To be sold by retail on the prescription of endocrinologist or internal medicine specialists only

SEMALIX™

1. Generic Name

Semaglutide Tablets 3 mg

Semaglutide Tablets 7 mg

Semaglutide Tablets 14 mg

2. Qualitative and quantitative Composition:

Semaglutide Tablets 3 mg

Each uncoated tablet contains:

Semaglutide….3 mg

Excipients……q.s.

Semaglutide Tablets 7 mg

Each uncoated tablet contains:

Semaglutide….7 mg

Excipients……q.s.

Semaglutide Tablets 14 mg

Each uncoated tablet contains:

Semaglutide….14 mg

Excipients……q.s.

3. Dosage form and strength

Dosage form: Uncoated Tablets

Strength: 3mg, 7mg, 14mg

4. Clinical particulars

4.1 Therapeutic indication

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

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

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 recommended single daily maintenance doses are 7 mg or 14 mg.

The maximum recommended single daily dose of semaglutide is 14 mg. Semaglutide should always be used as one tablet per day. Taking more than one tablet a day should not be done to achieve the effect of a higher dose.

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.

The blood glucose should be monitored for the dose adjustment of semaglutide as advised by the physician.

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.

Special populations

Elderly

No dose adjustment is required based on age.

Renal impairment

The phase III clinical trial in India was conducted in patients with eGFR > 60 mL/min/1.73 m^2.

No dose adjustment is required for patients with mild, moderate or severe renal impairment. Experience with the use of semaglutide in patients with end-stage kidney disease is limited.

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.

Paediatric population

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

Method of administration

Semaglutide is a tablet for once-daily oral use.

This medicinal product should be taken on an empty stomach after a recommended fasting period of at least 8 hours.

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.

4.3 Contraindications

Semaglutide is contraindicated in patients with:

- A personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).
- Hypersensitivity reaction to semaglutide or to any of the excipients in semaglutide.

4.4 Special warnings and precautions for use

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.

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.

Risk of Thyroid C-Cell Tumors

In mice and rats, semaglutide caused a dose-dependent and treatment-duration dependent increase in the incidence of thyroid C-cell tumors (adenomas and carcinomas) after lifetime exposure at clinically relevant plasma exposures. It is unknown whether semaglutide causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as human relevance of semaglutide-induced rodent thyroid C-cell tumors has not been determined.

Cases of MTC in patients treated with liraglutide, another GLP-1 receptor agonist, have been reported in the postmarketing period; the data in these reports are insufficient to establish or exclude a causal relationship between MTC and GLP-1 receptor agonist use in humans.

Semaglutide is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2. Counsel patients regarding the potential risk for MTC with the use of semaglutide and inform them of symptoms of thyroid tumors (e.g., a mass in the neck, dysphagia, dyspnea, persistent hoarseness).

Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with semaglutide. Such monitoring may increase the risk of unnecessary procedures, due to the low-test specificity for serum calcitonin and a high background incidence of thyroid disease. Significantly elevated serum calcitonin value may indicate MTC and patients with MTC usually have calcitonin values >50 ng/L. If serum calcitonin is measured and found to be elevated, the patient should be further evaluated. Patients with thyroid nodules noted on physical examination or neck imaging should also be further evaluated.

Acute Pancreatitis

Acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, has been observed in patients treated with GLP-1 receptor agonists, including semaglutide.

After initiation of semaglutide, observe patients carefully for signs and symptoms of pancreatitis, which may include persistent or severe abdominal pain (sometimes radiating to the back), and which may or may not be accompanied by nausea or vomiting. If pancreatitis is suspected, discontinue semaglutide and initiate appropriate management.

Diabetic Retinopathy Complications

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

In a 2-year CV outcomes trial with semaglutide injection involving patients with type 2 diabetes mellitus and high CV risk, diabetic retinopathy complications (which was a 4 component adjudicated endpoint) occurred in patients treated with semaglutide injection (3%) compared to placebo (1.8%). The absolute risk increase for diabetic retinopathy complications was larger among patients with a history of diabetic retinopathy at baseline (semaglutide injection 8.2%, placebo 5.2%) than among patients without a known history of diabetic retinopathy (semaglutide injection 0.7%, placebo 0.4%).

Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy. The effect of long-term glycemic control with semaglutide on diabetic retinopathy complications has not been studied. Patients with a history of diabetic retinopathy should be monitored for progression of diabetic retinopathy.

Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin

Patients receiving semaglutide in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin may have an increased risk of hypoglycemia, including severe hypoglycemia.

The risk of hypoglycemia may be lowered by a reduction in the dosage of sulfonylurea (or other concomitantly administered insulin secretagogue) or insulin. Inform patients using these concomitant medications of the risk of hypoglycemia and educate them on the signs and symptoms of hypoglycemia.

Acute Kidney Injury Due to Volume Depletion

There have been postmarketing reports of acute kidney injury, in some cases requiring hemodialysis, in patients treated with semaglutide. The majority of the reported events occurred in patients who experienced gastrointestinal reactions leading to dehydration such as nausea, vomiting, or diarrhea.

Monitor renal function in patients reporting adverse reactions to semaglutide that could lead to volume depletion, especially during dosage initiation and escalation of semaglutide.

Severe Gastrointestinal Adverse Reactions

Use of semaglutide has been associated with gastrointestinal adverse reactions, sometimes severe. In semaglutide clinical trials, severe gastrointestinal adverse reactions were reported more frequently among patients receiving semaglutide (7 mg 0.6%, 14 mg 2%) than placebo (0.3%). Severe gastrointestinal adverse reactions have also been reported postmarketing with GLP-1 receptor agonists.

Semaglutide is not recommended in patients with severe gastroparesis.

Hypersensitivity Reactions

Serious hypersensitivity reactions (e.g., anaphylaxis, angioedema) have been reported in patients treated with semaglutide. If hypersensitivity reactions occur, discontinue use of semaglutide; treat promptly per standard of care and monitor until signs and symptoms resolve. semaglutide is contraindicated in patients with a prior serious hypersensitivity reaction to semaglutide or to any of the excipients in semaglutide.

Anaphylaxis and angioedema have been reported with GLP-1 receptor agonists. Use caution in a patient with a history of angioedema or anaphylaxis with another GLP-1 receptor agonist

because it is unknown whether such patients will be predisposed to anaphylaxis with semaglutide.

Acute Gallbladder Disease

Acute events of gall bladder disease such as cholelithiasis or cholecystitis have been reported in GLP-1 receptor agonist trials and postmarketing. In placebo-controlled trials to improve glycemic control, cholelithiasis was reported in 1% of patients treated with semaglutide 7 mg. In a 4-year CV outcomes trial, cholelithiasis was reported in 1.1% of patients treated with semaglutide 14 mg and in 0.9% of placebo-treated patients. In trial, cholecystitis was reported in 1.1% of patients treated with semaglutide 14 mg and in 0.7% of placebo-treated patients. If cholelithiasis or cholecystitis is suspected, gallbladder studies and appropriate clinical follow-up are indicated.

Pulmonary Aspiration During General Anesthesia or Deep Sedation

Semaglutide delays gastric emptying. There have been rare postmarketing reports of pulmonary aspiration in patients receiving GLP-1 receptor agonists undergoing elective surgeries or procedures requiring general anesthesia or deep sedation who had residual gastric contents despite reported adherence to preoperative fasting recommendations.

Available data are insufficient to inform recommendations to mitigate the risk of pulmonary aspiration during general anesthesia or deep sedation in patients taking semaglutide, including whether modifying preoperative fasting recommendations or temporarily discontinuing semaglutide could reduce the incidence of retained gastric contents. Instruct patients to inform healthcare providers prior to any planned surgeries or procedures if they are taking semaglutide.

4.5 Drugs interactions

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.

4.6 Use in special populations (such as pregnant women, lactating women, Fertility etc.)

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. 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.

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, semaglutide 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.

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.

4.8 Undesirable effects

Summary of the safety profile

Adverse Events Reported In Phase-III Clinical Trial In Indian Patients With Type II Diabetes Mellitus:

In phase-III clinical trial conducted by Torrent Pharmaceutical Ltd. 236 Indian patients with Type 2 Diabetes Mellitus were exposed to semaglutide, equally randomized (1:1) to receive Torrent's Oral Semaglutide or the comparator (oral semaglutide, Rybelsus) alone or in

combination with other glucose-lowering medicinal products, as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus, for a treatment duration of 24 weeks. The most frequently reported adverse reactions (in >2% patients) in this clinical trial were gastrointestinal disorders, including nausea (16.1%), vomiting (6.8%), abdominal pain (5.1%), hyperchlorhydria (3.4%) and diarrhoea (3.4%).

