1. NAME OF THE MEDICINAL PRODUCT

Rybelsus® 3 mg
Rybelsus® 7 mg
Rybelsus® 14 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Rybelsus 3 mg tablets

Each tablet contains 3 mg semaglutide*.

Rybelsus 7 mg tablets

Each tablet contains 7 mg semaglutide*.

Rybelsus 14 mg tablets

Each tablet contains 14 mg semaglutide*.

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

Excipient with known effect

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

Rybelsus 3 mg tablets

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

Rybelsus 7 mg tablets

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

Rybelsus 14 mg tablets

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

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

4.2 Posology and method of administration

Posology

The starting dose of semaglutide is 3 mg once daily for one month. After one month, the dose should be increased to a maintenance dose of 7 mg once daily. After at least one month with a dose of 7 mg once daily, the dose can be increased to a maintenance dose of 14 mg once daily to further improve glycaemic control.

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

For information on switching between oral and subcutaneous (s.c.) semaglutide, see section 5.2.

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

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

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

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

Elderly
No dose adjustment is required based on age. Therapeutic experience in patients ≥75 years of age is limited (see section 5.2).

Renal impairment
No dose adjustment is required for patients with mild, moderate or severe renal impairment. Experience with the use of semaglutide in patients with severe renal impairment is limited. Semaglutide is not recommended in patients with end-stage renal disease (see section 5.2).

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

Paediatric population

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

Method of administration

Rybelsus is a tablet for once-daily oral use.

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name of the administered product should be clearly recorded. It is recommended to record the batch number as well.

General

Semaglutide should not be used for the treatment of diabetic ketoacidosis. Diabetic ketoacidosis has been reported in insulin-dependent patients who had rapid discontinuation or dose reduction of insulin when treatment with a GLP-1 receptor agonist is started (see section 4.2).

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

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

Aspiration in association with general anaesthesia or deep sedation

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

Gastrointestinal effects and dehydration

Use of GLP-1 receptor agonists may be associated with gastrointestinal adverse reactions. This should be considered when treating patients with impaired renal function, as nausea, vomiting, and diarrhoea may cause dehydration, which in rare cases can lead to a deterioration of renal function (see section 4.8). Patients treated with semaglutide should be advised of the potential risk of dehydration in relation to gastrointestinal side effects and take precautions to avoid fluid depletion.

Acute pancreatitis

Acute pancreatitis has been observed with the use of GLP-1 receptor agonists. Patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, semaglutide should be discontinued; if confirmed, semaglutide should not be restarted. Caution should be exercised in patients with a history of pancreatitis.

Hypoglycaemia

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

Diabetic retinopathy

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

Non-arteritic anterior ischaemic optic neuropathy (NAION)

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

Patients with gastroparesis

Semaglutide treated patients with gastroparesis may experience more serious or severe gastrointestinal adverse events. Semaglutide should be used with caution in these patients, and semaglutide is not recommended if gastroparesis is severe (see section 4.8).

Treatment response

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

Sodium content

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

4.5 Interaction with other medicinal products and other forms of interaction

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

Effects of semaglutide on other medicinal products

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

Warfarin and other coumarin derivatives
Semaglutide did not change the AUC or C_{max} of R- and S-warfarin following a single dose of warfarin, and the pharmacodynamic effects of warfarin as measured by the international normalised ratio (INR) were not affected in a clinically relevant manner. However, cases of decreased INR have been reported during concomitant use of acenocoumarol and semaglutide. Upon initiation of semaglutide treatment in patients on warfarin or other coumarin derivatives, frequent monitoring of INR is recommended.

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

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

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

Effects of other medicinal products on semaglutide

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

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

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

Pregnancy

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

Breast-feeding

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

Fertility

The effect of semaglutide on fertility in humans is unknown. Semaglutide did not affect male fertility in rats. In female rats, an increase in oestrous length and a small reduction in number of ovulations were observed at doses associated with maternal body weight loss (see section 5.3).

