Regulatory Operations

Insert: 2010-778x450-003
LIFT - Current 5

Physician leaflet

Colour:
PMS 280C + PMS Yellow C

2. Qualitative and quantitative composition

Wegovy® solution for injection in pre-filled pen 0.25 mg/0.5mL
Each single-use pre-filled pen contains 0.25 mg semaglutide* in 0.5 mL solution. One mL of solution contains 0.5 mg of semaglutide*.

Wegovy® solution for injection in pre-filled pen 0.5 mg/0.5mL
Each single-use pre-filled pen contains 0.5 mg semaglutide* in 0.5 mL solution. One mL of solution contains 1 mg of semaglutide*.

Wegovy® solution for injection in pre-filled pen 1 mg/0.5mL
Each single-use pre-filled pen contains 1 mg semaglutide* in 0.5 mL solution. One mL of solution contains 2 mg of semaglutide*.

Wegovy® solution for injection in pre-filled pen 1.7 mg/0.75mL
Each single-use pre-filled pen contains 1.7 mg semaglutide* in 0.75 mL solution. One mL of solution contains 2.27 mg of semaglutide*.

Wegovy® solution for injection in pre-filled pen 2.4 mg/0.75mL
Each single-use pre-filled pen contains 2.4 mg semaglutide* in 0.75 mL solution. One mL of solution contains 3.2 mg of semaglutide*.

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

For the full list of excipients, see section 6.1.

3. Pharmaceutical form
Solution for injection (injection)
Clear and colourless isotonic solution; pH=7.4.

4. Clinical particulars

4.1 Therapeutic indications
Wegovy® is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management, including weight loss and weight maintenance, in adults with an initial Body Mass Index (BMI) of

- ≥30 kg/m² (obesity), or
- ≥27 kg/m² to <30 kg/m² (overweight) in the presence of at least one weight-related comorbidity e.g. dysglycaemia (prediabetes or type 2 diabetes mellitus), hypertension, dyslipidaemia, obstructive sleep apnoea or cardiovascular disease.

4.2 Posology and method of administration
Posology
The maintenance dose of semaglutide 2.4 mg once-weekly is reached by starting with a dose of 0.25 mg. To reduce the likelihood of gastrointestinal symptoms, the dose should be escalated over a 16-week period to a maintenance dose of 2.4 mg once weekly (see Table 1). In case of significant gastrointestinal symptoms, consider delaying dose escalation or lowering to the previous dose until symptoms have improved.

Table 1 Dose escalation schedule

Dose escalation	Weekly dose
Week 1–4	0.25 mg
Week 5–8	0.5 mg
Week 9–12	1 mg
Week 13–16	1.7 mg
Maintenance dose	2.4 mg

Weekly doses higher than 2.4 mg are not recommended.

Patients with type 2 diabetes
When initiating semaglutide in patients with type 2 diabetes, consider reducing the dose of concomitantly administered insulin or insulin secretagogues (such as sulfonylureas) to reduce the risk of hypoglycaemia, see section 4.4.

Missed dose
If a dose is missed, it should be administered as soon as possible and within 5 days after the missed dose. If more than 5 days have passed, the missed dose should be skipped, and the next dose should be administered on the regularly scheduled day. In each case, patients can then resume their regular once weekly dosing schedule. If more doses are missed, reducing the starting dose for re-initiation should be considered.

Special populations
Elderly (≥65 years old)
No dose adjustment is required based on age. Therapeutic experience in patients ≥75 years of age is limited, and greater sensitivity of some older individuals cannot be excluded.

Patients with renal impairment
No dose adjustment is required for patients with mild or moderate renal impairment. Experience with the use of semaglutide in patients with severe renal impairment is limited. Semaglutide is not recommended for use in patients with severe renal impairment (eGFR <30 mL/min/1.73m²) including patients with end-stage renal disease (see sections 4.4, 4.8 and 5.2).

Patients with hepatic impairment
No dose adjustment is required for patients with mild or moderate hepatic impairment. Experience with the use of semaglutide in patients with severe hepatic impairment is limited. Semaglutide is not recommended for use in patients with severe hepatic impairment and should be used cautiously in patients with mild or moderate hepatic impairment (see sections 4.4 and 5.2).

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

Method of administration
Subcutaneous use.

Wegovy® is administered once weekly at any time of the day, with or without meals.

It is to be injected subcutaneously in the abdomen, in the thigh or in the upper arm. The injection site can be changed. It should not be administered intravenously or intramuscularly.

The day of weekly administration can be changed if necessary, as long as the time between two doses is at least 3 days (>72 hours). After selecting a new dosing day, once-weekly dosing should be continued.

When administering Wegovy®, the pen should be pressed firmly against the skin until the yellow bar has stopped moving. The injection takes about 5–10 seconds.

Patients should be advised to read the 'Instructions on how to use Wegovy® pen' on the other side of this leaflet carefully before administering the medicinal product.

For further information before administration see section 6.6.

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.

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. Patients 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 (see section 4.8). 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.
In the absence of other signs and symptoms of acute pancreatitis, elevations in pancreatic enzymes alone are not predictive of acute pancreatitis.

Patients with type 2 diabetes
Semaglutide should not be used as a substitute for insulin in patients with type 2 diabetes.

Semaglutide should not be used in combination with other GLP-1 receptor agonist products. It has not been evaluated and an increased risk of adverse reactions related to overdose is considered likely.

