## 1. NAME OF THE MEDICINAL PRODUCT

Wegovy 1.5 mg tablets
Wegovy 4 mg tablets
Wegovy 9 mg tablets
Wegovy 25 mg tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Wegovy 1.5 mg tablets

Each tablet contains 1.5 mg semaglutide*.

Wegovy 4 mg tablets

Each tablet contains 4 mg semaglutide*.

Wegovy 9 mg tablets

Each tablet contains 9 mg semaglutide*.

Wegovy 25 mg tablets

Each tablet contains 25 mg semaglutide*.

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

Excipient with known effect

Wegovy 25 mg tablets

Each tablet contains 23 mg sodium.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Tablet

Wegovy 1.5 mg tablets

White to light yellow and round (6.5 mm in diameter) debossed with ‘1.5’ on one side and ‘novo’ on the other side.

Wegovy 4 mg tablets

White to light yellow and round (6.5 mm in diameter) debossed with ‘4’ on one side and ‘novo’ on the other side.

Wegovy 9 mg tablets

White to light yellow and round (6.5 mm in diameter) debossed with '9' on one side and 'novo' on the other side.

Wegovy 25 mg tablets

White to light yellow, oval shaped (6.8 mm x 12 mm) debossed with '25' on one side and 'novo' on the other side.

## 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

- $\geq$ 30 kg/m$^2$ (obesity), or
- $\geq$ 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.

For trial results with respect to populations studied, see section 5.1.

### 4.2 Posology and method of administration

Posology

The starting dose for orally administered semaglutide is 1.5 mg once daily. After four weeks at this dose, the dose escalation steps for orally administered semaglutide once daily are 4 mg, 9 mg and 25 mg with a minimum duration of four weeks at each dose level. The dose should be escalated until 25 mg (maintenance dose). If needed, the dose can be maintained at the previous dose level.

The maximum recommended single daily dose of orally administered semaglutide is 25 mg. Orally administered semaglutide should always be taken as only one tablet per day. Taking more than one tablet, per day should not be done to achieve the effect of a higher dose.

*Switching from subcutaneous to oral semaglutide*

The effect of switching between subcutaneous and oral semaglutide cannot easily be predicted because oral semaglutide displays higher pharmacokinetic variability in absorption compared to subcutaneous semaglutide.

Patients treated with subcutaneous semaglutide 2.4 mg once weekly can be transitioned to oral semaglutide 25 mg once daily.
Patients can start oral semaglutide (Wegovy tablet) one week after their last dose of subcutaneous semaglutide.

*Patients with type 2 diabetes*

The risk of hypoglycaemia can be lowered by reducing the dose of sulfonylurea or insulin when initiating treatment with semaglutide (see sections 4.4 and 4.8).

*Missed dose*

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

*Special populations*

*Elderly (≥ 65 years of age)*
No dose adjustment is required based on age. Therapeutic experience in patients ≥ 85 years of age is limited.

*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/1.73m$^2$) including patients with end-stage renal disease (see sections 4.4, 4.8 and 5.2).

*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 orally administered semaglutide in children and adolescents below 18 years have not been established. No data is available.

Method of administration

Wegovy tablet is for oral use.

- This medicinal product should be taken on an empty stomach after a recommended fasting period of at least 8 hours (see section 5.2).
- It should be swallowed whole with a sip of water (up to half a glass of water equivalent to 120 mL). Tablets should not be split, crushed or chewed, as it is not known whether this impacts absorption of semaglutide.
- Patients should wait at least 30 minutes before eating, drinking or taking other oral medicinal products. Waiting less than 30 minutes decreases the absorption of semaglutide (see sections 4.5 and 5.2).

## 4.3 Contraindications

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

## 4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Aspiration in association with general anaesthesia or deep sedation

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

Gastrointestinal effects and dehydration

Use of GLP-1 receptor agonists may be associated with gastrointestinal adverse reactions. This

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

Acute pancreatitis

Acute pancreatitis has been observed with the use of GLP-1 receptor agonists (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.

Non-arteritic anterior ischaemic optic neuropathy (NAION)

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

Patients with 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.

Compliance with the dosing regimen is recommended for the optimal effect of semaglutide. If the treatment response with semaglutide is lower than expected, the treating physician should be aware that the absorption of semaglutide is highly variable and may be minimal, and that the absolute bioavailability of semaglutide is low.
Furthermore, patients with diabetes have been predicted to have lower drug exposure and less weight reduction than patients without diabetes.