4.7 Effects on ability to drive and use machines

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

When it is used in combination with a sulfonylurea or insulin, patients should be advised to take precautions to avoid hypoglycaemia while driving and using machines (see section 4.4).

4.8 Undesirable effects

Summary of the safety profile

In 10 phase 3a trials, 5,707 patients were exposed to semaglutide alone or in combination with other glucose-lowering medicinal products. The duration of the treatment ranged from 26 weeks to 78 weeks. The most frequently reported adverse reactions in clinical trials were gastrointestinal disorders, including nausea (very common), diarrhoea (very common) and vomiting (common).

Tabulated list of adverse reactions

Table 1 lists adverse reactions identified in phase 3 trials (further described in section 5.1) and post marketing reports in patients with type 2 diabetes mellitus. The frequencies of the adverse reactions (except diabetic retinopathy complications and dysaesthesia, see footnotes in Table 1) are based on a pool of the phase 3a trials excluding the cardiovascular outcomes trial.

The reactions are listed below by system organ class and absolute frequency. Frequencies are defined as: very common: (≥1/10); common: (≥1/100 to <1/10); uncommon: (≥1/1,000 to <1/100); rare: (≥1/10,000 to <1/1,000) and very rare: (<1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1 Frequency of adverse reactions of oral semaglutide

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

		Abdominal distension Constipation Dyspepsia Gastritis Gastro-oesophageal reflux disease Flatulence				
Hepatobiliary disorders			Cholelithiasis			
General disorders and administration site conditions		Fatigue				
Investigations		Increased lipase Increased amylase	Weight decreased			

[a)] Hypoglycaemia defined as blood glucose <3.0 mmol/L or <54 mg/dL.
[b)] Diabetic retinopathy complications are a composite of retinal photocoagulation, treatment with intravitreal agents, vitreous haemorrhage and diabetes-related blindness (uncommon). Frequency is based on the cardiovascular outcomes trial with subcutaneous semaglutide, but it cannot be excluded that the risk of diabetic retinopathy complications identified also applies to Rybelsus.
[c)] Grouped term covering also adverse events related to hypersensitivity such as rash and urticaria.
[d)] From post-marketing reports.
[e)] The frequency is based on the PIONEER PLUS trial results for 25 mg and 50 mg. Please refer to dysaesthesia subheading below for more information. There were no imbalances of dysaesthesia events with Rybelsus 3 mg, 7 mg and 14 mg in phase 3a trials, however, events have been reported in the post-marketing experience.
[f)] Grouped term covering PTs 'intestinal obstruction', 'ileus', 'small intestinal obstruction'.

Description of selected adverse reactions

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

Gastrointestinal adverse reactions
Nausea occurred in 15%, diarrhoea in 10%, and vomiting in 7% of patients when treated with semaglutide. Most events were mild to moderate in severity and of short duration. The events led to treatment discontinuation in 4% of subjects. The events were most frequently reported during the first months on treatment.

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

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

Diabetic retinopathy complications
A 2-year clinical trial with subcutaneous semaglutide investigated 3,297 patients with type 2 diabetes, with high cardiovascular risk, long duration of diabetes and poorly controlled blood glucose. In this trial, adjudicated events of diabetic retinopathy complications occurred in more patients treated with subcutaneous semaglutide (3.0%) compared to placebo (1.8%). This was observed in insulin-treated patients with known diabetic retinopathy. The treatment difference appeared early and persisted throughout the trial. Systematic evaluation of diabetic retinopathy complication was only performed in the cardiovascular outcomes trial with subcutaneous semaglutide. In clinical trials with Rybelsus of up to 18 months duration involving 6,352 patients with type 2 diabetes, adverse events related to diabetic retinopathy were reported in similar proportions in subjects treated with semaglutide (4.2%) and comparators (3.8%).

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

Immunogenicity
Consistent with the potential immunogenic properties of medicinal products containing proteins or peptides, patients may develop antibodies following treatment with semaglutide. The proportion of subjects tested positive for anti-semaglutide antibodies at any time point after baseline was low (0.5%) and no subjects had neutralising anti-semaglutide antibodies or anti-semaglutide antibodies with neutralising effect on endogenous GLP-1 at end-of-trial.