Hypoglycaemia in patients with type 2 diabetes
Insulin and sulfonylureas are known to cause hypoglycaemia. Patients treated with semaglutide in combination with a sulfonylurea or insulin may have an increased risk of hypoglycaemia. The risk of hypoglycaemia can be lowered by reducing the dose of sulfonylurea or insulin when initiating treatment with a GLP-1 receptor agonist. The addition of Wegovy® in patients treated with insulin has not been evaluated.

Diabetic retinopathy in patients with type 2 diabetes
In patients with diabetic retinopathy treated with semaglutide, an increased risk of developing diabetic retinopathy complications has been observed (see section 4.8). Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy, but other mechanisms cannot be excluded. Patients with diabetic retinopathy using semaglutide should be monitored closely and treated according to clinical guidelines. There is no experience with Wegovy® in patients with type 2 diabetes with uncontrolled or potentially unstable diabetic retinopathy. In these patients, treatment with Wegovy® is not recommended.

Populations not studied
The safety and efficacy of Wegovy® have not been investigated in patients:
– treated with other products for weight management,
– with type 1 diabetes,
– with severe renal impairment (see section 4.2),
– with severe hepatic impairment (see section 4.2),
– with congestive heart failure New York Heart Association (NYHA) class IV.

Use in these patients is not recommended.

There is limited experience with Wegovy® in patients:
– aged 75 years or more (see section 4.2),
– with mild or moderate hepatic impairment (see section 4.2),
– with inflammatory bowel disease,
– with diabetic gastroparesis.

Use with caution in these patients.

Sodium content
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction
Semaglutide delays gastric emptying and could potentially influence the absorption of concomitantly administered oral medicinal products. No clinically relevant effect on the rate of gastric emptying was observed with semaglutide 2.4 mg, probably due to a tolerance effect. Semaglutide should be used with caution in patients receiving oral medicinal products that require rapid gastrointestinal absorption.

Paracetamol
Semaglutide delays the rate of gastric emptying as assessed by paracetamol pharmacokinetics during a standardised meal test. Paracetamol $AUC_{0-60min}$ and C_{max} were decreased by 27% and 23%, respectively, following concomitant use of semaglutide 1 mg. The total paracetamol exposure (AUC_{0-5h}) was not affected. No clinically relevant effect on paracetamol was observed with semaglutide. No dose adjustment of paracetamol is necessary when administered with semaglutide.

Oral contraceptives
Semaglutide is not anticipated to decrease the effectiveness of oral contraceptives. It did not change the overall exposure of ethinylestradiol and levonorgestrel to a clinically relevant degree, when an oral contraceptive combination medicinal product (0.03 mg ethinylestradiol/0.15 mg levonorgestrel) was co-administered with semaglutide. Exposure of ethinylestradiol was not affected; an increase of 20% was observed for levonorgestrel exposure at steady state. C_{max} was not affected for any of the compounds.

Atorvastatin
Semaglutide did not change the overall exposure of atorvastatin following a single dose administration of atorvastatin (40 mg). Atorvastatin C_{max} was decreased by 38%. This was assessed not to be clinically relevant.

Digoxin
Semaglutide did not change the overall exposure or C_{max} of digoxin following a single dose of digoxin (0.5 mg).

Metformin
Semaglutide did not change the overall exposure or C_{max} of metformin following dosing of 500 mg twice daily over 3.5 days.

Warfarin
Semaglutide did not change overall exposure or C_{max} of R- and S-warfarin following a single dose of warfarin (25 mg), and the pharmacodynamic effects of warfarin as measured by the international normalised ratio were not affected in a clinically relevant manner. However, upon initiation of semaglutide treatment in patients on warfarin or other coumarin derivatives, frequent monitoring of international normalised ratio (INR) is recommended.

4.6 Fertility, pregnancy and lactation
Women of childbearing potential
Women of childbearing potential are recommended to use contraception when treated with semaglutide (see section 4.5).

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
In lactating rats, semaglutide was excreted in milk. 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 or use machines. However, dizziness can be experienced mainly during the dose escalation period. Driving or use of machines should be done cautiously if dizziness occurs.

Patients with type 2 diabetes
If semaglutide 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 safety profile
In four phase 3a trials, 2,650 patients were exposed to Wegovy®. The duration of the trials were 68 weeks. The most frequently reported adverse reactions were gastrointestinal disorders including nausea, diarrhoea, constipation and vomiting.

Tabulated list of adverse reactions
Table 2 lists adverse reactions identified in phase 3a clinical trials. The frequencies are based on a pool of the phase 3a trials.

Adverse reactions associated with Wegovy® are listed by system organ class and frequency. Frequency categories 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).

Table 2 Adverse reactions from controlled phase 3 trials

MedDRA system organ class	Very common	Common	Uncommon	Rare
Immune system disorders				Anaphylactic reaction
Metabolism and nutrition disorders		Hypoglycaemia in patients with type 2 diabetes[a]		
Nervous system disorders	Headache[b]	Dizziness[b]		
Eye disorders		Diabetic retinopathy in patients with type 2 diabetes[a]		
Cardiac disorders			Hypotension Orthostatic hypotension Increased heart rate[a,c]	
Gastrointestinal disorders	Vomiting[a,b] Diarrhoea[a,b] Constipation[a,b] Nausea[a,b] Abdominal pain[b,c]	Gastritis[b,c] Gastrooesophageal reflux disease[b] Dyspepsia[b] Eructation[b] Flatulence[b] Abdominal distension[b]	Acute pancreatitis[a]	
Hepatobiliary disorders		Cholelithiasis[a]		
Skin and subcutaneous tissue disorders		Hair loss[a]		Angioedema
General disorders and administration site conditions	Fatigue[b,c]	Injection site reactions[c]		
Investigations			Increased amylase[c] Increased lipase[c]	

