This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION

Rybelsus® semaglutide

1. NAME OF THE MEDICINE

Rybelsus (semaglutide) 3 mg tablet blister pack
Rybelsus (semaglutide) 7 mg tablet blister pack
Rybelsus (semaglutide) 14 mg tablet blister pack

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

3. PHARMACEUTICAL FORM

Tablet for oral administration.

Tablets are white to light yellow, oval shaped, debossed with '3', '7' or '14' on one side and 'novo' on the other side.

One tablet contains 3 mg, 7 mg or 14 mg semaglutide.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

- as monotherapy if metformin is considered inappropriate due to intolerance or contraindications; or
- in combination with other medicinal products for the treatment of type 2 diabetes mellitus.

4.2 Dose and Method of Administration

Dosage

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 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 Dosage Adjustment).

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.

Dosage Adjustment
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 Warning and Precautions).

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.

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

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

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 section 5.2 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 endstage renal disease (see section 5.2 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.

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

4.4 Special Warnings and Precautions for Use
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 in patients with congestive heart failure New York Heart Association (NYHA) class IV and semaglutide is therefore not recommended in these patients.

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

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

Use in hepatic impairment
See section 5.2 – Special Populations

Use in renal impairment
See section 5.2 – Special Populations

Use in elderly
See section 5.2 – Special Populations

Paediatric use
The safety and efficacy of semaglutide in children and adolescents aged below 18 years has not been studied.

Effects on laboratory tests
No data available.

4.5 Interaction with Other Medicines and Other Form of 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 Rybelsus at the same time as levothyroxine.

Warfarin
Semaglutide did not change the AUC or Cmax 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 coadministered 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 Cmax 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 Rybelsus

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 Cmax 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).

4.6 Fertility, Pregnancy and Lactation

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

Effects on fertility
The effect of semaglutide on fertility in humans is unknown. Semaglutide did not affect male fertility in rats at subcutaneous doses up to 828 µg/kg/day (yielding 27 times the systemic exposure in patients at the maximum recommended human dose, based on plasma AUC). 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 (≥30 µg/kg/day SC, resulting in subclinical exposure).

Use in pregnancy
Pregnancy Category: D
Studies in animals have shown reproductive toxicity at clinically relevant exposure levels. 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.

In pregnant rats, embryofoetal toxicity (lethality, impaired growth and an increased incidence of foetal abnormalities) was observed with subcutaneous administration of semaglutide at ≥30 µg/kg/day, yielding systemic exposure (plasma AUC) below that of patients at the maximum recommended oral dose with Rybelsus. Mechanistic studies suggest a direct GLP-1 receptor mediated role of semaglutide on some of the effects in rats (species specific). In pregnant rabbits, pharmacologically mediated reductions in maternal body weight gain and food consumption were observed at all dose levels. Early pregnancy losses and increased incidences of minor visceral (kidney, liver) and skeletal (sternebra) foetal abnormalities were observed at ≥2.5 µg/kg/day SC, yielding subclinical exposure. In pregnant cynomolgus monkeys, pharmacologically mediated, marked initial maternal body weight loss and reductions in body weight gain and food consumption coincided with the occurrence of sporadic abnormalities (vertebra, sternebra, ribs) and with an increase in early pregnancy losses at ≥ 75 µg/kg SC twice weekly (≥ 6 fold clinical exposure with oral administration at 14 mg/day). Exposures at the no observed adverse effect level in the three laboratory animal species were below or only marginally higher than the plasma AUC at the maximum recommended dose in patients, and a direct effect of semaglutide on the foetus cannot be excluded.

Use in lactation

In lactating rats, semaglutide was excreted in milk. As a risk to a breast-fed child cannot be excluded, Rybelsus should not be used during breast-feeding.

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 Adverse Effects (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.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

Tabulated List of Adverse Events

Table 1: Treatment-emergent adverse events with frequency ≥ 5% comparing Rybelsus with comparators

Adverse Event Term	Rybelsus[#] % (n=4116)	Comparator[*] % (n=2236)
Nausea	15.4	6.3
Nasopharyngitis	10.4	9.9
Diarrahoea	10.1	5.7
Vomiting	6.6	2.8
Headache	5.9	5.2
Constipation	5.8	3.7
Decreased appetite	5.0	2.0

[#] Data from all three oral semaglutide doses (3, 7 and 14 mg).