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

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: http://sideeffects.health.gov.il.

4.9 Overdose

Effects of overdose with semaglutide in clinical studies may be associated with gastrointestinal disorders. In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms. A prolonged period of observation and treatment of the symptoms may be necessary, taking into account the long half-life of semaglutide of approximately 1 week (see section 5.2). There is no specific antidote for overdose with semaglutide.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

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

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

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

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

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

Pharmacodynamic effects

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

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

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

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

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

Clinical efficacy and safety

The efficacy and safety of Rybelsus have been evaluated in eight global randomised controlled phase 3a trials. In seven trials, the primary objective was the assessment of the glycaemic efficacy; in one trial (PIONEER 6), the primary objective was the assessment of cardiovascular outcomes.

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

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

PIONEER 1 – Monotherapy
In a 26-week double-blind trial, 703 patients with type 2 diabetes inadequately controlled with diet and exercise were randomised to semaglutide 3 mg, semaglutide 7 mg, semaglutide 14 mg or placebo once daily.

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

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

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

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

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

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

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

PIONEER 3 – Semaglutide vs. sitagliptin, both in combination with metformin or metformin with sulfonylurea
In a 78-week, double-blind, double-dummy trial, 1,864 patients with type 2 diabetes were randomised to semaglutide 3 mg, semaglutide 7 mg, semaglutide 14 mg or sitagliptin 100 mg once daily, all in combination with metformin alone or metformin and sulfonylurea. Reductions in HbA_{1c} and body weight were sustained throughout the trial duration of 78 weeks.

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

	Semaglutide 7 mg	**Semaglutide 14 mg**	**Sitagliptin 100 mg**
Full analysis set (N)	465	465	467

Week 26			
HbA_{1c} (%)			
Baseline	8.4	8.3	8.3
Change from baseline[1]	−1.0	−1.3	−0.8
Difference from sitagliptin[1] [95% CI]	−0.3 [−0.4; −0.1]*	−0.5 [−0.6; −0.4]*	-
Patients (%) achieving HbA_{1c} <7.0%	44§	56§	32
FPG (mmol/L)			
Baseline	9.4	9.3	9.5
Change from baseline[1]	−1.2	−1.7	−0.9
Difference from sitagliptin[1] [95% CI]	−0.3 [−0.6; 0.0]§	−0.8 [−1.1; −0.5]§	-
Body weight (kg)			
Baseline	91.3	91.2	90.9
Change from baseline[1]	−2.2	−3.1	−0.6
Difference from sitagliptin[1] [95% CI]	−1.6 [−2.0; −1.1]*	−2.5 [−3.0; −2.0]*	-
Week 78			
HbA_{1c} (%)			
Change from baseline[1]	−0.8	−1.1	−0.7
Difference from sitagliptin[1] [95% CI]	−0.1 [−0.3; 0.0]	−0.4 [−0.6; −0.3]§	-
Patients (%) achieving HbA_{1c} <7.0%	39§	45§	29
Body weight (kg)			
Change from baseline[1]	−2.7	−3.2	−1.0
Difference from sitagliptin[1] [95% CI]	−1.7 [−2.3; −1.0]§	−2.1 [−2.8; −1.5]§	-

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

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

In a 52-week double-blind, double-dummy trial, 711 patients with type 2 diabetes were randomised to semaglutide 14 mg, liraglutide 1.8 mg subcutaneous injection or placebo once daily, all in combination with metformin or metformin and an SGLT2 inhibitor.

