Applicant	Novo Nordisk (Pty) Ltd	**Dosage form and strength**	Solution for injection; Semaglutide 0,25 mg Solution for injection; Semaglutide 0,5 mg Solution for injection; Semaglutide 1 mg Solution for injection; Semaglutide 1,7 mg Solution for injection; Semaglutide 2,4 mg
Product name	Wegovy® 0,25 mg, 0,5 mg, 1 mg, 1,7 mg, 2,4 mg		

PROFESSIONAL INFORMATION

WARNING: RISK OF THYROID C-CELL TUMORS

- **In rodents, semaglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures. It is unknown whether WEGOVY® 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**
- **WEGOVY® is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).**
- **Counsel patients regarding the potential risk for MTC with the use of WEGOVY® 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 WEGOVY®**

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINAL PRODUCT

Wegovy® 0,25 mg, solution for injection in pre-filled pen

Wegovy® 0,5 mg, solution for injection in pre-filled pen

Wegovy® 1 mg, solution for injection in pre-filled pen

Wegovy® 1,7 mg, solution for injection in pre-filled pen

Wegovy® 2,4 mg, solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Applicant	Novo Nordisk (Pty) Ltd	**Dosage form and strength**	Solution for injection; Semaglutide 0,25 mg Solution for injection; Semaglutide 0,5 mg Solution for injection; Semaglutide 1 mg Solution for injection; Semaglutide 1,7 mg Solution for injection; Semaglutide 2,4 mg
Product name	Wegovy® 0,25 mg, 0,5 mg, 1 mg, 1,7 mg, 2,4 mg		

Wegovy® 0,25 mg solution for injection

Each pre-filled pen contains 1 mg semaglutide* in 1,5 mL of solution. One mL of solution contains 0,68 mg semaglutide*. One pre-filled pen contains 4 doses of 0,25 mg

Wegovy® 0,5 mg solution for injection

Each pre-filled pen contains 2 mg semaglutide* in 1,5 mL solution. One mL of solution contains 1,34 mg semaglutide*. One pre-filled pen contains 4 doses of 0,5 mg.

Wegovy® 1 mg solution for injection

Each pre-filled pen contains 4 mg semaglutide* in 3 mL solution. One mL of solution contains 1,34 mg semaglutide*. One pre-filled pen contains 4 doses of 1 mg.

Wegovy® 1,7 mg solution for injection

Each pre-filled pen contains 6,8 mg semaglutide* in 3 mL solution. One mL of solution contains 2,27 mg semaglutide*. One pre-filled pen contains 4 doses of 1,7 mg.

Wegovy® 2,4 mg solution for injection

Each pre-filled pen contains 9,6 mg semaglutide* in 3 mL solution. One mL of solution contains 3,2 mg semaglutide*. One pre-filled pen contains 4 doses of 2,4 mg.

*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.

Applicant	Novo Nordisk (Pty) Ltd	**Dosage form and strength**	Solution for injection; Semaglutide 0,25 mg Solution for injection; Semaglutide 0,5 mg Solution for injection; Semaglutide 1 mg Solution for injection; Semaglutide 1,7 mg Solution for injection; Semaglutide 2,4 mg
Product name	Wegovy® 0,25 mg, 0,5 mg, 1 mg, 1,7 mg, 2,4 mg		

3. PHARMACEUTICAL FORM

Solution for injection

Clear and colourless isotonic solution; Ph = 7,4.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults

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/m^2 (obesity), or
- ≥27 kg/m^2 to < 30 kg/m^2 (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.

Adolescents (≥ 12 years)

Wegovy® is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management in adolescents ages 12 years and above with

- obesity* and
- body weight above 60 kg.

Treatment with Wegovy® should be discontinued and re-evaluated if adolescent patients have not reduced their BMI by at least 5 % after 12 weeks on the 2,4 mg or maximum tolerated dose.