In patients with type 2 diabetes with an inadequate response to oral semaglutide, consider switching to subcutaneous semaglutide.

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 agonist.

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.

Patients with gastroparesis

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

Populations not studied

The safety and efficacy of subcutaneous or oral semaglutide 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 subcutaneous or oral semaglutide in patients:
- aged 85 years or more (see section 4.2),
- with mild or moderate hepatic impairment (see section 4.2),
- with inflammatory bowel disease,
- with type 2 diabetes and $HbA_{1c}$ < 8% for the 25 mg oral semaglutide,
- with type 2 diabetes on concomitant insulin for the 25 mg oral semaglutide.

Use with caution in these patients.

Excipient with known effect

*Sodium*

Wegovy 1.5 mg, 4 mg and 9 mg tablets contain less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

Wegovy 25 mg tablets contain 23 mg sodium per tablet, equivalent to 1% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

## 4.5 Interaction with other medicinal products and other forms of interaction

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

Effects of semaglutide on other medicinal products

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

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

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

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

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

Effects of other medicinal products on semaglutide

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

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

Paediatric population

Interaction studies have only been performed in adults.

## 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

No measurable concentrations of semaglutide were found in breast milk of lactating women. Salcaprozate sodium was present in breast milk and some of its metabolites were excreted in breast milk at low concentrations. A risk to newborns/infants cannot be excluded. Wegovy 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

The most frequently reported adverse reactions were gastrointestinal disorders including nausea, diarrhoea, constipation, abdominal pain, dyspepsia and vomiting. These reactions were mainly seen in the dose-escalation period (see Description of selected adverse reactions).

The safety profile of oral semaglutide was consistent with the safety profile of subcutaneous semaglutide.

Tabulated list of adverse reactions

Table 1 lists adverse reactions identified in clinical studies in adults and post-marketing reports. The frequencies are based, unless otherwise specified, on a pool of the subcutaneous semaglutide phase 3a trials (STEP 1-4), where 2650 adult patients were exposed to Wegovy. The duration of the trials was 68 weeks. The adverse reactions in OASIS 4 (204 adults with obesity or overweight with at least one weight-related comorbidity were exposed to oral semaglutide for 64 weeks) had similar frequencies to the subcutaneous phase 3a trials, except for dyspepsia which had a higher frequency category. Events not relevant for oral administration are omitted in the following overview.

Adverse reactions are listed by MedDRA 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) and not known (cannot be estimated from the available data). Within each frequency category, adverse reactions are presented in order of decreasing seriousness.

**Table 1 Adverse reactions**

| MedDRA system organ class | Very common | Common | Uncommon | Rare | Very rare | Not known |
|---|---|---|---|---|---|---|
| Immune system disorders | | | | Anaphylactic reaction | | |
| Metabolism and nutrition disorders | | Hypoglycaemia in patients with type 2 diabetes[a] | | | | |
| Nervous system disorders | Headache[b] | Dizziness[b]<br>Dysgeusia[b,c]<br>Dysaesthesia[a,c,g] | | | | |
| Eye disorders | | Diabetic retinopathy in patients with type 2 diabetes[a] | | | Non-arteritic anterior ischaemic optic neuropathy (NAION) | |
| Cardiac disorders | | | Increased heart rate[a,c] | | | |
| Vascular disorders | | | Hypotension<br>Orthostatic hypotension | | | |

| MedDRA system organ class | Very common | Common | Uncommon | Rare | Very rare | Not known |
|---|---|---|---|---|---|---|
| Gastrointestinal disorders | Vomiting[a,b]<br>Diarrhoea[a,b]<br>Constipation[a,b]<br>Dyspepsia[b,d]<br>Nausea[a,b]<br>Abdominal pain[b,c] | Gastritis[b,c]<br>Gastrooesophageal reflux disease[b]<br>Eructation[b]<br>Flatulence[b]<br>Abdominal distension[b] | Acute pancreatitis[a]<br>Delayed gastric emptying | | | Intestinal obstruction[c,e,f] |
| Hepatobiliary disorders | | Cholelithiasis[a] | | | | |
| Skin and subcutaneous tissue disorders | | Hair loss[a] | | Angioedema | | |
| General disorders and administration site conditions | Fatigue[b,c] | | | | | |
| Investigations | | | Increased amylase[c]<br>Increased lipase[c] | | | |