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

	Semaglutide 14 mg	**Liraglutide 1.8 mg**	**Placebo**
Full analysis set (N)	285	284	142
Week 26			
HbA_{1c} (%)			
Baseline	8.0	8.0	7.9
Change from baseline[1]	−1.2	−1.1	−0.2
Difference from liraglutide[1] [95% CI]	−0.1 [−0.3; 0.0]	-	-
Difference from placebo[1] [95% CI]	−1.1 [−1.2; −0.9]*	-	-
Patients (%) achieving HbA_{1c} <7.0%	68§,a	62	14
FPG (mmol/L)			
Baseline	9.3	9.3	9.2
Change from baseline[1]	−2.0	−1.9	−0.4
Difference from liraglutide[1] [95% CI]	−0.1 [−0.4; 0.1]	-	-
Difference from placebo[1] [95% CI]	−1.6 [−2.0; −1.3]§	-	-

Body weight (kg)			
Baseline	92.9	95.5	93.2
Change from baseline[1]	−4.4	−3.1	−0.5
Difference from liraglutide[1] [95% CI]	−1.2 [−1.9; −0.6]*	-	-
Difference from placebo[1] [95% CI]	−3.8 [−4.7; −3.0]*	-	-
Week 52			
HbA_{1c} (%)			
Change from baseline[1]	−1.2	−0.9	−0.2
Difference from liraglutide[1] [95% CI]	−0.3 [−0.5; −0.1]§	-	-
Difference from placebo[1] [95% CI]	−1.0 [−1.2; −0.8]§	-	-
Patients (%) achieving HbA_{1c} <7.0%	61§,a	55	15
Body weight (kg)			
Change from baseline[1]	−4.3	−3.0	−1.0
Difference from liraglutide[1] [95% CI]	−1.3 [−2.1; −0.5]§	-	-
Difference from placebo[1] [95% CI]	−3.3 [−4.3; −2.4]§	-	-

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

PIONEER 5 – Semaglutide vs. placebo, both in combination with basal insulin alone, metformin and basal insulin or metformin and/or sulfonylurea, in patients with moderate renal impairment
In a 26-week double-blind trial, 324 patients with type 2 diabetes and moderate renal impairment (eGFR 30-59 mL/min/1.73 m^2) were randomised to semaglutide 14 mg or placebo once daily. Trial product was added to the patient's stable pre-trial antidiabetic regimen.

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

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

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

PIONEER 7 – Semaglutide vs. sitagliptin, both in combination with metformin, SGLT2 inhibitors, sulfonylurea or thiazolidinediones. Flexible-dose-adjustment trial

In a 52-week open-label trial, 504 patients with type 2 diabetes were randomised to semaglutide (flexible dose adjustment of 3 mg, 7 mg, and 14 mg once daily) or sitagliptin 100 mg once daily, all in combination with 1-2 oral glucose-lowering medicinal products (metformin, SGLT2 inhibitors, sulfonylurea or thiazolidinediones). The dose of semaglutide was adjusted every 8 weeks based on patient's glycaemic response and tolerability. The sitagliptin 100 mg dose was fixed. The efficacy and safety of semaglutide were evaluated at week 52.

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

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

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

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

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

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

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

	Semaglutide 7 mg	**Semaglutide 14 mg**	**Placebo**
Full analysis set (N)	182	181	184
Week 26 (insulin dose capped to baseline level)			
HbA_{1c} (%)			
Baseline	8.2	8.2	8.2
Change from baseline[1]	−0.9	−1.3	−0.1
Difference from placebo[1] [95% CI]	−0.9 [−1.1; −0.7]*	−1.2 [−1.4; −1.0]*	-
Patients (%) achieving HbA_{1c} <7.0%	43§	58§	7
FPG (mmol/L)			
Baseline	8.5	8.3	8.3
Change from baseline[1]	−1.1	−1.3	0.3
Difference from placebo[1] [95% CI]	−1.4 [−1.9; −0.8]§	−1.6 [−2.2; −1.1]§	-

Body weight (kg)			
Baseline	87.1	84.6	86.0
Change from baseline[1]	−2.4	−3.7	−0.4
Difference from placebo[1] [95% CI]	−2.0 [−3.0; −1.0]*	−3.3 [−4.2; −2.3]*	-
Week 52 (uncapped insulin dose)[+]			
HbA_{1c} (%)			
Change from baseline[1]	−0.8	−1.2	-0.2
Difference from placebo[1] [95% CI]	−0.6 [−0.8; −0.4][§]	−0.9 [−1.1; −0.7][§]	-
Patients (%) achieving HbA_{1c} <7.0%	40[§]	54[§]	9
Body weight (kg)			
Change from baseline[1]	−2.0	−3.7	0.5
Difference from placebo[1] [95% CI]	−2.5 [−3.6; −1.4][§]	−4.3 [−5.3; −3.2][§]	-

