Product Monograph

Including Patient Medication Information

RYBELSUS®

semaglutide tablets

Tablet for oral administration

Produced by recombinant DNA technology in Saccharomyces cerevisiae

3 mg, 7 mg and 14 mg tablets
or
1.5 mg, 4 mg and 9 mg tablets

Glucagon-like Peptide-1 (GLP-1) Receptor Agonist

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Part 1: Healthcare Professional Information

1. Indications

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

- as monotherapy when metformin is considered inappropriate due to intolerance or contraindications;
- in combination with other medicinal products for the treatment of diabetes (see 14. Clinical Trials for patient populations and drug combinations tested).
- to reduce the risk of major adverse cardiovascular (CV) events (CV death, non-fatal myocardial infarction or non-fatal stroke) in adults with type 2 diabetes mellitus who have established cardiovascular disease or are at high risk for these events.

1.1. Pediatrics

Pediatrics (< 18 years of age): The safety and efficacy of RYBELSUS® have not been studied in pediatric populations. RYBELSUS® is not indicated for use in pediatric patients.

1.2 Geriatrics

Geriatrics (≥ 65 years of age): Evidence from a pooled analysis of phase III clinical studies suggests that use in the geriatric population (n=1229) was associated with no significant differences in safety or efficacy, but greater sensitivity of some older individuals cannot be ruled out. Therapeutic experience in patients ≥ 75 years of age is limited (7.1.4 Geriatrics).

2. Contraindications

RYBELSUS® is contraindicated in patients who are hypersensitive to RYBELSUS® or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see Dosage Forms, Strengths, Composition and Packaging. See 7. Warnings and Precautions, Immune.

RYBELSUS® is contraindicated in patients who have a personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). See 7. Warnings and Precautions, Carcinogenesis and Mutagenesis.
RYBELSUS® should not be used during pregnancy or breastfeeding. See 7.1.1 Pregnant Women and 7.1.2 Breastfeeding.

3. Serious Warnings and Precautions Box

Risk of Thyroid C-cell Tumours

- Semaglutide causes treatment-dependent thyroid C-cell tumours at clinically relevant exposures in both genders of rats and mice (see 7. Warnings and Precautions and 16. Non-Clinical Toxicology). It is unknown whether semaglutide causes thyroid C-cell tumours, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be ruled out by clinical or nonclinical studies.
- RYBELSUS® is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). It is unknown whether monitoring with serum calcitonin or thyroid ultrasound will mitigate human risk of thyroid C-cell tumours. Patients should be counseled regarding the risk and symptoms of thyroid tumours (see 2. Contraindications, 7. Warnings and Precautions, and 16. Non-Clinical Toxicology).

4. Dosage and Administration

4.1. Dosing Considerations

- Do not take more than one tablet of RYBELSUS® daily. Do not take two or more tablets of RYBELSUS® to obtain a higher dose.

4.2. Recommended Dose and Dosage Adjustment

Different RYBELSUS® tablets are available:

- Initial Formulation of RYBELSUS® tablets: 3 mg, 7 mg, 14 mg.
- Optimized Formulation of RYBELSUS® tablets: 1.5 mg, 4 mg, 9 mg.

Initial Formulation of RYBELSUS® 3 mg, 7 mg, 14 mg tablets:
The starting dose of RYBELSUS® is 3 mg once daily. After 30 days, the dose should be increased to a maintenance dose of 7 mg once daily. If additional glycemic control is needed after at least 30 days on the 7 mg dose, the dose can be increased to a maintenance dose of 14 mg once daily. This regimen is intended to mitigate gastrointestinal symptoms during dose escalation.
The maximum recommended single daily dose of oral semaglutide is 14 mg.

Optimized Formulation of RYBELSUS® 1.5 mg, 4 mg, 9 mg tablets:
The starting dose of RYBELSUS® is 1.5 mg once daily. After 30 days, the dose should be increased to a maintenance dose of 4 mg once daily. If additional glycemic control is needed after at least 30 days on the 4 mg dose, the dose can be increased to a maintenance dose of 9 mg once daily. This regimen is intended to mitigate gastrointestinal symptoms during dose escalation.
The maximum recommended single daily dose of oral semaglutide is 9 mg.

The equivalent dosage between the initial and the optimized formulation of RYBELSUS® is shown in Table 1

Table 1 – RYBELSUS® equivalent tablets

Dose	One tablet of the optimized formulation of RYBELSUS®	equivalent to	One tablet of the initial formulation of RYBELSUS®
Starting dose	1.5 mg	=	3 mg
Maintenance dose	4 mg	=	7 mg
	9 mg	=	14 mg

The 1.5 mg tablet of the optimized formulation of RYBELSUS® and 3 mg tablets of the initial formulation of RYBELSUS® are intended for treatment initiation (starting dose) and are not intended for glycemic control.

The maximum recommended single daily dose of oral semaglutide is either 9 mg tablet of the optimized formulation of RYBELSUS® or 14 mg tablets of the initial formulation of RYBELSUS®
.
Taking more than one tablet to achieve a higher dose is not recommended.

The safety and efficacy of RYBELSUS® in children and adolescents below 18 years have not been studied (see 1.1 Pediatrics).

No dose adjustment of RYBELSUS® is recommended based on age, sex, race, ethnicity, upper gastrointestinal disease, or hepatic impairment.

Patients with Renal Insufficiency
No dose adjustment is required for patients with mild, moderate or severe renal impairment. Experience with the use of semaglutide in patients with end-stage kidney disease is limited (see 10.3. Pharmacokinetics). Monitor renal function, especially in the case of severe GI side effects (nausea, vomiting, diarrhea), because dehydration can worsen kidney function

4.4. Administration

RYBELSUS® must be taken on an empty stomach at least 30 minutes before the first food, beverage or other oral medications of the day. Waiting less than 30 minutes is likely to decrease the amount of semaglutide absorbed.

RYBELSUS® should be taken with no more than half a glass of water equivalent to 120 mL. A larger volume of water is likely to decrease the amount of semaglutide absorbed.
RYBELSUS® should be swallowed whole. Do not split, crush or chew.

4.5. Missed Dose

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

5. Overdose

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

Clinical trials have studied repeat doses of RYBELSUS® of up to 40 mg. Overdose with semaglutide may be associated with gastrointestinal disorders (e.g., nausea). All patients in

clinical studies who reported overdosing with semaglutide recovered without complications. Ensure that patients are instructed that only a single tablet of RYBELSUS® should be administered daily.

There is no specific antidote for overdose with RYBELSUS®. 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 for these symptoms may be necessary, taking into account the long half-life of RYBELSUS® of approximately 1 week.

6. Dosage Forms, Strengths, Composition, and Packaging

Table 2 – Dosage Forms, Strengths, and Composition

Route of Administration	Dosage Form/ Strength/Composition	Non-medicinal Ingredients
Oral	Initial Formulation of RYBELSUS® Tablet / 3 mg, 7 mg, 14 mg	Magnesium stearate, microcrystalline cellulose, povidone K 90 and salcaprozate sodium (SNAC)
Oral	Optimized Formulation of RYBELSUS® Tablet / 1.5 mg, 4 mg, 9 mg	Magnesium stearate, Salcaprozate sodium (SNAC)

Each Initial Formulation of RYBELSUS® tablet contains 3 mg, 7 mg or 14 mg of semaglutide and 300 mg of SNAC.
Each Optimized Formulation of RYBELSUS® tablet contains 1.5 mg, 4 mg or 9 mg of semaglutide and 100 mg of SNAC.
SNAC is a semaglutide absorption enhancer.

The physical characteristics of the tablets and their packaging are as follows:

Initial Formulation of RYBELSUS® 3 mg, 7 mg and 14 mg tablets:
- 3 mg tablets are white to light yellow, oval shaped debossed with "3" on one side and "novo" on the other side. The tablets are supplied in green coloured cartons containing alu/alu blisters in pack sizes of 30, 60 or 90 tablets.
- 7 mg tablets are white to light yellow, oval shaped debossed with "7" on one side and "novo" on the other side. The tablets are supplied in red coloured cartons containing alu/alu blisters in pack sizes of 30, 60 or 90 tablets.
- 14 mg tablets are white to light yellow, oval shaped debossed with "14" on one side and "novo" on the other side. The tablets are supplied in blue coloured cartons containing alu/alu blisters in pack sizes of 30, 60 or 90 tablets.

Optimized Formulation of RYBELSUS® 1.5 mg, 4 mg and 9 mg tablets:
- 1.5 mg tablets are white to light yellow, round tablets debossed with "1.5" on one side and "novo" on the other side. The tablets are supplied in green coloured cartons containing alu/alu blisters in pack sizes of 30 tablets.
- 4 mg tablets are white to light yellow, round tablets debossed with "4" on one side and "novo" on the other side. The tablets are supplied in red coloured cartons containing alu/alu blisters in pack sizes of 30 or 90 tablets.

- 9 mg tablets are white to light yellow, round tablets debossed with “9” on one side and “novo” on the other side. The tablets are supplied in blue coloured cartons containing alu/alu blisters in pack sizes of 30 or 90 tablets.

7. Warnings and Precautions

General

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

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

Carcinogenesis and Genotoxicity

Risk of Thyroid C-Cell Tumours
In mice and rats, semaglutide caused a treatment-duration-dependent increase in the incidence of thyroid C-cell tumours (adenomas and carcinomas) after lifetime exposure at clinically relevant plasma exposures (see 16. Non-Clinical Toxicology). It is unknown whether semaglutide causes thyroid C-cell tumours, including Medullary Thyroid Carcinoma (MTC), in humans as human relevance could not be determined. Thyroid C-cell tumours in rodents are a known class effect for GLP-1 receptor agonists.

Cases of MTC have been observed in patients treated with GLP-1 receptor agonists in clinical trials and the post-marketing period. The data is insufficient to establish or exclude a causal relationship between MTC and GLP-1 receptor agonists use in humans.

It is unknown whether monitoring with serum calcitonin or thyroid ultrasound will mitigate the potential risk of MTC, and such monitoring may increase the risk of unnecessary procedures, due to low test specificity for serum calcitonin and a high background incidence of thyroid disease. Patients with thyroid nodules noted on physical examination or neck imaging obtained for other reasons should be referred to an endocrinologist for further evaluation. Although routine monitoring of serum calcitonin is of uncertain value in patients treated with RYBELSUS® if serum calcitonin is measured and found to be elevated, the patient should be referred to an endocrinologist for further evaluation.

Cardiovascular

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.

Heart Rate Increase
Semaglutide causes an increase in heart rate (see 10. Clinical Pharmacology). Caution should be observed in patients who have cardiac conditions that might be worsened by an increase in heart rate, such as tachyarrhythmias (see 9. Drug Interactions).

PR Interval Prolongation
Semaglutide causes a prolongation of the PR interval of the electrocardiogram (see 10. Clinical Pharmacology). Caution should be observed in patients with pre-existing conduction system

abnormalities (e.g., marked first-degree AV block or second- or third-degree AV block) or a history of rhythm disturbances (e.g., tachyarrhythmias).

Driving and Operating Machinery

In rare cases, RYBELSUS® has the potential to cause hypoglycemia, which may impact an individual's ability to drive or use machines. When RYBELSUS® is used in combination with a sulfonylurea or insulin, patients should be advised to take precautions to avoid hypoglycemia while driving and using machines.

Dizziness can be experienced initially during dose escalation. Driving or use of machines should be avoided if dizziness occurs.

Endocrine and Metabolism

Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin
Patients treated with semaglutide in combination with an insulin secretagogue (e.g., sulfonylureas) or insulin may have an increased risk of hypoglycemia. The risk of hypoglycemia may be lowered by reducing the dose of the secretagogue or insulin when initiating treatment with RYBELSUS®.

Gastrointestinal

Use of GLP-1 receptor agonists may be associated with severe gastrointestinal disease (ileus). (see 8.5 Post-Market Adverse Reactions).

In placebo-controlled clinical trials, mild-moderate gastrointestinal events occurred more frequently in patients receiving RYBELSUS® than placebo, and included nausea, diarrhea, and vomiting (see 8.2 Clinical Trial Adverse Reactions). Gastrointestinal adverse events may be co-reported with dizziness.

Patients with gastroparesis

Semaglutide treated patients with gastroparesis may experience more serious or severe gastrointestinal adverse events. Semaglutide is not recommended in patients with severe gastroparesis (see 8. Adverse Reactions).

Events of delayed gastric emptying, dysgeusia, intestinal obstruction, and ileus have been reported in the post marketing database.

Hepatic/Biliary/Pancreatic

Pancreatic
Acute pancreatitis has been observed with the use of GLP-1 receptor agonists. In glycemic control trials, pancreatitis was reported as a serious adverse event in 6 RYBELSUS®-treated patients (0.1 cases per 100 patient years) versus 1 in comparator-treated patients (<0.1 cases per 100 patient years).

In phase 3b cardiovascular outcome trial SOUL, the frequency of acute pancreatitis confirmed by adjudication was 0.4 % for semaglutide and 0.4 % for placebo.

Patients should be informed of the characteristic symptoms of acute pancreatitis. After initiation of RYBELSUS®, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back and which may or may not be accompanied by vomiting). If pancreatitis is suspected, RYBELSUS® should be discontinued and appropriate management initiated; if confirmed, RYBELSUS® should not be restarted.

