1. Name of the medicinal product

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

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, not for first line therapy, or in addition to other medicinal products metformin, sulphonylurea, DPP-4 inhibitors, SGLT-2 inhibitor, an alpha-glucosidase inhibitor, a thiazolidinedione and insulin 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 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, 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 and the batch number of the administered product should be clearly recorded.

General

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

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, 5707 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, see footnote 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: (≥1/1000 to <1/100); rare: (≥1/10000 to <1/1000); very rare: (<1/10000) and 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**	**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 Headache	Dysgeusia		
Eye disorders		Diabetic retinopathy complications[b]			
Cardiac disorders			Increased heart rate		

Gastrointestinal disorders	Nausea Diarrhoea	Vomiting Abdominal pain Abdominal distension Constipation Dyspepsia Gastritis Gastro-oesophageal reflux disease Flatulence	Eructation Delayed gastric emptying	Acute pancreatitis	Intestinal obstruction[d,e]
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)] 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.

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

Diabetic retinopathy complications
A 2-year clinical trial with subcutaneous semaglutide investigated 3297 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%).

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®.

Reporting of suspected adverse reactions
Healthcare professionals are asked to report any suspected adverse reactions to Novo Nordisk Indonesia at IDJKAgree@novonordisk.com or to BPOM (Badan Pengawas Obat dan Makanan) at e-meso.pom.go.id.

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_{0-1h}) 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, the primary objective was the assessment of cardiovascular outcomes.

The trials included 8842 randomised patients with type 2 diabetes (5169 treated with semaglutide), including 1165 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;	−1.6 [−2.1;	-

	−0.8][§]	−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 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 3 – Semaglutide vs. sitagliptin, both in combination with metformin or metformin with sulfonylurea

In a 78-week, double-blind, double-dummy trial, 1864 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]	−1.0 [−1.2;	-	-

[95% CI]	−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

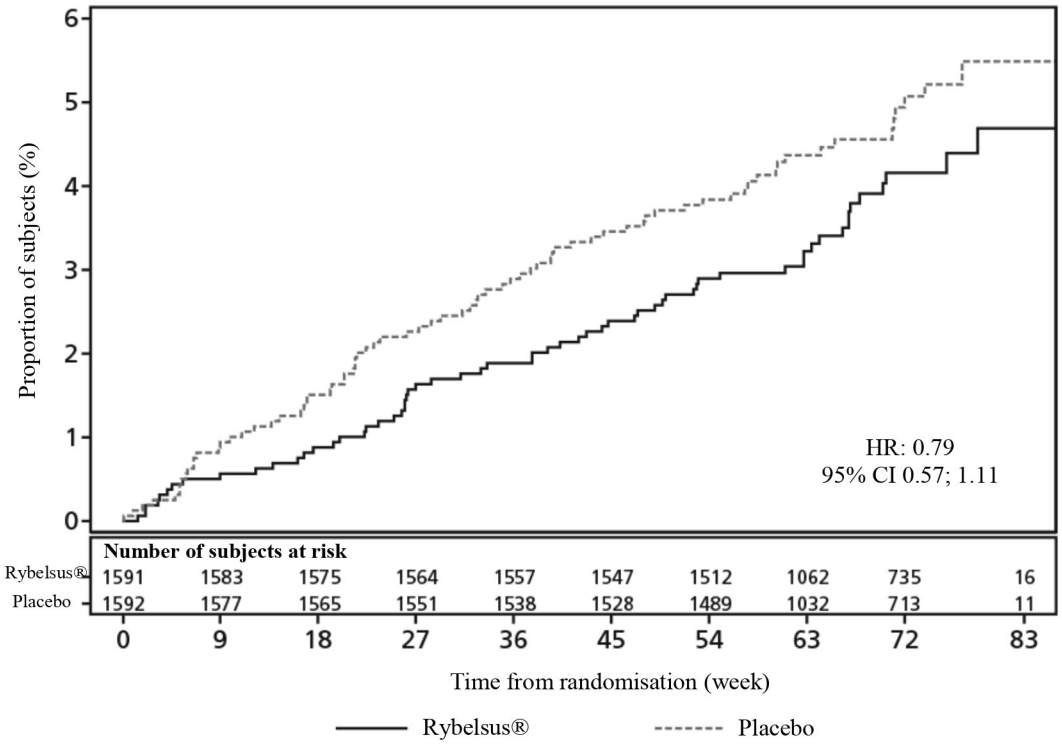
In a double-blind trial (PIONEER 6), 3183 patients with type 2 diabetes at high cardiovascular risk were randomised to Rybelsus® 14 mg once daily or placebo in addition to standard-of-care. The median observation period was 16 months.