[*] Comparator: sitagliptin, empagliflozin, liraglutide, dulaglutide and placebo.

Adverse Reactions

Table 2 lists adverse reactions identified in all phase 3a trials in patients with type 2 diabetes (further described in section 5.1). 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.

Table 2: Adverse reactions from controlled phase 3a trials

MedDRA system organ class		Very common	Common	Uncommon	Rare
Immune-system disorders					Anaphylactic reaction
Metabolism and nutrition disorders		Hypoglycaemia [a] when used with insulin or sulfonylurea[a]	Hypoglycaemia [a] 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	Eructation	Acute pancreatitis

			Abdominal distension Constipation Dyspepsia Gastritis Gastro-oesophageal reflux disease Flatulence		
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 subcutaeous semaglutide, but it cannot be excluded that the risk of diabetic retinopathy complications identified also applies to Rybelsus

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

complication was only performed in the cardiovascular outcomes trial with subcutaneous semaglutide.

In clinical trials with Rybelsus of up to 18 months duration involving 6,352 patients with type 2 diabetes, adverse events related to diabetic retinopathy were reported in similar proportions in subjects treated with semaglutide (4.2%) and comparators (3.8%).

Discontinuation due to an adverse event
Discontinuation of treatment due to adverse events was 9% for patients treated with Rybelsus. The rate of discontinuation increased with semaglutide dose and occurred more frequently in the dose-escalation phase. The events leading to discontinuation were predominantly gastrointestinal, particularly nausea and vomiting.

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.

Reporting adverse events
Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

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. 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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

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 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. GLP-1 receptors are also expressed in the heart, vasculature and immune system and kidney from where it may mediate cardiovascular and microvascular effects. Compared to native GLP-1, semaglutide has a prolonged half-life of around 1 week. The principal mechanism of protraction is albumin binding, which results in decreased renal clearance and protection from metabolic degradation.

Furthermore, semaglutide is stabilised against degradation by the DPP-4 enzyme. Semaglutide reduces blood glucose through a mechanism where it stimulates insulin secretion and lowers glucagon secretion, both in a glucose-dependent manner. Thus, when blood glucose is high, insulin secretion is stimulated and glucagon secretion is inhibited. 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. Semaglutide reduces body weight and body fat mass through lowered energy intake, involving an overall reduced appetite, which includes increased satiety and reduced hunger, as well as improved control of eating and decreased food cravings. Insulin resistance is also reduced, probably through reduction in body weight. In addition, semaglutide reduces the preference for high fat foods. Semaglutide had a beneficial effect on plasma lipids, lowered systolic blood pressure and reduced inflammation in clinical studies. In animal studies, semaglutide attenuates the development of atherosclerosis by preventing aortic plaque progression and reducing inflammation in the plaque.

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 plasma glucose and postprandial increments

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.

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 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 trials
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 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 phase 3a trials comprised 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, empagliflozin, sitagliptin, liraglutide and dulaglutide.

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 – 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 3: Results of a 26-week monotherapy trial comparing semaglutide with placebo (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	69§	77§	31
FPG (mmol/l)			
Baseline	9.0	8.8	8.9
Change from baseline	-1.5	-1.8	-0.2
Difference from placebo [95% CI]	-1.4 [-1.9; -0.8]§	-1.6 [-2.1; -1.2]§	
Body weight (kg)			
Baseline	89.0	88.1	88.6
Change from baseline	-2.3	-3.7	-1.4
Difference from placebo [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, 822 patients with type 2 diabetes were randomised to Rybelsus 14 mg 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 4: Results of a 52 week trial comparing semaglutide with empagliflozin (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	−1.3	−0.9
Difference from empagliflozin[1] [95% CI]	−0.4 [−0.6; −0.3]*	-
Patients (%) achieving HbA_{1c} <7%[2]	67§	40
FPG (mmol/l)		
Baseline	9.5	9.7
Change from baseline[1]	−2.0	−2.0
Difference from empagliglozin[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 HbA1c <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, 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 5: Results of a 78 week trial comparing semaglutide with sitagliptin (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 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 an SGLT2 inhibitor

In a 52-week double-blind, double-dummy trial (26-week primary endpoint), 711 patients with type 2 diabetes were randomized 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 6: Results of a 52 week trial comparing semaglutide with liraglutide and placebo (PIONEER 4)

	Rybelsus® 14 mg	Liraglutide 1.8 mg	Placebo
Full analysis set (N)	285	284	142
Week 26			
HbA_{1c} (%)			
Baseline	8.0	8.0	7.9
Change from baseline[1]	−1.2	−1.1	−0.2
Difference from liraglutide[1] [95% CI]	−0.1 [−0.3; 0.0]	-	-
Difference from placebo[1] [95% CI]	−1.1 [−1.2; −0.9]*	-	-
Patients (%) achieving HbA_{1c} <7.0%	68§	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 m^2) were randomised to Rybelsus 14 mg or placebo once daily. Trial product was added to the patient's stable pretrial 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% was 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 HbA1c and body weight compared with placebo.