There is limited clinical experience regarding the safety profile of RYBELSUS® in patients with mild, moderate or severe hepatic insufficiency.

Acute Gall Bladder Disease
Acute events of gallbladder disease such as cholelithiasis or cholecystitis have been reported in GLP-1 receptor agonist trials and post-market (see 8. Adverse Reactions). Patients should be informed of the characteristic symptoms of gallbladder disease (e.g., severe or persistent abdominal pain, fever, jaundice). Evaluate patients with suspected gallbladder disorders promptly and instruct patients to contact their physician for appropriate clinical follow-up if gallbladder disease is suspected. If cholelithiasis or cholecystitis are suspected, gallbladder studies and appropriate clinical follow-up are indicated.

Immune

Hypersensitivity
Serious hypersensitivity reactions, including anaphylaxis, may occur with any GLP-1 receptor agonist, including RYBELSUS®. If a hypersensitivity reaction occurs, the patient should discontinue RYBELSUS® and promptly seek medical advice. Do not use in patients with a previous hypersensitivity to RYBELSUS®. Caution should be exercised with a history of angioedema or anaphylaxis with another GLP-1 receptor agonist because it is unknown whether such patients will be predisposed to anaphylaxis with RYBELSUS®.

Monitoring and Laboratory Tests

Regular self-monitoring of blood glucose is not needed in order to adjust the dose of RYBELSUS®. However, when initiating treatment with RYBELSUS® in combination with a sulfonylurea or insulin it may become necessary to reduce the dose of the sulfonylurea or insulin in order to reduce the risk of hypoglycemia.

However, patients should be informed that response to all diabetic therapies should be monitored by periodic measurement of HbA_{1C} levels, with a goal of decreasing these levels towards the normal range. HbA_{1C} is especially useful for evaluating long-term glycemic control.

Ophthalmologic

Diabetic Retinopathy
In a pooled analysis of glycemic control trials with RYBELSUS®, patients reported diabetic retinopathy related adverse reactions during the trial (4.2% with RYBELSUS® and 3.8% with comparator).

Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy. Long-term glycemic 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.

Non-arteritic anterior ischaemic optic neuropathy (NAION)
Data from epidemiological studies suggest an increased risk of non-arteritic anterior ischaemic optic neuropathy (NAION) with a very rare frequency during treatment with semaglutide. There is no identified time interval for when NAION may develop following treatment start. Patients reporting a sudden loss of vision (including partial loss) should be urgently referred for ophthalmological examination and treatment with semaglutide should be discontinued if NAION is confirmed.

Perioperative Considerations

Aspiration in association with general anaesthesia or sedation

RYBELSUS® delays gastric emptying. Pulmonary aspiration has been reported in patients receiving GLP-1 receptor agonists undergoing general anaesthesia or sedation. This should be considered prior to such procedures.

Renal

Renal Insufficiency and dehydration
Use of GLP-1 receptor agonists may be associated with gastrointestinal adverse reactions. This should be considered when treating patients with impaired renal function as nausea, vomiting, and diarrhoea, may cause dehydration, which could cause a deterioration of renal function. Monitor renal function in patients with renal insufficiency reporting severe adverse gastrointestinal reactions.

In patients treated with GLP-1 receptor agonists, there have been post-marketing reports of acute renal failure and worsening of chronic renal failure, which may sometimes require hemodialysis. Some of these events were reported in patients without known underlying renal disease.

The safety and efficacy of RYBELSUS® was evaluated in a 26-week clinical study that included patients with moderate renal impairment (eGFR 30 to 59 mL/min/1.73m^2) and no overall differences in safety were observed.

Reproductive Health

- **Fertility**

The effect of semaglutide on fertility in humans is unknown. In female rats, following administration of subcutaneous semaglutide, an increase in oestrous length and a small reduction in number of ovulations were observed at doses associated with maternal body weight loss.

7.1. Special Populations

7.1.1. Pregnancy

The extent of exposure in pregnancy during clinical trials was very limited and there are no adequate and well-controlled studies of RYBELSUS® in pregnant women. Therefore, RYBELSUS® should not be used during pregnancy. Women of childbearing potential are recommended to use contraception when treated with semaglutide. 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 of semaglutide (see 10. Clinical Pharmacology).

Use of RYBELSUS® during pregnancy may cause fetal harm based on animal studies. Animal studies with subcutaneous semaglutide have shown reproductive and developmental toxicity at exposures below human exposure levels. Adverse developmental effects included fetal malformations in rats, rabbits, and monkeys and pre- and post-natal losses in monkeys. In addition, SNAC was shown to result in fetotoxicity in rats (increase in the number of dams with stillborn pups) at a maternal dose of 1000 mg/kg/day (see 16. Non-Clinical Toxicology).
As semaglutide and SNAC have both been demonstrated to cause developmental toxicity in animals, there may be a potential risk for an additive adverse developmental effect from exposure to RYBELSUS® during pregnancy.

7.1.2. Breastfeeding

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

No measurable concentrations of semaglutide were found in breastmilk of lactating women. Salcaprozate sodium was present in breastmilk and some of its metabolites were excreted in breastmilk at low concentrations. As a risk to a breast-fed child cannot be excluded, RYBELSUS® should not be used during breast-feeding.

7.1.3. Pediatrics

Pediatrics (< 18 years): The safety and efficacy of RYBELSUS® have not been studied in pediatric populations. RYBELSUS® is not indicated for use in pediatric patients.

7.1.4. Geriatrics

Geriatrics (≥65 years of age): In the pool of glycemic control trials, 1229 (29.9%) RYBELSUS®-treated patients were 65 years of age or over and 199 RYBELSUS®-treated patients (4.8%) patients were 75 years of age and over. In PIONEER 6, the cardiovascular outcome trial, 891 (56.0%) RYBELSUS®-treated patients were 65 years of age or older and 200 RYBELSUS®-treated patients (12.6%) were 75 years of age and over.
No overall differences in safety were detected between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8. Adverse Reactions

8.1. Adverse Reaction Overview

The most frequently reported adverse reactions in clinical trials and post marketing reports in patients with type 2 diabetes were gastrointestinal disorders (including nausea, diarrhea, and vomiting). In general, these reactions were mild or moderate in severity, although some post-

marketing reports described severe reactions. More patients taking RYBELSUS® versus comparator drugs had severe or serious adverse events and/or discontinued treatment due to gastrointestinal disorders.

The following serious adverse reactions are described below or elsewhere in the Product Monograph (see 7. Warnings and Precautions):

- Risk of Thyroid C-cell Tumours
- Pancreatitis
- Diabetic Retinopathy
- Hypoglycemia with Concomitant Use of Insulin or Sulfonylureas
- Renal Insufficiency
- Hypersensitivity
- Ileus

8.2. Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

In 10 phase 3a trials, 5707 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, diarrhea and vomiting. In general, these reactions were mild or moderate in severity and of short duration.

In the cardiovascular outcomes trial (SOUL), including 9 650 adults with type 2 diabetes and established cardiovascular disease and/or chronic kidney disease, the safety profile was consistent with the safety profile of RYBELSUS® seen in the phase 3a trials.

Pool of Placebo-Controlled Trials

The data in Table 2 are derived from 2 placebo-controlled trials [1 monotherapy trial (PIONEER 1) and 1 trial in combination with insulin (PIONEER 8)] in patients with type 2 diabetes (see 14. Clinical Trials). These data reflect exposure of 1071 patients to RYBELSUS® and a mean duration of exposure to RYBELSUS® of up to 41.8 weeks. Across the treatment arms, the mean age of patients was 58 years, 3.9% were 75 years or older and 52% were male. In these trials 63% were White, 6% were Black or African American, and 27% were Asian; 19% identified as Hispanic or Latino ethnicity. At baseline, patients had type 2 diabetes for an average of 9.4 years and had a mean HbA_{1c} of 8.1%. At baseline, 20.1% of the population reported retinopathy. Baseline estimated renal function was normal (eGFR ≥ 90 mL/min/1.73m2) in 66.2%, mildly impaired (eGFR 60 to 90 mL/min/1.73m2) in 32.4% and moderately impaired (eGFR 30 to 60 mL/min/1.73m2) in 1.4% of patients.

Pool of Placebo- and Active-Controlled Trials

In a pool of 9 phase 3a trials, 4116 patients were exposed to RYBELSUS® with a mean duration of exposure to RYBELSUS® of 55.5 weeks. The mean age of patients was 58 years, 5.0% were 75 years or older and 55% were male. In these trials 65% were White, 6% were Black or African

American, and 24% were Asian; 15% identified as Hispanic or Latino ethnicity. At baseline, patients had type 2 diabetes for an average of 8.8 years and had a mean HbA_{1c} of 8.2%. At baseline, 16.6% of the population reported retinopathy. Baseline estimated renal function was normal (eGFR ≥ 90 mL/min/1.73m2) in 65.9%, mildly impaired (eGFR 60 to 90 mL/min/1.73m2) in 28.5% and moderately impaired (eGFR 30 to 60 mL/min/1.73m2) in 5.4% of patients.

Common Adverse Reactions

Table 2 shows common adverse reactions, excluding hypoglycemia, associated with the use of RYBELSUS® in the pool of placebo-controlled trials (PIONEER 1 and PIONEER 8). These adverse reactions occurred more commonly on RYBELSUS® than on placebo, and occurred in at least 1% of patients treated with RYBELSUS®.

Table 3 – Adverse Reactions in Placebo-Controlled Trials Reported in ≥1% of RYBELSUS®-Treated Patients with Type 2 Diabetes Mellitus[a]

	RYBELSUS® 7 mg (N=356) %	RYBELSUS® 14 mg (N=356) %	Placebo (N=362) %
Eye Disorders			
Dry eye	1.7	0	0.3
Diabetic Retinopathy	3.7	2.8	2.8
Gastrointestinal			
Nausea	11.0	19.7	6.4
Diarrhea	8.7	10.1	4.1
Vomiting	6.2	8.4	3.0
Constipation	5.9	5.3	2.5
Abdominal pain	10.1	10.7	4.1
Abdominal Distension	1.7	2.8	1.1
Gastrooesophageal reflux disease	1.7	2.2	0.3
Eructation	0.6	2.0	0
Flatulence	1.7	1.1	0
Gastritis	1.7	1.7	0.8
Dyspepsia	3.1	0.6	0.6
General Disorders and Administration Site Conditions			
Pyrexia	0.8	1.7	1.1
Fatigue	3.7	2.8	0
Infections and Infestations			
Upper Respiratory Tract Infection	2.2	3.9	3.6
Urinary Tract Infections	1.7	3.7	3.3
Influenza	3.4	3.4	2.5
Injury, Poisoning and Procedural Complications			
Contusion	0.6	2.2	0.8
Fall	1.1	0.6	0.3
Hepatobiliary Disorders			
Cholelithiasis	1.1	0	0
Investigations			
Weight Decreased	0.6	1.4	0.3

Blood Creatinine Phosphokinase Increased	1.1	1.4	0
Lipase Increased	2.8	1.1	0.3
Metabolism and Nutrition Disorders			
Decreased Appetite	5.9	9.0	0.8
Nervous System Disorders			
Headache	4.8	4.5	3.9
Dizziness	1.1	2.8	2.2
Vertigo	1.4	1.4	0
Respiratory, Thoracic and Mediastinal Disorders			
Pharyngitis	1.7	2.0	1.7
Sinusitis	2.5	1.4	1.9
Respiratory Tract Infection Viral	0	1.1	0.8
Upper Respiratory Tract Inflammation	1.1	0.8	0.3

The values are proportions of subjects with at least one event from a pool of two clinical trials, PIONEER 1 (26 weeks) and PIONEER 8 (52 weeks).
Refer to Table 1 for equivalence between the 3 mg, 7 mg, and 14 mg and the 1.5 mg, 4 mg, 9 mg.

In the pool of glycemic controlled trials, the types and frequency of common adverse reactions, excluding hypoglycemia, were similar to those listed in Table 2.

Gastrointestinal Adverse Reactions
In the pool of placebo-controlled trials, gastrointestinal adverse reactions occurred more frequently among patients receiving RYBELSUS® than placebo (placebo 21.3%, RYBELSUS® 7 mg 31.8%, RYBELSUS® 14 mg 41.0%). The majority of the reports of nausea, vomiting, and/or diarrhea occurred during dose escalation. More patients receiving RYBELSUS® 7 mg (4.5%) and RYBELSUS® 14 mg (7.9%) prematurely discontinued trial product due to gastrointestinal adverse reactions than patients receiving placebo (0.6%). Rates of gastrointestinal adverse events were increased in both female patients and patients with a lower BMI, correlating with higher RYBELSUS® exposure observed in these patient populations.

Patients with gastroparesis may experience more serious or severe gastrointestinal effects when treated with semaglutide.

Other Adverse Reactions
Hypoglycemia
Table 4 summarizes the frequency of events related to hypoglycemia by various definitions in the placebo-controlled trials.