A total of 138 adverse events (AEs) were reported overall in 88 patients (37.3%) during the study. Among these, 70 AEs were reported in 48 patients (40.7%) who received Torrent's semaglutide oral tablets.

Global clinical trial 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 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: (≥1/1,000 to <1/100); rare: (≥1/10,000 to <1/1,000); very rare: (<1/10,000) 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	Hypoglycaemia when used with other oral antidiabetic products[a] Decreased appetite			
Nervous system disorders		Dizziness Headache	Dysgeusia		Dysesthesia[d]
Eye disorders		Diabetic retinopathy complications[b]			
Cardiac disorders			Increased heart rate		

MedDRA system organ class	Very common	Common	Uncommon	Rare	Not Known
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		
Renal disorders					Acute kidney injury[d]
Skin and Subcutaneous Tissue disorders					Alopecia[d]
General disorders and administration site conditions		Fatigue			
Investigations		Increased lipase Increased amylase	Weight decreased		

a) Hypoglycaemia defined as blood glucose <3.0 mmol/L or <54 mg/dL.
b) Diabetic retinopathy complications is a composite of retinal photocoagulation, treatment with intravitreal agents, vitreous haemorrhage and diabetes-related blindness (uncommon). Frequency is based on the cardiovascular outcomes trial with S.C. semaglutide, but it cannot be excluded that the risk of diabetic retinopathy complications identified also applies to Semaglutide.
c) Grouped term covering also adverse events related to hypersensitivity such as angioedema, 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 PIONEER 6 the frequency of acute pancreatitis confirmed by adjudication was 0.1% for semaglutide and 0.2% for placebo. In phase 3b cardiovascular outcomes trial SOUL, the frequency of acute pancreatitis confirmed by adjudication was 0.4% for semaglutide and 0.4% for placebo.

Diabetic retinopathy complications

A 2-year clinical trial with subcutaneous semaglutide investigated 3 297 patients with type 2 diabetes, with high cardiovascular risk, long duration of diabetes and poorly controlled blood glucose. In this trial, adjudicated events of diabetic retinopathy complications occurred in more patients treated with subcutaneous semaglutide (3.0%) compared to placebo (1.8%). This was observed in insulin-treated patients with known diabetic retinopathy. The treatment difference appeared early and persisted throughout the trial. Systematic evaluation of diabetic retinopathy complication was only performed in the cardiovascular outcomes trial with subcutaneous semaglutide. In clinical trials with semaglutide 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%). In the SOUL trial, adverse events of diabetic retinopathy were reported in similar proportions in subjects treated with oral semaglutide (20.1%) and placebo (19.6%) with low proportions of subjects having events identified due to eye symptoms (0.3% and 0.3%, respectively).

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 Semaglutide.

Reporting of 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. To report Suspected Adverse Reactions, contact Torrent pharmaceuticals Limited at email: pv@torrentpharma.com or call on 1800-120-3001 or through company website www.torrentpharma.com-> contact us->reporting of adverse event.

4.9 Overdose

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

5 Pharmacological properties

5.1 Mechanism of Action

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

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

Semaglutide reduces blood glucose in a glucose-dependent manner by stimulating insulin secretion and lowering glucagon secretion when 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.

The exact mechanism of cardiovascular risk reduction has not been established.

5.2 Pharmacodynamic Properties

Phase-III Clinical Trial In Indian Patients with Type 2 Diabetes Mellitus:

Summary of efficacy

In a 24-week, randomized, multi-centric, double-blind, double-dummy, active controlled, parallel-group, non-inferiority, phase-III clinical trial, 236 patients with type 2 diabetes were randomised to Torrent's semaglutide 3 mg, semaglutide 7 mg, semaglutide 14 mg oral tablets or the comparator (Rybelsus®, semaglutide 3 mg, semaglutide 7 mg, semaglutide 14 mg oral tablets) in a once daily dose, all in patients who were inadequately controlled on background antidiabetic therapy with metformin either alone or in combination with SU or SGLT-2 inhibitor. Reductions in HbA1c and body weight were sustained throughout the trial duration of 24 weeks.