[a] see description of selected adverse reactions below
[b] mainly seen in the dose-escalation period
[c] Grouped preferred terms

Description of selected adverse reactions
Gastrointestinal adverse reactions
Over the 68 weeks trial period, nausea occurred in 43.9% of patients when treated with semaglutide (16.1% for placebo), diarrhoea in 29.7% (15.9% for placebo) and vomiting in 24.5% (6.3% for placebo). Most events were mild to moderate in severity and of short duration. Constipation occurred in 24.2% of patients treated with semaglutide (11.1% for placebo) and was mild to moderate in severity and of longer duration. In patients treated with semaglutide, median duration of nausea was 8 days, vomiting 2 days, diarrhoea 3 days, and constipation 47 days.

Patients with moderate renal impairment (eGFR ≥30 mL/min/1.73m²) may experience more gastrointestinal effects when treated with semaglutide.

The gastrointestinal events led to permanent treatment discontinuation in 4.3% of patients.

Acute pancreatitis
The frequency of adjudication-confirmed acute pancreatitis reported in phase 3a clinical trials was 0.2% for semaglutide and <0.1% for placebo, respectively.

Acute gallstone disease/Cholelithiasis
Cholelithiasis was reported in 1.6% and led to cholecystitis in 0.6% of patients treated with semaglutide. Cholelithiasis and cholecystitis was reported in 1.1% and 0.3%, respectively, of patients treated with placebo.

Hair loss
Hair loss was reported in 2.5% of patients treated with semaglutide and in 1.0% of patients treated with placebo. The events were mainly of mild severity and most patients recovered while on continued treatment. Hair loss was reported more frequently in patients with a greater weight loss (≥20%).

Increased heart rate
In the phase 3a trials, a mean increase of 3 beats per minute (bpm) from a baseline mean of 72 bpm was observed in patients treated with semaglutide. The proportions of subjects with an increase in pulse from baseline ≥10 bpm at any timepoint during the on-treatment period were 67.0% in the semaglutide group vs. 50.1% in the placebo group.

Immunogenicity
Consistent with the potentially immunogenic properties of medicinal products containing proteins or peptides, patients may develop antibodies following treatment with semaglutide. The proportion of patients testing positive for anti-semaglutide antibodies at any time post-baseline was low (2.9%) and no patients had anti-semaglutide neutralising antibodies or anti-semaglutide antibodies with endogenous GLP-1 neutralising effect at end-of-trial. During treatment, high semaglutide concentrations might have lowered the sensitivity of the assays, hence the risk of false negatives cannot be excluded. However, in subjects testing positive for antibodies during and after treatment, the presence of antibodies was transient and with no apparent impact on efficacy and safety.

Hypoglycaemia in patients with type 2 diabetes
In STEP 2, clinically significant hypoglycaemia was observed in 6.2% (0.1 events/patient year) of subjects treated with semaglutide compared with 2.5% (0.03 events/patient year) of subjects treated with placebo. Hypoglycaemia with semaglutide was seen both with and without concomitant use of sulfonylurea. One episode (0.2% of subjects, 0.002 events/patient year) was reported as severe in a subject not concomitantly treated with a sulfonylurea. The risk of hypoglycaemia was increased when semaglutide was used with a sulfonylurea.

Diabetic retinopathy in patients with type 2 diabetes
A 2-year clinical trial investigated semaglutide 0.5 mg and 1 mg vs. placebo in 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 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. In STEP 2, retinal disorders were reported by 6.9% of patients treated with Wegovy®, 6.2% of patients treated with semaglutide 1 mg, and 4.2% of patients treated with placebo. The majority of events were reported as diabetic retinopathy (4.0%, 2.7%, and 2.7%, respectively) and non-proliferative retinopathy (0.7%, 0%, and 0%, respectively).

4.9 Overdose
Overdose with semaglutide may be associated with gastrointestinal disorders which could lead to dehydration. In the event of overdose the patient should be observed for clinical signs and appropriate supportive treatment initiated.

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 regulator of appetite and calorie intake, and the GLP-1 receptor is present in several areas of the brain involved in appetite regulation.

Animal studies show that semaglutide works in the brain through the GLP-1 receptor. Semaglutide has direct effects on areas in the brain involved in homeostatic regulation of food intake in the hypothalamus and the brainstem. Semaglutide may affect the hedonic reward system through direct and indirect effects in brain areas including the septum, thalamus and amygdala.

Clinical studies show that semaglutide reduces energy intake, increases feelings of satiety, fullness and control of eating, reduces feelings of hunger, and frequency and intensity of cravings. In addition, semaglutide reduces the preference for high fat foods.

Semaglutide orchestrates the homeostatic and hedonic contributions with executive function to regulate caloric intake, appetite, reward and food choice.

In addition, in clinical studies semaglutide have shown to reduce 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.

GLP-1 receptors are also expressed in the heart, vasculature, immune system and kidneys. Semaglutide has a beneficial effect on plasma lipids, lowered systolic blood pressure and reduced inflammation in clinical studies. Furthermore, animal studies have shown that semaglutide attenuated the development of atherosclerosis and had an anti-inflammatory action in the cardiovascular system.

