Summary Report of Benefit-Risk Assessment

OZEMPIC 1MG/DOSE SOLUTION FOR INJECTION IN PRE-FILLED PEN 1.34MG/ML
OZEMPIC 0.25MG, 0.5MG/DOSE SOLUTION FOR INJECTION IN PRE-FILLED PEN 1.34MG/ML

NEW DRUG APPLICATION

Active Ingredient(s)	Semaglutide
Product Registrant	Novo Nordisk Pharma (Singapore) Pte Ltd
Product Registration Number	SIN16164P, SIN16165P
Application Route	Abridged Evaluation
Date of Approval	21 April 2021

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A INTRODUCTION

Ozempic Solution for Injection is indicated as monotherapy when metformin is considered inappropriate due to intolerance or contraindications, or as addition to other medicinal products for treatment of adults with insufficiently controlled type 2 diabetes mellitus (T2DM).

The active substance, semaglutide, is a human glucagon-like peptide-1 (GLP-1) analogue for once-weekly subcutaneous administration. Semaglutide stimulates insulin secretion from the pancreatic islets in a glucose-dependent manner.

Ozempic Solution for Injection is available as solution containing 1.34/mL of semaglutide presented in pre-filled pen that allows delivery of doses of 0.25 mg/dose, 0.5 mg/dose, and 1 mg/dose. Other ingredients in the solution are disodium phosphate dihydrate, propylene glycol, phenol, hydrochloric acid), sodium hydroxide and water for injections.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, semaglutide, is manufactured at Novo Nordisk A/S, Kalundborg, Denmark. The drug products, Ozempic 0.25mg/dose, 0.5mg/dose and 1mg/dose solution for injection in pre-filled pens are manufactured at Novo Nordisk A/S, Bagsvaerd, Denmark.

Drug substance:

Adequate controls have been presented for the cell banks and reagents. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate. The drug substance manufacturer is compliant with Good Manufacturing Practice (GMP). Process validation was conducted on three consecutive production-scale batches.

The characterisation of the drug substance and its impurities are in accordance with ICH guidelines. Potential and actual impurities are adequately controlled.

The drug substance specifications are established in accordance with ICH Q6B and the impurity limits are considered appropriately qualified. The analytical methods used are adequately described and non-compendial methods are appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing was presented.

The stability data presented for semaglutide drug substance are adequate to support the approved storage condition and shelf life period. The packaging is 5L and 10L high density polyethylene (HDPE) plastic containers closed with HDPE plastic screw caps. The drug substance is approved for storage at -20^{o}C with a shelf life of 60 months.

Drug product:

The manufacturing process utilises aseptic processing.

All manufacturing sites involved are compliant with Good Manufacturing Practice (GMP). Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications are established in accordance with ICH Q6B and impurity limits are considered adequately qualified. The analytical methods used are adequately described and non-compendial methods are appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data submitted are adequate to support the approved shelf-life of 36 months when stored at 2ºC to 8 ºC. The in-use period after opening is 6 weeks when stored at or below 30°C or in the refrigerator at 2-8°C and is supported with appropriate data. The container closure system is pre-filled pen containing 1.5 ml or 3 ml cartridge made of clear, colourless type I hydrolytic glass closed at one end with a rubber plunger and the other end with a laminated rubber disc.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of semaglutide as mono- and combination therapy (primarily in combination with metformin, sulphonylurea (SU) and/or insulin) for the treatment of T2DM was based on 6 pivotal Phase 3 clinical trials - Studies 3623, 3626, 3624, 3625, 3627 and 4216 with a follow-up of 30-56 weeks. Cardiovascular outcomes and long-term efficacy were assessed in the Phase 3 Study 3744 with a follow-up of 104 weeks. Two additional supportive Phase 3 Studies 4091 and 4092 were submitted to evaluate semaglutide for treatment of T2DM in Japanese subjects. All the trials were randomised, parallel group, multi-centre trials comparing semaglutide with placebo or active comparator drugs used for treatment of diabetes. Overall, these studies provided the evidence to support the proposed use as monotherapy in treatment initiation in treatment-naïve patients, or as add-on therapy for treatment optimisation in patients inadequately controlled with metformin, SU and/or insulin.

- Study 3623 was a randomised, double-blind, parallel group, placebo-controlled trial in adult T2DM subjects who had not achieved adequate glycaemic control (HbA_{1c}: 7.0−10.0 %, both inclusive) on lifestyle modification through diet and exercise. The effects on glycaemic control and body weight after 30 weeks of treatment with once-weekly dosing of semaglutide (0.5 mg and 1 mg) were compared to placebo. Overall, 388 subjects were randomised to semaglutide 0.5 mg (N = 129), semaglutide 1 mg (N = 130) and placebo (N = 129). Subject demographics and baseline characteristics were balanced across the study with a mean age of 53.7 years (range: 18 - 88 years), mean body weight of 91.93 kg (range: 39.8 – 185.3 kg) and mean HbA_{1c} of 8.05 % (range: 6.40 – 10.30 %).

- Study 3626 was a randomised, double-blind, active-controlled trial in T2DM subjects who had not achieved adequate glycaemic control (HbA_{1c}: 7.0−10.5 %, both inclusive) on metformin, thiazolidinediones (TZD) or a combination of metformin/TZD. With the background anti-diabetic medications maintained at the stable, pre-trial dose and frequency, the effects of adding on once-weekly dosing semaglutide (0.5 mg or 1 mg) on glycaemic control and body weight after 56 weeks of treatment was compared to control with add-on sitagliptin 100 mg once-daily. Overall, 1231 subjects were randomised to receive semaglutide 0.5 mg (N = 410), semaglutide 1 mg (N = 410) and sitagliptin (N = 411). Subject demographics and baseline characteristics were balanced across the study with a mean age of 55.1 years (range: 23 - 83 years), mean body weight of 89.48 kg (range: 43.6 – 167.0 kg) and mean HbA_{1c} of 8.07 % (range: 5.90 – 11.40 %).

- Study 3624 was a randomised, open-label, active-controlled trial in T2DM subjects who had not achieved adequate glycaemic control (HbA_{1c}: 7.0−10.5 %, both inclusive) on metformin, TZD and/or SU. With the background anti-diabetic medications maintained at the stable, pre-trial dose and frequency, the effects of adding on once-weekly dosing semaglutide 1mg on glycaemic control and body weight after 56 weeks of treatment was compared to control which add-on exenatide ER 2 mg once-weekly. Overall, 813 subjects were randomised to receive semaglutide 1mg (N = 406) and exenatide ER (N = 407). Subject demographics and baseline characteristics were balanced across the study with a mean age of 56.6 years (range: 20 - 83 years), mean body weight of 95.79 kg (range: 49.9 – 198.3 kg) and mean HbA_{1c} of 8.35 % (range: 6.50 – 11.20 %).

- Study 3625 was a randomised, open-label, active-controlled trial in T2DM subjects who had not achieved adequate glycaemic control (HbA_{1c}: 7.0−10.5 %, both inclusive) on metformin or metformin and SU. With the background anti-diabetic medications maintained at the stable, pre-trial dose and frequency, the effects of adding on once-weekly dosing semaglutide (0.5 mg or 1mg) on glycaemic control and body weight after 30 weeks of treatment was compared to control with add-on insulin glargine once-daily. Overall, 1089 subjects were randomised to receive semaglutide 0.5 mg (N = 362), semaglutide 1mg (N = 362) and insulin glargine (N = 365). Subject demographics and baseline characteristics were balanced across the study with a mean age of 56.5 years (range: 22 - 82 years), mean body weight of 93.45 kg (range: 43.0 – 187.8 kg) and mean HbA_{1c} of 8.17 % (range: 5.50 – 11.70 %).

- Study 3627 was a randomised, double-blind, placebo-controlled trial in T2DM subjects who had not achieved adequate glycaemic control (HbA_{1c}: 7.0−10.0 %, both inclusive) on basal insulin alone or in combination with metformin. With the background basal insulin with or without metformin, the effects of adding on once-weekly dosing semaglutide (0.5 mg or 1mg) on glycaemic control and body weight after 30 weeks of treatment was compared to placebo. Overall, 397 subjects were randomised to receive semaglutide 0.5 mg (N = 132), semaglutide 1mg (N = 132) and placebo (N = 133). Subject demographics and baseline characteristics were balanced across the study with a mean age of 58.8 years (range: 19 - 86 years), mean body weight of 91.70 kg (range: 47.50 – 165.6 kg) and mean HbA_{1c} of 8.37 % (range: 6.80 – 11.10 %).

- Study 4216 was a randomised, open-label, active-controlled trial in T2DM subjects who had not achieved adequate glycaemic control (HbA_{1c}: 7.0−10.5 %, both inclusive) on metformin. With the background anti-diabetic medications maintained at the stable, pre-trial dose and frequency, the effects of adding on once-weekly dosing semaglutide (0.5 mg or 1mg) on glycaemic control and body weight after 40 weeks of treatment was compared to control with add-on dulaglutide (0.75 mg or 1.5 mg). Overall, 1201 subjects were randomised to receive semaglutide 0.5 mg (N = 301), semaglutide 1mg (N = 300), dulaglutide 0.75 mg (N = 300) and dulaglutide 1.5 mg (N = 300). Subject demographics and baseline characteristics were balanced across the study with a mean age of 56.0 years (range: 22 - 84 years), mean body weight of 95.2 kg (range: 46.0 – 209.6 kg) and mean HbA_{1c} of 8.2 % (range: 6.60 – 11.40 %).

- Study 3744 assessed the cardiovascular outcomes and the long-term efficacy and safety of semaglutide with continued treatment up to 104 weeks. This study was a randomised double-blind, parallel arm, placebo-controlled trial in T2DM subjects with high cardiovascular (CV) risks who had not achieved adequate glycaemic control with current standard-of-care. The primary objective was to confirm treatment with semaglutide does not result in an unacceptable increase in CV risk. Efficacy of semaglutide 0.5 mg and 1 mg

once-weekly compared to placebo was assessed as secondary objective. Overall, 3297 subjects were randomised to receive semaglutide 0.5 mg (N = 826), semaglutide 1mg (N = 822) and placebo (N = 1649). Subject demographics and baseline characteristics were balanced across the study with a mean age of 64.6 years (range: 50 - 89 years), mean body weight of 92.09 kg (range: 40.70 – 216.82 kg) and mean HbA_{1c} of 8.7 % (range: 5.90 – 17.90 %).

Studies 4091 and 4092 were designed to generate safety data in Japanese T2DM patients. Efficacy was the secondary objective and provided further supportive evidence of efficacy in Asian patient population.

- Study 4091 was a randomised, open-label, active-controlled trial in T2DM subjects who had not achieved adequate glycaemic control (HbA_{1c}: 7.0−10.5 %, both inclusive) on diet/exercise therapy or oral antidiabetic drug (OAD) monotherapy with SU, glinide, α-glucosidase inhibitor, or TZD. With the background anti-diabetic medications (if any) maintained at the stable, pre-trial dose and frequency, the effects of adding on once-weekly dosing semaglutide (0.5 mg or 1 mg) on glycaemic control and body weight after 56 weeks of treatment was compared to control with add-on 1 OAD (of either DPP-4 inhibitor, SU, glinide, biguanide, α-GI, or TZD). Overall, 601 subjects were randomised to receive semaglutide 0.5 mg (N = 239), semaglutide 1mg (N = 241) and control (N = 121). Subject demographics and baseline characteristics were balanced across the study with a mean age of 58.5 years (range: 26 - 83 years), mean body weight of 71.53 kg (range: 39.50 – 142.0 kg) and mean HbA_{1c} of 8.09 % (range: 6.70 – 13.10 %).

- Study 4092 was a randomised, open-label, active-controlled trial in subjects with T2DM who had not achieved adequate glycaemic control (HbA_{1c}: 7.0−10.5 %, both inclusive) on diet/exercise therapy or OAD monotherapy. For subjects on pre-trial OAD, the medication was stopped and subjects entered 8-week washout before randomization. The study compared the effect of once-weekly dosing of semaglutide (0.5 mg or 1 mg) as monotherapy with sitagliptin 100 mg monotherapy after 30 days of treatment. Overall, 308 subjects were randomised to receive semaglutide 0.5 mg (N = 103), semaglutide 1mg (N = 102) and sitagliptin (N = 103). Subject demographics and baseline characteristics were balanced across the study with a mean age of 58.3 years (range: 22 - 83 years), mean body weight of 68.65 kg (range: 39.10 – 129.4 kg) and mean HbA_{1c} of 8.15 % (range: 6.70 – 11.20 %).

The placebo-controlled studies were designed to claim superiority if the upper limit of 95% confidence interval (95% CI) of the difference in HbA_{1c} reduction was below 0. Studies with an active control were designed as non-inferiority studies with a pre-defined margin of 0.3% (0.4 % for Study 4216) and superiority was tested when non-inferiority was met. In the 9 trials, treatment with semaglutide 0.5 mg or 1 mg resulted in a reduction in HbA_{1c} starting after 4 weeks of treatment. The reduction in HbA_{1c} from baseline at the end of the study treatment were 1.09 % – 1.87 % with semaglutide 0.5 mg and 0.92 % – 2.18 % with semaglutide 1 mg. The improvement in HbA_{1c} was superior with semaglutide compared to placebo or active comparators across all the clinical trials. The reduction was maintained with continued treatment up to 104 weeks in Study 3744. The magnitude of the HbA_{1c} improvement with semaglutide was considered clinically relevant with the treatment differences greater than 0.3%.

Between the two doses of semaglutide, the reduction in baseline HbA_{1c} with semaglutide 1 mg was consistently larger than semaglutide 0.5 mg.

Summary of HbA_{1c} reductions in Studies 3623, 3626, 3624, 3625, 3627, 4216, 4091, 4092 and 3744

Trial No. (Treatment groups)	**3623 (Sema 0.5 Sema 1.0 Placebo)**	**3626 (Sema 0.5 Sema 1.0 Sita)**	**3624 (Sema 1.0 Exe ER 2.0)**	**3625 (Sema 0.5 Sema 1.0 IGlar)**	**3627 (Sema 0.5 Sema 1.0 Placebo)**	**4216 (Sema 0.5 Sema 1.0 Dula 0.75 Dula 1.5)**	**4091 (Sema 0.5 Sema 1.0 OAD)**	**4092 (Sema 0.5 Sema 1.0 Sita)**	**3744 (Sema 0.5 Sema 1.0 Placebo)**
Treatment Duration (Weeks)	30	56	56	30	30	40	56	30	104
Mean change from baseline at 'end-of-treatment', HbA_{1c} (%)	-1.45 -1.55 -0.02	-1.32 -1.61 -0.55	-1.54 -0.92	-1.21 -1.64 -0.83	-1.45 -1.85 -0.09	-1.51 -1.78 -1.11 -1.37	-1.74 -2.03 -0.67	-1.87 -2.18 -0.74	-1.09 -1.41 -0.44 -0.36
Treatment difference at 'end-of-treatment', % mean diff (95%CI)*									
Sema 0.5 mg *minus* Control	-1.43 (-1.71; -1.15)	-0.77 (-0.92; -0.62)	NA	-0.38 (-0.52; -0.24)	-1.35 (-1.61; -1.10)	-0.40 (-0.55; -0.25)	-1.08 (-1.24; -0.91)	-1.13 (-1.32; -0.94)	-0.66 (-0.80; -0.52)
Sema 1.0 mg *minus* Control	-1.53 (-1.81; -1.25)	-1.06 (-1.21; -0.91)	-0.62 (-0.80; -0.44)	-0.81 (-0.96; -0.67)	-1.75 (-2.01; -1.50)	-0.41 (-0.57; -0.25)	-1.37 (-1.53; -1.20)	-1.44 (-1.63; -1.24)	-1.05 (-1.19; -0.91)
*Superiority concluded if the upper limit of the 95 % CI of the diff between Test and Control below 0 %									

With respect to body weight reduction, semaglutide significantly reduced body weight in all 9 trials compared with placebo (both as monotherapy and in combination with insulin) or active comparators including sitagliptin, exenatide ER, dulaglutide and insulin glargine. There was a dose-response reduction from baseline body weight of up to 4.56kg and 6.53 kg with semaglutide 0.5 mg and 1 mg, respectively, and was sustained through the entire treatment period of up to 104 weeks in the Study 3744.