*Obesity (BMI ≥ 95th percentile) as defined on sex- and age-specific BMI growth charts (CDC.gov) (see Table 1).

Table 1 BMI cut-off points for obesity (≥ 95th percentile) by sex and age for paediatric patients aged 12 and older (CDC criteria)

Age (years)	**BMI (kg/m^2) at 95th Percentile**	
	Males	**Females**
12	24,2	25,2
12,5	24,7	25,7
13	25,1	26,3
13,5	25,6	26,8
14	26,0	27,2
14,5	26,4	27,7
15	26,8	28,1
15,5	27,2	28,5
16	27,5	28,9
16,5	27,9	29,3
17	28,2	29,6
17,5	28,6	30,0

4.2 Posology and method of administration

Posology

Adults

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 2). In case of significant gastrointestinal symptoms, consider delaying dose escalation or lowering to the previous dose until symptoms have improved. Weekly doses higher than 2,4 mg are not recommended.

Table 2 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

Adolescents

For adolescents ages 12 years and above, the same dose escalation schedule as for adults should be applied (see Table 2). The dose should be increased until 2,4 mg (maintenance dose) or maximum tolerated dose has been reached. Weekly doses higher than 2,4 mg are not recommended.

Patients with type 2 diabetes

Wegovy® should not be used in combination with other GLP-1 receptor agonist products.

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 subjects (≥ 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, moderate or severe 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/1,73 m^2) 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 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

No dose adjustment is required for adolescents ages 12 years and above.

The safety and efficacy of semaglutide in children below 12 years of age have not been established.

Method of administration

Subcutaneous use.

Wegovy® is administered once weekly at any time of the day, with or without meals. Wegovy® is to be injected subcutaneously in the abdomen, in the thigh or in the upper arm. The injection site can be changed. Wegovy® 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.

Patients should be advised to read the instructions for use included in the patient information leaflet carefully before administering Wegovy®.

For further information on 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 must 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 sulfonylurea 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 agonists. The addition of Wegovy® in patients treated with insulin

has not been evaluated.

Diabetic retinopathy in patients with type 2 diabetes

Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy. Long-term glycaemic control decreases the risk of diabetic retinopathy. Patients with a history of diabetic retinopathy should be monitored for worsening and treated according to local clinical guidelines.

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 medicine contains less than 1 mmol sodium (23 mg) per dose, i.e., 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 $AUC_{0\text{-}60min}$ and C_{max} were decreased by 27 % and 23 %, respectively, following concomitant use of semaglutide 1 mg. The total paracetamol exposure ($AUC_{0\text{-}5h}$) 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 as semaglutide 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. Women of childbearing potential are recommended to use contraception when treated with semaglutide. 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 3 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 body system 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 3 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]	Acute pancreatitis[a]	

		Abdominal distension[b]		
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/1,73 m^2) 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 Wegovy® 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 Wegovy® compared with 2,5 % (0,03 events/patient year) of subjects treated with placebo. One episode (0,2 % of subjects, 0,002 events/patient year) was reported as severe. The risk of hypoglycaemia was increased when Wegovy® 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).

Paediatric population

In a clinical trial conducted in adolescents of 12 years to below 18 years with obesity or overweight with at least one weight-related comorbidity, 133 patients were exposed to Wegovy®. The trial duration was 68 weeks.

Overall, the frequency, type and severity of adverse reactions in the adolescents were comparable to that observed in the adult population. Cholelithiasis was reported in 3,8 % of patients treated with Wegovy® and 0 % of patients treated with placebo.

No effects on growth or pubertal development were found after 68 weeks of treatment

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse

Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

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

Class of the medicine: A.21.13.

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.

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.

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 affects the hedonic reward system through direct and indirect effects in brain areas including the septum, thalamus and amygdala. Semaglutide has shown an effect to change food intake away from more rewarding high fat and sweet items.