The primary end point was mean change from baseline in HbA1c at week 24. The mean baseline HbA1c levels were comparable between both the treatment groups, measuring 8.08% in the test group and 8.16% in the comparator group, and both groups demonstrated a similar rate of reduction over time.

The mean change from baseline in HbA1c at week 24 was had significantly decreased by -1.30% (95% CI -1.45 to -1.16, p <.0001 for change in baseline to week 24) and -1.47% (95% CI -1.63 to -1.31, p <.0001 for change in baseline to week 24) in the test and comparator groups respectively from baseline to week 24. The estimated treatment difference between both groups was 0.16% (95% CI -0.01 to infinity; p <.0001).

Torrent's semaglutide 3 mg, 7 mg, 14 mg oral tablets demonstrated non-inferiority to RYBELSUS® (semaglutide 3 mg, 7 mg, 14 mg) oral tablets.

Table 2 Analysis of mean change from baseline in HbA1c at Week 24

	Statistics	Test (N= 117)	Comparator (N= 116)
Baseline	Mean(SD)	8.08 (0.655)	8.16 (0.656)
Week 24	Mean(SD)	6.77 (0.678)	6.69 (0.802)
Mean Change form baseline in HbA1c at week 24	Mean(SD)	-1.30 (0.771)	-1.47 (0.876)
	95 % CI	-1.45, -1.16	-1.63, -1.31
	Mean Difference (95% CI)	0.16 (0.108) (-0.01 : Infinity)	
	p-value	<0.0001	

The pharmacodynamic evaluations described below were performed with orally administered semaglutide after 12 weeks of treatment in other global clinical trials.

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 semaglutide have been evaluated in eight global randomised controlled phase 3a trials. Phase 3a studies were conducted with tablets containing 3 mg, 7 mg and 14 mg semaglutide which are bioequivalent to 1.5 mg, 4 mg and 9 mg semaglutide, respectively. 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 8842 randomised patients with type 2 diabetes (5 169 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.

A phase 3b cardiovascular outcomes trial (SOUL) including 9 650 patients was conducted to investigate whether oral semaglutide lowers the risk of major adverse cardiovascular events (MACE) compared to placebo in addition to standard of care, in patients with type 2 diabetes and established cardiovascular disease and/or chronic kidney disease.

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 3 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 4 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)		

	Semaglutide 14 mg	Empagliflozin 25 mg
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 HbA1c <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 HbA1c and body weight were sustained throughout the trial duration of 78 weeks.

Table 5 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	−1.6 [−2.0; −1.1][*]	−2.5 [−3.0; −2.0][*]	-

	Semaglutide 7 mg	Semaglutide 14 mg	Sitagliptin 100 mg
sitagliptin[1] [95% CI]			
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 HbA1c <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 S.C. injection or placebo once daily, all in combination with metformin or metformin and an SGLT2 inhibitor.

Table 6 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]*	-	-

	Semaglutide 14 mg	Liraglutide 1.8 mg	Placebo
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 HbA1c <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 m2) were randomised to semaglutide 14 mg or placebo once daily. Trial product was added to the patient's stable pre-trial antidiabetic regimen.

Table 7 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 HbA1c <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 8 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 HbA1c <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 9 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;	-

	Semaglutide 7 mg	Semaglutide 14 mg	Placebo
		−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 HbA1c <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 outcomes

SOUL: Cardiovascular outcomes trial in patients with type 2 diabetes

In a double-blind, placebo-controlled, event driven trial, 9650 patients, 50 years of age or older with type 2 diabetes at high cardiovascular risk, defined as having established cardiovascular disease and/or chronic kidney disease, were randomised to either semaglutide 14 mg once-daily or placebo once daily added to standard of care.