Pharmacodynamic effects
Appetite, energy intake and food choice
Semaglutide reduces appetite by increasing feelings of fullness and satiety, while lowering hunger and prospective food consumption. After 20 weeks of dosing, energy intake during an ad libitum meal was 35% lower with semaglutide compared to placebo. This was supported by improved control of eating, less food cravings and a relative lower preference for high fat food.

Fasting and postprandial lipids
Semaglutide 1 mg compared to placebo lowered fasting triglyceride and very low density lipoproteins (VLDL) concentrations by 12% and 21%, respectively. The postprandial triglyceride and VLDL response to a high fat meal was reduced with >40%.

Clinical efficacy and safety
The efficacy and safety of semaglutide for weight management in combination with a reduced calorie intake and increased physical activity were evaluated in four double-blinded randomised placebo-controlled phase 3a trials (STEP 1-4). A total of 4,684 patients (2,652 randomised to treatment with semaglutide) were included in the trials.

Treatment with semaglutide demonstrated superior, clinically meaningful, and sustained weight loss compared with placebo in patients with obesity (BMI ≥30 kg/m²), or overweight (BMI ≥27 kg/m² to <30 kg/m²) and at least one weight-related comorbidity. Furthermore, across the trials, a higher proportion of patients achieved ≥5%, ≥10%, ≥15% and ≥20% weight loss with semaglutide compared with placebo. The reduction in body weight occurred irrespective of the presence of gastrointestinal symptoms such as nausea, vomiting or diarrhoea.

Treatment with semaglutide also showed statistically significant improvements in waist circumference, systolic blood pressure and physical functioning compared to placebo.

Efficacy was demonstrated regardless of age, sex, race, ethnicity, baseline body weight, BMI, presence of type 2 diabetes and level of renal function. Variations in efficacy existed within all subgroups. Relatively greater weight loss was observed in women and in patients without type 2 diabetes as well as in patients with a lower versus higher baseline body weight.

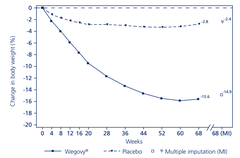
STEP 1: Weight management
In a 68-week double-blind trial, 1,961 patients with obesity (BMI ≥30 kg/m²), or with overweight (BMI ≥27 kg/m² to <30 kg/m²) and at least one weight-related comorbidity were randomised to semaglutide or placebo. All patients were on a reduced-calorie diet and increased physical activity throughout the trial.

Weight loss occurred early and continued throughout the trial. At end of treatment (week 68), the weight loss was superior and clinically meaningful compared with placebo (see Table 3 and Figure 1). Furthermore, a higher proportion of patients achieved ≥5%, ≥10%, ≥15% and ≥20% weight loss with semaglutide compared with placebo (see Table 3). Among patients with prediabetes at baseline, a higher proportion of patients had a normo-glycaemic status at end of treatment with semaglutide compared to placebo (84.1% vs. 47.8%).

Table 3 STEP 1: Results at week 68

	Wegovy®	Placebo
Full analysis set (N)	1,306	655
Body weight		
Baseline (kg)	105.4	105.2
Change (%) from baseline[1,2]	-14.9	-2.4
Difference (%) from placebo[1] [95% CI]	-12.4 [-13.4; -11.5]*	-
Change (kg) from baseline	-15.3	-2.6
Difference (kg) from placebo[1] [95% CI]	-12.7 [-13.7; -11.7]	-
Patients (%) achieving weight loss ≥5%[3]	83.5*	31.1
Patients (%) achieving weight loss ≥10%[3]	66.1*	12.0
Patients (%) achieving weight loss ≥15%[3]	47.9*	4.8
Waist circumference (cm)		
Baseline	114.6	114.8
Change from baseline[1]	-13.5	-4.1
Difference from placebo[1] [95% CI]	-9.4 [-10.3; -8.5]*	-
Systolic blood pressure (mmHg)		
Baseline	126	127
Change from baseline[1]	-6.2	-1.1
Difference from placebo[1] [95% CI]	-5.1 [-6.3; -3.9]*	-

* p<0.0001 (unadjusted 2-sided) for superiority.
[1] Estimated using an ANCOVA model using multiple imputation based on all data irrespective of discontinuation of randomised treatment or initiation of other anti-obesity medication or bariatric surgery.
[2] During the trial, randomised treatment was permanently discontinued by 17.1% and 22.4% of patients randomised to semaglutide 2.4 mg and placebo, respectively. Assuming that all randomised patients stayed on treatment and did not receive additional anti-obesity therapies, the estimated changes from randomisation to week 68 for body weight based on a Mixed Model for Repeated Measures including all observations until first discontinuation were -16.9% and -2.4% for semaglutide 2.4 mg and placebo respectively.
[3] Estimated from binary regression model based on same imputation procedure as in primary analysis.



Observed values for patients completing each scheduled visit, and estimates with multiple imputations (MI) from retrieved dropouts

Figure 1 STEP 1: Mean change in body weight (%) from baseline to week 68

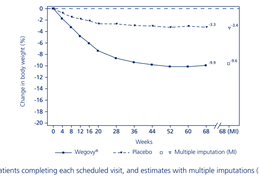
STEP 2: Weight management in patients with type 2 diabetes
In a 68-week, double-blind trial, 1,210 patients with overweight or obesity (BMI ≥27 kg/m²) and type 2 diabetes were randomised to either semaglutide 2.4 mg, semaglutide 1 mg once-weekly or placebo. Patients included in the trial had insufficiently controlled diabetes (HbA_{1c} 7–10%) and were treated with either: diet and exercise alone or 1–3 oral antidiabetic drugs. All patients were on a reduced-calorie diet and increased physical activity throughout the trial.