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, 1797 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]$_{95\% \text{ CI}}$.



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.

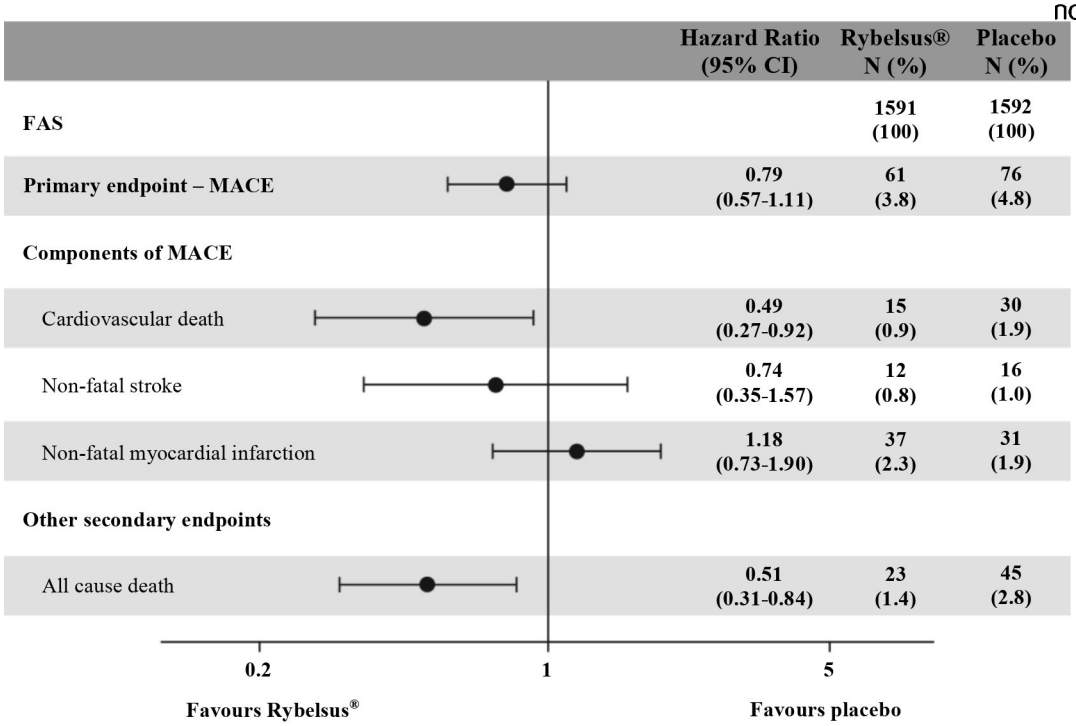


Figure 2 Treatment effect for the primary composite endpoint, its components and all cause death (PIONEER 6)

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

Semaglutide is not a pro-drug. There is no active metabolite in semaglutide. Chirality is not applicable for semaglutide. Semaglutide is freely soluble in the water. Pharmacokinetic data were obtained from healthy subjects and subjects with type 2 diabetes.

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 6.7 nmol/L and 14.6 nmol/L with semaglutide 7 mg and 14 mg, respectively; with 90% of subjects treated with semaglutide 7 mg having an average concentration between 1.7 and 22.7 nmol/L and 90% of subjects treated with semaglutide 14 mg having an average concentration between 3.7 and 41.3 nmol/L. Systemic exposure of semaglutide increased in a dose-proportional manner.

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 1.0 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.