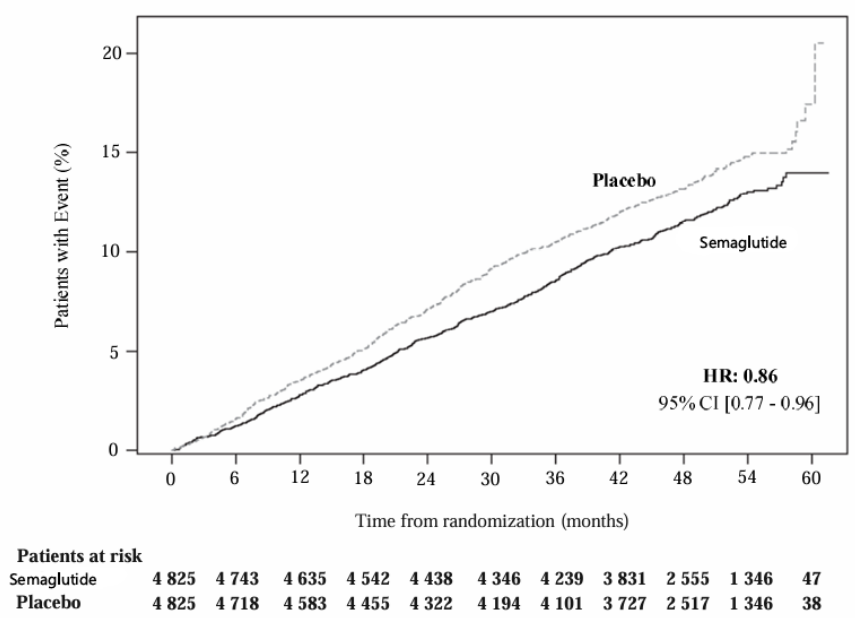
In total, 5468 patients (56.7%) had established cardiovascular disease without chronic kidney disease, 1241 (12.9%) had chronic kidney disease only and 2620 (27.2%) had both cardiovascular disease and kidney disease. The mean age at baseline was 66.1 years, and 71.1% of the patients were men. The mean duration of diabetes was 15.4 years, the mean HbA1c was 8.0%, the mean BMI was 31.1 kg/m^2, and the mean eGFR was 73.8 mL/min/1.73 m^2. Medical history included stroke (15.4%), myocardial infarction (40.0%), and peripheral artery disease (15.7%). At baseline, 26.9% of the patients were treated with sodium-glucose cotransporter-2 (SGLT2) inhibitors.

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. The primary endpoint, time to first MACE, occurred in 1247 of the 9650 included patients, 579 first MACE (12.0%) were recorded among the 4825 patients treated with semaglutide, compared to 668 first MACE (13.8%) among the 4825 patients treated with placebo.

Superiority of semaglutide versus placebo for MACE was confirmed with a hazard ratio of 0.86 [0.77; 0.96] [95% CI], corresponding to a relative risk reduction in MACE of 14 % (see Figure 1). The reduction of MACE with semaglutide was consistent across subgroups of age, sex, race, ethnicity, BMI at baseline, or level of kidney function impairment.

Analysis of the first composite kidney event (the first confirmatory secondary endpoint) resulted in a hazard ratio of 0.91 [0.80; 1.05] [95% CI].

Figure 1: Time from randomisation to first MACE Cumulative incidence function plot