Summary of body weight reductions in Studies 3623, 3626, 3624, 3625, 3627, 4216, 4091, 4092 and 3744

Trial No. (Treatment groups)	**3623 (Sema 0.5 Sema 1.0 Placebo)**	**3626 (Sema 0.5 Sema 1.0 Sita)**	**3624 (Sema 1.0 Exe ER 2.0)**	**3625 (Sema 0.5 Sema 1.0 IGlar)**	**3627 (Sema 0.5 Sema 1.0 Placebo)**	**4216 (Sema 0.5 Sema 1.0 Dula 0.75 Dula 1.5)**	**4091 (Sema 0.5 Sema 1.0 OAD)**	**4092 (Sema 0.5 Sema 1.0 Sita)**	**3744 (Sema 0.5 Sema 1.0 Placebo)**
Treatment Duration (Weeks)	30	56	56	30	30	40	56	30	104
Mean change from baseline at 'end-of-treatment', body weight (kg)	-3.73 -4.53 -0.98	-4.28 -6.13 -1.93	-5.63 -1.85	-3.47 -5.17 1.15	-3.67 -6.42 -1.36	-4.56 -6.53 -2.30 -2.98	-1.43 -3.18 0.41	-2.21 -3.87 -0.02	-3.57 -4.88 -0.62
Treatment difference at 'end-of-treatment', % mean diff (95%CI)*									
Sema 0.5 mg *minus* Control	-2.75 (-3.92; -1.58)	-2.35 (-3.06; -1.63)	NA	-4.62 (-5.27; -3.96)	-2.31 (-3.33; -1.29)	-2.26 (-3.02; -1.51)	-1.84 (-2.67; -1.01)	-2.22 (-3.02; -1.42)	-2.95 (-3.47; -2.44)
Sema 1.0 mg *minus* Control	-3.56 (-4.74; -2.38)	-4.20 (-4.91; -3.49)	-3.78 (-4.58; -2.98)	-6.33 (-6.99; -5.67)	-5.06 (-6.08; -4.04)	-3.55 (-4.32; -2.78)	-3.59 (-4.43; -2.75)	-3.88 (-4.70; -3.07)	-4.27 (-4.78; -3.75)
*Superiority concluded if the upper limit of the 95 % CI of the diff between Test and Control below 0 kg									

In conclusion, the studies demonstrated clinically meaningful and sustained reduction in HbA_{1c} from baseline when semaglutide was used either as monotherapy in treatment initiation in patients who were either treatment-naïve and as add-on therapy for treatment optimisation in patients inadequately controlled with OADs and/or insulin. The improvement in the glycaemic control was accompanied by a significant reduction in the body weight.

D ASSESSMENT OF CLINICAL SAFETY

The clinical safety of semaglutide was based on safety data from a total of 9292 patients who received at least one dose of study treatment: 2497 subjects in the semaglutide 0.5 mg arm, 2896 subjects in the semaglutide 1 mg arm, 3899 subjects in the comparators arm. There were 3286 subjects (823 subjects in semaglutide 0.5 mg arm, 819 subjects in semaglutide 1 mg arm and 1644 subjects in the placebo arm) from Study 3744 were exposed to treatment for a mean period of 1.8 years.

Overview of safety profile – On-treatment

Trial No. (Treatment groups)	**3623 (Sema 0.5 Sema 1.0 Placebo)**	**3626 (Sema 0.5 Sema 1.0 Sita)**	**3624 (Sema 1.0 Exe ER 2.0)**	**3625 (Sema 0.5 Sema 1.0 IGlar)**	**3627 (Sema 0.5 Sema 1.0 Placebo)**	**4216 (Sema 0.5 Sema 1.0 Dula 0.75 Dula 1.5)**	**4091 (Sema 0.5 Sema 1.0 OAD)**	**4092 (Sema 0.5 Sema 1.0 Sita)**	**3744 (Sema 0.5 Sema 1.0 Placebo 0.5 Placebo 1.0)**
Number of subjects	128 130 129	409 409 407	404 405	362 360 360	132 131 133	301 300 299 299	239 241 120	103 102 103	823 819 819 825
Any AEs, n (%)	82 (64.1) 73 (56.2) 69 (53.5)	306 (74.8) 292 (71.4) 292 (71.7)	303 (75.0) 309 (76.3)	253 (69.9) 264 (73.3) 235 (65.3)	91 (68.9) 84 (64.1) 77 (57.9)	204 (67.8) 207 (69.0) 186 (62.2) 221 (73.9)	206 (86.2) 212 (88.0) 86 (71.7)	77 (74.8) 73 (71.6) 68 (66.0)	732 (88.9) 722 (88.2) 730 (89.1) 723 (87.6)
Mild, n (%)	71 (55.5) 60 (46.2) 58 (45.0)	268 (65.5) 265 (64.8) 260 (63.9)	250 (61.9) 277 (68.4)	221 (61.0) 230 (63.9) 193 (53.6)	81 (61.4) 68 (51.9) 64 (48.1)	175 (58.1) 178 (59.3) 168 (56.2) 193 (64.5)	202 (84.5) 209 (86.7) 80 (66.7)	73 (70.9) 68 (66.7) 67 (65.0)	646 (78.5) 633 (77.3) 645 (78.8) 640 (77.6)
Moderate, n (%)	35 (27.3) 31 (23.8) 26 (20.2)	122 (29.8) 109 (26.7) 114 (28.0)	159 (39.4) 148 (36.5)	108 (29.8) 110 (30.6) 104 (28.9)	42 (31.8) 32 (24.4) 28 (21.1)	97 (32.2) 92 (30.7) 73 (24.4) 92 (30.8)	29 (12.1) 29 (12.0) 15 (12.5)	13 (12.6) 9 (8.8) 10 (9.7)	476 (57.8) 476 (58.1) 466 (56.9) 468 (56.7)
Severe, n (%)	9 (7.0) 8 (6.2) 4 (3.1)	26 (6.4) 21 (5.1) 21 (5.2)	41 (10.1) 30 (7.4)	27 (7.5) 20 (5.6) 10 (2.8)	5 (3.8) 10 (7.6) 6 (4.5)	20 (6.6) 20 (6.7) 16 (5.4) 19 (6.4)	10 (4.2) 3 (1.2) 2 (1.7)	2 (1.9) 1 (1.0) 2 (1.9)	185 (22.5) 185 (22.6) 186 (22.7) 180 (21.8)
Serious AEs, n (%)	7 (5.5) 7 (5.4) 5 (3.9)	30 (7.3) 30 (7.3) 29 (7.1)	38 (9.4) 24 (5.9)	22 (6.1) 17 (4.7) 18 (5.0)	8 (6.1) 12 (9.2) 9 (6.8)	17 (5.6) 23 (7.7) 24 (8.0) 22 (7.4)	19 (7.9) 12 (5.0) 8 (6.7)	6 (5.8) 2 (2.0) 2 (1.9)	264 (32.1) 240 (29.3) 297 (36.3) 277 (33.6)
Discontinuations due to AE	8 (6.3) 7 (5.4) 3 (2.3)	33 (8.1) 39 (9.5) 12 (2.9)	38 (9.4) 29 (7.2)	20 (5.5) 27 (7.5) 4 (1.1)	6 (4.5) 8 (6.1) 1 (0.8)	24 (8.0) 29 (9.7) 14 (4.7) 20 (6.7)	14 (5.9) 26 (10.8) 0 (0.0)	3 (2.9) 11 (10.8) 2 (1.9)	95 (11.5) 119 (14.5) 47 (5.7) 63 (7.6)
Deaths	0 (0) 0 (0) 0 (0)	2 (0.5) 1 (0.2) 3 (0.7)	2 (0.5) 0 (0)	4 (1.1) 0 (0) 2 (0.6)	0 (0) 0 (0) 0 (0)	0 (0) 1 (0.3) 2 (0.7) 2 (0.7)	1 (0.4) 0 (0.0) 1 (0.8)	0 (0) 0 (0) 0 (0)	24 (2.9) 23 (2.8) 25 (3.1) 19 (2.3)

AEs were reported in higher proportions of subjects with the semaglutide than with the comparator products. The most commonly reported AEs with semaglutide (0.5 mg and 1 mg) were gastrointestinal (GI) disorders including nausea, diarrhoea, vomiting, constipation and dyspepsia which are known common side effects of GLP-1 analogues. The long-term AE

profile of semaglutide observed in the Study 3744 was generally consistent with AE profiles observed in the other Phase 3 studies.

Gastro-intestinal adverse events by system organ class, high level group term and preferred term – On-treatment

Trial No. (Treatment groups)	**3623 (Sema 0.5 Sema 1.0 Placebo)**	**3626 (Sema 0.5 Sema 1.0 Sita)**	**3624 (Sema 1.0 Exe ER 2.0)**	**3625 (Sema 0.5 Sema 1.0 IGlar)**	**3627 (Sema 0.5 Sema 1.0 Placebo)**	**4216 (Sema 0.5 Sema 1.0 Dula 0.75 Dula 1.5)**	**4091 (Sema 0.5 Sema 1.0 OAD)**	**4092 (Sema 0.5 Sema 1.0 Sita)**	**3744 (Sema 0.5 Sema 1.0 Placebo 0.5 Placebo 1.0)**
GI Disorder	49 (38.3) 50 (38.5) 19 (14.7)	178 (43.5) 163 (39.9) 96 (23.6)	169 (41.8) 135 (33.3)	149 (41.2) 156 (43.3) 54 (15.0)	36 (27.3) 45 (34.4) 21 (15.8)	129 (42.9) 133 (44.3) 100 (33.4) 143 (47.8)	129 (54.0) 130 (53.9) 24 (20.0)	39 (37.9) 42 (41.2) 17 (16.5)	415 (50.4) 426 (52.0) 282 (34.4) 282 (34.2)
Gastrointestinal signs and symptoms	39 (30.5) 38 (29.2) 16 (12.4)	128 (31.3) 121 (29.6) 60 (14.7)	144 (35.6) 95 (23.5)	112 (30.9) 125 (34.7) 29 (8.1)	26 (19.7) 35 (26.7) 14 (10.5)	95 (31.6) 101 (33.7) 75 (25.1) 107 (35.8)	66 (27.6) 85 (35.3) 6 (5.0)	24 (23.3) 28 (27.5) 3 (2.9)	282 (34.3) 320 (39.1) 177 (21.6) 152 (18.4)
Nausea	26 (20.3) 31 (23.8) 10 (7.8)	73 (17.8) 72 (17.6) 30 (7.4)	90 (22.3) 48 (11.9)	77 (21.3) 80 (22.2) 13 (3.6)	15 (11.4) 22 (16.8) 6 (4.5)	68 (22.6) 63 (21.0) 39 (13.0) 60 (20.1)	29 (12.1) 46 (19.1) 1 (0.8)	11 (10.7) 13 (12.7) 0 (0.0)	142 (17.3) 178 (21.7) 61 (7.4) 66 (8.0)
Vomiting	5 (3.9) 9 (6.9) 2 (1.6)	33 (8.1) 41 (10.0) 11 (2.7)	29 (7.2) 25 (6.2)	24 (6.6) 37 (10.3) 11 (3.1)	8 (6.1) 15 (11.5) 4 (3.0)	31 (10.3) 31 (10.3) 12 (4.0) 29 (9.7)	13 (5.4) 14 (5.8) 2 (1.7)	4 (3.9) 2 (2.0) 1 (1.0)	84 (10.2) 119 (14.5) 44 (5.4) 33 (4.0)
Diarrhoea	16 (12.5) 14 (10.8) 3 (2.3)	54 (13.2) 53 (13.0) 29 (7.1)	46 (11.4) 34 (8.4)	59 (16.3) 69 (19.2) 16 (4.4)	6 (4.5) 9 (6.9) 2 (1.5)	43 (14.3) 41 (13.7) 23 (7.7) 53 (17.7)	24 (10.0) 38 (15.8) 8 (6.7)	7 (6.8) 9 (8.8) 2 (1.9)	145 (17.6) 145 (17.7) 94 (11.5) 83 (10.1)
Constipation	8 (6.3) 5 (3.8) 1 (0.8)	18 (4.4) 23 (5.6) 8 (2.0)	26 (6.4) 21 (5.2)	11 (3.0) 11 (3.1) 2 (0.6)	5 (3.8) 3 (2.3) 3 (2.3)	16 (5.3) 14 (4.7) 10 (3.3) 15 (5.0)	45 (18.8) 36 (14.9) 5 (4.2)	15 (14.6) 12 (11.8) 4 (3.9)	46 (5.6) 78 (9.5) 33 (4.0) 36 (4.4)
Dyspepsia	7 (5.5) 5 (3.8) 3 (2.3)	26 (6.4) 20 (4.9) 9 (2.2)	27 (6.7) 19 (4.7)	12 (3.3) 24 (6.7) 2 (0.6)	2 (1.5) 2 (1.5) 2 (1.5)	10 (3.3) 14 (4.7) 14 (4.7) 12 (4.0)	7 (2.9) 11 (4.6) 1 (0.8)	2 (1.9) 3 (2.9) 0 (0.0)	51 (6.2) 63 (7.7) 20 (2.4) 18 (2.2)
Abdominal discomfort	4 (3.1) 4 (3.1) 2 (1.6)	13 (3.2) 7 (1.7) 1 (0.2)	18 (4.5) 14 (3.5)	8 (2.2) 6 (1.7) 4 (1.1)	4 (3.0) 2 (1.5) 1 (0.8)	11 (3.7) 9 (3.0) 10 (3.3) 11 (3.7)	1 (0.4) 0 (0.0) 0 (0.0)	4 (3.9) 7 (6.9) 0 (0.0)	35 (4.3) 38 (4.6) 22 (2.7) 13 (1.6)
Abdominal pain upper	3 (2.3) 3 (2.3) 3 (2.3)	16 (3.9) 12 (2.9) 10 (2.5)	16 (4.0) 15 (3.7)	3 (0.8) 10 (2.8) 1 (0.3)	2 (1.5) 2 (1.5) 3 (2.3)	4 (1.3) 9 (3.0) 6 (2.0) 10 (3.3)	10 (4.2) 7 (2.9) 1 (0.8)	4 (3.9) 3 (2.9) 2 (1.9)	33 (4.0) 42 (5.1) 20 (2.4) 18 (2.2)
Abdominal distension	0 (0.0) 1 (0.8) 1 (0.8)	11 (2.7) 12 (2.9) 5 (1.2)	11 (2.7) 7 (1.7)	14 (3.9) 15 (4.2) 1 (0.3)	0 (0.0) 1 (0.8) 0 (0.0)	6 (2.0) 10 (3.3) 7 (2.3) 13 (4.3)	6 (2.5) 11 (4.6) 0 (0.0)	1 (1.0) 1 (1.0) 0 (0.0)	17 (2.1) 24 (2.9) 14 (1.7) 8 (1.0)
Abdominal pain	5 (3.9) 3 (2.3) 1 (0.8)	13 (3.2) 9 (2.2) 4 (1.0)	11 (2.7) 11 (2.7)	16 (4.4) 10 (2.8) 4 (1.1)	2 (1.5) 2 (1.5) 3 (2.3)	7 (2.3) 9 (3.0) 9 (3.0) 12 (4.0)	1 (0.4) 2 (0.8) 1 (0.8)	0 (0.0) 2 (2.0) 0 (0.0)	45 (5.5) 34 (4.2) 32 (3.9) 32 (3.9)
Eructation	5 (3.9) 2 (1.5) 0 (0.0)	3 (0.7) 7 (1.7) 2 (0.5)	15 (3.7) 1 (0.2)	5 (1.4) 4 (1.1) 0 (0.0)	2 (1.5) 1 (0.8) 0 (0.0)	3 (1.0) 13 (4.3) 3 (1.0) 5 (1.7)	1 (0.4) 1 (0.4) 0 (0.0)	1 (1.0) 1 (1.0) 0 (0.0)	10 (1.2) 19 (2.3) 0 (0.0) 0 (0.0)
Flatulence	1 (0.8) 0 (0.0) 2 (1.6)	3 (0.7) 6 (1.5) 3 (0.7)	6 (1.5) 3 (0.7)	2 (0.6) 9 (2.5) 0 (0.0)	2 (1.5) 1 (0.8) 0 (0.0)	7 (2.3) 8 (2.7) 5 (1.7) 4 (1.3)	1 (0.4) 0 (0.0) 0 (0.0)	0 (0.0) 0 (0.0) 0 (0.0)	13 (1.6) 26 (3.2) 10 (1.2) 5 (0.6)
Gastritis	1 (0.8) 1 (0.8) 1 (0.8)	12 (2.9) 4 (1.0) 2 (0.5)	7 (1.7) 1 (0.2)	3 (0.8) 3 (0.8) 1 (0.3)	0 (0.0) 1 (0.8) 1 (0.8)	4 (1.3) 1 (0.3) 2 (0.7)	6 (2.5) 3 (1.2) 1 (0.8)	0 (0.0) 2 (2.0) 1 (1.0)	17 (2.1) 22 (2.7) 10 (1.2)