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

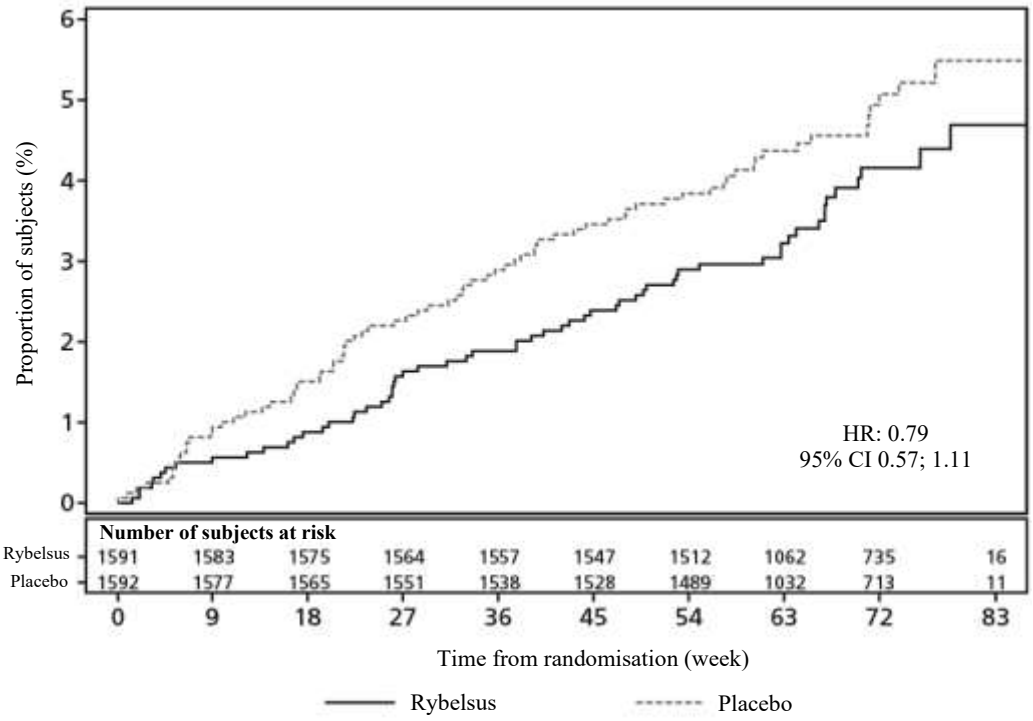
Cardiovascular evaluation

In a double-blind trial (PIONEER 6), 3,183 patients with type 2 diabetes at high cardiovascular risk were randomised to Rybelsus 14 mg once daily or placebo in addition to standard-of-care. The median observation period was 16 months.

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

Patients eligible to enter the trial were: 50 years of age or older and with established cardiovascular disease and/or chronic kidney disease, or 60 years of age or older and with cardiovascular risk factors only. In total, 1,797 patients (56.5%) had established cardiovascular disease without chronic kidney disease, 354 (11.1%) had chronic kidney disease only and 544 (17.1%) had both cardiovascular disease and kidney disease. 488 patients (15.3%) had cardiovascular risk factors only. The mean age at baseline was 66 years, and 68% of the patients were men. The mean duration of diabetes was 14.9 years and the mean BMI was 32.3 kg/m^2. Medical history included stroke (11.7%) and myocardial infarction (36.1%).