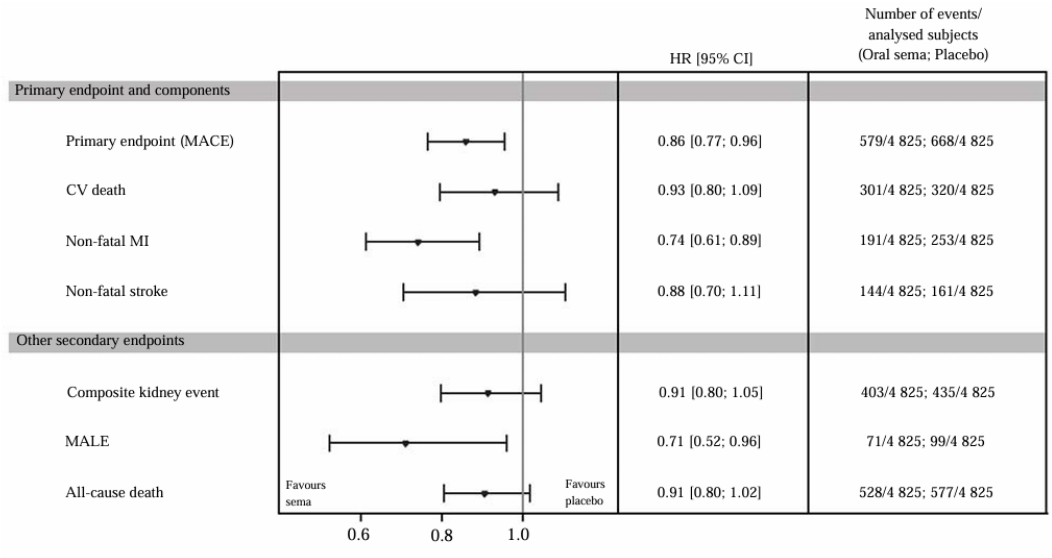


Patients at risk											
Semaglutide	4 825	4 743	4 635	4 542	4 438	4 346	4 239	3 831	2 555	1 346	47
Placebo	4 825	4 718	4 583	4 455	4 322	4 194	4 101	3 727	2 517	1 346	38

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

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

Figure 2: Treatment effect for the primary endpoint, its components and other secondary endpoints (SOUL)



Data from the in-trial period and based on full analysis set. Time from randomisation to each endpoint was analysed using a Cox proportional hazards model with treatment as categorical fixed factor. Subjects without events of interest were censored at the end of their in-trial period. For the primary endpoint the HR and CI were adjusted for the group sequential design using likelihood ratio ordering. CV death includes both cardiovascular death and undetermined cause of death.

HR: hazard ratio CI: Confidence interval CV: cardiovascular, MI: myocardial infarction.

Composite kidney event: endpoint consisting of cardiovascular death, kidney death, onset of persistent ≥ 50% reduction in estimated glomerular filtration rate (CKD-EPI) compared with baseline, onset of persistent eGFR

(CKD-EPI) < 15 mL/min/1.73 m2 or initiation of chronic kidney replacement therapy (dialysis or kidney transplantation).

MALE: major adverse limb events; composite endpoint consisting of acute or chronic limb ischemia hospitalisation.

PIONEER 6: Cardiovascular outcomes trial in patients with type 2 diabetes

In a double-blind trial (PIONEER 6), 3 183 patients, 50 years of age or older with type 2 diabetes at high cardiovascular risk were randomised to semaglutide 14 mg once daily or placebo in addition to standard-of-care. The median observation period was 16 months. PIONEER 6 was a pre−approval CVOT designed to establish CV safety.

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.

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 $[0.57; 1.11]_{95\% CI}$.

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.

In the cardiovascular outcomes trial SOUL, a reduction in body weight from baseline to week 104 was observed with semaglutide vs placebo, in addition to standard-of-care (4.22 kg vs 1.27 kg).

Blood pressure

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

Paediatric population

The MHRA has deferred the obligation to submit the results of studies with semaglutide in one or more subsets of the paediatric population in type 2 diabetes.

5.3 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 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. Different dosing schedules of semaglutide have been investigated. Studies show that longer pre- and 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.

6 Nonclinical properties

6.1. Animal Toxicology or Pharmacology

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.

7 Description

Semaglutide Tablets 3 mg is

White to off white, oval shaped, biconvex uncoated tablets, debossed with "III" on one side and torrent logo (Capital "T" with step up) on another side.

Semaglutide Tablets 7 mg is

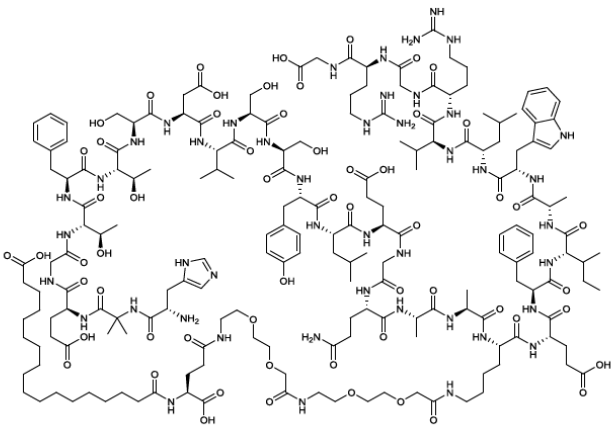
White to off white, oval shaped, biconvex uncoated tablets, debossed with "VII" on one side and torrent logo (Capital "T" with step up) on another side.