Treatment with semaglutide for 68 weeks resulted in superior and clinically meaningful reduction in body weight and in HbA_{1c} compared to placebo (see Table 4 and Figure 2).

Table 4 STEP 2: Results at week 68

	Wegovy®	Placebo
Full analysis set (N)	404	403
Body weight		
Baseline (kg)	99.9	100.5
Change (%) from baseline[1,2]	-9.6	-3.4
Difference (%) from placebo[1] [95% CI]	-6.2 [-7.3; -5.2]*	-
Change (kg) from baseline	-9.7	-3.5
Difference (kg) from placebo[1] [95% CI]	-6.1 [-7.2; -5.0]	-
Patients (%) achieving weight loss ≥5%[3]	67.4*	30.2
Patients (%) achieving weight loss ≥10%[3]	44.5*	10.2
Patients (%) achieving weight loss ≥15%[3]	25.0*	4.3
Waist circumference (cm)		
Baseline	114.5	115.5
Change from baseline[1]	-9.4	-4.5
Difference from placebo[1] [95% CI]	-4.9 [-6.0; -3.8]*	-
Systolic blood pressure (mmHg)		
Baseline	130	130
Change from baseline[1]	-3.9	-0.5
Difference from placebo[1] [95% CI]	-3.4 [-5.6; -1.3]**	-
HbA_{1c} (mmol/mol (%))		
Baseline	65.3 (8.1)	65.3 (8.1)
Change from baseline[1]	-17.5 (-1.6)	-4.1 (-0.4)
Difference from placebo[1] [95% CI]	-13.5 [-15.5; -11.4] (-1.2 [-1.4; -1.1])*	- -

* p<0.0001 (unadjusted 2-sided) for superiority; **p<0.05 (unadjusted 2-sided) for superiority
[1] Estimated using an ANCOVA model using multiple imputation based on all data irrespective of discontinuation of randomised treatment or initiation of other anti-obesity medication or bariatric surgery.
[2] During the trial, randomised treatment was permanently discontinued by 11.6% and 13.9% of patients randomised to semaglutide 2.4 mg and placebo, respectively. Assuming that all randomised patients stayed on treatment and did not receive additional anti-obesity therapies, the estimated changes from randomisation to week 68 for body weight based on a Mixed Model for Repeated Measures including all observations were -10.6% and -3.1% for semaglutide 2.4 mg and placebo respectively
[3] Estimated from binary regression model based on same imputation procedure as in primary analysis.



Observed values for patients completing each scheduled visit, and estimates with multiple imputations (MI) from retrieved dropouts

Figure 2 STEP 2: Mean change in body weight (%) from baseline to week 68

STEP 3: Weight management with intensive behavioural therapy
In a 68-week double-blind trial, 611 patients with obesity (BMI ≥30 kg/m²), or with overweight (BMI ≥27 kg/m² to <30 kg/m²) and at least one weight-related comorbidity were randomised to semaglutide or placebo. During the trial, all patients received intensive behavioural therapy (IBT) consisting of a very restrictive diet, increased physical activity and behavioural counselling.

Treatment with semaglutide and IBT for 68 weeks resulted in superior and clinically meaningful reduction in body weight compared to placebo (see Table 5).

Table 5 STEP 3: Results at week 68

	Wegovy®	Placebo
Full analysis set (N)	407	204
Body weight		
Baseline (kg)	106.9	103.7
Change (%) from baseline[1,2]	-16.0	-5.7
Difference (%) from placebo[1] [95% CI]	-10.3 [-12.0;-8.6]*	-
Change (kg) from baseline	-16.8	-6.2
Difference (kg) from placebo[1] [95% CI]	-10.6 [-12.5;-8.8]	-
Patients (%) achieving weight loss ≥5%[3]	84.8*	47.8
Patients (%) achieving weight loss ≥10%[3]	73.0*	27.1
Patients (%) achieving weight loss ≥15%[3]	53.5*	13.2
Waist circumference (cm)		
Baseline	113.6	111.8
Change from baseline[1]	-14.6	-6.3
Difference from placebo[1] [95% CI]	-8.3 [-10.1; -6.6]*	-
Systolic blood pressure (mmHg)		
Baseline	124	124
Change from baseline[1]	-5.6	-1.6
Difference from placebo[1] [95% CI]	-3.9 [-6.4; -1.5]*	

* p<0.005 (unadjusted 2-sided) for superiority
[1] Estimated using an ANCOVA model using multiple imputation based on all data irrespective of discontinuation of randomised treatment or initiation of other anti-obesity medication or bariatric surgery.
[2] During the trial, randomised treatment was permanently discontinued by 16.7% and 18.6% of patients randomised to semaglutide 2.4 mg and placebo, respectively. Assuming that all randomised patients stayed on treatment and did not receive additional anti-obesity therapies, the estimated changes from randomisation to week 68 for body weight based on a Mixed Model for Repeated Measures including all observations until first discontinuation were -17.6% and -5.0% for semaglutide 2.4 mg and placebo respectively
[3] Estimated from binary regression model based on same imputation procedure as in primary analysis.