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
Povidone K90
Cellulose, microcrystalline
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months (3 mg)
30 months (7 mg & 14 mg)
Expiry date is stated on the blister package and carton after 'Expiry'.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Alu/Alu blisters.
Pack size of 30 tablets (available strengths: 3 mg, 7 mg and 10 mg)

HARUS DENGAN RESEP DOKTER
Reg. No.: DKI2364605310A1 (3 mg)
DKI2364605310B1 (7 mg)
DKI2364605310C1 (14 mg)

6.6 Special precautions for disposal

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

7. Manufactured by:

Novo Nordisk A/S
Novo Nordisk Park
DK-2760 Måløv
Denmark

Packed by:
Novo Nordisk A/S
Hallas Allé
DK-4400 Kalundborg
Denmark

Released by:
Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark

Registered by:

PT Ferron Par Pharmaceuticals
Bekasi – Indonesia

Distributed by:
PT Anugrah Argon Medica
Indonesia

Based on approval date: …….

Text for frontpage:

Rybelsus®

semaglutide

Teks untuk halaman depan:

Rybelsus®

semaglutide

Brosur kemasan: Informasi untuk pasien

Rybelsus® tablet 3 mg
Rybelsus® tablet 7 mg
Rybelsus® tablet 14 mg
semaglutide

Bacalah seluruh bagian brosur ini dengan teliti sebelum Anda mulai menggunakan obat ini karena brosur ini mengandung informasi yang penting untuk Anda.
- Simpan brosur ini. Anda mungkin perlu membacanya lagi.
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakan kepada dokter, apoteker atau perawat Anda.
- Obat ini telah diresepkan hanya untuk Anda. Jangan memberikannya kepada orang lain. Obat ini mungkin membahayakan mereka, meskipun jika tanda-tanda penyakit mereka sama dengan Anda.
- Jika Anda mengalami efek samping apapun, bicarakan dengan dokter, apoteker atau perawat Anda. Termasuk kemungkinan efek samping apapun yang tidak tercantum dalam brosur ini. Lihat bagian 4.

Apa yang terdapat dalam brosur ini

1. Apa itu Rybelsus® dan untuk apa kegunaannya

Rybelsus® mengandung zat aktif semaglutide 3 mg, 7 mg dan 14 mg. Rybelsus® adalah obat yang digunakan untuk menurunkan kadar gula darah.

Rybelsus® digunakan untuk pengobatan orang dewasa (berusia 18 tahun dan ke atas) dengan diabetes tipe 2 ketika diet dan olahraga tidak cukup:
- secara tunggal, tidak untuk terapi lini pertama, atau
- dengan obat lain untuk diabetes (metformin, sulfonilurea, penghambat DPP-4, penghambat SGLT-2, penghambat *alpha-glucosidase*, thiazolidinedione dan insulin) – jika obat lain tidak cukup untuk mengontrol kadar gula darah Anda. Obat lain tersebut mungkin obat yang diberikan secara oral atau disuntikkan seperti insulin.

Penting bagi Anda untuk melanjutkan rencana diet dan olahraga Anda yang disetujui oleh dokter, apoteker atau perawat Anda.

Apa itu diabetes tipe 2?
Diabetes tipe 2 adalah suatu kondisi dimana tubuh Anda tidak cukup memproduksi insulin, dan insulin yang diproduksi oleh tubuh Anda tidak menurunkan kadar gula darah Anda seperti yang seharusnya. Dalam beberapa kasus, tubuh Anda dapat menghasilkan terlalu

banyak gula darah. Jika kadar gula darah Anda meningkat dan tetap tinggi dalam jangka waktu yang lama, hal tersebut dapat menyebabkan efek berbahaya seperti gangguan jantung, penyakit ginjal, gangguan mata, dan sirkulasi yang buruk di anggota tubuh Anda. Hal tersebut adalah alasan mengapa penting untuk menjaga kadar gula darah Anda dalam kisaran normal.

2. Apa yang Anda perlu ketahui sebelum menggunakan Rybelsus®

Jangan menggunakan Rybelsus®
- jika Anda alergi terhadap semaglutide atau salah satu zat lainnya dalam obat ini (tercantum di bagian 6).

Peringatan dan pencegahan
Bicarakan dengan dokter, apoteker atau perawat Anda sebelum menggunakan Rybelsus®.

Penelusuran
Untuk meningkatkan penelusuran produk obat biologis, catatlah nama dan nomor lot (terdapat di karton luar dan blister) obat yang Anda gunakan dan berikan informasi tersebut saat pelaporan efek samping.