						2 (0.7)			10 (1.2)
Gastro-oesophageal reflux	3 (2.3) 1 (0.8) 0 (0.0)	7 (1.7) 9 (2.2) 1 (0.2)	7 (1.7) 9 (2.2)	4 (1.1) 19 (5.3) 3 (0.8)	2 (1.5) 3 (2.3) 0 (0.0)	5 (1.7) 6 (2.0) 7 (2.3) 13 (4.3)	5 (2.1) 8 (3.3) 1 (0.8)	1 (1.0) 2 (2.0) 2 (1.9)	30 (3.6) 35 (4.3) 10 (1.2) 13 (1.6)

The proportion of subjects who experienced severe or blood glucose (BG) confirmed symptomatic hypoglycaemia was similar between semaglutide and comparators when semaglutide was used as monotherapy or as add-on to OADs other than SU. An increase incidence was observed when semaglutide was added on to existing therapy with SU or insulin compared to monotherapy and as add-on to non-SU OADs. Nonetheless, the risk of severe hypoglycaemia remained low and could be managed with reduction in dose of SU or insulin when semaglutide was added on to existing therapy.

Episodes of severe or blood glucose confirmed symptomatic hypoglycaemia by baseline background medication

	Sema 0.5		**Sema 1.0**		**Comparators**	
	Phase 3 Pool % (n/N)	**CVOT % (n/N)**	**Phase 3 Pool % (n/N)**	**CVOT % (n/N)**	**Phase 3 Pool % (n/N)**	**CVOT % (n/N)**
Severe or Blood Glucose Confirmed Symptomatic Hypoglycaemia						
Monotherapy	0 (0/299)	--	0.4 (1/300)	--	0 (0/237)	--
Add-on to SU	6.5 (16/255)	13.9 (32/230)	10.4 (45/436)	15.5 (34/219)	14.0 (62/435)	11.3 (49/434)
Add-on to insulin	8.3 (11/132))	29.1 (104/358)	10.7 (14/131))	29.6 (102/345)	5.3 (7/133)	31.0 (210/678)
Add-on to other OADs	1.3 (9/687)	7.6 (9/118)	1.2 (11/910)	1.6 (2/124)	1.1 (10/851)	4.3 (11/256)
ADA Severe Hypoglycaemia						
Monotherapy	0 (0/299)	--	0 (0/300)	--	0 (0/237)	--
Add-on to SU	0.8 (2/255)	1.3 (3/230)	1.2 (5/436)	1.4 (3/219)	0.9 (4/435)	0.5 (2/434)
Add-on to insulin	0 (0/132)	2.2 (8/358)	1.5 (2/131)	0.9 (3/345)	0 (0/133)	2.1 (14/687)
Add-on to other OADs	0 (0/687)	0.8 (1/118)	0.1 (1/910)	0 (0/124)	0.3 (3/851)	0.4 (1/256)

Cardiovascular safety of semaglutide was investigated in Study 3744 where cardiovascular (CV) death, non-fatal myocardial infarction (MI) and non-fatal stroke events reported in the study were adjudicated by an independent committee. The composite of these adjudicated events comprised the major adverse cardiovascular event (MACE). A total of 254 MACEs were reported during the trial. The proportion of subjects with first MACE was lower with semaglutide than with placebo (6.6 % vs 8.9 %). Semaglutide did not result in an increase in cardiovascular risk as compared to placebo as the upper limit of the two-sided 95% CI of the hazard ratio ($HR_{sema:placebo}$ = 0.74, 95%CI: 0.53 – 0.95) were below 1.0.

Diabetic retinopathy complications consisting of need for retinal photocoagulation or treatment with intravitreal agents, or vitreous haemorrhage events, or diabetes-related blindness (visual loss at time of evaluation: Snellen visual acuity of 20/200 or less) were also adjudicated in the study. A total of 98 events of diabetic retinopathy complications were observed in 79 subjects with the proportion of the subjects significantly higher in the semaglutide arm compared to the placebo arm (semaglutide vs Placebo: 3.0 % vs 1.8 %; HR of 1.76, 95%CI: 1.11; 2.78; p-value = 0.0159). There were 6 patients who met the criteria for events of diabetes-related blindness - 5 with semaglutide and 1 with placebo. All 5 semaglutide-treated patients who developed event of diabetes-related blindness had pre-existing proliferative diabetic retinopathy and other eye diseases (eg, cataract), and all had received treatment with laser therapy and/or intravitreal agents prior to entering the trial. Further post-study information available for 3 of the 5

semaglutide-treated patients revealed that none of these 3 subjects continued to fulfill the criteria for diabetes-related blindness (2 patients 18 months post event, and 1 patient 21 days post event), indicating the visual loss was transient.

Diabetic retinopathy complications were more commonly reported in the subgroup of patients with pre-existing diabetic retinopathy at baseline or co-use of insulin indicating that patients with these baseline characteristics may be at higher risk of developing retinopathy complications with semaglutide. There was no increase in risk of diabetic retinopathy complications with semaglutide vs placebo in patients without pre-existing diabetic retinopathy (semaglutide vs placebo: 10% vs 13.8%).

Overall, the safety profile of semaglutide is generally consistent with those reported for other drugs in the GLP-1 class with gastrointestinal adverse events, such as nausea, diarrhoea, vomiting, constipation, dyspepsia, being the most commonly reported AEs. Results from the cardiovascular safety study showed that treatment with semaglutide did not result in an increase in cardiovascular outcomes. Nonetheless, an increase in the risk of retinopathy complications was observed with semaglutide. Information on risk mitigation including identifying patients who may be predisposed to this risk and monitored during the course of therapy for early intervention has been adequately reflected in the label.

E ASSESSMENT OF BENEFIT-RISK PROFILE

Semaglutide demonstrated significant reductions in the baseline HbA_{1c} in T2DM patients when used either as monotherapy or in combination with other anti-diabetic treatments. The improvement from baseline HbA_{1c} was clinically relevant and was not observed to be accompanied by any significant increased risk of severe hypoglycaemia. The magnitude of reduction in HbA_{1c} was notably larger than existing therapies suggesting that semaglutide could be an alternative for patients who required more intensive control on their condition.

In-addition to the glycaemic control, semaglutide also showed a reduction in body weight which may be a potential advantage in over-weight T2DM patients. In this regard, semaglutide may provide an alternative for patients who have concern with body weight increase with existing therapies such as SU and insulin.

The safety profile of semaglutide is generally consistent with those reported for other drugs in the GLP-1 class. Nausea, diarrhoea, vomiting and constipation were frequent adverse events with semaglutide. The majority of these events were mild to moderate in intensity and generally resolved within a short duration. Most of the events occurred during the treatment initiation and the incidences decreased with continued treatment due to development of tolerance.

Risk of diabetic retinopathy related complications was higher in the semaglutide group especially in patients with history of retinopathy or baseline insulin treatment. For these patients, appropriate risk mitigation and close monitoring are recommended to enable early identification and prompt treatment of the complication.

Overall, the benefit-risk was considered favourable in view of the benefits are demonstrated and risk of treatment could be managed.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the approval of semaglutide for treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise was granted on 21 Apr 2021.

APPROVED PACKAGE INSERT AT REGISTRATION

Ozempic®
0.25 mg, 0.5 mg/dose
Solution for injection in pre-filled pen

Qualitative and quantitative composition
One ml of solution contains 1.34 mg of semaglutide*. One pre-filled pen contains 2 mg semaglutide* in 1.5 ml solution.

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

For the full list of excipients, see *List of excipients.*

Pharmaceutical form
Solution for injection.
Clear and colourless or almost colourless, isotonic solution; pH=7.4.

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

- as monotherapy when metformin is considered inappropriate due to intolerance or contraindications

- in addition to other medicinal products for the treatment of diabetes.

For study results with respect to combinations, effects on glycaemic control and cardiovascular events, and the populations studied, see *Special warnings and precautions for use, Interaction with other medicinal products and other forms of interaction* and *Pharmacodynamic properties.*

Posology and method of administration
Posology
The starting dose is 0.25 mg semaglutide once weekly. After 4 weeks the dose should be increased to 0.5 mg once weekly. After at least 4 weeks with a dose of 0.5 mg once weekly, the dose can be increased to 1 mg once weekly to further improve glycaemic control.

Semaglutide 0.25 mg is not a maintenance dose. Weekly doses higher than 1 mg are not recommended.

When Ozempic® is added to existing metformin and/or thiazolidinedione therapy, the current dose of metformin and/or thiazolidinedione can be continued unchanged.

When Ozempic® is added to existing therapy of sulfonylurea or insulin, a reduction in the dose of sulfonylurea or insulin should be considered to reduce the risk of hypoglycaemia (see *Special warnings and precautions for use* and *Undesirable effects*).

Self-monitoring of blood glucose is not needed in order to adjust the dose of Ozempic®. Blood glucose self-monitoring is necessary to adjust the dose of sulfonylurea and insulin, particularly when Ozempic® is started and insulin is reduced. A stepwise approach to insulin reduction is recommended

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.

Special populations

Elderly

No dose adjustment is required based on age. Therapeutic experience in patients ≥75 years of age is limited (see *Pharmacokinetic properties*).

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 end-stage renal disease (see *Pharmacokinetic properties*).

Hepatic impairment

No dose adjustment is required for patients with hepatic impairment. Experience with the use of semaglutide in patients with severe hepatic impairment is limited. Caution should be exercised when treating these patients with semaglutide (see *Pharmacokinetic properties*).

Paediatric population

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

Method of administration

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

Ozempic® is to be injected subcutaneously in the abdomen, in the thigh or in the upper arm. The injection site can be changed without dose adjustment. Ozempic® 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 2 days (>48 hours).

For further information on administration, see *Special precautions for disposal and other handling.*

Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in *List of excipients.*

Special warnings and precautions for use

Semaglutide should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. Semaglutide is not a substitute for insulin.

There is no experience in patients with congestive heart failure NYHA class IV and semaglutide is therefore not recommended in these patients.

Gastrointestinal effects

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 could cause a deterioration of renal function (see *Undesirable effects*).

Acute pancreatitis

Acute pancreatitis has been observed with the use of GLP-1 receptor agonists. Patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, semaglutide should be discontinued; if confirmed, semaglutide should not be restarted. Caution should be exercised in patients with a history of pancreatitis.

Hypoglycaemia

Patients treated with semaglutide in combination with a sulfonylurea or insulin may have an increased risk of hypoglycaemia. The risk of hypoglycaemia can be lowered by reducing the dose of sulfonylurea or insulin when initiating treatment with semaglutide (see *Undesirable effects*).

Diabetic retinopathy
In the 2-year cardiovascular outcomes trial involving patients with type 2 diabetes and high cardiovascular risk, an increase of developing diabetic retinopathy complications has been observed (see *Undesirable effects*). Caution should be exercised when using semaglutide in patients with history diabetic retinopathy or treated with insulin. The effect of long-term glycaemic control with semaglutide on diabetic retinopathy complications has not been studied. These patients should be monitored closely and treated according to clinical guidelines. Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy, but other mechanisms cannot be excluded.

Sodium content
This medicine contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium-free'.

Interaction with other medicinal products and other forms of interaction
Semaglutide delays gastric emptying and has the potential to impact the rate of absorption of concomitantly administered oral medicinal products. 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 dose adjustment of paracetamol is necessary when administered with semaglutide.

Oral contraceptives
Semaglutide is not anticipated to decrease the effect 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 the 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 (INR) 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 INR is recommended.

Fertility, pregnancy and lactation
Women of childbearing potential
Women of childbearing potential are recommended to use contraception when treated with semaglutide.

Pregnancy

Studies in animals have shown reproductive toxicity (see *Preclinical safety data*). 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 *Pharmacokinetic properties*).

Breast-feeding
In lactating rats, semaglutide was excreted in milk. As a risk to a breast-fed child cannot be excluded, semaglutide should not be used during breast-feeding.

Fertility
The effect of semaglutide on fertility in humans is unknown. Semaglutide did not affect male fertility in rats. In female rats, an increase in oestrous length and a small reduction in number of ovulations were observed at doses associated with maternal body weight loss (see *Preclinical safety data*).

Effects on ability to drive and use machines
Semaglutide has no or negligible influence on the ability to drive or use machines. When it is used in combination with a sulfonylurea or insulin, patients should be advised to take precautions to avoid hypoglycaemia while driving and using machines (see *Special warnings and precautions for use*).

Undesirable effects
Summary of safety profile
In 8 phase 3a trials 4,792 patients were exposed to semaglutide. The most frequently reported adverse reactions in clinical trials were gastrointestinal disorders, including nausea (very common), diarrhoea (very common), vomiting (common) and constipation (common). In general, these reactions were mild or moderate in severity and of short duration (except for constipation).

Tabulated list of adverse reactions
Table 1 lists adverse reactions identified in all phase 3a trials in patients with type 2 diabetes mellitus (further described in *Pharmacodynamic properties*). The frequencies of the adverse reactions are based on a pool of the phase 3a trials excluding the cardiovascular outcomes trial (see text below the table for additional details).

The reactions are listed below by system organ class and absolute frequency. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1 Adverse reactions from long-term controlled phase 3a trials including the cardiovascular outcomes trial

MedDRA system organ class	**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)**
Immune system disorders			Hypersensitivity[c]	Anaphylactic reaction
Metabolism and nutrition disorders	Hypoglycaemia[a] when used with insulin or sulfonylurea	Hypoglycaemia[a] when used with other OADs Decreased appetite		
Nervous system disorders		Dizziness	Dysgeusia	
Eye disorders		Diabetic retinopathy complications[b]		

Cardiac disorders			Increased heart rate	
Gastrointestinal disorders	Nausea Diarrhoea	Vomiting Abdominal pain Abdominal distension Constipation Dyspepsia Gastritis Gastro-oesophageal reflux disease Eructation Flatulence	Acute pancreatitis	
Hepatobiliary disorders		Cholelithiasis		
General disorders and administration site conditions		Fatigue	Injection site reactions	
Investigations		Increased lipase Increased amylase Weight decreased		

[a)] Hypoglycaemia defined as severe (requiring the assistance of another person) or symptomatic in combination with a blood glucose <3.1 mmol/l
[b)] Diabetic retinopathy complications is a composite of: retinal photocoagulation, treatment with intravitreal agents, vitreous haemorrhage, diabetes-related blindness (uncommon). Frequency based on cardiovascular outcomes trial.
[c)] Grouped term covering also adverse events related to hypersensitivity such as rash and urticaria.