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 was 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. In a phase 1 trial, energy intake during an ad libitum meal was 35 % lower with semaglutide compared to placebo after 20 weeks of dosing. This was supported by improved control of eating, less food cravings and a relative lower preference for high fat food. Food cravings were further assessed in STEP 5 by a Control of Eating Questionnaire (CoEQ). At week 104, the estimated treatment difference both for control of cravings and craving of savoury food significantly favoured semaglutide, whereas no clear effect was seen for craving of sweet 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/m^2), or overweight (BMI ≥ 27 kg/m^2 to < 30 kg/m^2) 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.

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.

In addition, a dedicated cardiovascular outcomes trial was conducted with semaglutide 0,5 mg and 1 mg once-weekly in patients with type 2 diabetes (T2D) at high cardiovascular risk. Treatment with semaglutide resulted in a significant (26 %) risk reduction in cardiovascular death, non-fatal myocardial infarction or non-fatal stroke compared with placebo.

STEP 1: Weight Management

In a 68-week double-blind trial, 1 961 patients with obesity (BMI ≥ 30 kg/m^2), or with overweight (BMI ≥ 27 kg/m^2 to < 30 kg/m^2) 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 4 and Figure 1). Furthermore, a higher proportion of patients achieved ≥ 5 %, ≥ 10 %, ≥ 15 % and ≥ 20 % weight loss with semaglutide compared with placebo (see Table 4). Among patients with pre-diabetes at baseline, a higher proportion of patients had a normo- glycaemic status at end of treatment with semaglutide than to placebo (see Table 4). 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 4 STEP 1: Results at week 68

	Semaglutide	**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 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 and placebo respectively.

[3] Estimated from binary regression model based on same imputation procedure as in primary analysis.

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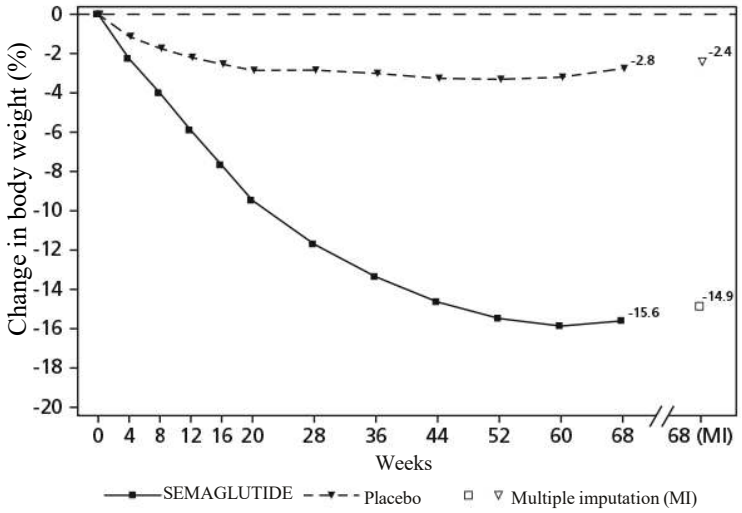
Product name	Wegovy® 0,25 mg, 0,5 mg, 1 mg, 1,7 mg, 2,4 mg		



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/m^2) 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 anti-diabetic 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 5).

Table 5 STEP 2: Results at week 68

	Semaglutide	**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]	-4,9 [-6,0; -3,8]*	-