Umum
Obat ini tidak sama dengan insulin dan Anda seharusnya tidak menggunakannya jika:
- Anda mengalami diabetes tipe 1 (tubuh Anda tidak memproduksi insulin)
- Anda mengalami ketoasidosis diabetes. Hal tersebut adalah komplikasi diabetes dengan kadar gula darah yang tinggi, kesulitan bernapas, kebingungan, rasa haus yang berlebihan, bau napas yang manis atau rasa manis atau logam di mulut.

Jika Anda mengetahui bahwa Anda akan menjalani operasi dimana Anda akan dibius anestesi (tertidur), beritahu dokter Anda bahwa Anda sedang mengkonsumsi Rybelsus®. Kasus aspirasi pulmonal (masuknya zat selain udara, dalam hal ini isi lambung, ke dalam saluran pernafasan) telah dilaporkan pada pasien penerima obat sejenis agonis reseptor GLP-1 (*glucagon-like peptide*-1) yang menjalani anestesi umum atau sedasi hingga tertidur.

Gangguan di lambung dan usus dan dehidrasi
Selama pengobatan dengan obat ini, Anda mungkin merasa sakit (mual) atau sakit (muntah), atau diare. Efek samping tersebut dapat menyebabkan dehidrasi (kehilangan cairan). Penting bagi Anda untuk minum cukup cairan untuk mencegah dehidrasi. Hal tersebut penting khususnya jika Anda mengalami gangguan ginjal. Bicarakan dengan dokter Anda jika Anda memiliki pertanyaan atau kekhawatiran.

Nyeri perut yang parah dan berkelanjutan yang dapat disebabkan oleh peradangan pankreas
Jika Anda mengalami nyeri parah dan berkelanjutan di area perut - segera temui dokter karena hal tersebut dapat menjadi tanda peradangan pankreas (pankreatitis akut).

Kadar gula darah rendah (hipoglikemia)

Mengonsumsi sulfonilurea atau insulin dengan Rybelsus® mungkin meningkatkan risiko terkena kadar gula darah yang rendah (hipoglikemia). Lihat bagian 4 untuk tanda peringatan kadar gula darah yang rendah.

Dokter Anda mungkin meminta Anda untuk melakukan tes kadar gula darah Anda. Hal tersebut akan membantu untuk memutuskan apakah dosis sulfonilurea atau insulin perlu diubah untuk mengurangi risiko kadar gula darah yang rendah.

Penyakit mata diabetes (retinopati)
Peningkatan yang cepat dalam pengendalian kadar gula darah mungkin menyebabkan perburukan sementara penyakit mata diabetes. Jika Anda mengalami penyakit mata diabetes dan mengalami gangguan mata saat menggunakan obat ini, bicarakan dengan dokter Anda.

Respon pengobatan
Jika respon pengobatan dengan semaglutide lebih rendah dari yang diharapkan, hal tersebut mungkin karena rendahnya absorpsi yang disebabkan oleh variabilitas dalam absorpsi dan bioavailabilitas absolut yang rendah. Anda seharusnya mengikuti instruksi yang diberikan di bagian 3 untuk efek semaglutide yang optimal.

Anak-anak dan remaja
Obat ini tidak direkomendasikan pada anak-anak dan remaja berusia di bawah 18 tahun karena keamanan dan efikasinya pada kelompok usia ini belum dikembangkan.

Obat-obatan lain dan Rybelsus®
Beritahu dokter atau apoteker Anda jika Anda sedang, baru saja atau mungkin menggunakan obat lain.

Secara khusus, beritahu dokter, apoteker atau perawat Anda jika Anda menggunakan obat-obatan yang mengandung salah satu zat berikut ini:
- Levothyroxine yang digunakan untuk penyakit tiroid. Hal tersebut karena dokter Anda mungkin perlu memeriksa kadar tiroid Anda jika Anda menggunakan Rybelsus® bersama dengan levotiroksin.
- Warfarin atau obat serupa yang digunakan secara oral untuk mengurangi pembekuan darah (antikoagulan oral). Anda mungkin perlu sering melakukan tes darah untuk memeriksa seberapa cepat darah Anda menggumpal.
- Jika Anda menggunakan insulin, dokter Anda akan memberitahu Anda bagaimana cara mengurangi dosis insulin dan akan merekomendasikan Anda untuk memantau lebih sering kadar gula darah Anda, untuk menghindari hiperglikemia (kadar gula darah yang tinggi) dan ketoasidosis diabetes (komplikasi diabetes yang terjadi ketika tubuh tidak mampu memecah glukosa karena tidak ada cukup insulin).