STEP 4: Sustained weight management
In a 68-week double-blind trial, 902 patients with obesity (BMI ≥30 kg/m²), or with overweight (BMI ≥27 kg/m² to <30 kg/m²) and at least one weight-related comorbidity were included in the trial. All patients were on a reduced-calorie diet and increased physical activity throughout the trial. From week 0 to week 20 (run-in), all patients received semaglutide. At week 20 (baseline), patients who had reached the maintenance dose of 2.4 mg were randomised to continue treatment or switch to placebo. At week 0 (start of run-in period) patients had a mean body weight of 107.2 kg and a mean BMI of 38.4 kg/m².

Patients who had reached the maintenance dose of 2.4 mg at week 20 (baseline) and continued treatment with semaglutide for 48 weeks (week 20–68) continued losing weight and had a superior and clinically meaningful reduction in body weight compared to those switched to placebo (see Table 6 and Figure 3). The body weight increased steadily from week 20 to week 68 in patients switching to placebo at week 20 (baseline). Nevertheless, the observed mean body weight was lower at week 68 than at start of the run-in period (week 0) (see Figure 3). Patients treated with semaglutide from week 0 (run-in) to week 68 (end of treatment) achieved a mean change in body weight of 17.4%, with weight loss ≥5% achieved by 87.8%, ≥10% achieved by 78.0%, ≥15% achieved by 62.2% and ≥20% achieved by 38.6% of these patients.

1. Name of the medicinal product

wegovy®

0.25 mg **0.5 mg** **1 mg** **1.7 mg** **2.4 mg**

Wegovy® solution for injection in pre-filled pen 0.25mg /0.5ml
Wegovy® solution for injection in pre-filled pen 0.5 mg/0.5ml
Wegovy® solution for injection in pre-filled pen 1 mg/0.5ml
Wegovy® solution for injection in pre-filled pen 1.7 mg/0.75ml
Wegovy® solution for injection in pre-filled pen 2.4 mg/0.75ml

semaglutide

Use Wegovy® one time each week

novo nordisk®

Wegovy® is a trademark owned by Novo Nordisk A/S, Denmark

© 2022
Novo Nordisk A/S

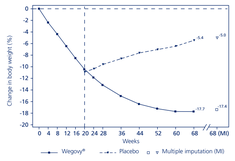
novo nordisk®

8-9570-00-001-1

Table 6 STEP 4: Results from week 20 to week 68

	Wegovy®	Placebo
Full analysis set (N)	535	268
Body weight		
Baseline[1] (kg)	96.5	95.4
Change (%) from baseline[1,2,3]	-7.9	6.9
Difference (%) from placebo[2] [95% CI]	-14.8 [-16.0; -13.5]*	-
Change (kg) from baseline	-7.1	6.1
Difference (kg) from placebo[2] [95% CI]	-13.2 [-14.3; -12.0]	-
Waist circumference (cm)		
Baseline	105.5	104.7
Change from baseline[1]	-6.4	3.3
Difference from placebo[2] [95% CI]	-9.7 [-10.9; -8.5]*	-
Systolic blood pressure (mmHg)		
Baseline[1]	121	121
Change from baseline[1,2]	0.5	4.4
Difference from placebo[2] [95% CI]	-3.9 [-5.8; -2.0]*	

* p<0.0001 (unadjusted 2-sided) for superiority,
[1] Baseline = week 20
[2] Estimated using an ANCOVA model using multiple imputation based on all data irrespective of discontinuation of randomised treatment or initiation of other anti-obesity medication or bariatric surgery.
[3] During the trial, randomised treatment was permanently discontinued by 5.8% and 11.6% of patients randomized to semaglutide 2.4 mg and placebo, respectively. Assuming that all randomised patients stayed on treatment and did not receive additional anti-obesity therapies, the estimated changes from randomisation to week 68 for body weight based on a Mixed Model for Repeated Measures including all observations until first discontinuation were -8.1% and 6.5% for semaglutide 2.4 mg and placebo respectively.



Observed values for patients completing each scheduled visit, and estimates with multiple imputations (MI) from retrieved dropouts

Figure 3 STEP 4: Mean change in body weight (%) from week 0 to week 68

Effect on body composition
In a sub-study in STEP 1 (N = 140), body composition was measured using dual energy X-ray absorptiometry (DEXA). The results of the DEXA assessment showed that treatment with semaglutide was accompanied by greater reduction in fat mass than in lean body mass leading to an improvement in body composition compared to placebo after 68 weeks. Furthermore, this reduction in total fat mass was accompanied by a reduction in visceral fat. These results suggest that most of the total weight loss was attributable to a reduction in fat tissue, including visceral fat.

Improvement in physical functioning
Semaglutide showed small improvements in physical functioning scores. Physical functioning was assessed using both the generic health-related quality of life questionnaire Short Form-36v2 Health Survey, Acute Version (SF-36) and the obesity-specific questionnaire Impact of Weight on Quality of Life Lite Clinical Trials Version (IWQOL-Lite-CT).

Cardiovascular evaluation
In the SUSTAIN 6 trial, 3,297 patients with insufficiently controlled type 2 diabetes and at high risk of cardiovascular events were randomised to semaglutide s.c. 0.5 mg or 1 mg once-weekly or placebo in addition to standard-of-care. The treatment duration was 104 weeks. The mean age was 65 years and the mean BMI was 33 kg/m².

The primary endpoint was the 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 the MACE was 254, including 108 (6.6%) with semaglutide and 146 (8.9%) with placebo.

The cardiovascular safety of treatment with semaglutide 0.5 or 1 mg was confirmed as the hazard ratio (HR) for semaglutide vs. placebo was 0.74, [0.58, 0.95] [95% CI], driven by a decrease in the rate of non-fatal stroke and non-fatal myocardial infarction with no difference in cardiovascular death (see Figure 4).