2-year cardiovascular outcomes and safety trial
In cardiovascular high risk population the adverse reaction profile was similar to that seen in the other phase 3a trials (described in *Pharmacodynamic properties*).

Description of selected adverse reactions
Hypoglycaemia
No episodes of severe hypoglycaemia were observed when semaglutide was used as monotherapy. Severe hypoglycaemia was primarily observed when semaglutide was used with a sulfonylurea (1.2% of subjects, 0.03 events/patient year) or insulin (1.5% of subjects, 0.02 events/patient year). Few episodes (0.1% of subjects, 0.001 events/patient year) were observed with semaglutide in combination with oral antidiabetics other than sulfonylureas.

Gastrointestinal adverse reactions
Nausea occurred in 17.0% and 19.9% of patients when treated with semaglutide 0.5 mg and 1 mg, respectively, diarrhoea in 12.2% and 13.3%, vomiting in 6.4% and 8.4% and constipation in 6.9% and 6.2%. Most events were mild to moderate in severity and of short duration (except constipation). The events led to treatment discontinuation in 3.9% and 5% of patients. The events were most frequently reported during the first months on treatment.
Patients with low body weight may experience more gastrointestinal side effects when treated with semaglutide.

Acute pancreatitis
The frequency of adjudication-confirmed acute pancreatitis reported in phase 3a clinical trials was 0.3% for semaglutide and 0.2% for the comparator, respectively. In the 2-year cardiovascular outcomes trial the frequency of acute pancreatitis confirmed by adjudication was 0.5% for semaglutide and 0.6% for placebo (see Special warnings and precautions for use).

Diabetic retinopathy complications
A 2-year clinical trial investigated 3,297 patients with type 2 diabetes, with high cardiovascular risk, long duration of diabetes and poorly controlled blood glucose. In this trial, adjudicated events of diabetic retinopathy complications occurred in more patients treated with semaglutide (3.0%) compared to placebo (1.8%). This was observed in insulin-treated patients with known diabetic retinopathy. The treatment difference appeared early and persisted throughout the trial. Systematic evaluation of diabetic retinopathy complication was only performed in the cardiovascular outcomes trial. In clinical trials up to 1 year involving 4,807 patients with type 2 diabetes, adverse events related to diabetic retinopathy were reported in similar proportions of subjects treated with semaglutide (1.7%) and comparators (2.0%).

Discontinuation due to an adverse event
The incidence of discontinuation of treatment due to adverse events was 6.1% and 8.7% for patients treated with semaglutide 0.5 mg and 1 mg, respectively, vs. 1.5% for placebo. The most frequent adverse events leading to discontinuation were gastrointestinal.

Injection site reactions
Injection site reactions (e.g. injection site rash, erythema) have been reported by 0.6% and 0.5% of patients receiving semaglutide 0.5 mg and 1 mg, respectively. These reactions have usually been mild.

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 tested positive for anti-semaglutide antibodies at any time point post-baseline was low (1-2%) and no patients had anti-semaglutide neutralising antibodies or anti-semaglutide antibodies with endogenous GLP-1 neutralising effect at end-of-trial.

Heart rate increase
Increased heart rate has been observed with GLP-1 receptor agonists. In the phase 3a trials, mean increases of 1 to 6 beats per minute (bpm) from a baseline of 72 to 76 bpm were observed in subjects treated with Ozempic®. In a long-term trial in subjects with cardiovascular risk factors, 16% of Ozempic®-treated subjects had an increase in heart rate of >10 bpm compared to 11% of subjects on placebo after 2 years of treatment.

Overdose
Overdoses of up to 4 mg in a single dose, and up to 4 mg in a week have been reported in clinical trials. The most commonly reported adverse reaction was nausea. All patients recovered without complications.

There is no specific antidote for overdose with semaglutide. In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms. A prolonged period of observation and treatment for these symptoms may be necessary, taking into account the long half-life of semaglutide of approximately 1 week (see *Pharmacokinetic properties*).

Pharmacodynamic properties
Pharmacotherapeutic group: Drugs used in diabetes, Glucagon-like peptide-1 (GLP-1) analogues, ATC code: A10BJ06

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

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

Semaglutide reduces blood glucose in a glucose dependent manner by stimulating insulin secretion and lowering glucagon secretion when blood glucose is high. The mechanism of blood glucose lowering also involves a minor delay in gastric emptying in the early postprandial phase. During hypoglycaemia, semaglutide diminishes insulin secretion and does not impair glucagon secretion.

Semaglutide reduces body weight and body fat mass through lowered energy intake, involving an overall reduced appetite. In addition, semaglutide reduces the preference for high fat foods.

GLP-1 receptors are also expressed in the heart, vasculature, immune system and kidneys.
Semaglutide had a beneficial effect on plasma lipids, lowered systolic blood pressure and reduced inflammation in clinical studies. In animal studies, semaglutide attenuates the development of atherosclerosis by preventing aortic plaque progression and reducing inflammation in the plaque.

Pharmacodynamic effects
All pharmacodynamic evaluations were performed after 12 weeks of treatment (including dose escalation) at steady state with semaglutide 1 mg once weekly.

Fasting and postprandial glucose
Semaglutide reduces fasting and postprandial glucose concentrations. In patients with type 2 diabetes, treatment with semaglutide 1 mg resulted in reductions in glucose in terms of absolute change from baseline (mmol/l) and relative reduction compared to placebo (%) for fasting glucose (1.6 mmol/l; 22% reduction), 2 hour postprandial glucose (4.1 mmol/l; 37% reduction), mean 24 hour glucose concentration (1.7 mmol/l; 22% reduction) and postprandial glucose excursions over 3 meals (0.6–1.1 mmol/l) compared with placebo. Semaglutide lowered fasting glucose after the first dose.

Beta-cell function and insulin secretion
Semaglutide improves beta-cell function. Compared to placebo, semaglutide improved first- and second-phase insulin response with a 3- and 2-fold increase, respectively, and increased maximal beta-cell secretory capacity in patients with type 2 diabetes. In addition, semaglutide treatment increased fasting insulin concentrations compared to placebo.

Glucagon secretion
Semaglutide lowers the fasting and postprandial glucagon concentrations. In patients with type 2 diabetes, semaglutide resulted in the following relative reductions in glucagon compared to placebo: fasting glucagon (8–21%), postprandial glucagon response (14–15%) and mean 24 hour glucagon concentration (12%).

Glucose dependent insulin and glucagon secretion
Semaglutide lowered high blood glucose concentrations by stimulating insulin secretion and lowering glucagon secretion in a glucose dependent manner. With semaglutide, the insulin secretion rate in patients with type 2 diabetes was comparable to that of healthy subjects.

During induced hypoglycaemia, semaglutide compared to placebo did not alter the counter regulatory responses of increased glucagon and did not impair the decrease of C-peptide in patients with type 2 diabetes.

Gastric emptying
Semaglutide caused a minor delay of early postprandial gastric emptying, thereby reducing the rate at which glucose appears in the circulation postprandially.

Appetite, energy intake and food choice

Semaglutide compared to placebo lowered the energy intake of 3 consecutive *ad libitum* meals by 18–35%. This was supported by a semaglutide-induced suppression of appetite in the fasting state as well as postprandially, improved control of eating, less food cravings and a relative lower preference for high fat food.

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

Cardiac electrophysiology (QTc)
The effect of semaglutide on cardiac repolarization was tested in a thorough QTc trial. Semaglutide did not prolong QTc intervals at supra-therapeutic dose levels (up to 1.5 mg at steady state).

Clinical efficacy and safety
Both improvement of glycaemic control and reduction of cardiovascular morbidity and mortality are an integral part of the treatment of type 2 diabetes.

The efficacy and safety of Ozempic® 0.5 mg and 1 mg once weekly were evaluated in six randomised controlled phase 3a trials that included 7,215 patients with type 2 diabetes mellitus (4,107 treated with semaglutide). Five trials (SUSTAIN 1–5) had the glycaemic efficacy assessment as the primary objective, while one trial (SUSTAIN 6) had cardiovascular outcome as the primary objective.

An additional trial including 1,201 patients was conducted to compare the efficacy and safety of Ozempic® 0.5 mg and 1 mg once weekly to dulaglutide 0.75 mg and 1.5 mg once weekly, respectively.

Treatment with semaglutide demonstrated sustained, statistically superior and clinically meaningful reductions in HbA_{1c} and body weight for up to 2 years compared to placebo and active control treatment (sitagliptin, insulin glargine, exenatide ER and dulaglutide).

The efficacy of semaglutide was not impacted by age, gender, race, ethnicity, BMI at baseline, body weight (kg) at baseline, diabetes duration and level of renal function impairment.

SUSTAIN 1 – Monotherapy
In a 30-week double-blind placebo-controlled trial, 388 patients inadequately controlled with diet and exercise, were randomised to Ozempic® 0.5 mg or Ozempic® 1 mg once weekly or placebo.

Table 2 SUSTAIN 1: Results at week 30

	Semaglutide 0.5 mg	**Semaglutide 1 mg**	**Placebo**
Intent-to-Treat (ITT) Population (N)	128	130	129
HbA_{1c} (%)			
Baseline (mean)	8.1	8.1	8.0
Change from baseline at week 30	-1.5	-1.6	0
Difference from placebo [95% CI]	-1.4 [-1.7, -1.1][a]	-1.5 [-1.8, -1.2][a]	-
Patients (%) achieving HbA_{1c} <7%	74	72	25
FPG (mmol/l)			
Baseline (mean)	9.7	9.9	9.7
Change from baseline at week 30	-2.5	-2.3	-0.6
Body weight (kg)			
Baseline (mean)	89.8	96.9	89.1
Change from baseline at week 30	-3.7	-4.5	-1.0
Difference from placebo [95% CI]	-2.7 [-3.9, -1.6][a]	-3.6 [-4.7, -2.4][a]	-

[a]p <0.0001 (2-sided) for superiority

SUSTAIN 2 – Ozempic® vs. sitagliptin both in combination with 1–2 oral antidiabetic drugs (metformin and/or thiazolidinediones)
In a 56-week active-controlled double-blind trial, 1,231 patients were randomised to Ozempic® 0.5 mg once weekly, Ozempic® 1 mg once weekly or sitagliptin 100 mg once daily, all in combination with metformin (94%) and/or thiazolidinediones (6%).

Table 3 SUSTAIN 2: Results at week 56

	Semaglutide 0.5 mg	**Semaglutide 1 mg**	**Sitagliptin 100 mg**
Intent-to-Treat (ITT) Population (N)	409	409	407
HbA_{1c} (%)			
Baseline (mean)	8.0	8.0	8.2
Change from baseline at week 56	-1.3	-1.6	-0.5
Difference from sitagliptin [95% CI]	-0.8 [-0.9, -0.6][a]	-1.1 [-1.2, -0.9][a]	-
Patients (%) achieving HbA_{1c} <7%	69	78	36
FPG (mmol/l)			
Baseline (mean)	9.3	9.3	9.6
Change from baseline at week 56	-2.1	-2.6	-1.1
Body weight (kg)			
Baseline (mean)	89.9	89.2	89.3
Change from baseline at week 56	-4.3	-6.1	-1.9
Difference from sitagliptin [95% CI]	-2.3 [-3.1, -1.6][a]	-4.2 [-4.9, -3.5][a]	-

[a]p <0.0001 (2-sided) for superiority

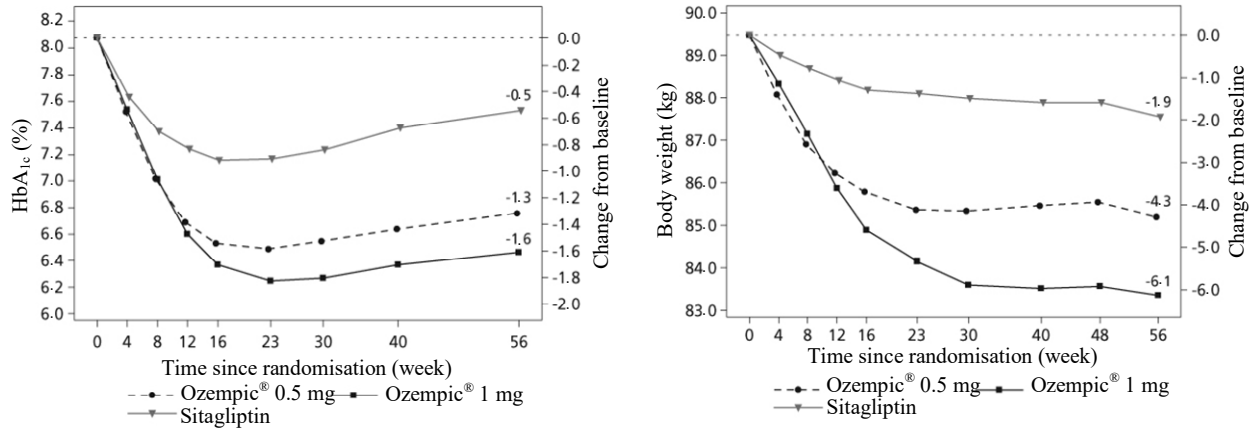


Figure 1 Mean change in HbA_{1c} (%) and body weight (kg) from baseline to week 56

SUSTAIN 7 – Ozempic® vs. dulaglutide both in combination with metformin
In a 40-week, open-label trial, 1,201 patients on metformin were randomised 1:1:1:1 to once weekly Ozempic® 0.5 mg, dulaglutide 0.75 mg , Ozempic® 1 mg or dulaglutide 1.5 mg, respectively.
The trial compared 0.5 mg of Ozempic® to 0.75 mg of dulaglutide and 1 mg of Ozempic® to 1.5 mg of dulaglutide.

Gastrointestinal disorders were the most frequent adverse events, and occurred in similar proportion of patients receiving Ozempic® 0.5 mg (129 patients [43%]), Ozempic® 1 mg (133 [44%]), and dulaglutide 1.5 mg (143 [48%]); fewer patients had gastrointestinal disorders with dulaglutide 0.75 mg (100 [33%]).
At week 40, the increase in pulse rate for Ozempic® (0.5 mg and 1 mg) and dulaglutide (0.75 mg and 1.5 mg) was 2.4, 4.0, and 1.6, 2.1, beats/min, respectively.