Kehamilan dan menyusui
Jika Anda sedang hamil atau menyusui, merasa Anda mungkin hamil atau berencana untuk memiliki bayi, mintalah saran dari dokter Anda sebelum menggunakan obat ini.

Obat ini seharusnya tidak digunakan selama kehamilan, karena tidak diketahui apakah obat ini memengaruhi bayi Anda yang belum lahir. Oleh karena itu, Anda harus menggunakan kontrasepsi saat menggunakan obat ini. Jika Anda ingin hamil, diskusikan bagaimana cara mengubah pengobatan Anda dengan dokter Anda karena Anda seharusnya berhenti menggunakan obat ini setidaknya 2 bulan sebelumnya. Jika Anda hamil saat menggunakan obat ini, segera bicarakan dengan dokter Anda, karena pengobatan Anda akan perlu diubah.

Jangan menggunakan obat ini jika Anda sedang menyusui. Obat ini masuk ke dalam ASI, dan tidak diketahui bagaimana pengaruh obat ini terhadap bayi Anda.

Mengemudi dan menggunakan mesin
Rybelsus® hampir tidak memengaruhi kemampuan Anda mengendarai dan menggunakan mesin.

Beberapa pasien mungkin merasakan pusing ketika mengonsumsi Rybelsus®. Jika Anda merasa pusing, berhati-hatilah ketika mengendarai atau menggunakan mesin. Bicarakan dengan dokter Anda untuk informasi lebih lanjut.

Jika Anda menggunakan obat ini dikombinasikan dengan sulfonilurea atau insulin, kadar gula darah yang rendah (hipoglikemia) mungkin terjadi yang mungkin mengurangi kemampuan Anda untuk berkonsentrasi. Jangan mengemudi atau menggunakan mesin jika Anda mengalami tanda kadar gula darah yang rendah. Lihat bagian 2, 'Peringatan dan pencegahan' untuk informasi tentang peningkatan risiko kadar gula darah yang rendah dan bagian 4 untuk tanda peringatan kadar gula darah yang rendah. Bicarakan dengan dokter Anda untuk informasi lebih lanjut.

Rybelsus® mengandung natrium
Obat ini mengandung 23 mg natrium (komponen utama garam masak/garam meja) pada setiap tabletnya. Hal tersebut setara dengan 1% dari asupan natrium harian maksimum yang direkomendasikan untuk orang dewasa.

3. Bagaimana cara menggunakan Rybelsus®

Selalu gunakan obat ini sama seperti yang disampaikan oleh dokter Anda. Periksa dengan dokter atau apoteker Anda jika Anda tidak yakin.

Berapa banyak yang digunakan
- Dosis awal adalah satu tablet 3 mg sekali sehari selama satu bulan.
- Setelah satu bulan, dokter Anda akan meningkatkan dosis Anda menjadi satu tablet 7 mg sekali sehari.
- Dokter Anda akan menginstruksikan Anda untuk menggunakan satu dosis selama minimum satu bulan sebelum meningkatkan ke dosis yang lebih tinggi.
- Dokter Anda mungkin meningkatkan dosis Anda menjadi satu tablet 14 mg sekali sehari jika perlu.
- Dokter Anda akan meresepkan kekuatan yang tepat untuk Anda. Jangan mengubah dosis Anda kecuali dokter Anda memberitahu Anda.

- Rybelsus® seharusnya digunakan satu tablet sehari sekali. Anda seharusnya tidak menggunakan dua tablet untuk mendapatkan efek dosis yang lebih tinggi.