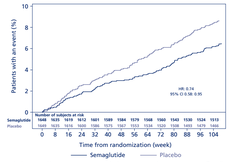


Figure 4: Kaplan-Maier plot of time to first occurrence of the composite outcome: Cardiovascular death, non-fatal myocardial infarction or non-fatal stroke (SUSTAIN 6)

5.2 Pharmacokinetic properties
Compared to native GLP-1, semaglutide has a prolonged half-life of around 1 week making it suitable for once weekly subcutaneous administration. The principal mechanism of protraction is albumin binding, which results in decreased renal clearance and protection from metabolic degradation. Furthermore, semaglutide is stabilised against degradation by the DPP-4 enzyme.

Absorption
The average semaglutide steady state concentration following s.c. administration of the semaglutide maintenance dose was approximately 75 nmol/L in patients with overweight (BMI ≥27 kg/m² to <30 kg/m²) or obesity (BMI ≥ 30 kg/m²) based on data from phase 3a trials, where 90% of patients had average concentrations between 51 nmol/L and 110 nmol/L. Bioequivalence was established between exposure associated with semaglutide administered with the marketed drug product and the exposure obtained with the drug product used in phase 3a trials. The steady state exposure of semaglutide increased proportionally with doses from 0.25 mg up to 2.4 mg once weekly. Steady state exposure was stable with time as assessed up to week 68. Similar exposure was achieved with s.c. administration of semaglutide in the abdomen, thigh, or upper arm. The absolute bioavailability of semaglutide was 89%.

Distribution
The mean volume of distribution of semaglutide following s.c. administration in patients with overweight or obesity was approximately 12.4 L. Semaglutide is extensively bound to plasma albumin (>99%).

Metabolism/biotransformation
Prior to excretion, semaglutide is extensively metabolised through proteolytic cleavage of the peptide backbone and sequential beta-oxidation of the fatty acid side chain. The enzyme neutral endopeptidase (NEP) was identified as one of the active metabolic enzymes.

Elimination
The primary excretion routes of semaglutide-related material are via the urine and faeces. Approximately 3% of the absorbed dose was excreted in the urine as intact semaglutide.
The clearance of semaglutide in patients with overweight (BMI ≥27 kg/m² to <30 kg/m²) or obesity (BMI ≥30 kg/m²) was approximately 0.05 L/h. With an elimination half-life of approximately 1 week, semaglutide will be present in the circulation for approximately 7 weeks after the last dose of 2.4 mg.

Special populations
Elderly
Age had no effect on the pharmacokinetics of semaglutide based on data from phase 3 trials including patients 18–86 years of age.

Gender, race and ethnicity
Gender, race (White, Black or African American, Asian) and ethnicity (Hispanic or Latino, non-Hispanic or -Latino) had no effect on the pharmacokinetics of semaglutide based on data from phase 3a trials.

Body weight
Body weight had an effect on the exposure of semaglutide. Higher body weight was associated with lower exposure; a 20% difference in body weight between individuals will result in an approximate 18% difference in exposure. The 2.4 mg weekly dose of semaglutide provided adequate systemic exposures over the body weight range of 54.4–245.6 kg evaluated for exposure response in the clinical trials.

Renal impairment
Renal impairment did not impact the pharmacokinetics of semaglutide in a clinically relevant manner. This was shown with a single dose of 0.5 mg semaglutide for patients with different degrees of renal impairment (mild, moderate, severe or patients in dialysis) compared with patients with normal renal function. This was also shown for patients with overweight (BMI ≥27 kg/m² to <30 kg/m²) or obesity (BMI ≥30 kg/m²) and mild to moderate renal impairment based on data from phase 3a trials.

Hepatic impairment
Hepatic impairment did not have any impact on the exposure of semaglutide. The pharmacokinetics of semaglutide were evaluated in patients with different degrees of hepatic impairment (mild, moderate, severe) and compared with patients with normal hepatic function in a study with a single dose of 0.5 mg semaglutide.

Prediabetes and diabetes
Prediabetes and diabetes did not have any clinically relevant effect on the exposure of semaglutide based on data from phase 3 trials.

Immunogenicity
Development of anti-semaglutide antibodies when treated with semaglutide occurred infrequently (see section 4.8) and the response did not appear to influence semaglutide pharmacokinetics.

Paediatrics
Safety and efficacy of semaglutide in children and adolescents below 18 years of age have not been studied.

5.3 Preclinical safety data
Preclinical data reveal no special hazards for humans based on conventional studies of safety pharmacology, repeat-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 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
Disodium phosphate, dihydrate
Sodium chloride
Hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities
In the absence of compatibility studies this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life
Expiry date is stated on the pen label and carton after 'Expiry'.

Wegovy® may be stored unrefrigerated for up to 28 days at a temperature not above 30°C. Discard the pen if it has been out of the refrigerator for more than 28 days.

6.4 Special precautions for storage
Store in a refrigerator (2°C-8°C). Keep away from the cooling element.
Do not freeze and do not use Wegovy® if it has been frozen.
Store the pen in the original carton in order to protect from light.

6.5 Nature and contents of container
1 mL glass syringe (type I glass) with attached stainless steel needle, rigid needle shield (type II/polyisoprene) and a rubber plunger (type I/chlorobutyl).

Pack sizes
4 pre-filled pens

6.6 Special precautions for disposal and other handling
The pen is for single-use only
Wegovy® should not be used if it does not appear clear and colourless.
The pen should not be used if it has been frozen.