Semaglutide Tablets 14 mg is

White to off white, oval shaped, biconvex uncoated tablets, debossed with "XIV" on one side and torrent logo (Capital "T" with step up) on another side.

Semaglutide is (17-{[(1R)-3-[(2-{2-[({2-[2-({[(5S)-5-[(2S)-2-[(2S)-2-[(2S)-2-{2-[(2S)-2-[(2S)-2-[(2S)-2-[(2S)-2-[(2S)-2-[(2S)-2-[(2S)-2-[(2S,3R)-2-[(2S)-2-[(2S,3R)-2-{2-[(2S)-2-{2-[(2S)-2-amino-3-(1H-imidazol-5 yl)propanamido]-2-methylpropanamido}-4-carboxybutanamido]acetamido}-3 hydroxybutanamido]-3-phenylpropanamido]-3-hydroxybutanamido]-3-hydroxypropanamido]-3-carboxypropanamido]-3-methylbutanamido]-3 hydroxypropanamido]-3-hydroxypropanamido]-3-(4 hydroxyphenyl)propanamido]-4-methylpentanamido]-4 carboxybutanamido]acetamido}-4 carbamoylbutanamido]propanamido]propanamido]-5-{[(1S)-1-{[(1S)-1-{[(1S,2S)-1-{[(1S)-1-{[(1S)-1-{[(1S)-1-{[(1S)-1-{[(1S)-4-carbamimidamido-1-[({[(1S)-4-carbamimidamido-1-[(carboxymethyl)carbamoyl]butyl]carbamoyl}methyl)carbamoyl]butyl]carbamoyl}-2-methylpropyl]carbamoyl}-3-methylbutyl]carbamoyl}-2-(1H-indol-3-yl)ethyl]carbamoyl}ethyl]carbamoyl}-2-methylbutyl]carbamoyl}-2-phenylethyl]carbamoyl}-3-carboxypropyl]carbamoyl}pentyl]carbamoyl}methoxy)ethoxy]ethyl}carbamoyl)methoxy]ethoxy}ethyl)carbamoyl]-1-carboxypropyl]carbamoyl}heptadecanoic acid. having molecular formula of $C_{187}H_{291}N_{45}O_{59}$ molecular weight is 4114 g/mol the chemical structure is:

Structure of Semaglutide



Excipients: Salcaprozate Sodium, Sodium Caprate (Decanoate), Microcrystalline cellulose, Povidone (K 90F), Croscarmellose Sodium, Magnesium Stearate.

8 Pharmaceutical particulars

8.1 Incompatibilities

Not applicable.

8.2 Shelf-life

Do not use later than date of expiry.

8.3 Packaging information

Semaglutide Tablets is available in blisters strips of 10 Tablets each.

8.4 Storage and handing instructions

Store at a Temperature Not Exceeding 30°C. Store in the original blister package to protect from moisture and light.

Keep all medicine out of reach of children.

9 Patient Counselling Information

Ask the patients to inform the treating physicians in case of any of the below:

- Have any allergies
- Have kidney or liver problems
- Are pregnant or plan to become pregnant
- Are breastfeeding or plan to breastfeed
- Have any serious illness
- Are taking any medicines (prescription, over-the-counter, vitamins, or herbal products)

10 Details of manufacturer

Torrent Pharmaceuticals Ltd.,

Vill. Bhud & Makhnu Majra,

Tehsil: Baddi, - 173 205, Dist. Solan (H.P.), India.

11 Details of permission or licence number with date

MNB/05/183

12 For any consumer queries contact

Consumer care officer

Torrent Pharmaceuticals Limited,

“Avirat”, Thaltej Shilaj Road,

Ahmedabad – 380 059, Gujarat, India

Email ID: pv@torrentpharma.com

Contact Number: 1800-120-3001

13 Date of revision

Apr-2026

MARKETED BY

TORRENT PHARMA

TORRENT PHARMACEUTICALS LTD.

IN/SEMALIX™ (3 mg, 7 mg, 14 mg)/Apr-2026/02/PI