Menggunakan obat ini
- Konsumsi tablet Rybelsus® dalam keadaan perut kosong kapanpun sepanjang hari.
- Telan tablet utuh Rybelsus® dengan seteguk air (hingga 120 mL). Jangan membelah, menghancurkan atau mengunyah tablet, karena tidak diketahui apakah hal tersebut memengaruhi absorpsi semaglutide.
- Setelah meminum tablet Rybelsus® Anda tunggu setidaknya 30 menit sebelum makan, minum air atau minum obat oral lainnya. Menunggu kurang dari 30 menit menurunkan absorpsi semaglutide.

Jika Anda menggunakan Rybelsus® lebih banyak dari yang seharusnya
Jika Anda menggunakan Rybelsus® lebih banyak dari yang seharusnya, segera bicarakan dengan dokter Anda. Anda mungkin mengalami efek samping seperti merasa sakit (mual).

Jika Anda lupa menggunakan Rybelsus®
Jika Anda lupa menggunakan 1 dosis, lewati dosis yang terlewat dan gunakan dosis normal Anda pada hari berikutnya.

Jika Anda berhenti menggunakan Rybelsus®
Jangan berhenti menggunakan obat ini tanpa berbicara dengan dokter Anda. Jika Anda berhenti menggunakannya, kadar gula darah Anda mungkin meningkat.

Jika Anda memiliki pertanyaan lebih lanjut tentang penggunaan obat ini, tanyakan kepada dokter, apoteker atau perawat Anda.

4. Efek samping yang mungkin dirasakan

Seperti semua obat, obat ini dapat menimbulkan efek samping, meski tidak semua orang mengalaminya.

Efek samping yang serius

Umum (mungkin memengaruhi hingga 1 dari 10 orang)
- Komplikasi penyakit mata diabetes (retinopati). Anda seharusnya memberitahu dokter Anda jika Anda mengalami gangguan mata, seperti perubahan penglihatan, selama pengobatan dengan obat ini.

Jarang (mungkin memengaruhi hingga 1 dari 1.000 orang)
- Reaksi alergi yang serius (reaksi anafilaksis). Anda harus segera mendapatkan pertolongan medis dan menginformasikan dokter Anda jika Anda mengalami gejala seperti gangguan pernapasan, pembengkakan wajah dan tenggorokan, mengi, detak jantung yang cepat, kulit pucat dan dingin, merasa pusing atau lemas.
- Peradangan pankreas (pankreatitis akut) yang dapat menyebabkan nyeri parah di perut dan punggung yang tidak hilang. Anda seharusnya segera ke dokter jika mengalami gejala tersebut.

Tidak diketahui (frekuensi tidak dapat diperkirakan dari data yang tersedia)
- Kerusakan usus. Konstipasi yang parah dengan gejala tambahan seperti nyeri lambung, kembung, muntah dan lain-lain.

Efek samping lainnya

Sangat umum (mungkin memengaruhi lebih dari 1 dari 10 orang)
- Kadar gula darah yang rendah (hipoglikemia) ketika obat ini digunakan dengan obat-obatan yang mengandung sulfonilurea atau insulin. Dokter Anda mungkin mengurangi dosis obat-obatan tersebut sebelum Anda mulai menggunakan obat ini.
- Merasa sakit (mual) - biasanya hilang seiring waktu
- Diare - biasanya hilang seiring waktu

Tanda peringatan kadar gula darah yang rendah mungkin terjadi tiba-tiba. Hal tersebut meliputi: keringat dingin, kulit pucat dingin, nyeri kepala, detak jantung yang cepat, merasa sakit (mual) atau sangat lapar, perubahan penglihatan, merasa mengantuk atau lemas, merasa gugup, cemas atau bingung, sulit berkonsentrasi atau gemetar.
Dokter Anda akan memberitahu Anda bagaimana cara mengatasi kadar gula darah yang rendah dan apa yang harus dilakukan jika Anda mengalami tanda-tanda peringatan tersebut.