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



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

Figure 1 Cumulative incidence of first occurrence of MACE in PIONEER 6

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

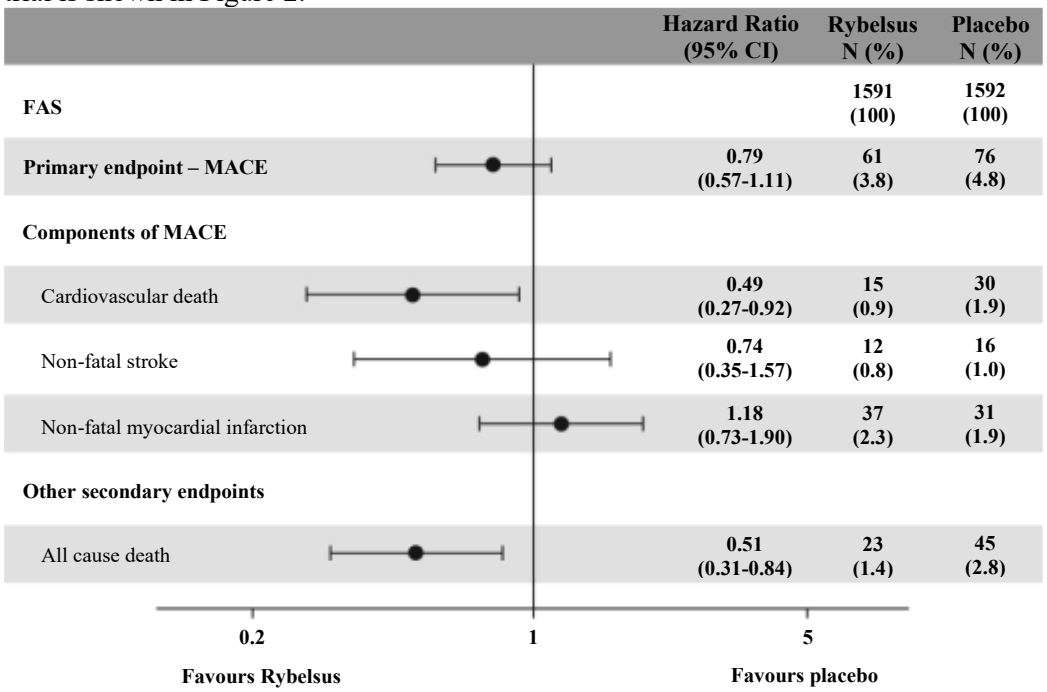


Figure 2 Treatment effect for the primary composite endpoint, its components and all cause death (PIONEER 6)

Body weight

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

Blood pressure

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

5.2 Pharmacokinetic properties

Absorption

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

The pharmacokinetics of semaglutide have been extensively characterised in healthy subjects and patients with type 2 diabetes. Following oral administration, maximum plasma concentration of semaglutide occurred approximately 1 hour post dose. Steady-state exposure was reached after 4–5 weeks of once-daily administration. In patients with type 2 diabetes, the average steady-state concentrations were approximately as listed below:
7 mg: Average concentration was 7 nmol/L with 90% of subjects treated with semaglutide 7 mg having an average concentration between 2 and 22 nmol/L.
14 mg: Average concentration was 15 nmol/L with 90% of subjects treated with semaglutide 14 mg having an average concentration between 4 and 45 nmol/L.

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

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

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

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

Distribution

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

Biotransformation

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

Elimination

The primary excretion routes of semaglutide-related material are via the urine and faeces. Approximately 3% of the absorbed dose is excreted as intact semaglutide via the urine.

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

Switching between oral and subcutaneous administration

The effect of switching between oral and subcutaneous semaglutide cannot easily be predicted because of the high pharmacokinetic variability of oral semaglutide. Exposure after oral semaglutide 14 mg once daily is comparable to subcutaneous semaglutide 0.5 mg once weekly. An oral dose equivalent to 1 mg of subcutaneous semaglutide has not been established.

Special populations

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

Gender
Gender had no clinically meaningful effects on the pharmacokinetics of semaglutide.

Race and ethnicity
Race (White, Black or African-American, Asian) and ethnicity (Hispanic or Latino, not Hispanic or Latino) had no effect on the pharmacokinetics of semaglutide.