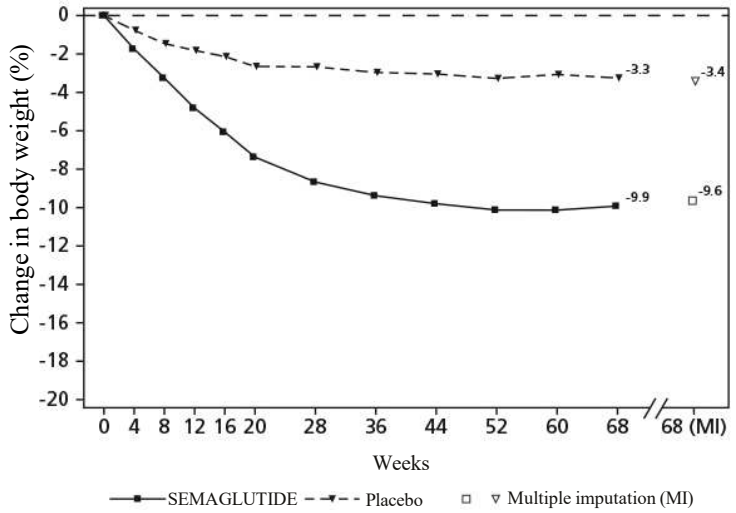
[95 % CI]		
Systolic blood pressure (mmHg)		
Baseline	130	130
Change from baseline[1]	-3,9	-0,5
Difference from placebo[1] [95 % CI]	-3,4 [-5,6; -1,3]**	-
HbA_{1c} (mmol/mol (%))		
Baseline	65,3 (8,1)	65,3 (8,1)
Change from baseline[1,2]	-17.5 (-1.6)	-4,1 (-0,4)
Difference from placebo[1] [95 % CI]	-13,5 [-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 until first discontinuation 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/m^2), or with overweight (BMI ≥ 27 kg/m^2 to < 30 kg/m^2) 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 6).

Table 6 STEP 3: Results at week 68

	Semaglutide	**Placebo**
Full analysis set (N)	407	204

Applicant	Novo Nordisk (Pty) Ltd	**Dosage form and strength**	Solution for injection; Semaglutide 0,25 mg Solution for injection; Semaglutide 0,5 mg Solution for injection; Semaglutide 1 mg Solution for injection; Semaglutide 1,7 mg Solution for injection; Semaglutide 2,4 mg
Product name	Wegovy® 0,25 mg, 0,5 mg, 1 mg, 1,7 mg, 2,4 mg		

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<0,0001 (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 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/m^2), or with overweight (BMI ≥ 27 kg/m^2 to < 30 kg/m^2) 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/m^2.

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 7 and Figure 3). On the other hand, in patients switching to placebo at week 20 (baseline), body weight increased steadily from week 20 to week 68. Nevertheless, the observed mean body weight was lower at week 68 than at start of the run- in period (week 0) (see Figure 4). 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.

Table 7 STEP 4: Results from week 20 to week 68

	Semaglutide	**Placebo**
Full analysis set (N)	535	268
Body weight		
Baseline[1] (kg)	96,5	95,4
Change (%) from baseline[1,2]	-7,9	6,9
Difference (%) from placebo[1] [95 % CI]	-14,8 [-16,0; -13,5]*	-
Change (kg) from baseline	-7,1	6,1

Difference (kg) from placebo[1] [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[1] [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]*	-

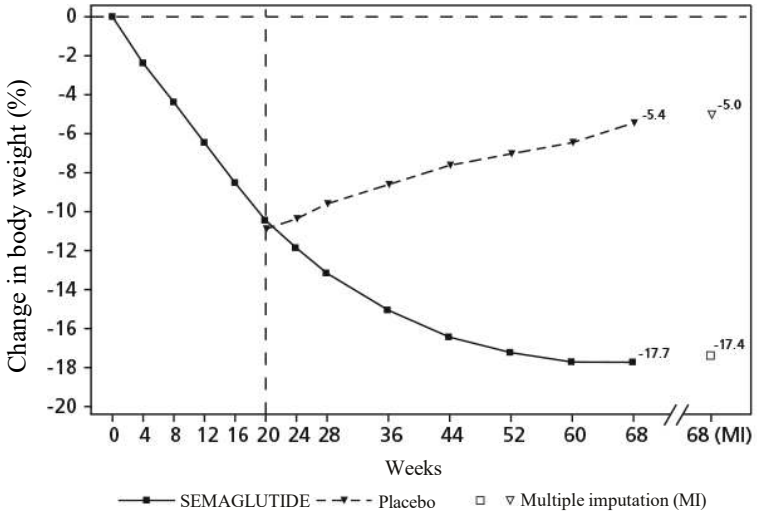
* p<0,0001 (unadjusted 2-sided) for superiority,

[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 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 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 Wegovy® 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/m^2.