Table 4 – Hypoglycemia Adverse Reactions in Placebo-Controlled Trials in Patients with Type 2 Diabetes Mellitus

	Placebo	RYBELSUS® 7 mg	RYBELSUS® 14 mg
Monotherapy (26 weeks)	**N = 178**	**N = 175**	**N = 175**
Severe[a] (Level 3)	0%	0.6%	0%
Clinically significant[b] (Level 2)	1.1%	0%	0%

Moderate renal impairment[c] (26 weeks)	**N = 161**	-	**N = 163**
Severe[a] (Level 3)	0%	-	0%
Clinically significant[b] (Level 2)	2.5%	-	5.5%
Add-on to insulin with or without metformin (52 weeks)	**N = 184**	**N = 181**	**N = 181**
Severe[a] (Level 3)	0.5%	0%	1.1%
Clinically significant[b] (Level 2)	27.2%	25.4%	26.5%

a. "Severe" hypoglycemia adverse reactions are episodes requiring the assistance of another person.
b. "Clinically significant" hypoglycemia adverse reactions are episodes with a plasma glucose of < 3.0 mmol/L
c. As an add-on to metformin and/or sulfonylurea, basal insulin alone or metformin in combination with basal insulin
d. Refer to Table 1 for equivalence between the 3 mg, 7 mg, and 14 mg and the 1.5 mg, 4 mg, 9 mg

Hypoglycemia was more frequent when RYBELSUS® was used in combination with insulin secretagogues (e.g. sulfonylurea) or insulin (see 7. Warnings and Precautions and 14. Clinical Trials).

Discontinuation due to an adverse event
In the placebo dose pool, discontinuation of treatment due to adverse events was higher in patients receiving RYBELSUS® than placebo (placebo 2.5%, RYBELSUS® 7 mg 6.5%, RYBELSUS® 14 mg 10.4%). The most frequent adverse events leading to discontinuation were gastrointestinal.

Heart Rate Increase
In placebo-controlled trials, RYBELSUS® 7 mg and 14 mg resulted in a mean increase in heart rate of 1 to 3 beats per minute. There was no change in heart rate in placebo-treated patients.

8.3. Less Common Clinical Trial Adverse Reactions

In addition to Table 2, the following Adverse Reactions have been identified based on an overall causality assessment including data from placebo- and active-controlled glycemic trials

Cardiovascular: Increased heart rate
Immune System: Anaphylactic reaction, Hypersensitivity (rash and urticaria)

Immunogenicity
Across the placebo- and active-controlled glycemic control trials with antibody measurements, 14 (0.5%) RYBELSUS®-treated patients developed anti-drug antibodies (ADAs) to the active ingredient in RYBELSUS® (i.e., semaglutide). Of the 14 semaglutide-treated patients that developed semaglutide ADAs, 7 patients (0.2% of the overall population) developed antibodies cross-reacting with native GLP-1. The in vitro neutralizing activity of the antibodies is uncertain at this time.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, the incidence of antibodies to semaglutide in the studies described below cannot be directly compared with the incidence of antibodies in other studies or to other

products.

8.4. Abnormal Laboratory Findings: Hematologic, Clinical Chemistry, and Other Quantitative Data

Increases in Amylase and Lipase
In placebo-controlled trials, patients exposed to RYBELSUS® 7 mg and 14 mg had a mean increase from baseline in amylase of 10% and 13%, respectively, and lipase of 30% and 34%, respectively. These changes were not observed in placebo-treated patients.

8.5. Post-Market Adverse Reactions

The following additional adverse reactions have been reported during post-approval use of RYBELSUS®. Because these events are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- *Hypersensitivity*: anaphylaxis, angioedema, rash, urticaria
- *Hepatobiliary*: cholecystitis, cholelithiasis requiring cholecystectomy
- *Gastrointestinal:* delayed gastric emptying (see 10.1 Mechanism of Action), intestinal obstruction (grouped term covering Intestinal obstruction, Ileus, small intestinal obstruction).
- *Nervous System Disorders:* dysgeusia, dizziness, headache, dysaesthesia
- *Ocular disorder:* Non-Arteritic Anterior Ischemic Optic Neuropathy (NAION)

9. Drug Interactions

9.2. Drug Interactions Overview

Semaglutide delays gastric emptying which may influence the absorption of other oral medications. Trials were conducted to study the potential effect of semaglutide on the absorption of oral medicinal products taken with semaglutide administered orally at steady-state exposure.

9.3. Drug-Behaviour Interactions

Interactions with lifestyle products have not been studied.

9.4. Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 5 – Established or Potential Drug-Drug Interactions

Common name	Source of Evidence	Effect	Clinical comment

Levothyroxine	CT	The AUC of thyroxine (adjusted for endogenous levels) was increased by 33% following administration of a single 600 ug dose of levothyroxine concurrently administered with semaglutide. Cmax was unchanged.	Monitoring of thyroid parameters should be considered when treating patients with RYBELSUS® at the same time as levothyroxine.
Metformin Furosemide Rosuvastatin	CT	No clinically relevant change in AUC or Cmax	None
Warfarin (S-warfarin and R-warfarin) and other coumarin derivatives	CT	Semaglutide did not change the AUC or Cmax	Cases of decreased INR have been reported during concomitant use of acenocoumarol and semaglutide. Upon initiation of semaglutide treatment in patients on warfarin or other coumarin derivatives, frequent monitoring of INR is recommended.
Digoxin Lisinopril Oral Contraceptives (containing ethinylestradiol and levonorestrel)	CT	Semaglutide did not change the AUC or Cmax	None

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

No clinically relevant drug-drug interaction with semaglutide was observed based on the evaluated medications. Therefore, no dose adjustment is required for drugs taken with RYBELSUS®.

Effects of other medicinal products on RYBELSUS®

No clinically relevant change in AUC or Cmax of semaglutide was observed when taken with omeprazole.

In a trial investigating the pharmacokinetics of semaglutide co-administered with five other tablets, the AUC_{0-24h} of semaglutide decreased by 34% and C_{max} by 32%. The presence of multiple tablets in the stomach influences the absorption of semaglutide if co-administered at the same time. Patients taking RYBELSUS® should wait at least 30 minutes before taking other oral medications (see 4.1 Dosing Considerations).

Drugs that Increase Heart Rate

RYBELSUS® causes an increase in heart rate (see 7. Warnings and Precautions and 10. Clinical Pharmacology). The impact on heart rate of co-administration of RYBELSUS® with other drugs that increase heart rate (e.g., sympathomimetic drugs) has not been evaluated in drug-drug interaction studies. As a result, co-administration of RYBELSUS® with these drugs should be undertaken with caution.

Drugs that Cause PR Interval Prolongation
RYBELSUS® causes an increase in the PR interval (see 7. Warnings and Precautions and 10. Clinical Pharmacology). The impact on the PR interval of co-administration of RYBELSUS® with other drugs that prolong the PR interval (including, but not limited to, antiarrhythmics, calcium channel blockers, beta-adrenoceptor blockers, digitalis glycosides, HIV protease inhibitors) has not been evaluated. As a result, co-administration of RYBELSUS® with these drugs should be undertaken with caution.

9.5. Drug-Food Interactions

Concomitant intake of food reduces the exposure of semaglutide.

9.6. Drug-Herb Interactions

Interactions with herbal products have not been studied.

9.7. Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been studied.

10. Clinical Pharmacology

10.1. 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 GLP-1 receptor is the target for native GLP-1, an endogenous incretin hormone that potentiates glucose-dependent insulin secretion from the pancreatic beta cells. Unlike native GLP-1, semaglutide has a half-life of approximately one week. This long plasma half-life is based on binding to albumin, which reduces renal clearance, and increased enzymatic stability towards the dipeptidyl peptidase (DPP-IV) enzyme.

Semaglutide action is mediated via a specific interaction with GLP-1 receptors, leading to an increase in cyclic adenosine monophosphate (cAMP). Semaglutide stimulates insulin secretion in a glucose-dependent manner. Simultaneously, semaglutide lowers glucagon secretion, also in a glucose-dependent manner. Thus, when blood glucose is high, insulin secretion is stimulated and glucagon secretion is inhibited. Conversely, when blood glucose is low semaglutide diminishes insulin secretion and does not impair glucagon secretion. The mechanism of blood glucose lowering also involves a delay in gastric emptying.

The mechanism of action of semaglutide for cardiovascular risk reduction is likely multifactorial, in part driven by reduction in HbA1c and effects on known cardio-kidney-metabolic risk factors including reduction in blood pressure, and body weight, improvements in lipid profile, and kidney function, and anti-inflammatory effects as demonstrated by reductions in hsCRP. The exact mechanism of cardiovascular risk reduction has not been established.

10.2. Pharmacodynamics

All pharmacodynamic evaluations were performed at steady state after 12 weeks of treatment (including dose escalation) with 1 mg subcutaneous semaglutide.

Fasting and Postprandial Glucose
Semaglutide lowered postprandial glucose concentration. In patients with type 2 diabetes, treatment with semaglutide resulted in a reduction compared to placebo for fasting glucose, 2-hour postprandial glucose, mean 24-hour glucose concentration and post prandial glucose excursions over 3 meals.

First and Second Phase Insulin Secretion
Both first-and second-phase insulin secretion are increased in patients with type 2 diabetes treated with semaglutide compared with placebo.

Glucagon Secretion
Semaglutide lowered fasting glucagon, postprandial glucagon response, and mean 24-hour glucagon concentrations compared to placebo in patients with type 2 diabetes.

Glucose dependent insulin and glucagon secretion
Semaglutide lowered high blood glucose concentrations by stimulating insulin secretion and lowering glucagon secretion in a glucose-dependent manner. With semaglutide, the insulin secretion rate in patients with type 2 diabetes was similar to that of healthy subjects.
During induced hypoglycemia, semaglutide did not alter the counter-regulatory responses of increased glucagon compared to placebo, and did not impair the decrease of C-peptide in patients with type 2 diabetes.

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

Fasting and postprandial lipids
Semaglutide compared to placebo lowered fasting triglyceride and very-low-density lipoproteins (VLDL) cholesterol concentrations. The postprandial triglyceride and VLDL cholesterol response to a high fat meal was reduced in patients with type 2 diabetes treated with semaglutide compared to placebo.

Cardiac electrophysiology (QTc)
The effect of semaglutide on cardiac repolarization was tested in a QTc trial using supratherapeutic doses of subcutaneous semaglutide. 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.

Heart Rate: Treatment with subcutaneous semaglutide was associated with an increase in heart rate at all dose levels (see 7. Warnings and Precautions and 9. Drug Interactions).

PR Interval: Treatment with subcutaneous semaglutide causes PR interval prolongation, with no evidence of dose-dependency over the 0.5 to 1.5 mg dose range studied (see 7. Warnings and Precautions and 9. Drug Interactions).

QTcI Interval: Treatment with subcutaneous semaglutide at doses of 0.5, 1.0, and 1.5 mg was associated with a QTcI-shortening effect over the 0-48 h time frame studied, with no evidence of dose-dependency.

10.3. Pharmacokinetics

Table 6 – Summary of semaglutide Pharmacokinetic Parameters in Patients with Type 2 Diabetes

	C_{max}	AUC_{0-24h}[a]	T_{max}	$t_{½}$	CL	Vd
Steady-State	7 mg: 7.6 nmol/L 14 mg: 16.5 nmol/L	7 mg: 161 nmol*h/L 14 mg: 350 nmol*h/L	1 hour	≈ 1 week	Estimated absolute clearance: 0.04 L/h	Estimated absolute volume of distribution: 8 L

a. Calculated from an average steady-state concentration of 6.7 nmol/L for patients treated with 7 mg semaglutide tablets, and 14.6 nmol/L for patients treated with 14 mg semaglutide tablets.

Equivalence between the optimized formulation of RYBELSUS® 1.5 mg, 4 mg, and 9 mg and the initial formulation of RYBELSUS® 3 mg, 7 mg, 14 mg, respectively, was demonstrated based on the mean area under the plasma concentration-time curve (AUC) and Cmax at the steady-state.

Absorption
Semaglutide has been co-formulated with salcaprozate sodium (SNAC), which facilitates the absorption of semaglutide after oral administration. The absorption of semaglutide predominantly occurs in the stomach.

Absorption of oral semaglutide is decreased if taken with food.

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

The estimated absolute bioavailability of semaglutide is approximately 1-2% 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.

Clearance of semaglutide in patients with type 2 diabetes is approximately 0.04 L/h. With an elimination half-life of approximately 1 week, semaglutide will be present in the circulation for about 5 weeks after the last dose.

Special populations and conditions
Based on a population pharmacokinetic analysis, age (18-92 years), sex, race, ethnicity, upper gastrointestinal disease and renal impairment (mild or moderate) do not have a clinically meaningful effect on the pharmacokinetics of semaglutide. Semaglutide exposure is inversely related to body weight. Lower body weight was associated with higher exposure and a greater incidence of gastrointestinal adverse events (see 8. Adverse Reactions, Gastrointestinal Adverse Reactions). However, RYBELSUS® doses of 7mg and 14mg provide adequate systemic exposure over the bodyweight range of 40-188kg evaluated in the clinical trials.

11. Storage, Stability, and Disposal

Store at room temperature (15ºC to 30ºC) out of the reach of children.

12. Special Handling Instructions

RYBELSUS® must be stored in the original blister packaging to protect from moisture and light

Take the tablet directly after removing from blister card.