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

7. Product Owner
Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark

Instructions on how to use Wegovy® pen

Important information before you start

The package contains one package leaflet and four Wegovy® pre-filled pens.

This part of the package leaflet instructs on how to use the pen. For further information regarding your medicine please refer to the other side of this package leaflet.

Each pen is only to be used once.
It comes with:

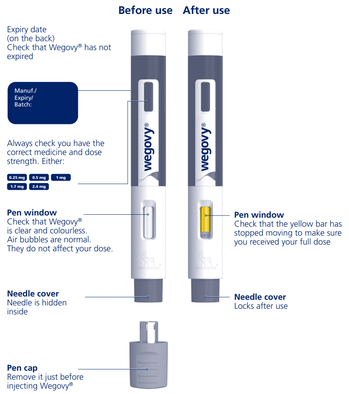
- **one pre-set dose.**
- **a needle cover** that hides the built-in needle before, during and after use.
- **an automatic dosing** mechanism that starts when the needle cover is pressed against your skin as described by your doctor or nurse.

When injecting the dose, a yellow bar will appear in the pen window. Do not lift the pen before the yellow bar has stopped moving. If you do, the automatic dosing will continue, but you may not receive your full dose.

The needle cover will lock when the pen is removed from your skin. You cannot pause the injection and restart it later.

People who are blind or have vision problems should not use Wegovy® pen without help from a person trained to use Wegovy®.

Always follow these user instructions and any directions given by your doctor or nurse.



How to use your Wegovy®

1. Prepare for your injection.

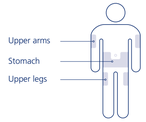
Check your Wegovy® pen and be careful not to use your pen if:

1. it has expired
2. it appears to have been used or damaged, e.g. if it has been dropped or stored incorrectly
3. the medicine looks cloudy.

Choose your injection site

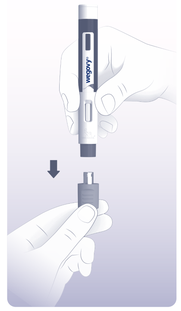
Choose an injection site in one of the body areas marked below. You can choose your upper arms, upper legs or stomach (keep a 5 cm distance from your belly button).

You may inject in the same body area each week, but make sure it is not in the same spot as used the last time.



2. Remove pen cap.

Pull the pen cap straight off your pen.



3. Inject Wegovy®.

Press the pen firmly against your skin until the yellow bar has stopped moving.

If the yellow bar does not start moving, press the pen more firmly against your skin.

How do I handle my pen safely?

For information regarding your medicine please refer to the other side of this package leaflet:

- The pen is for a single injection of Wegovy® under the skin once a week and should be used by one person only.
- Always refer to the instructions on the other side of this package leaflet and ensure you have been shown how to use these pens by your doctor or nurse.
- Always keep Wegovy® pens out of sight and reach of children. Also, keep the pen cap away from children to prevent them from swallowing it.
- Treat your pen with care and do not expose it to any kind of liquid. Rough handling or misuse may cause your pen to give less than the full dose or no dose at all.
- Keep the pen cap on until you are ready to inject. Your pen will no longer be sterile if you store an unused pen without the cap, if you pull the pen cap off and put it on again, or if the pen cap is missing. This could lead to an infection.
- Be careful when handling your pen before use and do not touch the needle or the needle cover. The hidden needle can cause needle stick injuries.
- Each pen contains one weekly dose and cannot be reused. Dispose of it after use.

How do I store my unused pens?

For information regarding storage see sections 6.3 and 6.4 on the other side of this package leaflet.

How do I dispose of my pens?

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

Project: Library - Artwork
Document: 8-9570-00-001-1_v10.pdf
Document description:
Document Lifecycle State: Approved
Version: 1
Version ID: 00002_0000203655
Downloaded: Feb 3, 2022 at 1:56 PM GMT+01:00
By: Johansen, Gitte Iele (GFOG@NOVONORDISK.COM)
Approval state: **Approved**

Stage Nr	Approver	Role / Group	Company/ Location	Date and Time	Action	Comment
1	V, Srinivas (SINV@NOVONORDISK.COM)	CREATOR	Novo Nordisk (Business Users)	Jan 27, 2022 at 9:15 AM GMT+01:00	Approved (1st Graphic Approval)	
2	R, Sowmya (SOYR@NOVONORDISK.COM)	CONTROLLER	Novo Nordisk (Business Users)	Jan 27, 2022 at 11:06 AM GMT+01:00	Approved (2nd Graphic Approval)	
3	Johansen, Gitte Iele (GFOG@NOVONORDISK.COM)	PROOFREADER / PROOFREADER_ENGLISH NEUTRAL	Novo Nordisk (Business Users)	Jan 28, 2022 at 5:50 AM GMT+01:00	Approved (1st Affiliate Approval)	
4	Kunkel, Ulla E. (UEK@NOVONORDISK.COM)	PROOFREADER / PROOFREADER_ENGLISH NEUTRAL	Novo Nordisk (Business Users)	Jan 31, 2022 at 2:19 PM GMT+01:00	Approved (2nd Affiliate Approval)	

Stage Nr	Approver	Role / Group	Company/ Location	Date and Time	Action	Comment
5	Iyer, Shobhana R (SIR@NOVONORDISK.COM)	QA APPROVER	Novo Nordisk (Business Users)	Feb 1, 2022 at 5:29 AM GMT+01:00	Approved (QA Approval)	