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 secondary endpoint was time from randomisation to first occurrence of an expanded composite cardiovascular outcome, defined as MACE, revascularisation (coronary and peripheral), unstable angina requiring hospitalisation or hospitalisation for heart failure. The total number of the primary component MACE was 254, including 108 (6,6 %) with semaglutide and 146 (8,9 %) with placebo.

Treatment with semaglutide reduced the rate of MACE vs. placebo with a risk reduction of 26 %, HR 0,74, [0,58, 0,95] [95% CI]. This was mainly driven by a significant (39 %) decrease in the rate of non-fatal stroke and a non-significant (26 %) decrease in non-fatal myocardial infarction with no difference in cardiovascular death (see Figure 4

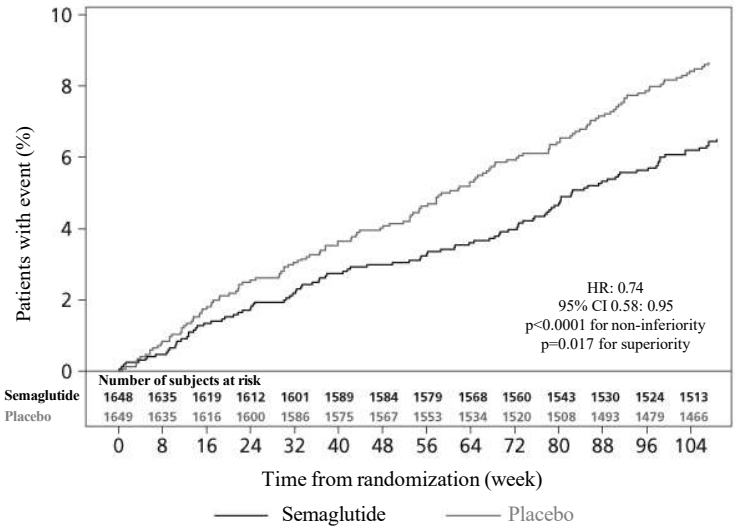


Figure 4: Kaplan-Maier plot of time to first occurrence of the composite outcome: Cardiovascular death, non-fatal myocardial infarction or non-fatal stroke (SUSTAIN 6)

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Wegovy® in one or more subsets of the paediatric population in the treatment of weight management (see section 4.2 for information on paediatric use).

STEP TEENS: Weight management in adolescent patients

In a 68-week double-blind trial 201 pubertal adolescents, ages 12 to < 18 years, with obesity or overweight and at least one weight-related comorbidity were randomised 2:1 to semaglutide or placebo. All patients were on a reduced-calorie diet and increased physical activity throughout the trial.

At end of treatment (week 68), the improvement in BMI with semaglutide was superior and clinically meaningful compared with placebo (see Table 8 and Figure 5). Furthermore, a higher proportion of patients achieved ≥ 5 %, 10 % and ≥ 15 % weight loss with semaglutide compared with placebo (see Table 8).