Table 7: Results of a 26 week trial comparing semaglutide with placebo in patients with type 2 diabetes and moderate renal impairment (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, all 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 randomized 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 8: Results of a 52 week flexible-dose-adjustment trial comparing semaglutide with sitagliptin (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 randomisation 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 randomisation. After the 26 weeks, patients were allowed to adjust the insulin dose as needed. At randomisation, 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 HbA1c and body weight compared with placebo (Table 8).

Table 9: Results of a 52 week trial comparing semaglutide with placebo in combination with insulin (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] [95% CI]	−0.6 [−0.8; −0.4]§	−0.9 [−1.1; −0.7]§	-
Patients (%) achieving HbA_{1c} <7.0%	40§	54§	9
Body weight (kg)			
Change from baseline[1]	−2.0	−3.7	0.5
Difference from placebo[1] [95% CI]	−2.5 [−3.6; −1.4]§	−4.3 [−5.3; −3.2]§	-

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

Cardiovascular evaluation

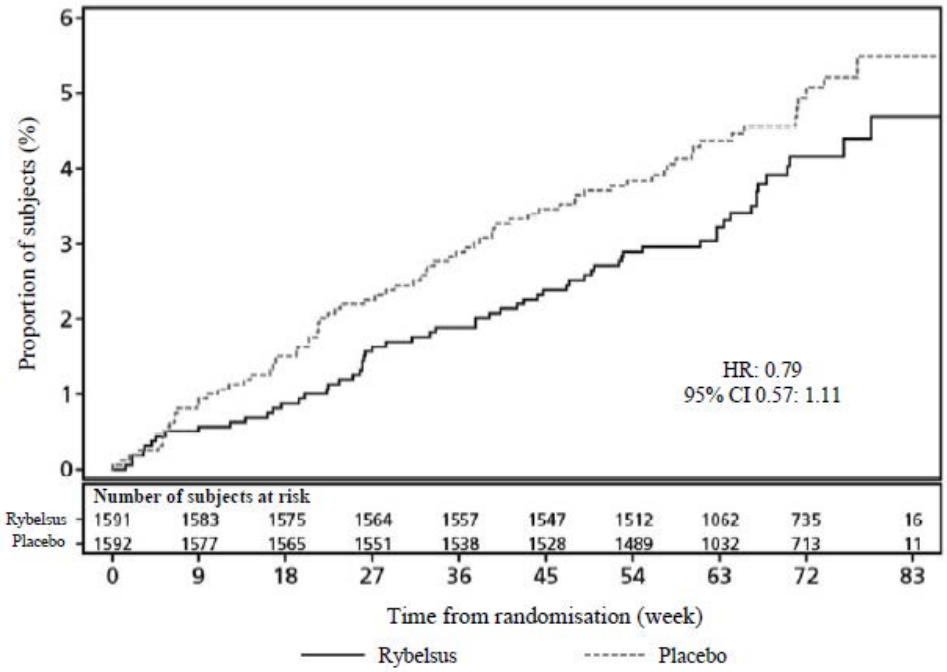
PIONEER 6

In a double-blind cardiovascular outcomes 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 32.3 kg/m^2. Medical history included stroke (11.7%) and myocardial infarction (36.1%).

The total number of first MACE (cardiovascular death, non-fatal myocardial infarction or non -fatal stroke) was 137: 61 (3.8%) with Rybelsus and 76 (4.8%) with placebo. The analysis of time to first MACE (cardiovascular death, non-fatal myocardial infarction or non -fatal stroke) resulted in a HR of 0.79 (95% CI: 0.57, 1.11).



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 1: 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.