Part 2: Scientific Information

13. Pharmaceutical Information

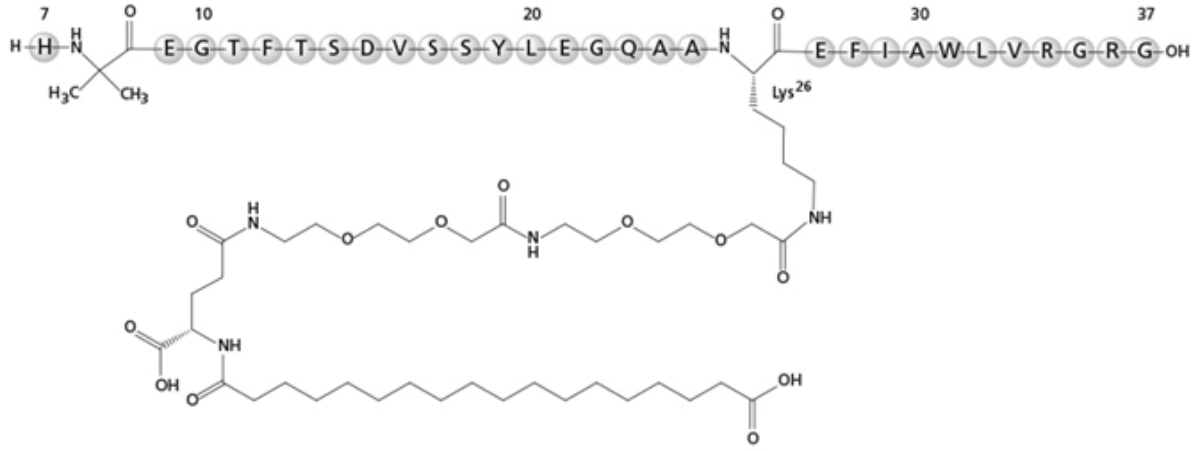
Drug Substance

Proper name: RYBELSUS®

Chemical name: semaglutide

Molecular formula and molecular mass: C_{187} H_{291} N_{45} O_{59} and 4113.6 Dalton

Structure:



Physicochemical properties: Semaglutide is a white to almost white hygroscopic powder

14. Clinical Trials

14.1. Clinical Trials by Indication

Glycemic Control in Adults with Type 2 Diabetes Mellitus

The efficacy and safety of RYBELSUS® have been evaluated in seven global randomised controlled phase 3a trials that comprised 8,336 randomised patients with type 2 diabetes (4,915 treated with RYBELSUS®), including 1,162 patients with moderate renal impairment. The efficacy of RYBELSUS® was compared with placebo, empagliflozin, sitagliptin and liraglutide. In six trials, the primary objective was the assessment of the glycemic efficacy; in one trial, the primary objective was the assessment of cardiovascular outcomes.

All the Phase 3a studies were conducted with tablets of the initial formulation of RYBELSUS® containing 3 mg, 7 mg and 14 mg semaglutide (Refer to Table 1 for formulation equivalence).

Table 7 summarizes the trial designs and study demographics of the pivotal trials.

Table 8 summarises the trial designs and study demographics for the cardiovascular outcomes trials (PIONEER 6 and SOUL).

Table 7 – Trial Design and Study Demographics: Summary of patient demographics for glycemic control clinical trials

Study #	Trial design and duration	Dosage and route of administration	Background medication	Study subjects (n[a])	Mean age (Range)	Sex N (%)
P1 - 4233	26-week, double-blind, placebo controlled	RYBELSUS® 3 mg oral, daily **OR** RYBELSUS® 7 mg oral, daily **OR** RYBELSUS® 14 mg oral, daily **OR** placebo, oral, daily	Monotherapy	703	55 (22 to 84)	Female: 346 (49%) Male: 357 (51%)
P2 – 4223	52-week, open label, active-controlled trial (26-week primary endpoint)	RYBELSUS® 14 mg oral, daily, **OR** empagliflozin 25 mg, oral, daily	Metformin	821	58 (27 to 84)	Female: 406 (49%) Male: 415 (51%)
P3 – 4222	78-week, double-blind, active-controlled trial (26-week primary endpoint)	RYBELSUS® 3 mg oral, daily **OR** RYBELSUS® 7 mg oral, daily **OR** RYBELSUS® 14 mg oral, daily **OR** sitagliptin 100 mg, oral, daily	Metformin ± a sulfonylurea	1863	58 (18 to 84)	Female: 879 (47%) Male: 984 (53%)
P4 – 4224	52-week, double-blind, placebo-and active-controlled, double-dummy trial (26-week primary endpoint)	RYBELSUS® 14 mg oral, daily **OR** liraglutide 1.8 mg, s.c., daily **OR** Placebo, oral, daily	Metformin ± an SGLT2 inhibitor	711	56 (27 to 83)	Female: 341 (48) Male: 370 (52%)

P5 – 4234	26-week, double-blind, placebo-controlled trial in patients with moderate renal impairment	RYBELSUS® 14 mg, oral, daily **OR** placebo oral, daily	Basal insulin, metformin ± basal insulin or metformin ± a sulfonylurea	324	70 (45 to 92)	Female: 168 (52%) Male: 156 (48%)
P8 – 4280	52-week double blind, placebo-controlled trial (26-week primary endpoint)	RYBELSUS® 3 mg oral, daily **OR** RYBELSUS® 7 mg oral, daily **OR** RYBELSUS® 14 mg oral, daily **OR** Placebo, oral, daily	Insulin ± metformin	731	61 (22 to 85)	Female: 336 (46%) Male: 395 (54%)

a. All randomized subjects in the full analysis set (FAS)
b. Refer to Table 1 for equivalence between the 3 mg, 7 mg, and 14 mg and the 1.5 mg, 4 mg, 9 mg

Table 8 – Summary of patient demographics for clinical trials Cardiovascular Outcomes Trials

Study #	Trial design and duration	Dosage and route of administration	Background medication	Study subjects (n[a])	Mean age (Range)	Sex N (%)
P6 – 4221	Multi-center, multi-national, placebo-controlled, double-blind cardiovascular outcomes trial	RYBELSUS® 14 mg oral, daily **OR** Placebo, oral, daily	Standard of care	3183	66 (50 to 88)	Female: 1007 (32%) Male: 2176 (68%)
SOUL 4473	Randomized, double-blind, parallel-group, placebo-controlled trial	RYBELSUS® 14 mg oral, daily **OR** Placebo, oral, daily	Standard of care	9650	66.1 (50 to 91)	Female: 2790 (28.9%) Male: 6860 (71.1%)

a) All randomized subjects in the full analysis set (FAS)

Study Results

PIONEER 1 - MONOTHERAPY

In a 26-week double-blind trial, 703 patients with type 2 diabetes inadequately controlled with diet and exercise were randomized to RYBELSUS® 3 mg, RYBELSUS® 7 mg or RYBELSUS® 14 mg once daily or placebo. The mean age of the trial population was 55 years and 51% were men. The mean duration of type 2 diabetes was 3.5 years, and the mean body weight at baseline was 88kg. Overall, 75% were White, 5% were Black or African American, and 17% were Asian; 26% identified as Hispanic or Latino ethnicity.

At week 26, monotherapy with RYBELSUS® 7 mg and RYBELSUS® 14 mg once daily had resulted in a statistically superior reduction in HbA_{1c} compared with placebo (see Table 9).

Table 9 – Study 4233 - Results at Week 26 in a Trial of RYBELSUS® as Monotherapy in Adult Patients with Type 2 Diabetes Mellitus Inadequately Controlled with Diet and Exercise (PIONEER 1)

	Placebo	RYBELSUS® 7 mg [d]	RYBELSUS® 14 mg
FAS (full analysis set) (N)[a]	178	175	175
HbA_{1c} (%)			
Baseline (mean)	7.9	8.0	8.0
Change at week 26[b]	−0.3	−1.2	−1.4
Difference from placebo[b] [95% CI]		−0.9 [−1.1; −0.6]	−1.1 [−1.3; −0.9]
p-value[b]		<0.0001	<0.0001
Patients (%) achieving HbA_{1c} <7.0%	31	69	77
FPG (mmol/l)			
Baseline (mean)	8.88	8.98	8.77
Change at week 26[b]	−0.18	−1.55	−1.82
Body weight (kg)			
Baseline (mean)	88.6	89.0	88.1
Change at week 26[b]	−1.4	−2.3	−3.7

a. The population includes all randomized patients in the FAS. At week 26, data for the primary endpoint HbA_{1c} were missing for 5.6%, 8.6% and 8.6% of patients randomized to placebo, RYBELSUS® 7 mg and RYBELSUS® 14 mg, respectively. Missing data were imputed by a pattern mixture model using multiple imputation (MI). Pattern was defined by randomized treatment and treatment status at week 26. During the trial, additional anti-diabetic medication was initiated as an add on to randomized treatment by 15%, 2% and 1% of patients randomized to placebo, RYBELSUS® 7 mg and RYBELSUS® 14 mg, respectively.
Estimated using an ANCOVA model based on data irrespectively of discontinuation of trial product or initiation of rescue medication adjusted for baseline value and region.
Two-sided p-value for superiority. Type I error rate controlled using a weighted Bonferroni-based closed testing procedure.
Refer to Table 1 for equivalence between the 3 mg, 7 mg, and 14 mg and the 1.5 mg, 4 mg, 9 mg

PIONEER 2 – RYBELSUS® vs. empagliflozin, both in combination with metformin

In a 52-week open label trial (primary efficacy evaluation at week 26), 821 patients with type 2 diabetes were randomized to RYBELSUS® 14 mg once daily or empagliflozin 25 mg once daily, both in combination with metformin. Patients had a mean age of 58 years and 51% were men.

The mean duration of type 2 diabetes was 7.4 years, and the mean body weight at baseline was 92 kg. Overall, 86% were White, 7% were Black or African American, and 6% were Asian; 24% identified as Hispanic or Latino ethnicity.

At week 26, treatment with RYBELSUS® 14 mg once daily had resulted in a statistically superior reduction in HbA_{1c} compared with empagliflozin 25 mg once daily (see Table 10).

Table 10 – Study 4223 - Results at Week 26 in a Trial of RYBELSUS® Compared to Empagliflozin in Adult Patients with Type 2 Diabetes Mellitus In Combination with Metformin (PIONEER 2)

	RYBELSUS® 14 mg	Empagliflozin 25 mg
FAS (full analysis set) (N)[a]	411	410
HbA_{1c} (%)		
Baseline (mean)	8.1	8.1
Change at week 26[b]	−1.3	−0.9
Difference from empagliflozin[b] [95% CI]	−0.4 [−0.6, −0.3]	
p-value[c]	<0.0001	
Patients (%) achieving HbA_{1c} < 7.0%	67	40
FPG (mmol/L)		
Baseline (mean)	9.52	9.66
Change at week 26[b]	-1.99	-2.01
Body weight (kg)		
Baseline (mean)	91.9	91.3
Change at week 26[b]	−3.8	−3.7

a. The population includes all randomized patients in the FAS. At week 26, the data for the primary endpoint HbA_{1c} were missing for 4.6% and 3.7% of patients randomized to RYBELSUS® 14 mg and empagliflozin 25 mg, respectively. Missing data were imputed by a pattern mixture model using multiple imputation (MI). Pattern was defined by randomized treatment and treatment status at week 26. At week 26, additional anti-diabetic medication was initiated as an add on to randomized treatment by 1.9% and 1.2 % of patients randomized to RYBELSUS® 14 mg and empagliflozin 25 mg, respectively.
Estimated using an ANCOVA based on data irrespectively of discontinuation of trial product or initiation of rescue medication adjusted for baseline value and region.
Two-sided p-value for superiority. Type I error rate controlled using a weighted Bonferroni-based closed testing procedure. Statistical superiority tested once non-inferiority was demonstrated using a non-inferiority margin of 0.4%.
Refer to Table 1 for equivalence between the 3 mg, 7 mg, and 14 mg and the 1.5 mg, 4 mg, 9 mg

At week 52, the mean changes from baseline in HbA_{1c} were -1.3% and -0.9% for RYBELSUS® 14 mg and empagliflozin 25 mg, respectively.

The mean changes from baseline for body weight at week 52 were -3.8 kg and -3.6 kg for RYBELSUS® 14 mg and empagliflozin 25 mg, respectively.

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

In a 78-week, double-blind, double-dummy trial (primary efficacy evaluation at week 26), 1863 patients with type 2 diabetes were randomized 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 53% were men. The mean duration of type 2 diabetes was 8.6 years, and the mean body weight at baseline was 91kg. Overall, 71% were White, 9% were Black or African American, and 13% were Asian; 17% identified as Hispanic or Latino ethnicity.

At week 26, treatment with RYBELSUS® 7 mg and RYBELSUS® 14 mg once daily had resulted in a statistically superior reduction in HbA_{1c} compared with sitagliptin 100 mg once daily (see Table 11).

