

Use the only used 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

*Exipient with known effect
Each tablet contains saccharate 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 'novio' on the other side

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

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

4. Clinical particulars

4.1 Therapeutic indication

Semaglutide is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus

- as monotherapy when metformin is considered inappropriate due to intolerance or contraindications
- in combination with other medical products for the treatment of diabetes

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 (SGLT2) or thiazolidinedione, the current dose of metformin and/or SGLT2/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; its use 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 who 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

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. 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 (C_{max} by 32%). This 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 in rats 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 is not considered clinically relevant.

Dopamine oral contraceptives, metformin, furosemide

No clinically relevant change in AUC or C_{max} of dopamine, oral contraceptives (containing ethinylstradiol 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 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.

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, saccharate 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 male rats, an increase in oestrous length and a small reduction in number of ovidulations 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 (≥1/10 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.

MedDRA system organ class	Very common	Common	Uncommon	Rare
Immune system disorders			Hypersensitivity	Anaphylactic reaction
Metabolism and nutrition disorders	Hypoglycaemia when used with insulin or sulfonylurea*	Hypoglycaemia when used with other oral antidiabetic products* Decreased appetite		
Eye disorders		Diabetic retinopathy complications*		
Cardiac disorders			Increased heart rate	
Gastrointestinal disorders	Nausea Diarrhoea	Vomiting Abdominal pain Abdominal distension Constipation Dyspepsia Gastritis Gastro-oesophageal reflux disease Flatulence	Erectation	Acute Pancreatitis
Hepatobiliary disorders			Cholestasis	
General disorders and administration site conditions		Fatigue		
Investigations	Increased lipase Increased amylase		Weight decreased	

*Hypoglycaemia defined as blood glucose <3.0 mmol/L or <54 mg/dL. 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®.

*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: A10B05

Pharmacodynamic effects

Rybelsus® lowers fasting glucose and self-measured plasma glucose. The onset happens 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 23% [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_{0-4h}) 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 QTc intervals 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 HbA_{1c} (fasting plasma glucose (FPG) and body weight. These effects were maintained up to a trial duration of 78 weeks.

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

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 comprised 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)

	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	-1.1	-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 ¹	77 ¹	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]*	-

¹Respective 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), 882 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.

Table 3 Results of a trial comparing Rybelsus® 14 mg once daily was superior at week 26 in reducing HbA_{1c} compared to empagliflozin 25 mg once daily (Table 3)

	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 ¹	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 ¹	43
Body weight (kg)		
Change from baseline ¹	-3.8	-3.6
Difference from empagliflozin ¹ [95% CI]	-0.2 [-0.9; 0.5]	-

¹Respective 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 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).

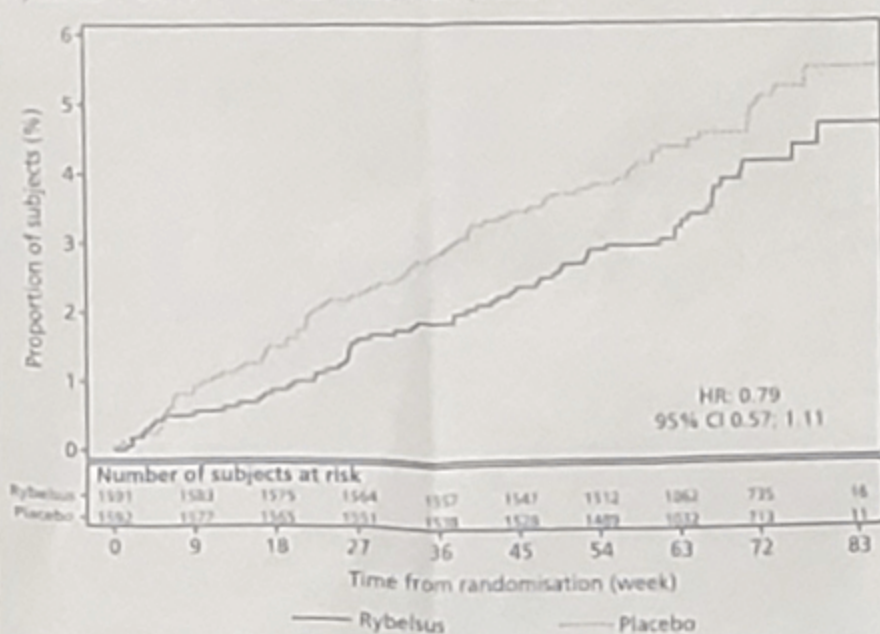
Table 4 Results of a trial comparing Rybelsus® with sitagliptin at week 78 (PIONEER 3)

	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 ¹	56 ¹	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 ¹	45 ¹	29
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]*	-

¹Respective 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 sitagliptin 100 mg.