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

Renal impairment
Renal impairment did not impact the pharmacokinetics of semaglutide in a clinically relevant manner. The pharmacokinetics of semaglutide were evaluated in patients with mild, moderate or severe renal impairment and patients with end-stage renal disease on dialysis compared with subjects with normal renal function in a study with 10 consecutive days of once-daily doses of semaglutide. This was also shown for subjects with type 2 diabetes and renal impairment based on data from phase 3a studies.

Hepatic impairment
Hepatic impairment did not impact the pharmacokinetics of semaglutide in a clinically relevant manner. The pharmacokinetics of semaglutide were evaluated in patients with mild, moderate or

severe hepatic impairment compared with subjects with normal hepatic function in a study with 10 consecutive days of once-daily doses of semaglutide.

Upper GI tract disease
Upper GI tract disease (chronic gastritis and/or gastroesophageal reflux disease) did not impact the pharmacokinetics of semaglutide in a clinically relevant manner. The pharmacokinetics were evaluated in patients with type 2 diabetes with or without upper GI tract disease dosed for 10 consecutive days with once-daily doses of semaglutide. This was also shown for subjects with type 2 diabetes and upper GI tract disease based on data from phase 3a studies.

Paediatric population

Semaglutide has not been studied in paediatric patients and is not indicated in this population.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity or genotoxicity.

Non-lethal thyroid C-cell tumours observed in rodents are a class effect for GLP-1 receptor agonists. In 2-year carcinogenicity studies in rats and mice, semaglutide caused thyroid C-cell tumours at clinically relevant exposures. No other treatment-related tumours were observed. The rodent C-cell tumours are caused by a non-genotoxic, specific GLP-1 receptor mediated mechanism to which rodents are particularly sensitive. The relevance for humans is considered to be low, but cannot be completely excluded.

In fertility studies in rats, semaglutide did not affect mating performance or male fertility. In female rats, an increase in oestrous cycle length and a small reduction in *corpora lutea* (ovulations) were observed at doses associated with maternal body weight loss.

In embryo-foetal development studies in rats, semaglutide caused embryotoxicity below clinically relevant exposures. Semaglutide caused marked reductions in maternal body weight and reductions in embryonic survival and growth. In foetuses, major skeletal and visceral malformations were observed, including effects on long bones, ribs, vertebrae, tail, blood vessels and brain ventricles. Mechanistic evaluations indicated that the embryotoxicity involved a GLP-1 receptor mediated impairment of the nutrient supply to the embryo across the rat yolk sac. Due to species differences in yolk sac anatomy and function, and due to the lack of GLP-1 receptor expression in the yolk sac of non-human primates, this mechanism is considered unlikely to be of relevance to humans. However, a direct effect of semaglutide on the foetus cannot be excluded.

In developmental toxicity studies in rabbits and cynomolgus monkeys, increased pregnancy loss and slightly increased incidence of foetal abnormalities were observed at clinically relevant exposures. The findings coincided with marked maternal body weight loss of up to 16%. Whether these effects are related to the decreased maternal food consumption as a direct GLP-1 effect is unknown.

Postnatal growth and development were evaluated in cynomolgus monkeys. Infants were slightly smaller at delivery, but recovered during the lactation period.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Salcaprozate sodium
Cellulose, microcrystalline
Magnesium stearate
Povidone K90

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging material.

6.4 Special precautions for storage

Store in the original blister package in order to protect from light and moisture. Store up to 30°C.

6.5 Nature and contents of container

Alu/Alu blisters.
Pack size of 3 mg tablets: 30 tablets.
Pack sizes of 7 mg tablets: 30 and 90 tablets.
Pack sizes of 14 mg tablets: 30 and 90 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MANUFACTURER

Novo Nordisk A/S
Novo Allé 1
DK-2880 Bagsværd
Denmark

8. REGISTRATION HOLDER

Novo Nordisk Ltd.
1 Atir Yeda St.
Kfar-Saba, 4464301

9. REGISTRATION NUMBER:

Rybelsus 3 mg: **166-72-36539**
Rybelsus 7 mg: **166-73-36540**
Rybelsus 14 mg: **166-74-36541**

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