[a)] See description of selected adverse reactions below
[b)] Mainly seen in the dose-escalation period
[c)] Grouped preferred terms
[d)] The frequency is based on the OASIS 4 phase 3 trial with oral semaglutide.
[e)] From post-marketing reports
[f)] Grouped term covering PTs Intestinal obstruction, Ileus, small intestinal obstruction
[g)] Grouped term covering PTs Dysaesthesia, Hyperaesthesia, Paraesthesia, Skin burning sensation, Burning sensation, Pain of skin, Sensitive skin, Skin discomfort, Skin sensitisation, Allodynia and Hyperpathia

Description of selected adverse reactions

The below adverse reactions are applicable for oral semaglutide. Frequencies on specific adverse reactions, unless otherwise specified, pertains to the OASIS 4 phase 3 trial.

*Gastrointestinal adverse reactions*

The events were most frequently reported during dose escalation. Over the 64 weeks trial period, nausea occurred in 46.6% of patients when treated with oral semaglutide (18.6% for placebo), vomiting in 30.9% (5.9% for placebo), dyspepsia in 18.1% (8.8% for placebo), diarrhoea in 17.6% (8.8% for placebo), and abdominal pain in 16.7% (7.8% for placebo). Most events were mild to moderate in severity and of short duration. Constipation occurred in 20.1% of patients treated with semaglutide (9.8% for placebo) and was mild to moderate in severity and of longer duration.

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

Patients with moderate renal impairment (eGFR $\geq$ 30 to < 60 mL/min/1.73 $m^2$) may experience more gastrointestinal effects when treated with semaglutide.

The gastrointestinal events led to permanent treatment discontinuation in 3.4% of patients treated with oral semaglutide.

*Acute pancreatitis*

Acute pancreatitis was reported in 0 % of patients treated with oral semaglutide and 1.0 % of patients treated with placebo. The frequency of adjudication-confirmed acute pancreatitis reported in the STEP phase 3a clinical studies was 0.2 % for semaglutide and < 0.1 % for placebo, respectively. In SELECT, the cardiovascular outcomes trial, the frequency of acute pancreatitis confirmed by adjudication was 0.2 % for semaglutide and 0.3 % for placebo.

*Acute gallstone disease/Cholelithiasis*

Cholelithiasis was reported in 2.5 % and led to cholecystitis in 0 % of patients treated with oral semaglutide. Cholelithiasis and cholecystitis were reported in 1 % and 0 %, respectively, of patients treated with placebo.

*Hair loss*

Hair loss was reported in 6.4 % of patients treated with oral semaglutide and in 2.0 % of patients treated with placebo. All events were mild or moderate and half of them recovered by end of the trial. Hair loss was reported more frequently in patients with a greater weight loss (≥ 20 %).

*Increased heart rate*

A mean increase of 2 beats per minute (bpm) from a baseline mean of 72 bpm was observed in patients treated with oral semaglutide. The proportions of subjects with an increase in pulse from baseline ≥ 20 bpm at any timepoint during the on-treatment period were 26.5 % in the semaglutide group vs. 20.8 % 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 with oral semaglutide 14 mg and 50 mg at any time post-baseline was low (0.5 % and 0.3 % for Rybelsus and Wegovy tablets, respectively) and no patients had anti-semaglutide neutralising antibodies or anti-semaglutide antibodies with endogenous GLP-1 neutralising effect. 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 anti-semaglutide antibodies, the presence of antibodies had 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 2.4 mg s.c 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 subcutaneous 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 semaglutide 2.4 mg, 6.2 % of patients treated with subcutaneous 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).

*Dysaesthesia*

Events related to a clinical picture of altered skin sensation such as sensitive skin, hyperaesthesia, paraesthesia, skin burning sensation and allodynia were reported in 4.9% of patients treated with oral semaglutide. No events were reported in patients treated with placebo. The events were mild to moderate in severity and most patients recovered while on continued treatment.

*Non-arteritic anterior ischaemic optic neuropathy (NAION)*

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

Other special populations

In the SELECT trial, in adults with established cardiovascular disease, the adverse reaction profile was similar to that seen in subcutaneous semaglutide in the weight management phase 3a trials.

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 professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie.

### 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: Medicinal product 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 has 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.