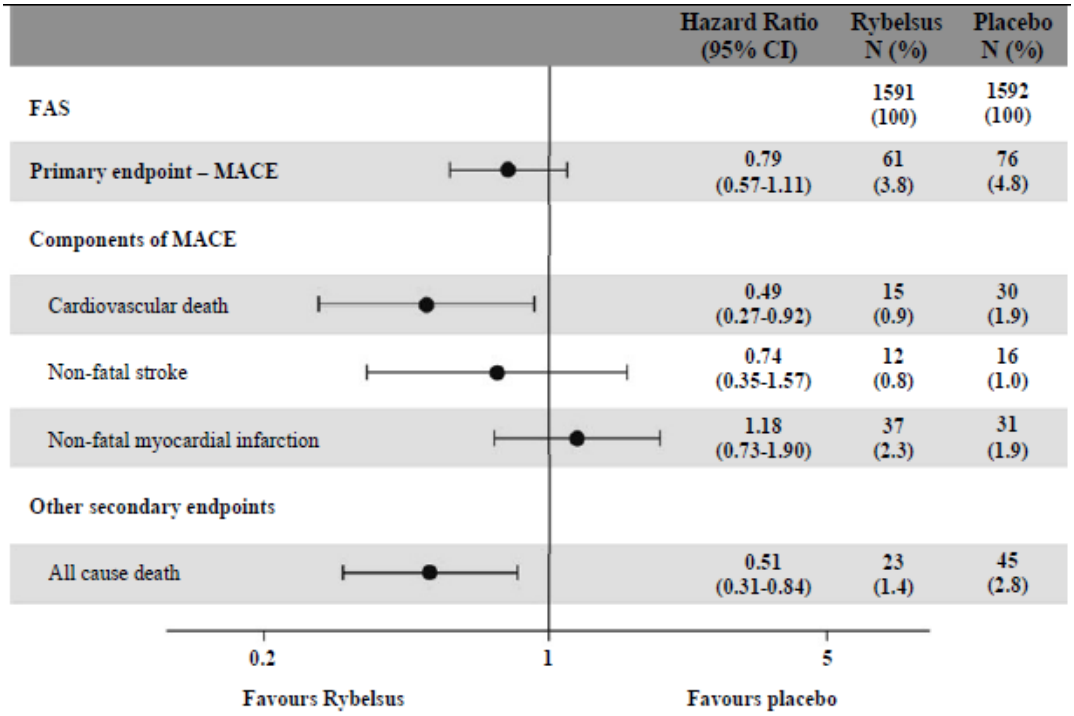


Figure 2: Forest plot: Treatment effect for the primary composite endpoint, its components and all cause death (PIONEER 6)

Body weight
By end-of-treatment, 27-45% of the patients had achieved a weight loss of ≥5% and 6-16% had achieved a weight loss of ≥10% with semaglutide, compared with 12-39% and 2-8%, respectively, with the active comparators.

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

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 antisemaglutide 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.

5.2 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 semaglutide 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%).

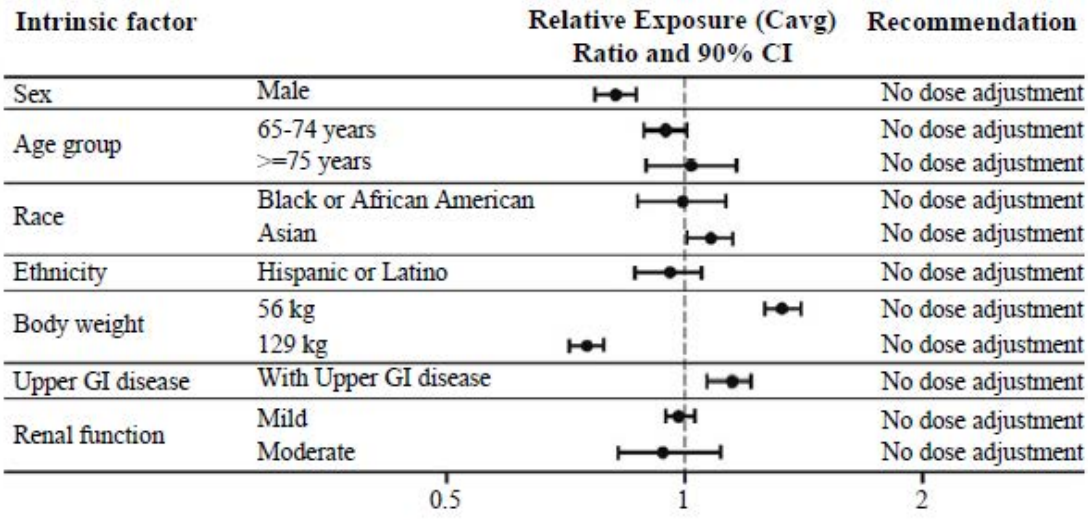
Metabolism
Semaglutide is metabolised through proteolytic cleavage of the peptide backbone and sequential beta-oxidation of the fatty acid sidechain.