Table 8 STEP TEENS: Results at week 68

	Semaglutide 2,4 mg	**Placebo**
Full analysis set (N)	134	67
BMI		
Baseline (BMI)	37,7	35,7
Change (%) from baseline[1,2]	-16,1	0,6
Difference (%) from placebo[1] [95% CI]	-16,7 [-20,3; -13,2]*	-
Baseline (BMI SDS)	3,4	3,1
Change from baseline in BMI SDS[1]	-1,1	-0,1
Difference from placebo[1] [95% CI]	-1,0 [-1,3; -0,8]	-
Body Weight		
Baseline (kg)	109,9	102,6
Change (%) from baseline[1]	-14,7	2,8

Difference (%) from placebo[1] [95% CI]	-17,4 [-21,1; -13,8]	-
Change (kg) from baseline[1]	-15,3	2,4
Difference (kg) from placebo[1] [95% CI]	-17,7 [-21,8; -13,7]	-
Patients (%) achieving weight loss ≥ 5 %[3]	72,5*	17,7
Patients (%) achieving weight loss ≥ 10 %[3]	61,8	8,1
Patients (%) achieving weight loss ≥ 15 %[3]	53,4	4,8
Waist circumference (cm)		
Baseline	111,9	107,3
Change from baseline[1]	-12,7	-0,6
Difference from placebo[1] [95% CI]	-12,1 [-15,6; -8,7]	-
Systolic blood pressure (mmHg)		
Baseline	120	120
Change from baseline[1]	-2,7	-0,8

Difference from placebo[1] [95% CI]	-1,9 [-5,0; 1,1]	-

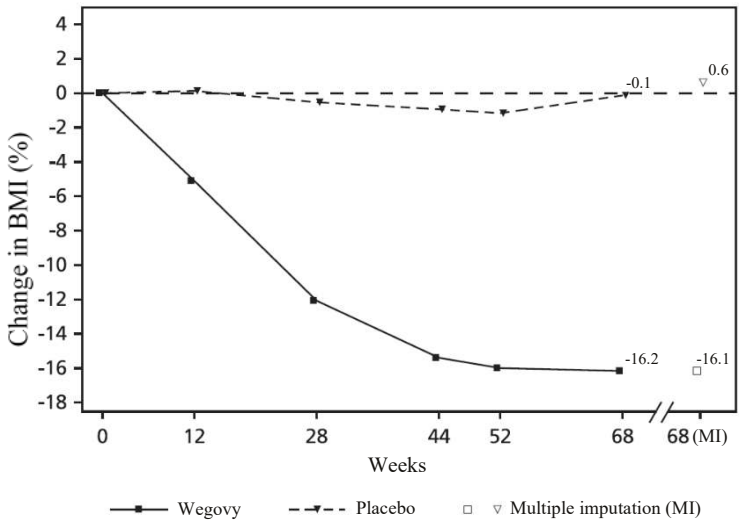
* p<0,0001 (unadjusted 2-sided) for superiority.

[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 10,4% and 10,4% 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 BMI based on a Mixed Model for Repeated Measures including all observations until first discontinuation were -17,9% and 0,6% for semaglutide 2,4 mg and placebo respectively

[3] Estimated from logistic regression model based on same imputation procedure as in primary analysis.

Figure 5 STEP TEENS: Mean change in BMI (%) from baseline to week 68



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

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 semaglutide 2,4 mg was approximately 75 nmol/L in patients with overweight (BMI ≥27 kg/m^2 to < 30 kg/m^2) or obesity (BMI ≥ 30 kg/m^2). The steady state exposure of semaglutide increased proportionally with doses up to 2,4 mg once weekly. 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) 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 was excreted in the urine as intact semaglutide.
The clearance of semaglutide in patients with overweight (BMI ≥ 27 kg/m^2 to < 30 kg/m^2) or obesity (BMI ≥ 30 kg/m^2) 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. 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/m^2 to < 30 kg/m^2) or obesity (BMI ≥ 30 kg/m^2) 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

Pharmacokinetic properties for semaglutide were assessed in a clinical trial for adolescent patients with obesity or overweight and at least one weight-related comorbidity ages 12 to < 18 years (124 patients, body weight 61,6 – 211,9 kg). The semaglutide exposure in adolescents was similar to that in adults with obesity or overweight.