Table 11 – Study 4222 – Results at Week 26 in a Trial of RYBELSUS® Compared to Sitagliptin 100 mg Once Daily in Adult Patients with Type 2 Diabetes mellitus In Combination with Metformin or Metformin with Sulfonylurea (PIONEER 3)

	RYBELSUS® 7 mg	RYBELSUS® 14 mg	Sitagliptin 100 mg
FAS (full analysis set) (N)[a]	465	465	467
HbA_{1c} (%)			
Baseline (mean)	8.4	8.3	8.3
Change at week 26[b]	−1.0	−1.3	−0.8
Difference from sitagliptin[b] [95% CI]	−0.3 [−0.4; −0.1]	−0.5 [−0.6; −0.4]	
p-value[c]	<0.0001	<0.0001	
Patients (%) achieving HbA_{1c} < 7.0%	44	56	32
FPG (mmol/L)			
Baseline (mean)	9.45	9.32	9.53
Change at week 26[b]	−1.18	−1.69	−0.86
Body weight (kg)			
Baseline (mean)	91.3	91.2	90.9
Change at week 26[b]	−2.2	−3.1	−0.6

a. The population includes all randomized patients in the FAS. At week 26, the data for the primary endpoint HbA_{1c} were missing for 5.8%, 6.2% and 4.5% of patients randomized to RYBELSUS® 7 mg, RYBELSUS® 14 mg and sitagliptin 100 mg, respectively. Missing values were imputed by a pattern mixture model using multiple imputation (MI). Pattern was defined by randomized treatment and treatment status at week 26. At week 26, additional anti-diabetic medication was initiated as an add on to randomized treatment by 2.4%, 1.1% and 2.8% of patients randomized to RYBELSUS® 7 mg, RYBELSUS® 14 mg and sitagliptin 100 mg, respectively.
Estimated using an ANCOVA based on data irrespectively of discontinuation of trial product or initiation of rescue medication adjusted for baseline value, background medication and region.
Two-sided p-value for superiority. Type I error rate controlled using a weighted Bonferroni-based closed testing procedure. Statistical superiority tested once non-inferiority was demonstrated using a non-inferiority margin of 0.3%.
Refer to Table 1 for equivalence between the 3 mg, 7 mg, and 14 mg and the 1.5 mg, 4 mg, 9 mg

At week 78, the mean changes from baseline for HbA_{1c} were -0.8%, -1.1% and -0.7% for RYBELSUS® 7 mg, RYBELSUS® 14 mg and sitagliptin 100 mg, respectively.

The mean changes from baseline in body weight at 78 weeks were, -2.7 kg, -3.2 kg and -1.0 kg for RYBELSUS® 7 mg, RYBELSUS® 14 mg and sitagliptin 100 mg, respectively.

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 (primary efficacy evaluation at week 26), 711 patients with type 2 diabetes were randomized to RYBELSUS® 14 mg once daily, liraglutide 1.8 mg s.c. injection once daily 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 52% were men. The mean duration of type 2 diabetes was 7.6 years, and the mean body weight at baseline was 94 kg. Overall, 73% were White, 4% were Black or African American, and 13% were Asian; 6% identified as Hispanic or Latino ethnicity.

At week 26, treatment with RYBELSUS® 14 mg once daily had resulted in a statistically superior reduction in HbA_{1c} compared with placebo. At week 26, treatment with RYBELSUS® 14 mg once daily was non-inferior to liraglutide 1.8 mg in reducing HbA_{1c} (non-inferiority margin of 0.4%; see Table 12.

Table 12 – Study 4224 – Results at Week 26 in a Trial of RYBELSUS® Compared to Liraglutide and Placebo in Adult Patients with Type 2 Diabetes Mellitus In Combination with Metformin or Metformin with SGLT2i (PIONEER 4)

	Placebo	Liraglutide 1.8 mg	RYBELSUS® 14 mg
FAS (full analysis set) (N)[a]	142	284	285
HbA_{1c} (%)			
Baseline (mean)	7.9	8.0	8.0
Change at week 26[b]	−0.2	−1.1	−1. 2
Difference from placebo[b] [95% CI]			−1.1 [−1.2; −0.9]
p-value[c]			<0.0001
Difference from liraglutide[b] [95% CI]			−0.1 [−0.3; 0.0]
p-value[b]			<0.0001
Patients (%) achieving HbA_{1c} < 7.0 %	14	62	68
FPG (mmol/L)			
Baseline (mean)	9.25	9.30	9.27
Change at week 26[b]	−0.36	−1.87	−2.00
Body weight (kg)			
Baseline (mean)	93	96	93
Change at week 26[b]	−0.5	−3.1	−4.4

a. The population includes all randomized patients in the FAS. At week 26, the data for the primary endpoint HbA_{1c} were missing for 5.6%, 4.2% and 2.5% of patients randomized to placebo, liraglutide 1.8 mg and RYBELSUS® 14 mg respectively. Missing values were imputed by a pattern mixture model using multiple imputation (MI). Pattern was defined by randomized treatment and treatment status at week 26. At week 26, additional anti-diabetic medication was initiated by 7.7%, 3.2% and 3.5% of patients randomized to placebo, liraglutide 1.8 mg and RYBELSUS® 14 mg respectively.
Estimated using an ANCOVA based on data irrespectively of discontinuation of trial product or initiation of rescue medication adjusted for baseline value, background medication and region
Two-sided p-value for non-inferiority (vs liraglutide) and superiority (vs placebo). Type I error rate controlled using a weighted Bonferroni-based closed testing procedure.
Refer to Table 1 for equivalence between the 3 mg, 7 mg, and 14 mg and the 1.5 mg, 4 mg, 9 mg

At week 52, the mean changes from baseline for HbA_{1c} were -0.2%, -0.9 % and -1.2% for placebo, liraglutide 1.8 mg and RYBELSUS® 14 mg, respectively.

At week 52, the mean changes from baseline in body weight were -1.0 kg, -3.0 kg and -4.3 kg for placebo, liraglutide 1.8 mg and RYBELSUS® 14 mg, respectively.

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 moderate renal impairment (eGFR 30−59 mL/min/1.73 m^2) were randomized to RYBELSUS® 14 mg or placebo once daily. RYBELSUS® was added to the patient's stable pre-trial antidiabetic regimen. The insulin dose was reduced by 20% at randomization for patients on basal insulin. Dose reduction of insulin and sulfonylurea was allowed in case of hypoglycemia; up titration of insulin was allowed but not beyond the pre-trial dose.

The mean age of the trial population was 70 years and 48% were men. The mean duration of type 2 diabetes was 14.0 years, and the mean body weight at baseline was 91 kg. Overall, 96% were White, 4% were Black or African American, and less than 1% were Asian; 6% identified as Hispanic or Latino ethnicity. 39.5% of patients had a eGFR value of 30 to 44 mL/min/1.73 m^2.

At week 26, treatment with RYBELSUS® 14 mg once daily had resulted in a statistically superior reduction in HbA_{1c} compared with placebo (see Table 13).

Table 13 – Study 4234 – Results at Week 26 in a Trial of RYBELSUS® Compared to Placebo in Patients With Moderate Renal Impairment (PIONEER 5)

	Placebo	RYBELSUS® 14 mg
FAS (full analysis set) (N)[a]	161	163
HbA_{1c} (%)		
Baseline (mean)	7.9	8.0
Change at week 26[b]	−0.2	−1.0
Difference from placebo[b] [95% CI]		−0.8 [−1.0; −0.6]
p-value[c]		<0.0001
Patients (%) achieving HbA_{1c} < 7.0%	23	58
FPG (mmol/L)		
Baseline (mean)	9.07	9.08
Change at week 26[b]	−0.37	−1.54
Body weight (kg)		
Baseline (mean)	90.4	91.3
Change at week 26[b]	−0.9	−3.4

a. The population includes all randomized patients in the FAS. At week 26, the data for the primary endpoint HbA_{1c} was missing for 3.7% and 5.5% of patients randomized to placebo and RYBELSUS® 14 mg, respectively. Missing values were imputed by a pattern mixture model using multiple imputation (MI). Pattern was defined by randomized treatment and treatment status at week 26. During the trial, rescue medication was initiated by 9.9% and 4.3% of patients randomized to placebo and RYBELSUS® 14 mg, respectively.

Estimated using an ANCOVA based on data irrespectively of discontinuation of trial product or initiation of rescue medication adjusted for baseline value, background medication, renal status and region.
Two-sided p-value for superiority.
Refer to Table 1 for equivalence between the 3 mg, 7 mg, and 14 mg and the 1.5 mg, 4 mg, 9 mg

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

In a 52-week double blind trial (primary efficacy evaluation at week 26), 731 patients with type 2 diabetes inadequately controlled on insulin (basal, basal/bolus or premixed) with or without metformin, were randomized to RYBELSUS® 3 mg, RYBELSUS® 7 mg and RYBELSUS® 14 mg or placebo once daily. All patients were recommended to reduce their insulin dose by 20% at randomization to reduce the risk of hypoglycemia. Patients were allowed to increase the insulin dose only up to the starting insulin dose prior to randomization for the first 26 weeks. At randomization, the total daily insulin dose were 55 U, 63 U, and 53 U for placebo, RYBELSUS® 7 mg and RYBELSUS® 14 mg, respectively.

The mean age of the trial population was 61 years and 54% were men. The mean duration of type 2 diabetes was 15.0 years, and the mean body weight at baseline was 86 kg. Overall, 51% were White, 7% were Black or African American, and 36% were Asian; 13% identified as Hispanic or Latino ethnicity.

At week 26, treatment with RYBELSUS® 7 mg and RYBELSUS® 14 mg once daily had resulted in a statistically superior reduction in HbA_{1c} compared with placebo (see Table 14).

Table 14 – Study 4280 – Results at Week 26 in a Trial of RYBELSUS® Compared to Placebo in Adult Patients with Type 2 Diabetes Mellitus In Combination with Insulin alone or with Metformin (PIONEER 8)

	Placebo	RYBELSUS® 7 mg [d]	RYBELSUS® 14 mg [d]
FAS (full analysis set) (N)[a]	184	182	181
HbA_{1c} (%)			
Baseline (mean)	8.2	8.2	8.2
Change at week 26[b]	−0.1	−0.9	−1.3
Difference from placebo[b] [95% CI]		−0.9 [−1.1; −0.7]	−1.2 [−1.4; −1.0]
p-value[c]		<0.0001	<0.0001
Patients (%) achieving HbA_{1c} <7.0%	7	43	58
FPG (mmol/L)			
Baseline (mean)	8.30	8.51	8.33
Change at week 26[b]	0.29	−1.08	−1.33
Body weight (kg)			
Baseline (mean)	86	87	85
Change at week 26[b]	−0.4	−2.4	−3.7

a. The population includes all randomized patients in the FAS. At week 26, the data for the primary endpoint HbA_{1c} endpoint were missing for 4.3%, 4.4% and 4.4% of patients randomized to placebo, RYBELSUS® 7 mg, RYBELSUS® 14 mg and placebo, respectively. Missing values were imputed by a

pattern mixture model using multiple imputation (MI). Pattern was defined by randomized treatment and treatment status at week 26. At week 26, additional anti-diabetic medication was initiated as an add on to randomized treatment by 4.9%, 1.1% and 2.2% of patients randomized to placebo, RYBELSUS® 7 mg and RYBELSUS® 14 mg, respectively.
Estimated using an ANCOVA based on data irrespectively of discontinuation of trial product or initiation of rescue medication adjusted for baseline value, background medication and region.
Two-sided p-value for superiority. Type I error rate controlled using a weighted Bonferroni-based closed testing procedure.
Refer to Table 1 for equivalence between the 3 mg, 7 mg, and 14 mg and the 1.5 mg, 4 mg, 9 mg

At week 52, the mean changes from baseline in HbA_{1c} were -0.2%, -0.8% and -1.2 % for placebo, RYBELSUS® 7 mg and RYBELSUS® 14 mg, respectively.

At week 52, the mean changes from baseline in body weight were 0.5 kg, -2.0 kg and -3.7 kg for placebo, RYBELSUS® 7 mg and RYBELSUS® 14 mg, respectively.

Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus and Cardiovascular Disease

PIONEER 6

PIONEER 6 was a multi-center, multi-national, double-blind trial in which RYBELSUS® or placebo were added to and used concomitantly with standard of care treatments for type 2 diabetes mellitus and cardiovascular disease. In this trial, 3,183 patients with inadequately controlled type 2 diabetes mellitus and atherosclerotic cardiovascular disease were randomized to the add-on placebo arm or the add-on RYBELSUS® 14 mg arm for a mean observation period of 16 months. The primary objective of the trial was to confirm that treatment with RYBELSUS® does not result in any unacceptable increase in cardiovascular risk compared to placebo (i.e. rule out 80% excess risk) in patients with type 2 diabetes mellitus at high risk of cardiovascular events. This was done by demonstrating that the upper limit of the two-sided 95% confidence interval (CI) of the hazard ratio for RYBELSUS® versus placebo is less than 1.8 when comparing time to first occurrence of a major adverse cardiovascular event (MACE). MACE was defined as cardiovascular death, non-fatal myocardial infarction or non-fatal stroke.