The mechanism of action of semaglutide for cardiovascular risk reduction is likely multifactorial, in part driven by weight loss effects and effects on known cardiovascular risk factors (reduction in blood pressure, improvements in lipid profile and glucose metabolism, and anti-inflammatory effects as demonstrated by reductions in high-sensitivity C-reactive protein (hsCRP)). The exact mechanism of cardiovascular risk reduction has not been established.

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.

*Fasting and postprandial lipids*

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

Clinical efficacy and safety

The efficacy and safety of 25 mg orally administered semaglutide (tablet) once daily for weight management in combination with a reduced calorie intake and increased physical activity have been evaluated in a 64-week double-blinded randomised placebo-controlled phase 3b trial (OASIS 4) including 307 patients (205 randomised to treatment with orally administered semaglutide).

Treatment with oral semaglutide demonstrated superior, clinically meaningful, and sustained weight loss compared with placebo in patients with obesity (BMI $\geq$ 30 kg/m$^2$), or overweight (BMI $\geq$ 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 $\geq$ 5%, $\geq$ 10%, $\geq$ 15% and $\geq$ 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 oral semaglutide also showed statistically significant improvements in waist circumference, and physical functioning compared to placebo.

Efficacy was demonstrated with oral semaglutide regardless of age, gender, 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.

In addition, the efficacy and safety of subcutaneous semaglutide for weight management in combination with a reduced calorie intake and increased physical activity were evaluated in four 68 weeks double-blinded randomised placebo-controlled phase 3a trials (STEP 1-4). A total of 4 684 patients (2 652 randomised to treatment with subcutaneously administered semaglutide) were included in these trials. The efficacy and safety were similar between OASIS 4 and STEP 1 regardless of the route of administration.

*OASIS 4: Weight management – once daily Wegovy 25 mg tablet (semaglutide 25 mg)*

In a 64-week phase 3b trial, 307 adult 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 once daily orally administered 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 64), the weight loss was superior and clinically meaningful compared with placebo (see Table 2 and Figure 1).

Furthermore, a higher proportion of patients achieved ≥ 5%, ≥ 10%, ≥ 15% and ≥ 20% weight loss with orally administered semaglutide compared with placebo (see Table 2). Among patients with prediabetes at baseline, a higher proportion of patients had a normo-glycaemic status at end of treatment with orally administered semaglutide compared to placebo (71.1% vs. 33.3%).

