet strength: green for 3 mg tablets, red for 7 mg tablets and blue for 14 mg tablets. The blister card contains 10 identical cavities, each containing 1 tablet. Batch specific information is printed on each blister card. The secondary packaging consists of an outer sales carton.

8. PHARMACEUTICAL PARTICULARS

List of excipients

Salcaprozate sodium 300 mg
Povidone K 90 (Ph Eur., USP, JP) 8 mg
Cellulose, microcrystalline (Ph Eur., USP, JP) 80 mg
Magnesium stearate (Ph Eur., USP, JP) 9.7 mg

8.1 Incompatibilities

Not applicable.

8.2 Shelf life

3 mg: 24 months
7 mg: 30 months
14 mg: 30 months.
(Refer pack for Expiry date)

8.3 Packaging information

The tablets are available in alu/alu blister cards in Pack sizes of 10, 30, 60 and 90 tablets. Not all pack sizes may be marketed.

8.4 Storage and handling instructions

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. The expiry date refers to the last day of that month.

Do not store above 30°C. Store in the original package to protect from moisture and light. Keep the tablet in the blister until you are ready to take it. Removing it too soon can prevent it from working as planned.

Do not use this medicine if you notice that the package is damaged or shows signs of being open.

Special precautions for disposal

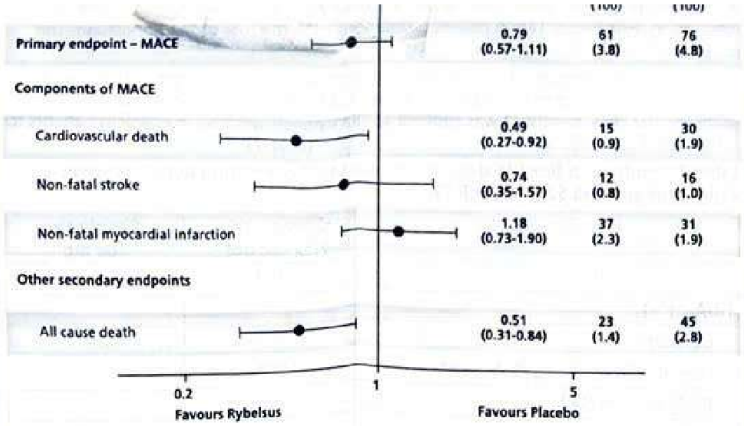
Any unused medicinal product or waste material should be disposed of in accordance with local requirements

9. Patient Counselling Information

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 4.8 "Undesirable Effects".

For product related complaints or Adverse event reporting you may write to us at INAgree@novonordisk.com or Contact us at: +91 8040303200



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Proportion of patients achieving HbA_{1c} targets

Up to 80% of the patients achieved HbA_{1c} <7.0%. The odds of achieving HbA1c <7.0% were statistically significantly greater with Rybelsus® than with sitagliptin, empagliflozin and placebo. Up to 68% of the patients achieved HbA_{1c} ≤6.5%. The odds of achieving HbA_{1c} ≤6.5% were statistically significantly greater with Rybelsus® than with sitagliptin, empagliflozin, liraglutide and placebo.

Up to 73% of the patients achieved HbA_{1c} <7.0% without severe or blood glucose confirmed symptomatic hypoglycaemia and without weight gain. The odds of achieving the target were statistically significantly greater with Rybelsus® than with placebo, sitagliptin, empagliflozin and liraglutide.

Body weight

Rybelsus® 14 mg was associated with sustained weight reduction over the duration of the trials (up to −5.0 kg from baseline to final time point). Rybelsus® 14 mg used as monotherapy or in combination with 1-2 glucose-lowering products resulted in statistically significant reduction in body weight compared with placebo, sitagliptin, liraglutide and empagliflozin. Up to 49% and 18% of patients achieved a weight loss of ≥5% and ≥10%, respectively. The odds of achieving a weight loss of ≥5% and ≥10% were statistically significantly greater with Rybelsus®14 mg than with placebo, sitagliptin and liraglutide.

Fasting plasma glucose

Treatment with Rybelsus® reduced FPG by up to 2.5 mmol/l across the phase 3a trials. The reductions were sustained through week 78.