Umum (mungkin memengaruhi hingga 1 dari 10 orang)
- Kadar gula darah yang rendah (hipoglikemia) jika obat ini digunakan dengan obat diabetes oral selain sulfonilurea atau insulin
- Nafsu makan berkurang
- Merasa pusing
- Sakit (muntah)
- Nyeri lambung
- Perut kembung
- Konstipasi
- Nyeri perut atau gangguan pencernaan
- Peradangan lambung ('gastritis') - tanda-tandanya termasuk nyeri lambung, merasa sakit (mual) atau sakit (muntah)
  Refluks atau maag - juga disebut 'penyakit refluks gastro-esofagus'
- Gas (flatulensi)
- Kelelahan
- Peningkatan enzim pankreas (seperti lipase dan amilase) pada tes darah
- Sakit kepala.

Tidak umum (mungkin memengaruhi hingga 1 dari 100 orang)
- Reaksi alergi seperti ruam atau gatal
- Perubahan dalam merasakan rasa makanan atau minuman
- Denyut nadi yang cepat
- Bersendawa
- Penundaan pengosongan lambung
- Batu empedu

- Penurunan berat badan

Pelaporan efek samping
Jika Anda mengalami efek samping apapun selama atau setelah penggunaan obat, bicarakan dengan dokter, apoteker atau perawat Anda. Termasuk kemungkinan efek samping apapun yang tidak tercantum di brosur ini. Anda juga dapat melaporkan efek samping tersebut secara langsung ke Novo Nordisk Indonesia melalui IDJKAgree@novonordisk.com. Dengan melaporkan efek samping, Anda dapat membantu menyediakan informasi lebih lanjut mengenai keamanan obat ini.

5. Bagaimana cara menyimpan Rybelsus®

Jauhkan obat ini dari pandangan dan jangkauan anak-anak.

Jangan menggunakan obat ini setelah tanggal kedaluwarsa yang tertera pada blister dan karton setelah 'Expiry'. Tanggal kedaluwarsa mengacu pada hari terakhir bulan tersebut.

Simpan dalam kemasan aslinya untuk melindungi dari cahaya dan kelembaban. Simpan di bawah 30°C.

Jangan membuang obat apa pun melalui air limbah atau limbah rumah tangga. Tanyakan apoteker Anda bagaimana cara membuang obat yang tidak Anda gunakan lagi. Tindakan tersebut akan membantu melindungi lingkungan.

6. Isi kemasan dan informasi lainnya

Apa yang terkandung dalam Rybelsus®
- Zat aktifnya adalah semaglutide. Setiap tablet mengandung semaglutide 3, 7 atau 14 mg semaglutide.

Zat lainnya adalah natrium salcaprozate, povidone K90, mikrokristalin selulosa, magnesium stearat. Lihat juga bagian 2, ‘Rybelsus® mengandung natrium’.

Seperti apa bentuk Rybelsus® dan isi kemasan
Rybelsus® tablet 3 mg berwarna putih hingga kuning muda dan berbentuk oval (7,5 mm x 13,5 mm). Terdapat angka '3' di satu sisi dan 'novo' di sisi lain.
Rybelsus® tablet 7 mg berwarna putih hingga kuning muda dan berbentuk oval (7,5 mm x 13,5 mm). Terdapat angka '7' di satu sisi dan 'novo' di sisi lain.
Rybelsus® tablet 14 mg berwarna putih hingga kuning muda dan berbentuk oval (7,5 mm x 13,5 mm). Terdapat angka '14' di satu sisi dan 'novo' di sisi lain.

Tablet 3 mg, 7 mg dan 14 mg tersedia dalam blister alu/alu dalam ukuran kemasan 30 tablet.

HARUS DENGAN RESEP DOKTER
Reg. No.: DKI2364605310A1 (3 mg)
DKI2364605310B1 (7 mg)
DKI2364605310C1 (14 mg)

Diproduksi oleh:
Novo Nordisk A/S
Novo Nordisk Park
DK-2760 Måløv
Denmark

Dikemas oleh:
Novo Nordisk A/S
Hallas Allé
DK-4400 Kalundborg
Denmark

Dirilis oleh:
Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark

Didaftarkan oleh:
PT Ferron Par Pharmaceuticals
Bekasi – Indonesia

Didistribusikan oleh:
PT Anugrah Argon Medica
Indonesia

Berdasarkan persetujuan tanggal: .....

Rybelsus® adalah merek dagang yang dimiliki oleh Novo Nordisk A/S, Denmark