Safety and efficacy of semaglutide in children below 12 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

Propylene glycol

Phenol

Hydrochloric acid (for pH adjustment)

Sodium hydroxide (for pH adjustment)

Water for injection

6.2 Incompatibilities

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

6.3 Shelf life

Before use: 3 years.

In-use shelf-life: 6 weeks. Store below 30 °C or in a refrigerator (2 °C to 8 °C).

6.4 Special precautions for storage

Store in a refrigerator (2 °C to 8 °C). Keep away from the cooling element.

Keep the pen cap on when the pen is not in use in order to protect it from light.

6.5 Nature and contents of container

Pre-filled pen, FlexTouch® (0,25, 0,5 mg)

1,5 mL glass cartridge (type I glass) closed at the one end with a rubber plunger (chlorobutyl) and at the other end with an aluminium cap with a laminated rubber sheet (bromobutyl/polyisoprene) inserted. The cartridge is assembled into a disposable pre-filled pen made of polypropylene, polyoxymethylene, polycarbonate and acrylonitrile butadiene styrene.

Pre-filled pen, FlexTouch® (1, 1,7 and 2,4 mg)

3 mL glass cartridge (type I glass) closed at the one end with a rubber plunger (chlorobutyl) and at the other end with an aluminium cap with a laminated rubber sheet (bromobutyl/polyisoprene) inserted. The cartridge is assembled into a disposable pre-filled pen made of polypropylene, polyoxymethylene, polycarbonate and acrylonitrile butadiene
styrene

Pack sizes

Pre-filled pen, FlexTouch® (0,25, 0,5, 1 and 1,7 mg)

Pack size of 1 pre-filled pen and 4 disposable NovoFine® Plus needles.

Applicant	Novo Nordisk (Pty) Ltd	**Dosage form and strength**	Solution for injection; Semaglutide 0,25 mg Solution for injection; Semaglutide 0,5 mg Solution for injection; Semaglutide 1 mg Solution for injection; Semaglutide 1,7 mg Solution for injection; Semaglutide 2,4 mg
Product name	Wegovy® 0,25 mg, 0,5 mg, 1 mg, 1,7 mg, 2,4 mg		

Pre-filled pen, FlexTouch® (2,4 mg)

Pack sizes:

1 pre-filled pen and 4 disposable NovoFine® Plus needles.

3 pre-filled pens and 12 disposable NovoFine® Plus needles.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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.

Pre-filled pen, FlexTouch®

This pen is for multi-use. It contains 4 doses.

The patient should be advised to discard the injection needle in accordance with local requirements after each injection and store the Wegovy® pen without an injection needle attached. This may prevent blocked needles, contamination, infection, leakage of solution and inaccurate dosing.

The pen is for use by one person only.

Wegovy® can be administered with 30 G, 31 G, and 32 G disposable needles up to a length of 8 mm.

Applicant	Novo Nordisk (Pty) Ltd	**Dosage form and strength**	Solution for injection; Semaglutide 0,25 mg Solution for injection; Semaglutide 0,5 mg Solution for injection; Semaglutide 1 mg Solution for injection; Semaglutide 1,7 mg Solution for injection; Semaglutide 2,4 mg
Product name	Wegovy® 0,25 mg, 0,5 mg, 1 mg, 1,7 mg, 2,4 mg		

7. HOLDER OF CERTIFICATE OF REGISTRATION

Novo Nordisk (Pty) Ltd

150 Rivonia Road

10 Marion Street Office Park Building C1

Sandton

Johannesburg

2196

8. REGISTRATION NUMBERS

Wegovy® 0,25 mg: 58/21.013/0223

Wegovy® 0,5 mg: 58/21.013/0224

Wegovy® 1 mg: 58/21.013/0225

Wegovy® 1,7 mg: 58/21.013/0226

Wegovy® 2,4 mg: 58/21.013/0227

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11 February 2025

10. DATE OF REVISION OF THE TEXT

N/A