Table 4 SUSTAIN 7: Results at week 40

	Semaglutide 0.5 mg	Semaglutide 1 mg	Dulaglutide 0.75 mg	Dulaglutide 1.5 mg
Intent-to-Treat (ITT) Population (N)	301	300	299	299
HbA_{1c} (%)				
Baseline (mean)	8.3	8.2	8.2	8.2
Change from baseline at week 40	-1.5	-1.8	-1.1	-1.4
Difference from dulaglutide [95% CI]	-0.4[b] [-0.6, -0.2][a]	-0.4[c] [-0.6, -0.3][a]	-	-
Patients (%) achieving HbA_{1c} <7%	68	79	52	67
FPG (mmol/l)				
Baseline (mean)	9.8	9.8	9.7	9.6
Change from baseline at week 40	-2.2	-2.8	-1.9	-2.2
Body weight (kg)				
Baseline (mean)	96.4	95.5	95.6	93.4
Change from baseline at week 40	-4.6	-6.5	-2.3	-3.0
Difference from dulaglutide [95% CI]	-2.3[b] [-3.0, -1.5][a]	-3.6[c] [-4.3, -2.8][a]	-	-

[a]p <0.0001 (2-sided) for superiority
[b]Ozempic® 0.5 mg vs. dulaglutide 0.75 mg
[c]Ozempic® 1 mg vs. dulaglutide 1.5 mg

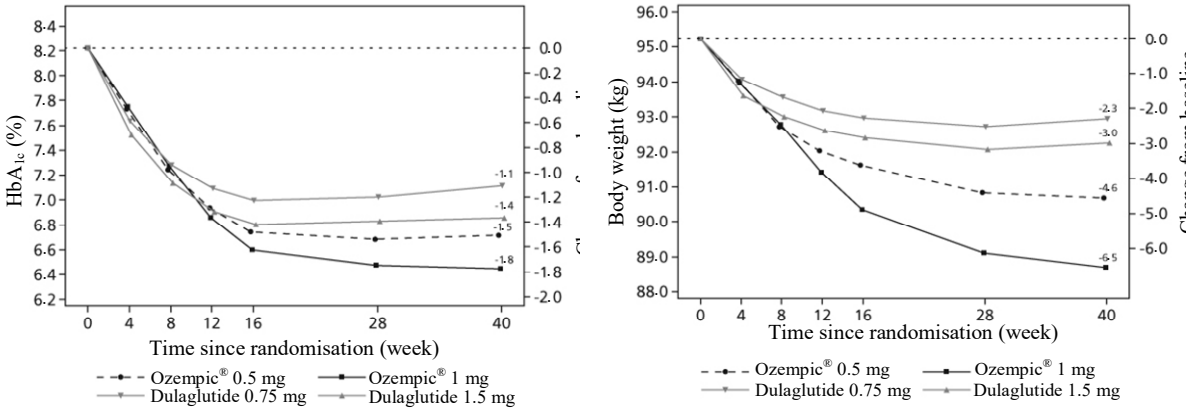


Figure 2 Mean change in HbA_{1c} (%) and body weight (kg) from baseline to week 40

SUSTAIN 3 – Ozempic® vs. exenatide ER both in combination with metformin or metformin with sulfonylurea

In a 56-week open-label trial, 813 patients on metformin alone (49%), metformin with sulfonylurea (45%) or other (6%) were randomised to Ozempic® 1 mg or exenatide ER 2 mg once weekly.

Table 5 SUSTAIN 3: Results at week 56

	Semaglutide 1 mg	Exenatide ER 2 mg
Intent-to-Treat (ITT) Population (N)	404	405
HbA_{1c} (%)		
Baseline (mean)	8.4	8.3
Change from baseline at week 56	-1.5	-0.9
Difference from exenatide [95% CI]	-0.6 [-0.8, -0.4][a]	-
Patients (%) achieving HbA_{1c} <7%	67	40
FPG (mmol/l)		
Baseline (mean)	10.6	10.4
Change from baseline at week 56	-2.8	-2.0

Body weight (kg)		
Baseline (mean)	96.2	95.4
Change from baseline at week 56	-5.6	-1.9
Difference from exenatide [95% CI]	-3.8 [-4.6, -3.0][a]	-

[a]p <0.0001 (2-sided) for superiority

SUSTAIN 4 – Ozempic® vs. insulin glargine both in combination with 1–2 oral antidiabetic drugs (metformin or metformin and sulfonylurea)
In a 30-week open-label comparator trial 1,089 patients were randomised to Ozempic® 0.5 mg once weekly, Ozempic® 1 mg once weekly, or insulin glargine once-daily on a background of metformin (48%) or metformin and sulfonylurea (51%).

Table 6 SUSTAIN 4: Results at week 30

	Semaglutide 0.5 mg	**Semaglutide 1 mg**	**Insulin Glargine**
Intent-to-Treat (ITT) Population (N)	362	360	360
HbA_{1c} (%)			
Baseline (mean)	8.1	8.2	8.1
Change from baseline at week 30	-1.2	-1.6	-0.8
Difference from insulin glargine [95% CI]	-0.4 [-0.5, -0.2][a]	-0.8 [-1.0, -0.7][a]	-
Patients (%) achieving HbA_{1c} <7%	57	73	38
FPG (mmol/l)			
Baseline (mean)	9.6	9.9	9.7
Change from baseline at week 30	-2.0	-2.7	-2.1
Body weight (kg)			
Baseline (mean)	93.7	94.0	92.6
Change from baseline at week 30	-3.5	-5.2	+1.2
Difference from insulin glargine [95% CI]	-4.6 [-5.3, -4.0][a]	-6.34 [-7.0, -5.7][a]	-

[a]p <0.0001 (2-sided) for superiority

SUSTAIN 5 – Ozempic® vs. placebo both in combination with basal insulin
In a 30-week double-blind placebo-controlled trial, 397 patients inadequately controlled with basal insulin with or without metformin were randomised to Ozempic® 0.5 mg once weekly, Ozempic® 1 mg once weekly or placebo.

Table 7 SUSTAIN 5: Results at week 30

	Semaglutide 0.5 mg	**Semaglutide 1 mg**	**Placebo**
Intent-to-Treat (ITT) Population (N)	132	131	133
HbA_{1c} (%)			
Baseline (mean)	8.4	8.3	8.4
Change from baseline at week 30	-1.4	-1.8	-0.1
Difference from placebo [95% CI]	-1.4 [-1.6, -1.1][a]	-1.8 [-2.0, -1.5][a]	-
Patients (%) achieving HbA_{1c} <7%	61	79	11
FPG (mmol/l)			
Baseline (mean)	8.9	8.5	8.6
Change from baseline at week 30	-1.6	-2.4	-0.5
Body weight (kg)			
Baseline (mean)	92.7	92.5	89.9
Change from baseline at week 30	-3.7	-6.4	-1.4
Difference from placebo [95% CI]	-2.3 [-3.3, -1.3][a]	-5.1 [-6.1, -4.0][a]	-

[a]p <0.0001 (2-sided) for superiority

Combination with sulfonylurea monotherapy
In SUSTAIN 6 (see subsection Cardiovascular disease) 123 patients were on sulfonylurea monotherapy at baseline. HbA_{1c} at baseline was 8.2%, 8.4% and 8.4% for Ozempic® 0.5 mg, Ozempic® 1 mg, and placebo, respectively. At week 30, the change in HbA_{1c} was -1.6%, -1.5% and 0.1% for Ozempic® 0.5 mg, Ozempic® 1 mg, and placebo, respectively.

Combination with premix insulin ± 1–2 OADs
In SUSTAIN 6 (see subsection Cardiovascular disease) 867 patients were on premix insulin (with or without OAD(s)) at baseline. HbA_{1c} at baseline was 8.8%, 8.9% and 8.9% for Ozempic® 0.5 mg, Ozempic® 1 mg, and placebo, respectively. At week 30, the change in HbA_{1c} was -1.3%, -1.8% and -0.4% for Ozempic® 0.5 mg, Ozempic® 1 mg, and placebo, respectively.

Cardiovascular disease
In a 104-week double-blind trial (SUSTAIN 6), 3,297 patients with type 2 diabetes mellitus at high cardiovascular risk were randomised to either Ozempic® 0.5 mg once weekly, Ozempic® 1 mg once weekly or corresponding placebo in addition to standard-of-care hereafter followed for 2 years. In total 98% of the patients completed the trial and the vital status was known at the end of the trial for 99.6% of the patients.

The trial population was distributed by age as: 1,598 patients (48.5%) ≥65 years, 321 (9.7%) ≥75 years, and 20 (0.6%) ≥85 years. There were 2,358 patients with normal or mild renal impairment, 832 with moderate and 107 with severe or end stage renal impairment. There were 61% males, the mean age was 65 years and mean BMI was 33 kg/m^2. The mean duration of diabetes was 13.9 years.

The primary endpoint was time from randomisation to first occurrence of a major adverse cardiovascular event (MACE): cardiovascular death, non-fatal myocardial infarction or non-fatal stroke.

The total number of primary component MACE endpoints was 254, including 108 (6.6%) with semaglutide and 146 (8.9%) with placebo. See figure 4 for results on primary and secondary cardiovascular endpoints. Treatment with semaglutide resulted in a 26% risk reduction in the primary composite outcome of death from cardiovascular causes, non-fatal myocardial infarction or non-fatal stroke. The total numbers of cardiovascular deaths, non-fatal myocardial infarctions and non-fatal strokes were 90, 111, and 71, respectively, including 44 (2.7%), 47 (2.9%), and 27 (1.6%), respectively, with semaglutide (figure 4). The risk reduction in the primary composite outcome was mainly driven by decreases in the rate of non-fatal stroke (39%) and non-fatal myocardial infarction (26%) (figure 3).

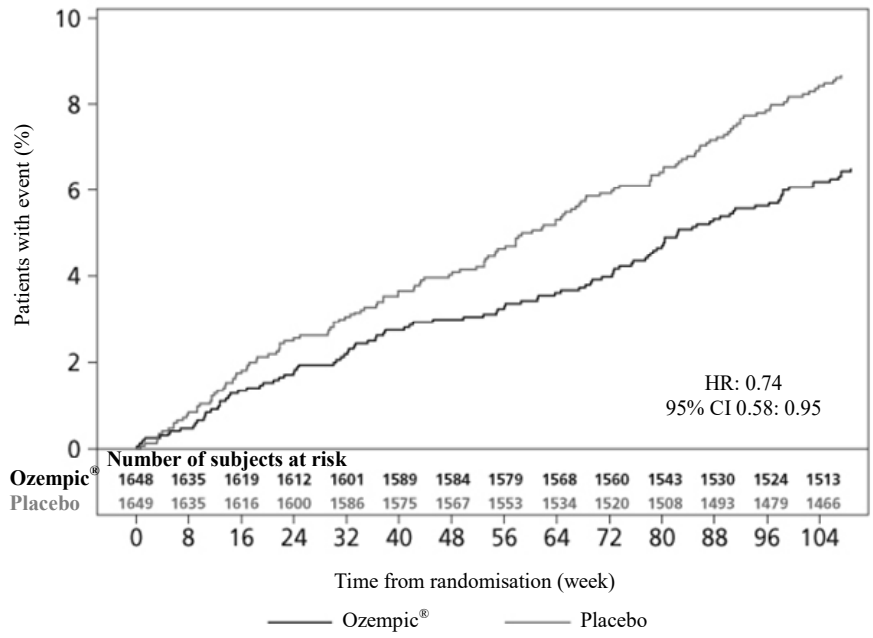


Figure 3 Kaplan-Meier plot of time to first occurrence of the composite outcome: cardiovascular death, non-fatal myocardial infarction or non-fatal stroke (SUSTAIN 6)

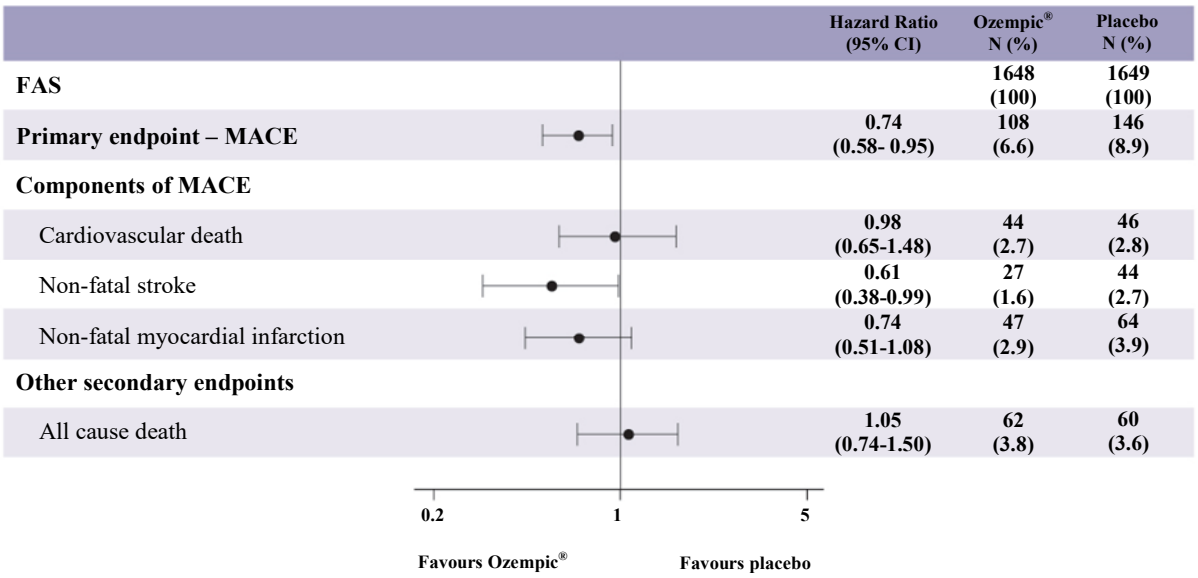


Figure 4 Forest plot: analyses of time to first occurrence of the composite outcome, its components and all cause death (SUSTAIN 6)

There were 158 events of new or worsening nephropathy. The hazard ratio [95% CI] for time to nephropathy (new onset of persistent macroalbuminuria, persistent doubling of serum creatinine, need for continuous renal replacement therapy and death due to renal disease) was 0.64 [0.46; 0.88] driven by new onset of persistent macroalbuminuria.

Body weight
After one year of treatment, a weight loss of ≥5% and ≥10% was achieved for more subjects with Ozempic® 0.5 mg (46% and 13%) and 1 mg (52–62% and 21–24%) compared with the active comparators sitagliptin (18% and 3%) and exenatide ER (17% and 4%).

In the 40-week trial vs. dulaglutide a weight loss of ≥5% and ≥10% was achieved for more subjects with Ozempic® 0.5 mg (44% and 14%) compared with dulaglutide 0.75 mg (23% and 3%) and Ozempic® 1 mg (up to 63% and 27%) compared with dulaglutide 1.5 mg (30% and 8%).

A significant and sustained reduction in body weight from baseline to week 104 was observed with Ozempic® 0.5 mg and 1 mg vs. placebo 0.5 mg and 1 mg, in addition to standard-of-care (-3.6 kg and -4.9 kg vs. -0.7 kg and -0.5 kg , respectively) in SUSTAIN 6.

Blood pressure
Significant reductions in mean systolic blood pressure were observed when Ozempic® 0.5 mg (3.5–5.1 mmHg) and 1 mg (5.4–7.3 mmHg) were used in combination with oral antidiabetic medicinal products or basal insulin. For diastolic blood pressure, there were no significant differences between semaglutide and comparators.

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
Maximum concentration was reached 1 to 3 days post dose. Steady state exposure was achieved following 4–5 weeks of once weekly administration. In patients with type 2 diabetes, the mean steady state concentrations following subcutaneous administration of 0.5 mg and 1 mg semaglutide were approximately 16 nmol/l and 30 nmol/l, respectively. Semaglutide exposure increased in a dose proportional manner for doses of 0.5 mg and 1 mg. Similar exposure was achieved with subcutaneous administration of semaglutide in the abdomen, thigh, or upper arm. Absolute bioavailability of subcutaneous semaglutide was 89%.

Distribution
The mean volume of distribution of semaglutide following subcutaneous administration in patients with type 2 diabetes was approximately 12.5 l. Semaglutide was 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 sidechain. The enzyme neutral endopeptidase (NEP) is expected to be involved in the metabolism of semaglutide.

Elimination
In a study with a single subcutaneous dose of radiolabelled semaglutide, it was found that the primary excretion routes of semaglutide-related material were via urine and faeces; approximately 2/3 of semaglutide-related material were excreted in urine and approximately 1/3 in faeces. Approximately 3% of the dose was excreted as intact semaglutide via urine. In patients with type 2 diabetes clearance of semaglutide was approximately 0.05 l/h. With an elimination half-life of approximately 1 week, semaglutide will be present in the circulation for about 5 weeks after the last dose.

Special population

Elderly
Age had no effect on the pharmacokinetics of semaglutide based on data from phase 3a studies including patients of 20–86 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.

Body weight
Body weight has an effect on the exposure of semaglutide. Higher body weight results in lower exposure; a 20% difference in body weight between individuals will result in an approximate 16% difference in exposure. Semaglutide doses of 0.5 mg and 1 mg provide adequate systemic exposure over a body weight range of 40–198 kg.