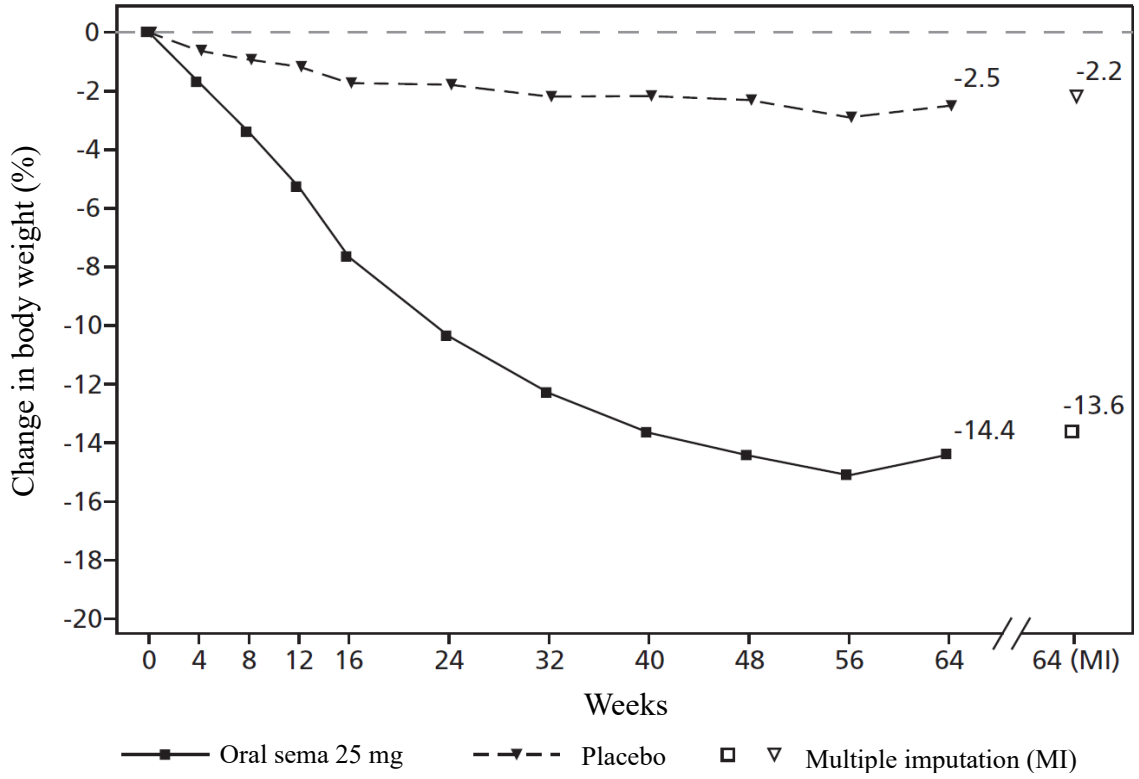
**Table 2 OASIS 4: Results at week 64**

| | **Semaglutide 25 mg tablet** | **Placebo** |
|---|---|---|
| Full analysis set (N) | 205 | 102 |
| **Body weight** | | |
| Baseline (kg) | 106.4 | 104.8 |
| Change (%) from baseline[1,2] | -13.6 | -2.2 |
| Difference (%) from placebo[1] [95% CI] | -11.4 [-13.9; -9]* | |
| Change (kg) from baseline[1] | -14.2 | -2.2 |
| Difference (kg) from placebo[1] [95% CI] | -12.0 [-14.6; -9.5]* | |
| Patients (%) achieving weight loss ≥ 5%[3] | 76.3* | 30.5 |
| Patients (%) achieving weight loss ≥ 10%[3] | 59.8* | 14.1 |
| Patients (%) achieving weight loss ≥ 15%[3] | 47.0* | 5.4 |
| Patients (%) achieving weight loss ≥ 20%[3] | 27.5* | 3 |
| **Waist circumference (cm)** | | |
| Baseline | 114 | 113.6 |
| Change from baseline[1] | -12.2 | -2.8 |
| Difference from placebo[1] [95% CI] | -9.5 [-12.4; -6.6]* | |
| **Systolic blood pressure (mmHg)** | | |
| Baseline | 131 | 131 |
| Change from baseline[1] | -6.8 | -5.4 |
| Difference from placebo[1] [95% CI] | -1.4 [-4.6; 1.8] | |

* p< 0.0001 (unadjusted 2-sided) for superiority.
1 Estimated using an ANCOVA model using multiple imputation based on all data irrespective of premature discontinuation of randomised treatment or initiation of other anti-obesity medicinal product or bariatric surgery.
2 During the trial, randomised treatment was permanently discontinued by 18% and 25.5% of patients randomised to oral semaglutide 25 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 64 for body weight based on a Mixed Model for Repeated Measures including all observations until first discontinuation were -16.6% and -2.8% for oral semaglutide 25 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 OASIS 4: Mean change in body weight (%) from baseline to week 64**

While some patients have not achieved the same exposure with oral semaglutide 25 mg and subcutaneous semaglutide 2.4 mg, data from the following trials with the subcutaneous formulation are considered informative for the oral formulation.

*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 subcutaneous 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. Furthermore, a higher proportion of patients achieved ≥ 5%, ≥ 10%, ≥ 15% and ≥ 20% weight loss with semaglutide compared with placebo.

*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 antidiabetic medicinal product. 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.

*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 subcutaneous 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.

*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 subcutaneous semaglutide. At week 20 (baseline), patients who had reached the maintenance dose of subcutaneous semaglutide 2.4 mg were randomised to continue treatment or switch to placebo.

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.

*Improvement in physical functioning*
Oral semaglutide showed statistically significant improvement in physical functioning scores and more patients with oral semaglutide achieved a clinically meaningful improvement compared to placebo. Physical functioning was assessed using the obesity-specific questionnaire Impact of Weight on Quality of Life Lite Clinical studies Version (IWQOL-Lite-CT).

*Cardiovascular evaluation*

*SELECT: Cardiovascular outcomes trial in patients with overweight or obesity*

No cardiovascular outcomes clinical studies have been performed with oral semaglutide 25 mg in individuals with established cardiovascular disease and BMI ≥ 27 kg/m$^2$.