Patients eligible to enter the trial were 1) 50 years of age or older and had established, stable, cardiovascular/cerebrovascular/peripheral artery disease, chronic kidney disease or NYHA class II or III heart failure or 2) were 60 years of age or older and had at least one of the following risk factors: microalbuminuria/proteinuria, hypertension and left ventricular hypertrophy, left ventricular systolic or diastolic dysfunction, and an ankle/brachial index <0.9. 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 risk factors only. The mean age at baseline was 66 years, and 68% were men. The mean duration of diabetes was 14.9 years, and mean BMI was 32 kg/m^2. Overall, 72% were White, 6% were Black or African American, and 20% were Asian; 16% identified as Hispanic or Latino ethnicity. Concomitant diseases of patients in this trial included, but were not limited to, heart failure (NYHA Class I, II or III (12%), history of ischemic stroke (8%) and history of a myocardial infarction (36%). In total, 99.7% of the patients completed the trial and the vital status was known at the end of the trial for 100%.

During the 16 months mean observation time, the proportion of patients who experienced at least one MACE event was 61/1,591 (3.8%) for RYBELSUS® and 76/1,592 (4.8%) for placebo. The estimated hazard ratio of MACE associated with RYBELSUS® relative to placebo was 0.79 with a 95% confidence interval of (0.57, 1.11) (See Figure 1). No increased risk for MACE was observed with RYBELSUS®.

The results, including the contribution of each component to the primary composite endpoint are shown in Figure 1.

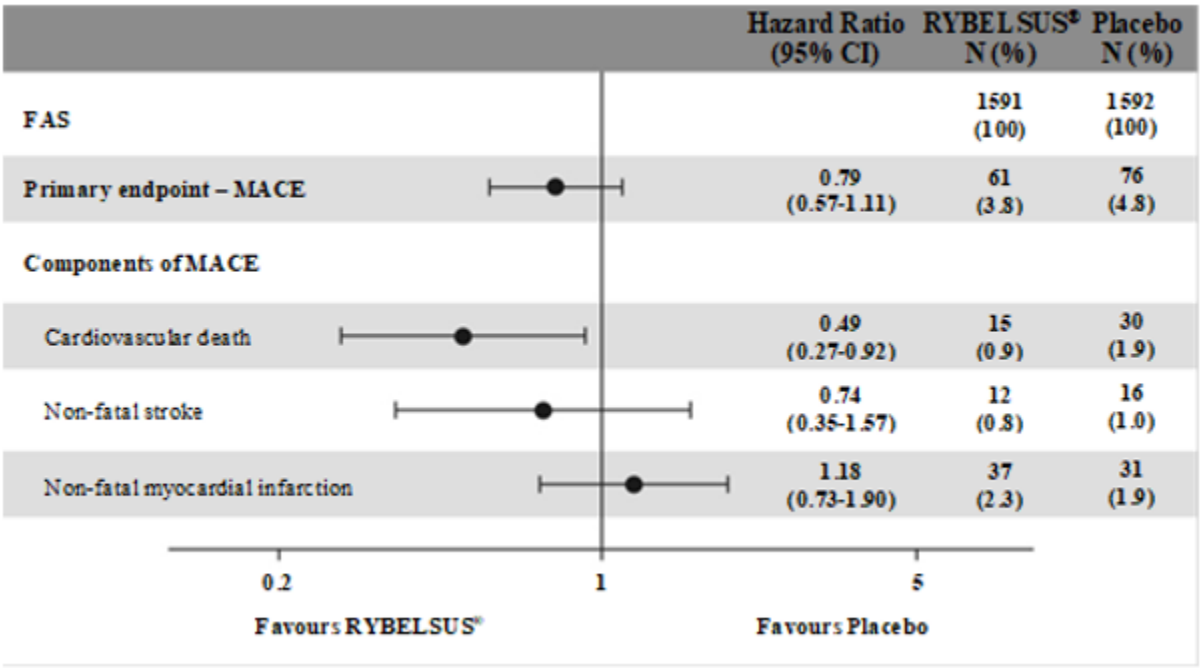


Figure 1 Treatment effect for the primary composite endpoint, MACE, and its components (PIONEER 6)

SOUL - Semaglutide cardiovascular outcomes trial in patients with type 2 diabetes and established Cardiovascular Disease

SOUL was a randomized, double-blind, parallel-group, placebo-controlled trial. In this trial, 9650 patients with type 2 diabetes mellitus and established cardiovascular disease (CVD) and/or chronic kidney disease (CKD), were randomised to either RYBELSUS® 14 mg once daily or placebo once daily.

The trial compared the risk of major adverse cardiovascular event (MACE) between RYBELSUS® and placebo when these were added to and used concomitantly with standard of care treatments for diabetes and cardiovascular disease. The primary endpoint, MACE, was the time to first occurrence of a three-part composite outcome which included cardiovascular death, non-fatal myocardial infarction and 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. In total, 5468 patients (56.7%) had established cardiovascular disease without chronic kidney disease, 1241 (12.9%) had chronic kidney disease only and 2620 (27.2%) had both cardiovascular disease and kidney disease.

Most patients (97.3%) used one or more glucose lowering medications at baseline, 75.9% of patients were being treated with metformin, 50.7% with insulin, 26.9% with SGLT2 inhibitors, 29.2% with a sulfonylurea, 23.2% with DPP4 inhibitors and 88.8% used lipid lowering drugs, 94.2% on cardiovascular medications at baseline.

The mean age at baseline was 66.1 years, and 71.1% of the patients were men. The mean duration of diabetes was 15.4 years, and the mean BMI was 31.1 kg/m2, the mean HbA1c was 8% and the mean eGFR was 73.8 mL/min/1.73 m2. Overall, 68.9% White, 2.6% were Black or African American, and 23.4% were Asian; 14.3% identified as Hispanic or Latino ethnicity. Concomitant diseases of patients in this trial included but were not limited to heart failure (23.1%), hypertension (90.8%), history of ischemic stroke (12.3%), history of myocardial infarction (40%) and history of peripheral artery disease (15.7%). Total 98.4% patients completed the trial, and the vital status was known at the end of the trial for 99.5%.

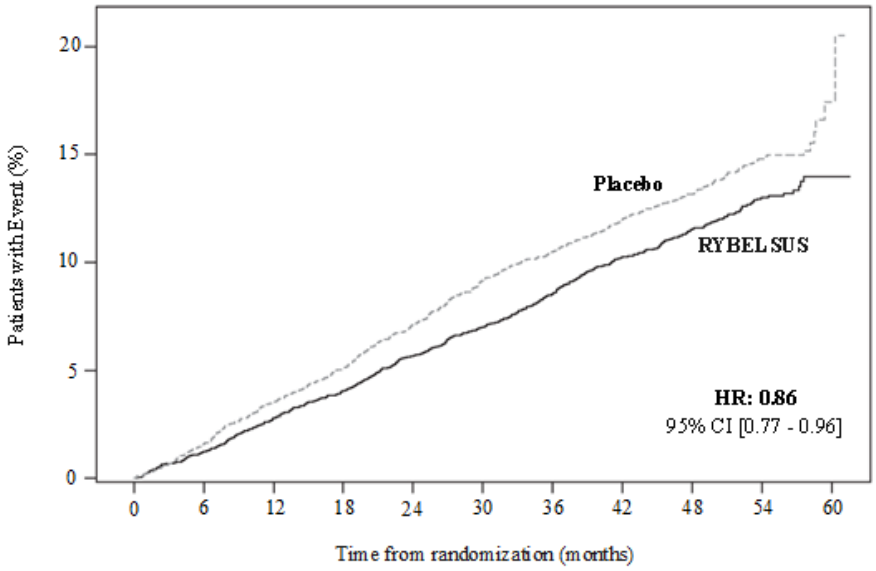
Superiority of semaglutide versus placebo for MACE was confirmed with a hazard ratio of 0.86 [0.77; 0.96] [95% CI], corresponding to a relative risk reduction in MACE of 14%.

Refer to Table 15 and Figure 2. The treatment effect for the primary composite endpoint including the contribution of each component in the SOUL trial is shown in Table 15.

Table 15 – Treatment Effect for the MACE and its Components in SOUL trial

	PLACEBO N = 4825	RYBELSUS® 14 mg N = 4825	Hazard ratio vs Placebo (95% CI)
Primary composite endpoint			
Composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke (time to first occurrence)	668 (13.8%)	579 (12.0%)	0.86 (0.77, 0.96)
Cardiovascular Death	320 (6.6%)	301 (6.2%)	0.93 (0.80,1.09)
Non-fatal Myocardial Infarction (MI)	253 (5.2%)	191 (4.0%)	0.74 (0.61,0.89)
Non-fatal Stroke	161 (3.3%)	144 (3.0%)	0.88 (0.70,1.11)

Note: Data from the in-trial period based on full analysis set. Time from randomization to each endpoint was analyzed using a Cox proportional hazards model with treatment as categorical fixed factor. Subjects without events of interest were censored at the end of their in-trial period. For the primary endpoint the HR and CI were adjusted for the group sequential design using likelihood ratio ordering. Secondary endpoints are not under multiplicity control. CV death includes both cardiovascular death and undetermined cause of death.

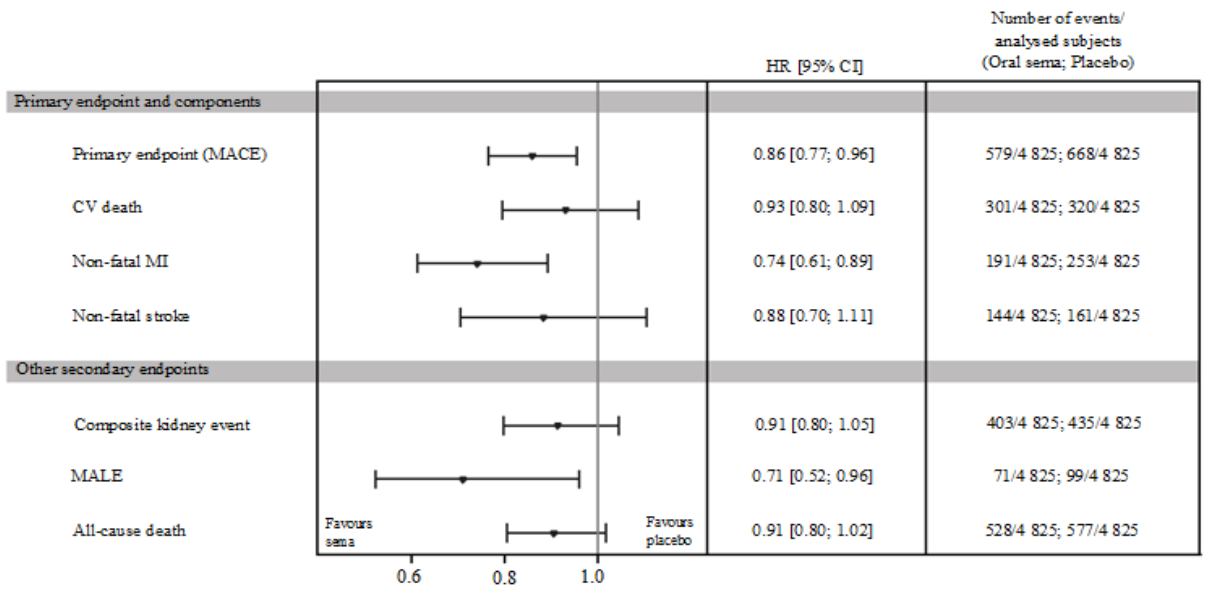


Patients at risk											
RYBELSUS	4825	4743	4635	4542	4438	4346	4239	3831	2555	1346	47
Placebo	4825	4718	4583	4455	4322	4194	4101	3727	2517	1346	38

Data from the in-trial period based on full analysis set. Cumulative incidence estimates are based on time from randomisation to first EAC-confirmed MACE with non-CV death modelled as competing risk using the Aalen-Johansen estimator. Subjects without events of interest were censored at the end of their in-trial observation period. Time from randomisation to first MACE was analysed using a Cox proportional hazards model with treatment as categorical fixed factor. The hazard ratio and confidence interval are adjusted for the group sequential design using the likelihood ratio ordering. The 95% CI refers to a nominal 95.4% CI adjusted for the group sequential design.

CV: cardiovascular, EAC: event adjudication committee, MACE: major adverse cardiovascular event.

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



Data from the in-trial period based on full analysis set. Time from randomisation to each endpoint was analysed using a Cox proportional hazards model with treatment as categorical fixed factor. Subjects without events of interest were censored at the end of their in-trial period. For the primary endpoint the HR and CI were adjusted for the group sequential design using likelihood ratio ordering. Secondary endpoints are not under multiplicity control. CV death includes both cardiovascular death and undetermined cause of death.
HR: hazard ratio CI: Confidence interval.
CV: cardiovascular, MI: myocardial infarction.
Composite kidney event: endpoint consisting of cardiovascular death, kidney death, onset of persistent ≥ 50% reduction in estimated glomerular filtration rate (CKD-EPI) compared with baseline, onset of persistent eGFR (CKD-EPI) < 15 mL/min/1.73 m2 or initiation of chronic kidney replacement therapy (dialysis or kidney transplantation).
MALE: major adverse limb events; composite endpoint consisting of acute or chronic limb ischemia hospitalisation.
Analysis of the first composite kidney event (the first confirmatory secondary endpoint) resulted in a hazard ratio of 0.91 [0.80; 1.05]95%CI. As superiority was not confirmed, the confirmatory secondary endpoints CV death and MALE were not tested for superiority. All-cause death was a secondary endpoint not included in the testing hierarchy.