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 subjects with normal renal function. This was also shown for subjects with type 2 diabetes and with renal impairment based on data from phase 3a studies, although the experience in patients with end-stage renal disease was limited.

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) compared with subjects with normal hepatic function in a study with a single-dose of 0.5 mg semaglutide.

Paediatric population
Semaglutide has not been studied in paediatric patients.

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.

List of excipients
Disodium phosphate dihydrate, propylene glycol, phenol, hydrochloric acid (for pH adjustment), sodium hydroxide (for pH adjustment) and water for injections.

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

Special precautions for storage
Before first use: Store in a refrigerator (2°C to 8°C). Keep away from the cooling element.
Do not freeze Ozempic® and do not use Ozempic® if it has been frozen.

After first use: After first use the medicinal product may be stored for a maximum of 6 weeks. Store below 30°C or in a refrigerator (2°C to 8°C). Do not freeze Ozempic® and do not use Ozempic® if it has been frozen.
Keep the pen cap on when the pen is not in use in order to protect it from light.

Always remove the injection needle after each injection and store the pen without a needle attached. This may prevent blocked needles, contamination, infection, leakage of solution and inaccurate dosing.

Nature and contents of container
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.

Pack size:
1 pre-filled pen and 6 disposable NovoFine® Plus needles.
Each pre-filled pen contains 1.5 ml of solution, delivering doses of 0.25 mg or 0.5 mg.

Special precautions for disposal and other handling
The patient should be advised to discard the injection needle after each injection and store the pen without an injection needle attached. This may prevent blocked needles, contamination, infection, leakage of solution and inaccurate dosing. Needles and other waste material should be disposed of in accordance with local requirements.

The pen is for use by one person only.
Ozempic® should not be used if it does not appear clear and colourless or almost colourless.
Ozempic® should not be used if it has been frozen.

Ozempic® can be administered with needles up to a length of 8 mm. The pen is designed to be used with NovoFine® or NovoTwist® disposable needles. NovoFine® Plus needles are included in the package.

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

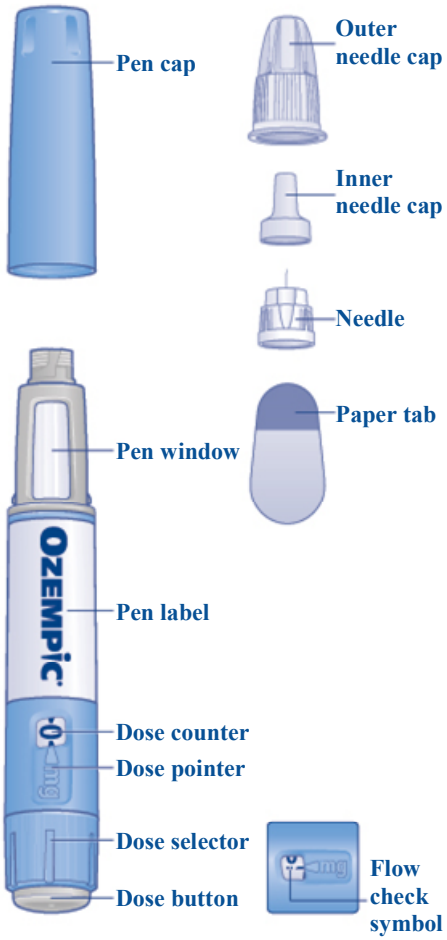
Ozempic®, NovoFine® and NovoTwist® are trademarks owned by Novo Nordisk A/S, Denmark.

Ozempic®
0.25mg, 0.5 mg/dose
solution for injection in pre-filled pen
Semaglutide

Instructions on how to use Ozempic® 0.25 mg, 0.5 mg/dose solution for injection in pre-filled pen

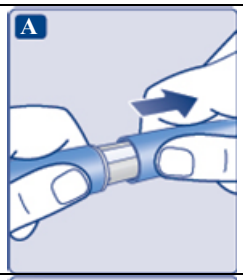
Please read these instructions carefully before using your Ozempic® pre-filled pen.
Do not use the pen without proper training from your doctor or nurse.
Start by checking your pen to **make sure that it contains Ozempic® 0.25 mg, 0.5 mg** then look at the illustrations below to get to know the different parts of your pen and needle.
If you are blind or have poor eyesight and cannot read the dose counter on the pen, do not use this pen without help. Get help from a person with good eyesight who is trained to use the Ozempic® pre-filled pen.
Your pen is a pre-filled dial-a-dose pen. It contains 2 mg of semaglutide, and you can select doses of 0.25 mg or 0.5 mg. Your pen is designed to be used with NovoFine® and NovoTwist® disposable needles up to a length of 8 mm.
NovoFine® Plus needles are included in the pack.

Ozempic® pre-filled pen and needle (example)

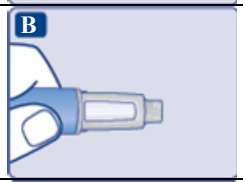


1. Prepare your pen with a new needle

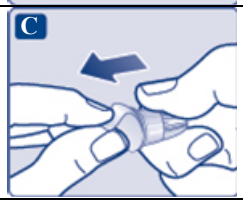
- **Check the name and coloured label** of your pen, to make sure that it contains Ozempic®. This is especially important if you take more than one type of injectable medicine. Using the wrong medicine could cause severe harm to your health.
- **Pull off the pen cap.**



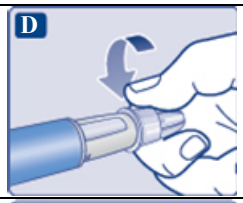
- **Check that the solution in your pen is clear** and colourless. Look through the pen window. If the solution looks cloudy or coloured, do not use the pen.



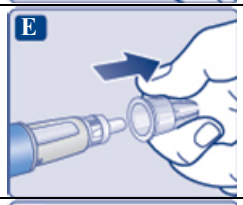
- **Take a new needle**
  Check the paper tab and the outer needle cap for damages that could affect sterility. If any damage is seen use a new needle.
- **Tear off the paper tab.**



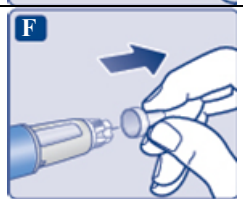
- **Push the needle straight onto the pen. Turn until it is on tight.**



- **Pull off the outer needle cap and keep it for later.** You will need it after the injection, to safely remove the needle from the pen.



- **Pull off the inner needle cap and throw it away.** If you try to put it back on, you may accidentally stick yourself with the needle.



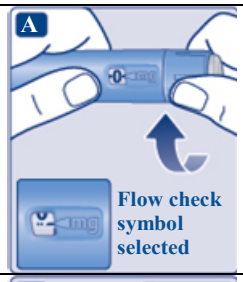
A drop of solution may appear at the needle tip. This is normal, but you must still check the flow, if you use a new pen for the first time. See step 2 'Check the flow'.
Do not attach a new needle to your pen until you are ready to take your injection.

⚠ **Always use a new needle for each injection.**
This reduces the risk of blocked needles, contamination, infection and inaccurate dosing.

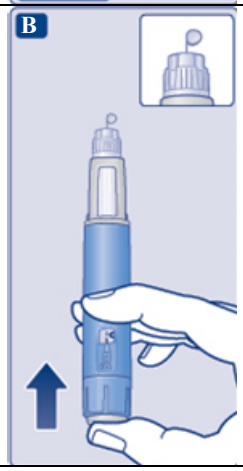
⚠ **Never use a bent or damaged needle.**

2. Check the flow

- **Before your first injection with each new pen, check the flow.** If your pen is already in use, go to step 3 'Select your dose'.
- Turn the dose selector **until the dose counter shows the flow check symbol** (▪▪ ▬).



- Hold the pen with the needle pointing up.
Press and hold in the dose button until the dose counter returns to 0. The 0 must line up with the dose pointer.
A drop of solution should appear at the needle tip.



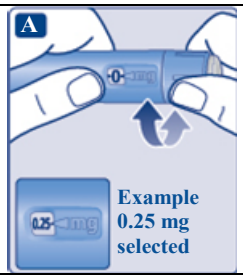
A small drop may remain at the needle tip, but it will not be injected.
If no drop appears, repeat step 2 'Check the flow' up to 6 times. If there is still no drop, change the needle and repeat step 2 'Check the flow' once more.
If a drop still does not appear, dispose of the pen and use a new one.

⚠ **Always make sure that a drop appears** at the needle tip before you use a new pen for the first time. This makes sure that the solution flows.
If no drop appears, you will **not** inject any medicine even though the dose counter may move. **This may indicate a blocked or damaged needle.**

If you do not check the flow before your first injection with each new pen, you may not get the prescribed dose and the intended effect of Ozempic®.

3. Select your dose

- **Turn the dose selector until the dose counter shows your prescribed dose (0.25 mg or 0.5 mg).**
  If you select the wrong dose, you can turn the dose selector forwards or backwards to the correct dose.

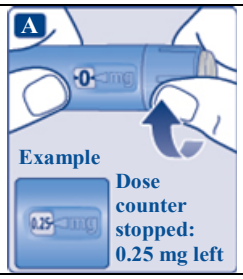


The dose selector changes the dose. Only the dose counter and dose pointer will show how many mg you select per dose.
The dose selector clicks differently when turned forwards, backwards or past the number of mg left. Do not count the pen clicks.

⚠ **Always use the dose counter and the dose pointer to see how many mg you have selected before injecting this medicine.**
Do not count the pen clicks.
The selected dose in the dose counter must line up precisely with the dose pointer to ensure that you get a correct dose.

How much solution is left

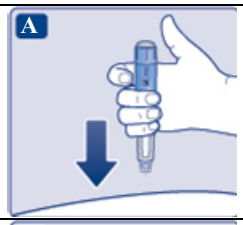
- **To see how much solution is left,** use the dose counter: Turn the dose selector until the **dose counter stops.** If it shows 0.5, **at least 0.5 mg** is left in your pen.
  If the **dose counter stops before 0.5 mg,** there is not enough solution left for a full dose of 0.5 mg.



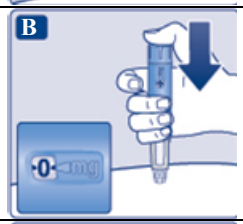
⚠ If there is not enough solution left in your pen for a full dose, do not use it. Use a new Ozempic® pen.

4. Inject your dose

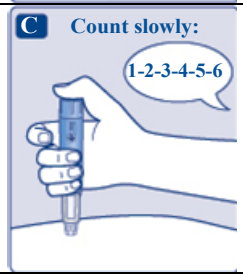
- **Insert the needle into your skin** as your doctor or nurse has shown you.
- **Make sure you can see the dose counter.** Do not cover it with your fingers. This could interrupt the injection.



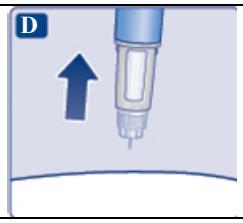
- **Press and hold down the dose button until the dose counter shows 0.** The 0 must line up with the dose pointer. You may then hear or feel a click.



- **Keep the needle in your skin** after the dose counter has returned to 0 and **count slowly to 6.** This is to make sure that you get your full dose.
- If the needle is removed earlier, you may see a stream of solution coming from the needle tip. If so, the full dose will not be delivered.



- **Remove the needle from your skin.** If blood appears at the injection site, press lightly. Do not rub the area.



You may see a drop of solution at the needle tip after injecting. This is normal and does not affect your dose.

⚠ **Always watch the dose counter to know how many mg you inject.** Hold the dose button down until the dose counter shows 0.

How to identify a blocked or damaged needle

– If 0 does not appear in the dose counter after continuously pressing the dose button, you may have used a blocked or damaged needle.
– In this case, you have **not** received any medicine – even though the dose counter has moved from the original dose that you have set.

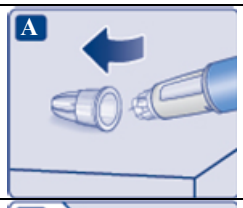
How to handle a blocked needle

Change the needle as described in step 5 'After your injection' and repeat all steps starting with step 1 'Prepare your pen with a new needle'. Make sure you select the full dose you need.

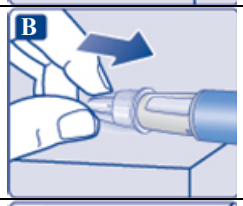
Never touch the dose counter when you inject. This can interrupt the injection.

5. After your injection

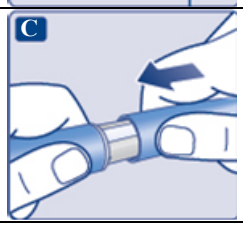
- **Lead the needle tip into the outer needle cap** on a flat surface without touching the needle or the outer needle cap.



- Once the needle is covered, **carefully push the outer needle cap completely on.**
- **Unscrew the needle** and dispose of it carefully in accordance with local guidelines. Ask your doctor, nurse or pharmacist about sharps disposal.



- **Put the pen cap on** your pen after each use to protect the solution from light.



Always dispose of the needle after each injection to ensure convenient injections and prevent blocked needles. If the needle is blocked, you will **not** inject **any** medicine.
When the pen is empty, throw it away **without** a needle on as instructed by your doctor, nurse, pharmacist or local authorities.

⚠ **Never try to put the inner needle cap back on the needle.** You may stick yourself with the needle.

⚠ **Always remove the needle from your pen immediately after each injection.**
This reduces the risk of blocked needles, contamination, infection, leakage of solution and inaccurate dosing.

⚠ **Further important information**

- Always keep your pen and needles **out of the sight and reach of others,** especially children.
- **Never share** your pen or your needles with other people.
- Caregivers must **be very careful when handling used needles** to prevent needle injury and cross-infection.

Caring for your pen

Treat your pen with care. Rough handling or misuse may cause inaccurate dosing. If this happens you might not get the intended effect of this medicine.
• **Do not inject Ozempic® which has been frozen.** If you do that, you might not get the intended effect of this medicine. • **Do not inject Ozempic® which has been exposed to direct sunlight.** If you do that, you might not get the intended effect of this medicine. • **Do not expose your pen to dust, dirt or liquid.** • **Do not wash, soak or lubricate your pen.** If necessary, clean it with a mild detergent on a moistened cloth. • **Do not drop your pen** or knock it against hard surfaces. If you drop it or suspect a problem, attach a new needle and check the flow before you inject. • **Do not try to refill your pen.** Once empty, it must be disposed of. • **Do not try to repair your pen** or pull it apart.

Ozempic®
1 mg/dose
Solution for injection in pre-filled pen

Qualitative and quantitative composition
One ml of solution contains 1.34 mg of semaglutide*. One pre-filled pen contains 4 mg semaglutide* in 3.0 ml solution. Each dose contains 1 mg of semaglutide in 0.74 ml solution.

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

For the full list of excipients, see *List of excipients.*

Pharmaceutical form
Solution for injection.
Clear and colourless or almost colourless, isotonic solution; pH=7.4.

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

- as monotherapy when metformin is considered inappropriate due to intolerance or contraindications

- in addition to other medicinal products for the treatment of diabetes.

For study results with respect to combinations, effects on glycaemic control and cardiovascular events, and the populations studied, see *Special warnings and precautions for use, Interaction with other medicinal products and other forms of interaction* and *Pharmacodynamic properties.*

Posology and method of administration
Posology
The starting dose is 0.25 mg semaglutide once weekly. After 4 weeks the dose should be increased to 0.5 mg once weekly. After at least 4 weeks with a dose of 0.5 mg once weekly, the dose can be increased to 1 mg once weekly to further improve glycaemic control.

Semaglutide 0.25 mg is not a maintenance dose. Weekly doses higher than 1 mg are not recommended.

When Ozempic® is added to existing metformin and/or thiazolidinedione therapy, the current dose of metformin and/or thiazolidinedione can be continued unchanged.

When Ozempic® is added to existing therapy of sulfonylurea or insulin, a reduction in the dose of sulfonylurea or insulin should be considered to reduce the risk of hypoglycaemia (see *Special warnings and precautions for use* and *Undesirable effects*).