Beta-cell function and insulin resistance

Beta-cell function measured by homeostasis model assessment for beta-cell function (HOMA-B) and insulin resistance measured by homeostasis model assessment for insulin resistance (HOMA-IR) overall improved with Rybelsus® 7 mg and Rybelsus® 14 mg

Cardiovascular risk factors

Treatment with Rybelsus® reduced systolic blood pressure by up to 7 mmHg and C-reactive protein concentrations by up to 35% and improved the fasting lipid profile (e.g. triglycerides reduction of up to around 13%).

5.3 Pharmacokinetic properties

Absorption

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

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

The pharmacokinetics of semaglutide have been extensively characterised in healthy subjects and patients with type 2 diabetes. Following oral administration, maximum plasma concentration of semaglutide occurred 1 hour post dose. Steady-state exposure was reached after 4–5 weeks of once-daily administration. In patients with type 2 diabetes, the average steady-state concentrations were approximately 6.7 nmol/L and 14.6 nmol/L with Rybelsus® 7 mg and 14 mg, respectively; with 90% of subjects treated with semaglutide 7 mg having an average concentration between 1.7 and 22.7 nmol/L and 90% of subjects treated with semaglutide 14 mg having an average concentration between 3.7 and 41.3 nmol/L. Systemic exposure of semaglutide increased in a dose-proportional manner.

Absorption of semaglutide is decreased if taken with food or large volumes of water. A longer post-dose fasting period results in higher absorption.

The estimated absolute bioavailability of semaglutide is approximately 1% following oral

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Distribution

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

Metabolism

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

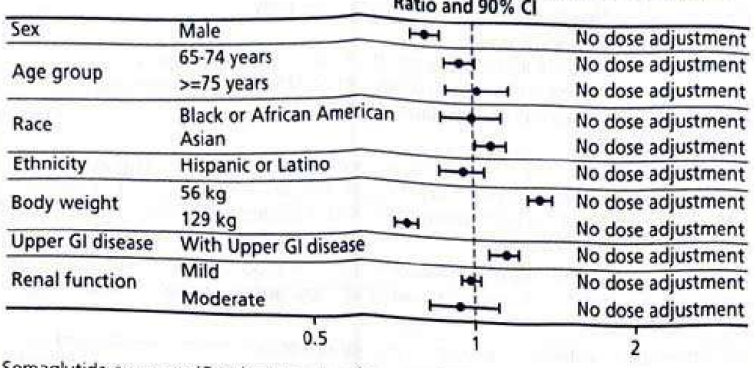
Elimination

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

Based on a population pharmacokinetic analysis, age, gender, race, ethnicity, upper GI tract disease and renal impairment did not have a clinically meaningful effect on the pharmacokinetics of semaglutide; therefore, no dose adjustment is needed. The effects of intrinsic factors on the pharmacokinetics of semaglutide are shown in Figure 5.



Semaglutide exposure (Cavg) relative to reference subject profile: White, non-Hispanic or Latino, female aged 18-64 years, with body weight of 85 kg, without upper GI disease or renal impairment, dosed 14 mg. Body weight categories (56 and 129 kg) represent the 5% and 95% percentiles in the dataset.
Abbreviations: Cavg: average semaglutide concentration. CI: Confidence interval. GI: gastrointestinal

Figure 5 Impact of intrinsic factors on semaglutide exposure

Age

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

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

Ethnicity

Ethnicity (Hispanic or Latino) had no effect on the pharmacokinetics of semaglutide.

Body weight

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

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 (**Figure 5).**

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 (**Figure 5).**

Paediatric population

Semaglutide has not been studied in paediatric patients.

GI: gastrointestinal

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6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

Pre-clinical data with semaglutide revealed no special hazards for human based on conventional studies of safety pharmacology, repeat-dose toxicity, or genotoxicity.

Non-lethal thyroid C-cell tumours observed in rodents are a class effect for GLP-1 receptor agonists. In 2 year carcinogenicity studies in rats and mice, semaglutide caused thyroid C-cell tumours at clinically relevant exposures. 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.