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

15. Microbiology

Not applicable

16. Non-Clinical Toxicology

Safety Pharmacology

Subcutaneous semaglutide

Acute effects of semaglutide on vital organ function (central nervous system, cardiovascular system and respiration) and renal function were evaluated following subcutaneous dosing in rats or telemetered conscious unrestrained cynomolgus monkeys. Semaglutide was generally well tolerated, but displayed pharmacologically-mediated effects of abnormal gait (walking on toes), decreased touch response, passivity, dirty muzzle, lethargy, piloerection, and increased acute transient diuresis in the rat, at doses equivalent to the human C_{max} exposure at the maximal recommended human dose (MRHD). In the monkey, no adverse effects were identified on acute cardiovascular function, at doses up to 27-fold the C_{max} exposure at the MRHD. In vitro investigations (hERG ion channel assay and isolated rabbit Purkinje fibres) indicated no effects on cardiac repolarisation.

General toxicity

Repeat dose toxicity studies with oral and subcutaneous semaglutide were conducted in mice (subcutaneously only), rats, and monkeys. In oral studies, semaglutide was administered in a formulation containing the SNAC excipient, which facilitates the absorption of semaglutide after oral administration. Generally, decreased food consumption was observed in all studies and was accompanied by reduced body weight gain and body weights. Secondary to these effects, non-adverse clinical pathology and organ weight changes were observed across species. Clinical signs of decreased activity, hunched posture, and piloerection were also observed, during the first few weeks of dosing at the highest doses.

Oral semaglutide
In a 26-week repeat-dose toxicity study, rats were orally administered 6, 20, and 60 mg/kg/day semaglutide (below human exposure, 1-, and 9-fold the human exposure at the MRHD) co-administered with 90, 300, and 900 mg/kg/day SNAC, respectively. Control groups included a negative vehicle control group, as well as groups administered SNAC alone at the same doses. Premature death was observed in two females of the high-dose oral semaglutide group, which were attributed to exaggerated pharmacodynamic effects of semaglutide on food consumption and body weight. Premature death was also observed in a total of 8 females and 3 males given ≥ 300 mg/kg/day SNAC alone (see below for further discussion). The NOAEL for the oral toxicity of SNAC alone was determined to be 90 mg/kg/day based on SNAC-related deaths at higher doses. The NOAEL for the oral toxicity of semaglutide co-formulated with SNAC was determined to be 6 mg/kg/day semaglutide with 90 mg/kg/day SNAC based on the NOAEL for SNAC.

In a 6-week repeat-dose toxicity study, cynomolgus monkeys were orally administered 5 and 10 mg/kg/day semaglutide (1.3 and 8-fold the human exposure at the MRHD) co-administered with 78 and 157 mg/kg/day SNAC, respectively. In the absence of any adverse effects, the NOAEL was established at 10 mg/kg/day semaglutide with 157 mg/kg/day SNAC.

Subcutaneous semaglutide
In a 13-week repeat-dose toxicity study, mice were subcutaneously administered semaglutide at doses of 1, 3 and 10 mg/kg/day (33-, 109-, and 332-fold the human AUC exposure at the MRHD of 14 mg). Thyroid C-cell hyperplasia was observed at all dose levels and consequently, a NOAEL could not be identified for this study.

In a 26-week repeat-dose toxicity study, rats were subcutaneously administered semaglutide at doses of 0.03, 0.13, and 0.6 mg/kg/day (2.6-, 11-, and 52-fold the human exposure at the MRHD). In the absence of any adverse findings, the NOAEL was determined to be 0.6 mg/kg/day.

In a 52-week repeat-dose toxicity study, cynomolgus monkeys were subcutaneously administered semaglutide at doses of 0.01, 0.06, and 0.36 mg/kg twice weekly (1.4-, 8.8-, and 52-fold the human exposure at the MRHD). Electrocardiography (ECG) recordings revealed a continuous left-bundle-branch-block ECG recording in Weeks 26 and 52 in one high-dose female. In addition, histopathology revealed multifocal myocardial vacuolation, with karyomegaly, in the left ventricle of one high-dose male. As it could not be excluded that these findings were treatment related, 0.06 mg/kg twice-weekly was determined to be the NOAEL.

SNAC

High doses of SNAC (≥ 300 mg/kg) have been observed to cause adverse clinical signs and/or mortality in mice, rats, and monkeys in separate single and repeat-dose oral studies conducted with SNAC alone. In these studies, clinical signs generally consisted of apathy, abnormal respiration, abnormal body carriage, eyes half closed, reduced alertness, startle response, touch response and body tone, hunched posture, passivity, loss of righting reflex, and, in some cases, convulsions. In monkeys, the clinical signs observed were consistent with hypoglycemia and decreased blood glucose concentrations were observed in one study at a dose of 1800 mg/kg/day. Decreases in plasma and CSF glucose levels were also observed in rats at doses at which clinical signs and mortalities were observed.

Genotoxicity

Subcutaneous semaglutide
Semaglutide was not mutagenic or clastogenic in a standard battery of genotoxicity tests (bacterial reverse mutation test, in vitro chromosomal aberration test in human peripheral blood lymphocytes, and in vivo rat bone marrow micronucleus test).

Carcinogenicity

Subcutaneous semaglutide
Non-lethal thyroid C-cell tumours observed in rodents are a class effect for GLP-1 receptor agonists. In a 2-year carcinogenicity study in CD-1 mice, subcutaneous doses of 0.3, 1 and 3 mg/kg/day semaglutide (8.8-, 33-, and 113-fold the human exposure, based on AUC, at the MRHD) was administered to the males, and 0.1, 0.3 and 1 mg/kg/day semaglutide (3.2-, 8.8-, and 33-fold the human exposure at the MRHD) was administered to the females. High incidence rates of focal/multifocal C-cell hyperplasia and C-cell adenoma were observed in both sexes at all doses. In control animals, the incidence rate of C-cell hyperplasia was very low and no incidences of C-cell adenoma were observed. The increase in thyroid C-cell adenomas was statistically significant in both sexes at all doses. A numerical increase in C-cell carcinomas was observed in males and females at all doses, while no incidences of C-cell carcinomas were observed in control animals. A NOAEL could not be identified for this study.

In a 2-year carcinogenicity study in Sprague Dawley rats, subcutaneous doses of 0.0025, 0.01, 0.025 and 0.1 mg/kg/day semaglutide were administered (below human exposure, below human exposure, 1.8-, and 11-fold the human exposure at the MRHD). An increase in incidence of focal C-cell hyperplasia of the thyroid was observed in males at all doses. A statistically significant increase in thyroid C-cell adenomas was observed in males and females at all doses, and a statistically significant increase in thyroid C-cell carcinomas was observed in males at ≥0.01 mg/kg/day, and in females at 0.1 mg/kg/day. The increases in the incidences of thyroid C-cell adenomas and carcinomas were largely dose-dependent. A NOAEL could not be identified for this study.

In both studies, the increased incidences of thyroid C-cell hyperplasia, adenoma, and carcinoma were determined to be treatment-related. Thyroid C-cell tumours are rare findings during carcinogenicity testing in mice and rats. The human relevance of thyroid C-cell tumours in these rodent species is unknown and could not be determined based on the results of the clinical or nonclinical studies (see 7. Warnings and Precautions, Carcinogenesis and Mutagenesis).

No other treatment-related tumours were observed in the carcinogenicity studies.

Reproductive and developmental toxicology

Subcutaneous semaglutide

In a combined fertility and embryo-fetal developmental toxicity study in rats, subcutaneous doses of 0.01, 0.03 and 0.09 mg/kg/day semaglutide (below human exposure, below human exposure, and 1.7-fold the human AUC exposure at the MRHD) were administered to male and female rats. Males were dosed for 4 weeks prior to mating, and females were dosed for 2 weeks prior to mating and throughout organogenesis until Gestation Day (GD) 17. No effects were observed on mating performance or male fertility. In females, an increase in estrus cycle length was observed at all dose levels, together with a small reduction in numbers of corpora lutea (ovulations) at ≥0.03 mg/kg/day. Semaglutide caused embryotoxicity below clinically relevant exposures. Semaglutide caused reductions in maternal body weight, and reduction in number of corpora lutea, leading to fewer implantations and reduced fetal growth. In fetuses, increased incidences of skeletal and visceral malformations were observed at the mid and high dose, consisting of short tibia/malrotated hindlimb at the high dose and retro-oesophageal aortic arch (cardiovascular malformation) in combination with variation in the origin of the right subclavian artery observed at the two highest doses. Increased incidences of minor abnormalities were also observed at the high-dose, including skeletal variations (partially fused, misaligned, or reduced ossification of skeletal components) and dilated lateral brain ventricles. Thus, the NOAEL for the embryo-fetal toxicity of semaglutide in rats was determined to be 0.01 mg/kg/day.

In an embryo-fetal developmental toxicity study in rabbits, subcutaneous doses of 0.001, 0.0025 and 0.0075 mg/kg/day semaglutide (below human exposure, below human exposure, and 4.4-fold the human exposure at the MRHD) were administered to female rabbits throughout organogenesis i.e. from GD6 to GD19. Semaglutide markedly reduced maternal body weight gain and food and water consumption. Semaglutide caused increased post-implantation losses and an increased incidence of incomplete ossification of metacarpals (skeletal variation) at the mid and the high dose, and increased incidences of other minor, non-adverse skeletal abnormalities at all dose levels. There was also an increased incidence of minor visceral abnormalities, consisting of dilated renal pelvis at the high dose, and increased incidences of forelimb/paw flexure at the mid and high doses. An increased number of visceral malformations were also observed at the mid and high dose that were not observed in controls, and consisted of multiple folded retina: absent vitreous humour, misshapen heart: dilated pulmonary trunk, absent kidney/ureter, absent adrenals, and bent scapula: hyperextension of the forelimb. Thus, the NOAEL for the embryo-fetal toxicity of semaglutide in rabbits was determined to be 0.001 mg/kg/day.

In an embryo-fetal developmental toxicity study in cynomolgus monkeys, subcutaneous doses of 0.015, 0.075, and 0.15 mg/kg semaglutide (1.9-, 9.9-, and 29-fold the human exposure at the MRHD) were administered to pregnant monkeys from GD 20 to 50 every 3 days. Marked maternal body weight loss and reduced food consumption was observed at all doses during the dosing period. A slightly increased incidence of fetal malformations was observed at the mid- and high-dose. The fetal abnormalities included skeletal abnormalities, consisting of shifts in the alignment of the vertebrae, ribs, and sternebrae at the cervico-thoracic border observed in one fetus of each of the mid- and high-dose groups, a misshapen right brain hemisphere, which was due to accumulation of blood between the dura mater and the brain, in a high-dose fetus, fused kidneys in a mid-dose fetus, and liver cysts in another mid-dose fetus. Thus, the NOAEL for the embryo-fetal toxicity of semaglutide in cynomolgus monkeys was determined to be 0.015 mg/kg administered every 3 days.

In a combined embryo-fetal and pre- and post-natal developmental toxicity study in cynomolgus monkeys, subcutaneous doses of 0.015, 0.075, and 0.15mg/kg semaglutide (1.3-, 6-, and 14-fold the human exposure at the MRHD) were administered to pregnant monkeys from GD 20 to 140 every 3 days. A higher incidence of pre-natal loss was observed in the mid- and high-dose groups. The incidence of pre-natal loss was 5/24 (21%), 5/22 (23%), 7/22 (32%), and 10/24 (42%) in the control, low-, mid-, and high-dose groups, respectively, with the most losses occurring between GD 20 and 50; early pre-natal loss was 2/24 (8.3%), 1/22 (4.5%), 5/22 (23%), and 8/24 (33%) in the control, low-, mid-, and high-dose groups, respectively. A higher incidence of post-natal loss was also observed at all doses. The incidence of post-natal loss was 0/19 (0%), 5/17(29%), 3/15(20%), and 3/14(21%) in the control, low-, mid-, and high-dose groups, respectively. Infants were also slightly smaller at delivery in the two highest dose groups, but recovered during the lactation period. The NOAEL for the developmental toxicity of semaglutide in cynomolgus monkeys was determined to be 0.015 mg/kg administered every 3 days.

SNAC

In a pre- and post-natal development study on SNAC alone, pregnant rats were orally administered 1000 mg/kg/day SNAC from GD 7 through postnatal day (PND) 20. SNAC prolonged the duration of gestation (3%), increased the number of dams with stillborn pups (46% compared to 21% in the vehicle control group), and increased the number of pups found dead from PND 2 to 4. A NOAEL could not be determined for this study due to fetotoxicity at the dose tested.

Juvenile toxicity

Subcutaneous semaglutide
In a juvenile toxicity study in rats, subcutaneous doses of 0.02, 0.13 and 0.6 mg/kg/day semaglutide (1.3-, 10-, and 43-fold the human exposure at the MRHD) were administered to young rats from Postnatal Day 21 to 98. As in other studies, lower body weight gain, body weights, and food consumption were observed in animals administered semaglutide when compared to control animals. Semaglutide also caused a delay in sexual maturation in both males and females. There were no consequential effects on estrus cycle length, the reproductive organs of either sex, the reproductive capacity of either sex, or on the ability of the females to maintain pregnancy.