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

The total number of first MACE endpoint was 137/61 (3.8%) with Rybelus® 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 Rybelus®.



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**

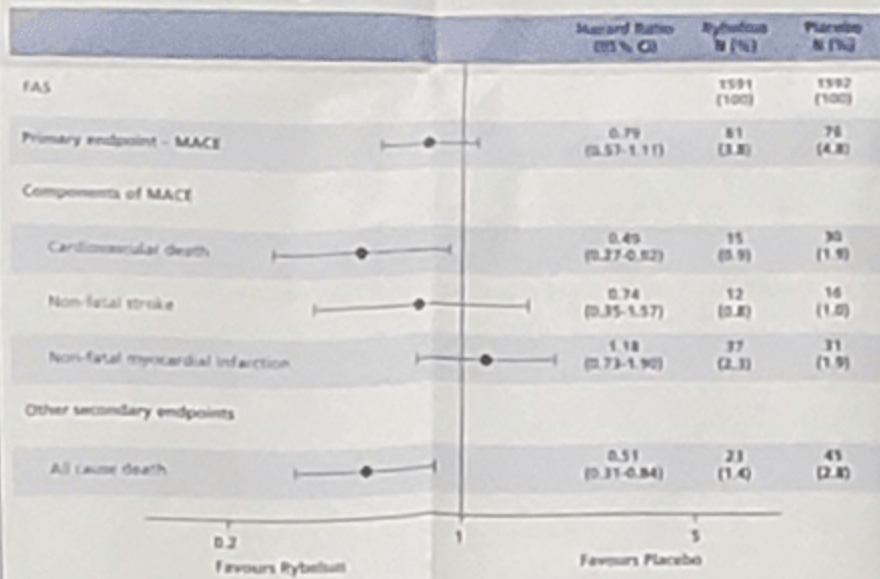


Figure 4 Forest plot: Treatment effect for the primary composite endpoint, its components and all cause death (PIONEER 6)

Combined analysis of SUSTAIN 6 and PIONEER 6
Consistent cardiovascular risk reduction was shown in SUSTAIN 6 and PIONEER 6. Consistent cardiovascular risk reduction was shown in 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 HbA_{1c} <7.0% were statistically significantly greater with Rybelus® 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 Rybelus® 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 Rybelus® than with placebo, sitagliptin, empagliflozin and liraglutide.

Body weight
Rybelus® 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). Rybelus® 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 Rybelus® 14 mg than with placebo, sitagliptin and liraglutide.

Fasting plasma glucose
Treatment with Rybelus® reduced FPG by up to 2.5 mmol/l across the phase 3a trials. The reductions were sustained through week 76.

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

Cardiovascular risk factors
Treatment with Rybelus® 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 dosing 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 Rybelus® 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 administration.

Distribution

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

Metabolism

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

Intrinsic factor	Relative Exposure (C _{avg}) Ratio and 90% CI	Recommendation
Sex	Male	No dose adjustment
Age group	65-74 years	No dose adjustment
	≥75 years	No dose adjustment
Race	Black or African American	No dose adjustment
	Asian	No dose adjustment
Ethnicity	Hispanic or Latino	No dose adjustment
Body weight	56 kg	No dose adjustment
	129 kg	No dose adjustment
Upper GI disease	With Upper GI disease	No dose adjustment
Renal function	Mild	No dose adjustment
	Moderate	No dose adjustment

Semaglutide exposure (C_{avg}) 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: C_{avg}: 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 impact the pharmacokinetics of semaglutide in patients with type 2 diabetes with or without upper GI tract disease 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.

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 agonists. In 2 year carcinogenicity studies in rats and mice, semaglutide caused thyroid agonists. In 2 year carcinogenicity studies in rats and mice, semaglutide caused thyroid agonists. In 2 year carcinogenicity studies in rats and mice, semaglutide caused thyroid agonists.

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-fetal 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.

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 NAAgree@novonordisk.com or Contact us at: +91 8040303200