Self-monitoring of blood glucose is not needed in order to adjust the dose of Ozempic®. Blood glucose self-monitoring is necessary to adjust the dose of sulfonylurea and insulin, particularly when Ozempic® is started and insulin is reduced. A stepwise approach to insulin reduction is recommended.

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.

Special populations

Elderly

No dose adjustment is required based on age. Therapeutic experience in patients ≥75 years of age is limited (see *Pharmacokinetic properties*).

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 end-stage renal disease (see *Pharmacokinetic properties*).

Hepatic impairment

No dose adjustment is required for patients with hepatic impairment. Experience with the use of semaglutide in patients with severe hepatic impairment is limited. Caution should be exercised when treating these patients with semaglutide (see *Pharmacokinetic properties*).

Paediatric population

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

Method of administration

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

Ozempic® is to be injected subcutaneously in the abdomen, in the thigh or in the upper arm. The injection site can be changed without dose adjustment. Ozempic® 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 2 days (>48 hours).

For further information on administration, see *Special precautions for disposal and other handling.*

Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in *List of excipients.*

Special warnings and precautions for use

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

There is no experience in patients with congestive heart failure NYHA class IV and semaglutide is therefore not recommended in these patients.

Gastrointestinal effects

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 could cause a deterioration of renal function (see *Undesirable effects*).

Acute pancreatitis

Acute pancreatitis has been observed with the use of GLP-1 receptor agonists. Patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, semaglutide should be discontinued; if confirmed, semaglutide should not be restarted. Caution should be exercised in patients with a history of pancreatitis.

Hypoglycaemia

Patients treated with semaglutide in combination with a sulfonylurea or insulin may have an increased risk of hypoglycaemia. The risk of hypoglycaemia can be lowered by reducing the dose of sulfonylurea or insulin when initiating treatment with semaglutide (see *Undesirable effects*).

Diabetic retinopathy
In the 2-year cardiovascular outcomes trial involving patients with type 2 diabetes and high cardiovascular risk, an increase of developing diabetic retinopathy complications has been observed (see *Undesirable effects*). Caution should be exercised when using semaglutide in patients with history diabetic retinopathy or treated with insulin. The effect of long-term glycaemic control with semaglutide on diabetic retinopathy complications has not been studied. These patients should be monitored closely and treated according to clinical guidelines. Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy, but other mechanisms cannot be excluded.

Sodium content
This medicine contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium-free'.

Interaction with other medicinal products and other forms of interaction
Semaglutide delays gastric emptying and has the potential to impact the rate of absorption of concomitantly administered oral medicinal products. 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 dose adjustment of paracetamol is necessary when administered with semaglutide.

Oral contraceptives
Semaglutide is not anticipated to decrease the effect 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 the 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 (INR) 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 INR is recommended.

Fertility, pregnancy and lactation

Women of childbearing potential
Women of childbearing potential are recommended to use contraception when treated with semaglutide.

Pregnancy
Studies in animals have shown reproductive toxicity (see *Preclinical safety data*). 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 *Pharmacokinetic properties*).

Breast-feeding
In lactating rats, semaglutide was excreted in milk. As a risk to a breast-fed child cannot be excluded, semaglutide should not be used during breast-feeding.

Fertility
The effect of semaglutide on fertility in humans is unknown. Semaglutide did not affect male fertility in rats. In female rats, an increase in oestrous length and a small reduction in number of ovulations were observed at doses associated with maternal body weight loss (see *Preclinical safety data*).

Effects on ability to drive and use machines
Semaglutide has no or negligible influence on the ability to drive or use machines. When it is used in combination with a sulfonylurea or insulin, patients should be advised to take precautions to avoid hypoglycaemia while driving and using machines (see *Special warnings and precautions for use*).

Undesirable effects
Summary of safety profile
In 8 phase 3a trials 4,792 patients were exposed to semaglutide. The most frequently reported adverse reactions in clinical trials were gastrointestinal disorders, including nausea (very common), diarrhoea (very common), vomiting (common) and constipation (common). In general, these reactions were mild or moderate in severity and of short duration (except for constipation).

Tabulated list of adverse reactions
Table 1 lists adverse reactions identified in all phase 3a trials in patients with type 2 diabetes mellitus (further described in *Pharmacodynamic properties*). The frequencies of the adverse reactions are based on a pool of the phase 3a trials excluding the cardiovascular outcomes trial (see text below the table for additional details).

The reactions are listed below by system organ class and absolute frequency. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1 Adverse reactions from long-term controlled phase 3a trials including the cardiovascular outcomes trial

MedDRA system organ class	**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)**
Immune system disorders			Hypersensitivity[c]	Anaphylactic reaction
Metabolism and nutrition disorders	Hypoglycaemia[a] when used with insulin or sulfonylurea	Hypoglycaemia[a] when used with other OADs Decreased appetite		

Nervous system disorders		Dizziness	Dysgeusia	
Eye disorders		Diabetic retinopathy complications[b]		
Cardiac disorders			Increased heart rate	
Gastrointestinal disorders	Nausea Diarrhoea	Vomiting Abdominal pain Abdominal distension Constipation Dyspepsia Gastritis Gastro-oesophageal reflux disease Eructation Flatulence	Acute pancreatitis	
Hepatobiliary disorders		Cholelithiasis		
General disorders and administration site conditions		Fatigue	Injection site reactions	
Investigations		Increased lipase Increased amylase Weight decreased		

[a)] Hypoglycaemia defined as severe (requiring the assistance of another person) or symptomatic in combination with a blood glucose <3.1 mmol/l

[b)] Diabetic retinopathy complications is a composite of: retinal photocoagulation, treatment with intravitreal agents, vitreous haemorrhage, diabetes-related blindness (uncommon). Frequency based on cardiovascular outcomes trial.

[c)] Grouped term covering also adverse events related to hypersensitivity such as rash and urticaria.

2-year cardiovascular outcomes and safety trial

In cardiovascular high risk population the adverse reaction profile was similar to that seen in the other phase 3a trials (described in *Pharmacodynamic properties*).

Description of selected adverse reactions

Hypoglycaemia

No episodes of severe hypoglycaemia were observed when semaglutide was used as monotherapy. Severe hypoglycaemia was primarily observed when semaglutide was used with a sulfonylurea (1.2% of subjects, 0.03 events/patient year) or insulin (1.5% of subjects, 0.02 events/patient year). Few episodes (0.1% of subjects, 0.001 events/patient year) were observed with semaglutide in combination with oral antidiabetics other than sulfonylureas.

Gastrointestinal adverse reactions

Nausea occurred in 17.0% and 19.9% of patients when treated with semaglutide 0.5 mg and 1 mg, respectively, diarrhoea in 12.2% and 13.3%, vomiting in 6.4% and 8.4% and constipation in 6.9% and 6.2%. Most events were mild to moderate in severity and of short duration (except constipation). The events led to treatment discontinuation in 3.9% and 5% of patients. The events were most frequently reported during the first months on treatment. Patients with low body weight may experience more gastrointestinal side effects when treated with semaglutide.

Acute pancreatitis

The frequency of adjudication-confirmed acute pancreatitis reported in phase 3a clinical trials was 0.3% for semaglutide and 0.2% for the comparator, respectively. In the 2-year cardiovascular outcomes trial the frequency of acute pancreatitis confirmed by adjudication was 0.5% for semaglutide and 0.6% for placebo (see *Special warnings and precautions for use*).

Diabetic retinopathy complications
A 2-year clinical trial investigated 3,297 patients with type 2 diabetes, with high cardiovascular risk, long duration of diabetes and poorly controlled blood glucose. In this trial, adjudicated events of diabetic retinopathy complications occurred in more patients treated with semaglutide (3.0%) compared to placebo (1.8%). This was observed in insulin-treated patients with known diabetic retinopathy. The treatment difference appeared early and persisted throughout the trial. Systematic evaluation of diabetic retinopathy complication was only performed in the cardiovascular outcomes trial. In clinical trials up to 1 year involving 4,807 patients with type 2 diabetes, adverse events related to diabetic retinopathy were reported in similar proportions of subjects treated with semaglutide (1.7%) and comparators (2.0%).

Discontinuation due to an adverse event
The incidence of discontinuation of treatment due to adverse events was 6.1% and 8.7% for patients treated with semaglutide 0.5 mg and 1 mg, respectively, vs. 1.5% for placebo. The most frequent adverse events leading to discontinuation were gastrointestinal.

Injection site reactions
Injection site reactions (e.g. injection site rash, erythema) have been reported by 0.6% and 0.5% of patients receiving semaglutide 0.5 mg and 1 mg, respectively. These reactions have usually been mild.

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 tested positive for anti-semaglutide antibodies at any time point post-baseline was low (1-2%) and no patients had anti-semaglutide neutralising antibodies or anti-semaglutide antibodies with endogenous GLP-1 neutralising effect at end-of-trial.

Heart rate increase
Increased heart rate has been observed with GLP-1 receptor agonists. In the phase 3a trials, mean increases of 1 to 6 beats per minute (bpm) from a baseline of 72 to 76 bpm were observed in subjects treated with Ozempic®. In a long-term trial in subjects with cardiovascular risk factors, 16% of Ozempic®-treated subjects had an increase in heart rate of >10 bpm compared to 11% of subjects on placebo after 2 years of treatment.

Overdose
Overdoses of up to 4 mg in a single dose, and up to 4 mg in a week have been reported in clinical trials. The most commonly reported adverse reaction was nausea. All patients recovered without complications.

There is no specific antidote for overdose with semaglutide. In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms. A prolonged period of observation and treatment for these symptoms may be necessary, taking into account the long half-life of semaglutide of approximately 1 week (see *Pharmacokinetic properties*).

Pharmacodynamic properties
Pharmacotherapeutic group: Drugs used in diabetes, Glucagon-like peptide-1 (GLP-1) analogues, ATC code: A10BJ06

Mechanism of action

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

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

Semaglutide reduces blood glucose in a glucose dependent manner by stimulating insulin secretion and lowering glucagon secretion when blood glucose is high. The mechanism of blood glucose lowering also involves a minor delay in gastric emptying in the early postprandial phase. During hypoglycaemia, semaglutide diminishes insulin secretion and does not impair glucagon secretion.

Semaglutide reduces body weight and body fat mass through lowered energy intake, involving an overall reduced appetite. In addition, semaglutide reduces the preference for high fat foods.

GLP-1 receptors are also expressed in the heart, vasculature, immune system and kidneys.
Semaglutide had a beneficial effect on plasma lipids, lowered systolic blood pressure and reduced inflammation in clinical studies. In animal studies, semaglutide attenuates the development of atherosclerosis by preventing aortic plaque progression and reducing inflammation in the plaque.

Pharmacodynamic effects
All pharmacodynamic evaluations were performed after 12 weeks of treatment (including dose escalation) at steady state with semaglutide 1 mg once weekly.

Fasting and postprandial glucose
Semaglutide reduces fasting and postprandial glucose concentrations. In patients with type 2 diabetes, treatment with semaglutide 1 mg resulted in reductions in glucose in terms of absolute change from baseline (mmol/l) and relative reduction compared to placebo (%) for fasting glucose (1.6 mmol/l; 22% reduction), 2 hour postprandial glucose (4.1 mmol/l; 37% reduction), mean 24 hour glucose concentration (1.7 mmol/l; 22% reduction) and postprandial glucose excursions over 3 meals (0.6–1.1 mmol/l) compared with placebo. Semaglutide lowered fasting glucose after the first dose.

Beta-cell function and insulin secretion
Semaglutide improves beta-cell function. Compared to placebo, semaglutide improved first- and second-phase insulin response with a 3- and 2-fold increase, respectively, and increased maximal beta-cell secretory capacity in patients with type 2 diabetes. In addition, semaglutide treatment increased fasting insulin concentrations compared to placebo.

Glucagon secretion
Semaglutide lowers the fasting and postprandial glucagon concentrations. In patients with type 2 diabetes, semaglutide resulted in the following relative reductions in glucagon compared to placebo: fasting glucagon (8–21%), postprandial glucagon response (14–15%) and mean 24 hour glucagon concentration (12%).

Glucose dependent insulin and glucagon secretion
Semaglutide lowered high blood glucose concentrations by stimulating insulin secretion and lowering glucagon secretion in a glucose dependent manner. With semaglutide, the insulin secretion rate in patients with type 2 diabetes was comparable to that of healthy subjects.

During induced hypoglycaemia, semaglutide compared to placebo did not alter the counter regulatory responses of increased glucagon and did not impair the decrease of C-peptide in patients with type 2 diabetes.

Gastric emptying

Semaglutide caused a minor delay of early postprandial gastric emptying, thereby reducing the rate at which glucose appears in the circulation postprandially.

Appetite, energy intake and food choice
Semaglutide compared to placebo lowered the energy intake of 3 consecutive *ad libitum* meals by 18–35%. This was supported by a semaglutide-induced suppression of appetite in the fasting state as well as postprandially, improved control of eating, less food cravings and a relative lower preference for high fat food.

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

Cardiac electrophysiology (QTc)
The effect of semaglutide on cardiac repolarization was tested in a thorough QTc trial. Semaglutide did not prolong QTc intervals at supra-therapeutic dose levels (up to 1.5 mg at steady state).

Clinical efficacy and safety
Both improvement of glycaemic control and reduction of cardiovascular morbidity and mortality are an integral part of the treatment of type 2 diabetes.

The efficacy and safety of Ozempic® 0.5 mg and 1 mg once weekly were evaluated in six randomised controlled phase 3a trials that included 7,215 patients with type 2 diabetes mellitus (4,107 treated with semaglutide). Five trials (SUSTAIN 1–5) had the glycaemic efficacy assessment as the primary objective, while one trial (SUSTAIN 6) had cardiovascular outcome as the primary objective.

An additional trial including 1,201 patients was conducted to compare the efficacy and safety of Ozempic® 0.5 mg and 1 mg once weekly to dulaglutide 0.75 mg and 1.5 mg once weekly, respectively.

Treatment with semaglutide demonstrated sustained, statistically superior and clinically meaningful reductions in HbA_{1c} and body weight for up to 2 years compared to placebo and active control treatment (sitagliptin, insulin glargine, exenatide ER and dulaglutide).

The efficacy of semaglutide was not impacted by age, gender, race, ethnicity, BMI at baseline, body weight (kg) at baseline, diabetes duration and level of renal function impairment.

SUSTAIN 1 – Monotherapy
In a 30-week double-blind placebo-controlled trial, 388 patients inadequately controlled with diet and exercise, were randomised to Ozempic® 0.5 mg or Ozempic® 1 mg once weekly or placebo.

Table 2 SUSTAIN 1: Results at week 30

	Semaglutide 0.5 mg	**Semaglutide 1 mg**	**Placebo**
Intent-to-Treat (ITT) Population (N)	128	130	129
HbA_{1c} (%)			
Baseline (mean)	8.1	8.1	8.0
Change from baseline at week 30	-1.5	-1.6	0
Difference from placebo [95% CI]	-1.4 [-1.7, -1.1][a]	-1.5 [-1.8, -1.2][a]	-
Patients (%) achieving HbA_{1c} <7%	74	72	25
FPG (mmol/l)			
Baseline (mean)	9.7	9.9	9.7
Change from baseline at week 30	-2.5	-2.3	-0.6
Body weight (kg)			

Baseline (mean)	89.8	96.9	89.1
Change from baseline at week 30	-3.7	-4.5	-1.0
Difference from placebo [95% CI]	-2.7 [-3.9, -1.6][a]	-3.6 [-4.7, -2.4][a]	-

[a]p <0.0001 (2-sided) for superiority

SUSTAIN 2 – Ozempic® vs. sitagliptin both in combination with 1–2 oral antidiabetic drugs (metformin and/or thiazolidinediones)

In a 56-week active-controlled double-blind trial, 1,231 patients were randomised to Ozempic® 0.5 mg once weekly, Ozempic® 1 mg once weekly or sitagliptin 100 mg once daily, all in combination with metformin (94%) and/or thiazolidinediones (6%).