SELECT was a randomised, double-blind, placebo-controlled, event driven trial which included 17 604 patients with established cardiovascular disease and BMI≥ 27 kg/m$^2$. Patients were randomised to either subcutaneous semaglutide 2.4 mg (n=8 803) or placebo (n=8 801) in addition to standard-of-care. The median time in trial was 41.8 months.

The study population consisted of female and male patients, with a mean age of 61.6 years. The mean BMI was 33.3 kg/m$^2$ and mean body weight was 96.7 kg. Patients with history of type 1 and type 2 diabetes were excluded.

The primary endpoint was the time from randomisation to first occurrence of major adverse cardiovascular events (MACE), defined as a composite endpoint consisting of cardiovascular death (including undetermined cause of death), non-fatal myocardial infarction, or non-fatal stroke.

Superiority of subcutaneous semaglutide 2.4 mg versus placebo for MACE was confirmed with a hazard ratio of 0.80 [0.72; 0.90][95% CI], corresponding to a relative risk reduction in MACE of 20

%. The reduction of MACE with subcutaneous semaglutide 2.4 mg was not impacted by age, gender, race, ethnicity, BMI at baseline, or level of renal function impairment.

## 5.2 Pharmacokinetic properties

Absorption

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

The pharmacokinetic profile of orally administered semaglutide has been characterised in healthy people and patients with overweight or obesity using population PK modelling. Following oral administration, maximum plasma concentration of semaglutide occurred 1 hour post dose. The half-life of semaglutide is approximately 1 week indicating that steady-state exposure will be reached after 4-5 weeks of once-daily administration. Average predicted concentration was approximately 77 nmol/L with 90% of subjects treated with semaglutide 25 mg having an average concentration between 27 and 186 nmol/L.

The steady-state concentrations increased approximately proportionally with doses up to 25 mg once daily. The total within and between participant variability in AUC following oral semaglutide dosing was estimated at 166% after a single dose. In steady state conditions, the variability in AUC is reduced due to daily dosing and the long half-life of semaglutide, resulting in 68% total variability (33% within participant variability).

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

The estimated absolute bioavailability of semaglutide is approximately 1-2% following oral administration.

Absorption of orally administered semaglutide is decreased if taken with food or large volumes of water. Different dosing schedules of semaglutide have been investigated. Studies show that longer pre- and post-dose fasting period results in higher absorption.

Distribution

The absolute volume of distribution of semaglutide in patients with overweight or obesity is approximately 8.9 L. Semaglutide is extensively bound to plasma proteins (> 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 absolute clearance of semaglutide in patients with overweight (BMI $\geq$ 27 kg/m$^2$ to < 30 kg/m$^2$) or obesity (BMI $\geq$ 30 kg/m$^2$) is approximately 0.04 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 oral semaglutide (tablet).

Special populations

*Elderly*

Age had no effect on the pharmacokinetics of semaglutide based on data from phase 3 trials including patients 18–92 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 based on subcutaneous semaglutide data. Subcutaneous and oral administration of semaglutide has provided clinically efficacious exposures over the body weight range of 54.4−245.6 kg in clinical studies.

*Renal impairment*

Renal impairment did not impact the pharmacokinetics of semaglutide in a clinically relevant manner. This was shown following 10 consecutive days of once-daily oral doses of 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 $\geq$ 27 kg/m$^2$ to < 30 kg/m$^2$) or obesity (BMI $\geq$ 30 kg/m$^2$) and mild to moderate renal impairment based on data from phase 3 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 studies following 10 consecutive days of once-daily oral doses of semaglutide.

*Upper gastrointestinal tract diseases*

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

*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.

*Paediatric population*

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

## 5.3 Preclinical safety data

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

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

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

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

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

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

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

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Salcaprozate sodium
Magnesium stearate

### 6.2 Incompatibilities

Non applicable.

### 6.3 Shelf life

3 years.

### 6.4 Special precautions for storage

Store in the original package in order to protect from moisture and light. This medicinal product does not require any special temperature storage conditions.

### 6.5 Nature and contents of container

Alu/Alu blisters of 10 tablets.
Pack sizes of: 10, 30 and 90 tablets.
Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal and other handling

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

## 7. MARKETING AUTHORISATION HOLDER

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

## 8. MARKETING AUTHORISATION NUMBER(S)

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## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 06 January 2022
Date of latest renewal: 21 September 2026

## 10. DATE OF REVISION OF THE TEXT

09/2026

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.