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PR RYBELSUS®

semaglutide tablets

This Patient Medication Information is written for the person who will be taking **RYBELSUS®**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **RYBELSUS®**, talk to a healthcare professional.

What RYBELSUS® is used for:

RYBELSUS® contains the active substance semaglutide. It is used to lower blood sugar (glucose) in adults with type 2 diabetes.

- RYBELSUS® is used on its own if your blood sugar level is not properly controlled by diet and exercise alone and you cannot use metformin.
- RYBELSUS® is used in combination with one or more other medicines for diabetes when they are not enough to control your blood sugar levels.
- RYBELSUS® is used to reduce the risk of serious heart issues (heart-related death, heart attacks, strokes) in adults with type 2 diabetes mellitus and established cardiovascular disease or are at high risk for those.

How RYBELSUS® works:

RYBELSUS® belongs to a class of medicines called GLP-1 receptor agonists (glucagon-like peptide-1 receptor agonists). RYBELSUS® helps your body make more insulin when your blood sugar is high.

The ingredients in RYBELSUS® are:

Medicinal ingredients: semaglutide

Non-medicinal ingredients for the initial formulation of RYBELSUS® tablets (3 mg, 7 mg and 14 mg).: magnesium stearate, microcrystalline cellulose, povidone K 90, salcaprozate sodium (SNAC)

Non-medicinal ingredients for the optimized formulation of RYBELSUS® tablets (1.5 mg, 4 mg and 9 mg).: magnesium stearate, salcaprozate sodium (SNAC).

RYBELSUS® comes in the following dosage forms:

Initial formulation of RYBELSUS® 3 mg, 7 mg and 14 mg tablets

3 mg tablets are white to light yellow, oval shaped debossed with “3” on one side and “novo” on the other side. The tablets are supplied in green coloured cartons and blister packaging.

7 mg tablets are white to light yellow, oval shaped debossed with “7” on one side and “novo” on

the other side. The tablets are supplied in red coloured cartons and blister packaging.

14 mg tablets are white to light yellow, oval shaped debossed with “14” on one side and “novo” on the other side. The tablets are supplied in blue coloured cartons and blister packaging.

Optimized formulation of RYBELSUS® 1.5 mg, 4 mg and 9 mg tablets
1.5 mg tablets are white to light yellow, round shaped debossed with “1.5” on one side and “novo” on the other side. The tablets are supplied in green coloured cartons and blister packaging.

4 mg tablets are white to light yellow, round shaped debossed with “4” on one side and “novo” on the other side. The tablets are supplied in red coloured cartons and blister packaging.

9 mg tablets are white to light yellow, round shaped debossed with “9” on one side and “novo” on the other side. The tablets are supplied in blue coloured cartons and blister packaging.

Do not use RYBELSUS® if:

- you are allergic to semaglutide or any of the other ingredients in this medication;
- you or a member of your family has ever had medullary thyroid cancer (MTC);
- you have Multiple Endocrine Neoplasia syndrome type 2 (MEN 2);
- you are pregnant or breastfeeding.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take RYBELSUS®. Talk about any health conditions or problems you may have, including if you:

- or a member of your family has or has had medullary thyroid carcinoma (MTC), or if you have Multiple Endocrine Neoplasia syndrome type 2 (MEN 2);
- have type 1 diabetes – a condition where your body does not produce any insulin;
- you develop diabetic ketoacidosis (increased ketones in the blood or urine);
- have ever had an allergic reaction to RYBELSUS®;
- have a high heart rate (fast pulse);
- have ever had pancreatitis;
- are breastfeeding or plan to breastfeed;
- are pregnant or plan to become pregnant;
- have end stage renal disease;
- have gastrointestinal (digestive) problems, including severe vomiting, diarrhea and/or dehydration;
- have liver or gall bladder problems;
- have diabetic retinopathy;
- you take blood thinners (ex. Warfarin/Coumadin).

Other warnings you should know about:

Cardiovascular
RYBELSUS® may increase heart rate and could cause changes known as PR prolongation, which are detected by electrocardiogram (ECG) tracings. Increased heart rate is the same as a faster pulse. These heart rhythm changes are more likely if you have heart disease, or if you are taking certain other drugs. It is important to follow your doctor's advice about the dose of

RYBELSUS® or about any special tests that you may need. See '*What are possible side effects from using RYBELSUS®?*'

Children and adolescents
RYBELSUS® is not recommended in children and adolescents under 18 years as the safety and efficacy in this age group have not yet been studied.

Pregnancy and Breastfeeding
Tell your doctor if you are pregnant, think you might be pregnant, or are planning to become pregnant. RYBELSUS® should not be used during pregnancy and for at least two months before a planned pregnancy because it is not known if it may affect your unborn child.

If you could become pregnant while using RYBELSUS®, it is recommended to use contraception.

Do not use RYBELSUS® if you are breastfeeding. RYBELSUS® passes into breast milk, and it is not known how it affects your baby.

Driving and Using Machines
If you use RYBELSUS® in combination with a sulfonylurea or insulin, low blood sugar (hypoglycemia) may occur which may reduce your ability to concentrate. Avoid driving or using machines if you get any signs of low blood sugar. Talk to your doctor for further information. You may feel dizzy when taking RYBELSUS®, especially if your dose is being increased. If you feel dizzy, avoid driving or using machines. Talk to your doctor for further information.

Severe and on-going stomach pain which could be due to acute pancreatitis or gallbladder disease
If you have severe and on-going pain in the stomach area or experience jaundice (yellowing of your skin, eyes or mucous membranes) while taking RYBELSUS® – see a doctor straight away as this could be a sign of acute pancreatitis (inflamed pancreas) or gallbladder disease.

Effects on the digestive system, including dehydration
During treatment with RYBELSUS®, you may feel sick (nausea) or be sick (vomiting), or have diarrhea. These side effects can cause dehydration (loss of fluids). It is important that you drink plenty of fluids to prevent dehydration. This is especially important if you have kidney problems. Talk to your doctor if you have any questions or concerns.

Patients with delayed stomach emptying (gastroparesis)
If you have slow (delayed) stomach emptying (called gastroparesis), use of RYBELSUS® may lead to serious or severe gastrointestinal adverse events. RYBELSUS® is not recommended if you have severe gastroparesis.

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

Sudden changes to your eyesight
If you notice a sudden loss of vision or rapidly worsening eyesight during treatment with RYBELSUS®, urgently contact your doctor. This may be caused by a very rare side effect called

non-arteritic anterior ischaemic optic neuropathy (NAION). Your doctor will refer you for an eye examination by an ophthalmologist and you may have to stop treatment with RYBELSUS®.

Low blood sugar (hypoglycemia)
Taking a sulfonylurea medicine or insulin with RYBELSUS® might increase the risk of getting low blood sugar levels (hypoglycemia). Your doctor may ask you to test your blood sugar levels. This will help your doctor decide if the dose of the sulfonylurea or insulin needs to be changed to reduce the risk of low blood sugar.

General Anesthesia or Deep Sedation
RYBELSUS® may delay how long your stomach takes to empty its contents. This may increase the risk of problems with food or liquid from the stomach getting into the lungs while under general anaesthesia or sedation. If you are about to have a procedure that requires you to be unconscious, tell your healthcare professional that you are taking RYBELSUS®.

Sodium Content
RYBELSUS® contains 23 mg of sodium per tablet. This is equivalent to 1% of the maximum daily intake of sodium per day for adults recommended by the World Health Organization.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

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

- sulfonylurea;
- insulin;
- levothyroxine – this is because your doctor may need to check your thyroid levels if you are taking RYBELSUS® together with levothyroxine.

The following may interact with RYBELSUS®:

The following list includes some, but not all, of the drugs that may increase your heart rate. You should check with your doctor or pharmacist before taking any other medication with RYBELSUS®:

- drugs to treat hypertension;
- drugs to treat heart failure;
- drugs to treat HIV infection;
- drugs to treat attention deficit-hyperactivity disorder;
- drugs to suppress appetite/cause weight loss;
- decongestants;
- drugs to treat asthma.

How to take RYBELSUS®:

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

Follow these instructions carefully:

- Take your RYBELSUS® tablet on an empty stomach.
- Swallow your RYBELSUS® tablet whole with a sip of water (up to 120 ml). Do not split, crush or chew the tablet.

- After taking your RYBELSUS® tablet wait at least 30 minutes before you have your first meal or drink of the day or taking other oral medicines.

Usual dose:

Initial Formulation of RYBELSUS® 3 mg, 7 mg and 14 mg tablets

- The starting dose is one 3 mg tablet once a day for 30 days.
- After 30 days of 3 mg once a day, your doctor will increase your dose to 7 mg once a day.
- Your doctor may increase your dose to 14 mg once a day if your blood sugar is not controlled well enough with a dose of 7 mg once a day.

Optimized Formulation of RYBELSUS® 1.5 mg, 4 mg and 9 mg tablets:

- The starting dose is one 1.5 mg tablet once a day for 30 days.
- After 30 days of 1.5 mg once a day, your doctor will increase your dose to 4 mg once a day.
- Your doctor may increase your dose to 9 mg once a day if your blood sugar is not controlled well enough with a dose of 4 mg once a day.

Your doctor will prescribe the strength that is right for you. Do not change your dose unless your doctor has told you so. Do not take more than one tablet of RYBELSUS® daily. Do not take two tablets of RYBELSUS® to obtain a higher dose.

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

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

Overdose:

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

If you think you, or a person you are caring for, have taken too much RYBELSUS®, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed dose:

If you forget to take a dose, just take one tablet on the morning after.

Possible side effects from using RYBELSUS®:

These are not all the possible side effects you may feel when taking RYBELSUS®. If you experience any side effects not listed here, contact your healthcare professional.

Very common: may affect more than 1 in 10 people

- feeling sick (nausea) – this usually goes away over time;
- diarrhea – this usually goes away over time;
- low blood sugar (hypoglycemia) when this medicine is used with insulin or sulfonylureas.

The warning signs of low blood sugar may come on suddenly. They can include: cold sweat, cool pale skin, headache, fast heartbeat, feeling sick (nausea) or very hungry, changes in vision, feeling sleepy or weak, feeling nervous, anxious or confused, difficulty concentrating or shaking.

Your doctor will tell you how to treat low blood sugar and what to do if you notice these warning signs.

Low blood sugar is more likely to happen if you also take a sulfonylurea or insulin. Your doctor may reduce your dose of these medicines before you start using this medicine.

Common: may affect up to 1 in 10 people
- being sick (vomiting);
- upset stomach or indigestion;
- inflamed stomach ('gastritis') – the signs include stomachache, feeling sick (nausea) or being sick (vomiting);
- reflux or heartburn – also called 'gastro-esophageal reflux disease' (GERD);
- stomach pain;
- bloating of the stomach;
- constipation;
- change in the way food or drink tastes;
- tiredness;
- less appetite;
- gas (flatulence);
- increase of pancreatic enzymes (such as lipase and amylase);
- feeling dizzy;
- headache.
- changed skin sensation

Uncommon: may affect up to 1 in 100 people
- weight loss;
- gallstones;
- burping;
- fast pulse;
- allergic reactions like rash, itching or hives;
- a delay in the emptying of the stomach.

Unknown:
- Intestinal obstruction including ileus: a condition where your intestine can't push food and waste out of your body (can cause bowel obstruction, a severe form of constipation with additional symptoms such as stomach ache, bloating, vomiting etc).

Rare: may affect up to 1 in 1,000 people
- serious allergic reactions (anaphylactic reactions). You should seek immediate medical help and inform your doctor straight away if you get symptoms such as breathing problems,

swelling of face and throat, wheezing, fast heartbeat, pale and cold skin, feeling dizzy or weak.

Serious side effects and what to do about them

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Common			
Diabetic retinopathy complications – complications of diabetic eye disease/diabetic eye problems		✓	
Gallbladder disease symptoms: severe or constant pain in your stomach area, fever or jaundice (yellowing of your skin, eyes or mucous membranes)		✓	
Uncommon			
Pancreatitis (severe and ongoing pain in the stomach area which could be a sign of inflamed pancreas)		✓	✓
Severe hypoglycemia* (low blood sugar) symptoms: feeling confused, fits and passing out.		✓	
Rare			
Severe allergic reaction (anaphylactic reaction) symptoms: breathing problems, swelling of face and throat and a fast heartbeat.		✓	✓
Very rare			
Non-Arteritic Anterior Ischemic Optic Neuropathy (NAION) symptoms: a sudden loss of vision or rapidly worsening eyesight		✓	✓

**The risk of severe hypoglycemia is higher depending on the other diabetes medications.*

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting side effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Do not use this medicine after the expiry date which is stated on the blister and carton after EXP. The expiry date refers to the last day of that month.
Store RYBELSUS® at room temperature (15 ºC to 30 ºC). RYBELSUS® must be stored in the original blister 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 tampering.

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

If you want more information about RYBELSUS®:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada Drug Product Database website (Drug Product Database: Access the database); the manufacturer's website www.novonordisk.ca, or by calling 1-800-465-4334.

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