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 3: 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 effect on 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 endstage 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 oncedaily 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 6).

Paediatrics
Semaglutide has not been studied in paediatric patients.

5.3 Preclinical Safety Data

Genotoxicity
Semaglutide was not mutagenic in the bacterial reverse mutation assay, and was not clastogenic in vitro (cytogenetic assay in human lymphocytes), or in vivo (rat bone marrow micronucleus test).

Carcinogenicity
Non-lethal thyroid C-cell tumours observed in rodents are a class effect for GLP-1 receptor agonists. In 2-year carcinogenicity studies in rats and mice, semaglutide caused thyroid C-cell tumours at clinically relevant exposures (≥ 7 times the clinical AUC at the maximum recommended human dose of 14 mg/day for mice, and below the clinical AUC in rats; a no effect level was not established in either species). 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.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients
Salcaprozate sodium
Povidone
Microcrystalline cellulose
Magnesium Stearate

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf Life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special Precautions for Storage

Store below 30°C.
Store in original blister package to protect from moisture and light

6.5 Nature and Contents of Container

Rybelsus is provided in alu/alu blister cards which contain 3 mg, 7 mg or 14 mg semaglutide tablets.

The tablets are available in pack sizes of 10 (excluding 3 mg), 30, 60 and 90 tablets*.
*Not all presentations or pack sizes may available.

6.6 Special Precautions for Disposal

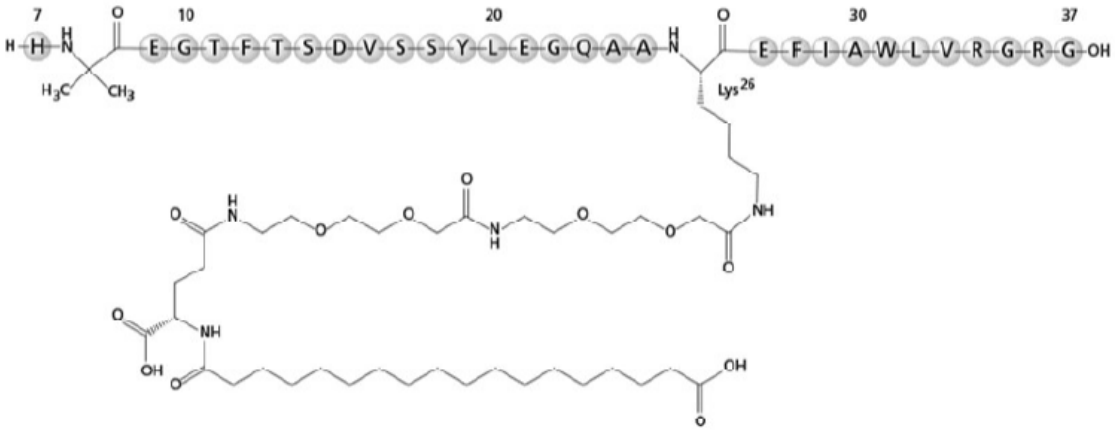
In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 Physicochemical Properties

Chemical structure

Molecular formula: $C_{187}H_{291}N_{45}O_{59}$

Molecular weight: 4113.58 Dalton



CAS number
CAS No. RN910463-68-2

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4

8. SPONSOR

Novo Nordisk Pharmaceuticals Pty Limited
Level 10, 118 Mount Street
North Sydney NSW 2060
Australia.

9. DATE OF FIRST APPROVAL

07 February 2022

10. DATE OF REVISION

N/A

Attachment 1: Product information for AusPAR - Rybelsus - semaglutide - Novo Nordisk Pharmaceuticals Pty Ltd - PM-2020-03921-1-5 Final 27 October 2022. This is the Product Information that was approved with the submission described in this AusPAR. It may have been superseded. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/products/australian-register-therapeutic-goods-artg/product-information-one>

Summary table of changes

Section changed	Summary of new information
N/A	New registration