Table 3 SUSTAIN 2: Results at week 56

	Semaglutide 0.5 mg	**Semaglutide 1 mg**	**Sitagliptin 100 mg**
Intent-to-Treat (ITT) Population (N)	409	409	407
HbA_{1c} (%)			
Baseline (mean)	8.0	8.0	8.2
Change from baseline at week 56	-1.3	-1.6	-0.5
Difference from sitagliptin [95% CI]	-0.8 [-0.9, -0.6][a]	-1.1 [-1.2, -0.9][a]	-
Patients (%) achieving HbA_{1c} <7%	69	78	36
FPG (mmol/l)			
Baseline (mean)	9.3	9.3	9.6
Change from baseline at week 56	-2.1	-2.6	-1.1
Body weight (kg)			
Baseline (mean)	89.9	89.2	89.3
Change from baseline at week 56	-4.3	-6.1	-1.9
Difference from sitagliptin [95% CI]	-2.3 [-3.1, -1.6][a]	-4.2 [-4.9, -3.5][a]	-

[a]p <0.0001 (2-sided) for superiority

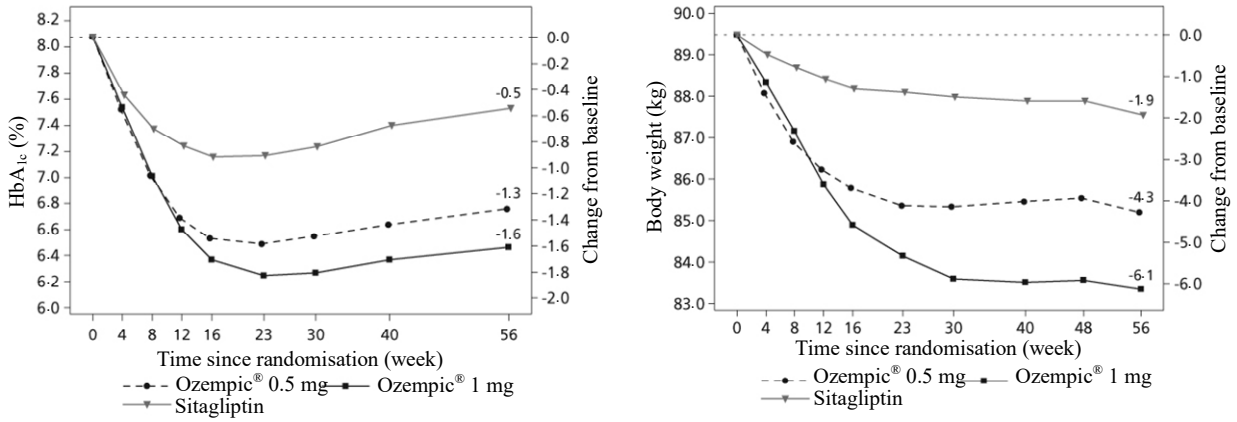


Figure 1 Mean change in HbA_{1c} (%) and body weight (kg) from baseline to week 56

SUSTAIN 7 – Ozempic® vs. dulaglutide both in combination with metformin

In a 40-week, open-label trial, 1,201 patients on metformin were randomised 1:1:1:1 to once weekly Ozempic® 0.5 mg, dulaglutide 0.75 mg , Ozempic® 1 mg or dulaglutide 1.5 mg, respectively.

The trial compared 0.5 mg of Ozempic® to 0.75 mg of dulaglutide and 1 mg of Ozempic® to 1.5 mg of dulaglutide.

Gastrointestinal disorders were the most frequent adverse events, and occurred in similar proportion of patients receiving Ozempic® 0.5 mg (129 patients [43%]), Ozempic® 1 mg (133 [44%]), and dulaglutide 1.5 mg (143 [48%]); fewer patients had gastrointestinal disorders with dulaglutide 0.75 mg (100 [33%]). At week 40, the increase in pulse rate for Ozempic® (0.5 mg and 1 mg) and dulaglutide (0.75 mg and 1.5 mg) was 2.4, 4.0, and 1.6, 2.1, beats/min, respectively.

Table 4 SUSTAIN 7: Results at week 40

	Semaglutide 0.5 mg	**Semaglutide 1 mg**	**Dulaglutide 0.75 mg**	**Dulaglutide 1.5 mg**
Intent-to-Treat (ITT) Population (N)	301	300	299	299
HbA_{1c} (%)				
Baseline (mean)	8.3	8.2	8.2	8.2
Change from baseline at week 40	-1.5	-1.8	-1.1	-1.4
Difference from dulaglutide [95% CI]	-0.4[b] [-0.6, -0.2][a]	-0.4[c] [-0.6, -0.3][a]	-	-
Patients (%) achieving HbA_{1c} <7%	68	79	52	67
FPG (mmol/l)				
Baseline (mean)	9.8	9.8	9.7	9.6
Change from baseline at week 40	-2.2	-2.8	-1.9	-2.2
Body weight (kg)				
Baseline (mean)	96.4	95.5	95.6	93.4
Change from baseline at week 40	-4.6	-6.5	-2.3	-3.0
Difference from dulaglutide [95% CI]	-2.3[b] [-3.0, -1.5][a]	-3.6[c] [-4.3, -2.8][a]	-	-

[a]p <0.0001 (2-sided) for superiority
[b]Ozempic® 0.5 mg vs. dulaglutide 0.75 mg
[c]Ozempic® 1 mg vs. dulaglutide 1.5 mg

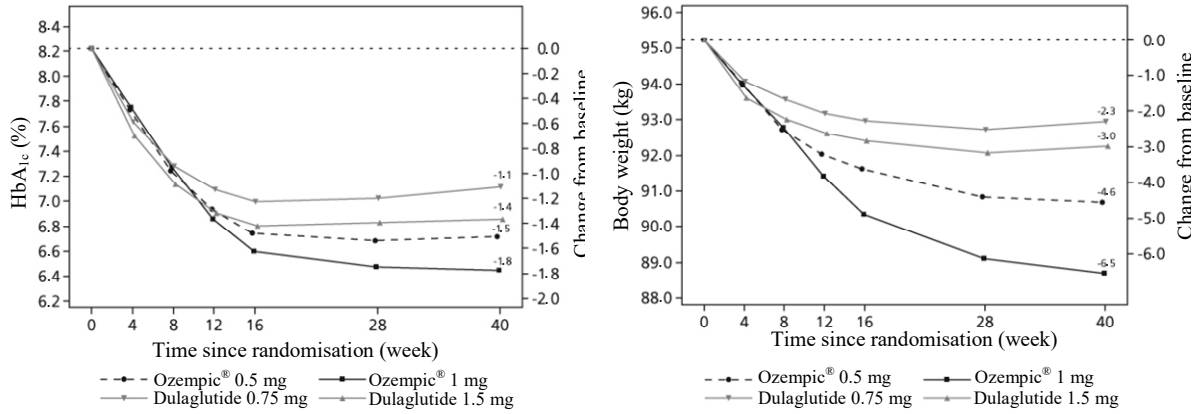


Figure 2 Mean change in HbA_{1c} (%) and body weight (kg) from baseline to week 40

SUSTAIN 3 – Ozempic® vs. exenatide ER both in combination with metformin or metformin with sulfonylurea
In a 56-week open-label trial, 813 patients on metformin alone (49%), metformin with sulfonylurea (45%) or other (6%) were randomised to Ozempic® 1 mg or exenatide ER 2 mg once weekly.

Table 5 SUSTAIN 3: Results at week 56

	Semaglutide 1 mg	**Exenatide ER 2 mg**

Intent-to-Treat (ITT) Population (N)	404	405
HbA_{1c} (%)		
Baseline (mean)	8.4	8.3
Change from baseline at week 56	-1.5	-0.9
Difference from exenatide [95% CI]	-0.6 [-0.8, -0.4][a]	-
Patients (%) achieving HbA_{1c} <7%	67	40
FPG (mmol/l)		
Baseline (mean)	10.6	10.4
Change from baseline at week 56	-2.8	-2.0
Body weight (kg)		
Baseline (mean)	96.2	95.4
Change from baseline at week 56	-5.6	-1.9
Difference from exenatide [95% CI]	-3.8 [-4.6, -3.0][a]	-

[a]p <0.0001 (2-sided) for superiority

SUSTAIN 4 – Ozempic® vs. insulin glargine both in combination with 1–2 oral antidiabetic drugs (metformin or metformin and sulfonylurea)
In a 30-week open-label comparator trial 1,089 patients were randomised to Ozempic® 0.5 mg once weekly, Ozempic® 1 mg once weekly, or insulin glargine once-daily on a background of metformin (48%) or metformin and sulfonylurea (51%).

Table 6 SUSTAIN 4: Results at week 30

	Semaglutide 0.5 mg	**Semaglutide 1 mg**	**Insulin Glargine**
Intent-to-Treat (ITT) Population (N)	362	360	360
HbA_{1c} (%)			
Baseline (mean)	8.1	8.2	8.1
Change from baseline at week 30	-1.2	-1.6	-0.8
Difference from insulin glargine [95% CI]	-0.4 [-0.5, -0.2][a]	-0.8 [-1.0, -0.7][a]	-
Patients (%) achieving HbA_{1c} <7%	57	73	38
FPG (mmol/l)			
Baseline (mean)	9.6	9.9	9.7
Change from baseline at week 30	-2.0	-2.7	-2.1
Body weight (kg)			
Baseline (mean)	93.7	94.0	92.6
Change from baseline at week 30	-3.5	-5.2	+1.2
Difference from insulin glargine [95% CI]	-4.6 [-5.3, -4.0][a]	-6.34 [-7.0, -5.7][a]	-

[a]p <0.0001 (2-sided) for superiority

SUSTAIN 5 – Ozempic® vs. placebo both in combination with basal insulin
In a 30-week double-blind placebo-controlled trial, 397 patients inadequately controlled with basal insulin with or without metformin were randomised to Ozempic® 0.5 mg once weekly, Ozempic® 1 mg once weekly or placebo.

Table 7 SUSTAIN 5: Results at week 30

	Semaglutide 0.5 mg	**Semaglutide 1 mg**	**Placebo**
Intent-to-Treat (ITT) Population (N)	132	131	133
HbA_{1c} (%)			
Baseline (mean)	8.4	8.3	8.4
Change from baseline at week 30	-1.4	-1.8	-0.1
Difference from placebo [95% CI]	-1.4 [-1.6, -1.1][a]	-1.8 [-2.0, -1.5][a]	-
Patients (%) achieving HbA_{1c} <7%	61	79	11
FPG (mmol/l)			

Baseline (mean)	8.9	8.5	8.6
Change from baseline at week 30	-1.6	-2.4	-0.5
Body weight (kg)			
Baseline (mean)	92.7	92.5	89.9
Change from baseline at week 30	-3.7	-6.4	-1.4
Difference from placebo [95% CI]	-2.3 [-3.3, -1.3][a]	-5.1 [-6.1, -4.0][a]	-

[a]p <0.0001 (2-sided) for superiority

Combination with sulfonylurea monotherapy
In SUSTAIN 6 (see subsection Cardiovascular disease) 123 patients were on sulfonylurea monotherapy at baseline. HbA_{1c} at baseline was 8.2%, 8.4% and 8.4% for Ozempic® 0.5 mg, Ozempic® 1 mg, and placebo, respectively. At week 30, the change in HbA_{1c} was -1.6%, -1.5% and 0.1% for Ozempic® 0.5 mg, Ozempic® 1 mg, and placebo, respectively.

Combination with premix insulin ± 1–2 OADs
In SUSTAIN 6 (see subsection Cardiovascular disease) 867 patients were on premix insulin (with or without OAD(s)) at baseline. HbA_{1c} at baseline was 8.8%, 8.9% and 8.9% for Ozempic® 0.5 mg, Ozempic® 1 mg, and placebo, respectively. At week 30, the change in HbA_{1c} was -1.3%, -1.8% and -0.4% for Ozempic® 0.5 mg, Ozempic® 1 mg, and placebo, respectively.

Cardiovascular disease
In a 104-week double-blind trial (SUSTAIN 6), 3,297 patients with type 2 diabetes mellitus at high cardiovascular risk were randomised to either Ozempic® 0.5 mg once weekly, Ozempic® 1 mg once weekly or corresponding placebo in addition to standard-of-care hereafter followed for 2 years. In total 98% of the patients completed the trial and the vital status was known at the end of the trial for 99.6% of the patients.

The trial population was distributed by age as: 1,598 patients (48.5%) ≥65 years, 321 (9.7%) ≥75 years, and 20 (0.6%) ≥85 years. There were 2,358 patients with normal or mild renal impairment, 832 with moderate and 107 with severe or end stage renal impairment. There were 61% males, the mean age was 65 years and mean BMI was 33 kg/m^2. The mean duration of diabetes was 13.9 years.

The primary endpoint was time from randomisation to first occurrence of a major adverse cardiovascular event (MACE): cardiovascular death, non-fatal myocardial infarction or non-fatal stroke.

The total number of primary component MACE endpoints was 254, including 108 (6.6%) with semaglutide and 146 (8.9%) with placebo. See figure 4 for results on primary and secondary cardiovascular endpoints. Treatment with semaglutide resulted in a 26% risk reduction in the primary composite outcome of death from cardiovascular causes, non-fatal myocardial infarction or non-fatal stroke. The total numbers of cardiovascular deaths, non-fatal myocardial infarctions and non-fatal strokes were 90, 111, and 71, respectively, including 44 (2.7%), 47 (2.9%), and 27 (1.6%), respectively, with semaglutide (figure 4). The risk reduction in the primary composite outcome was mainly driven by decreases in the rate of non-fatal stroke (39%) and non-fatal myocardial infarction (26%) (figure 3).

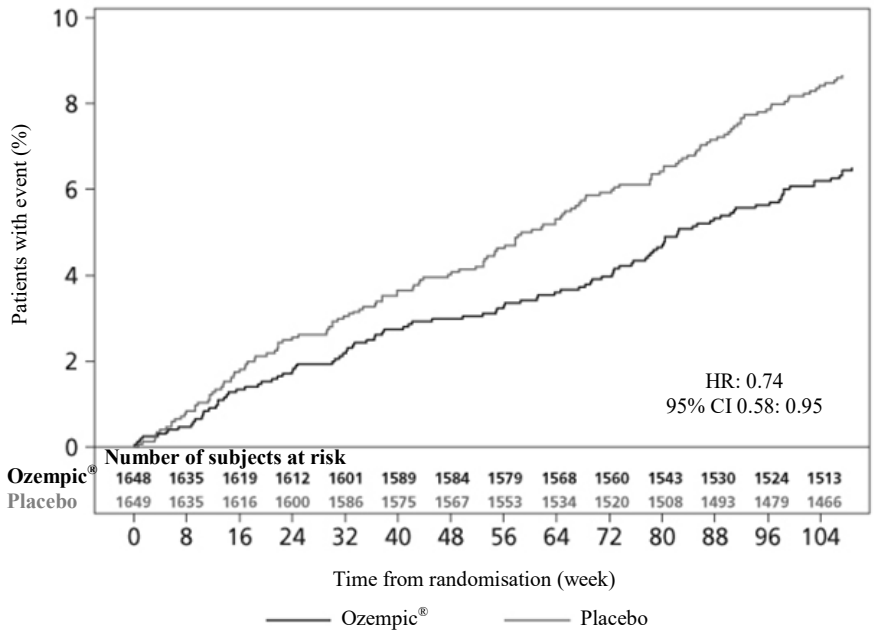


Figure 3 Kaplan-Meier plot of time to first occurrence of the composite outcome: cardiovascular death, non-fatal myocardial infarction or non-fatal stroke (SUSTAIN 6)

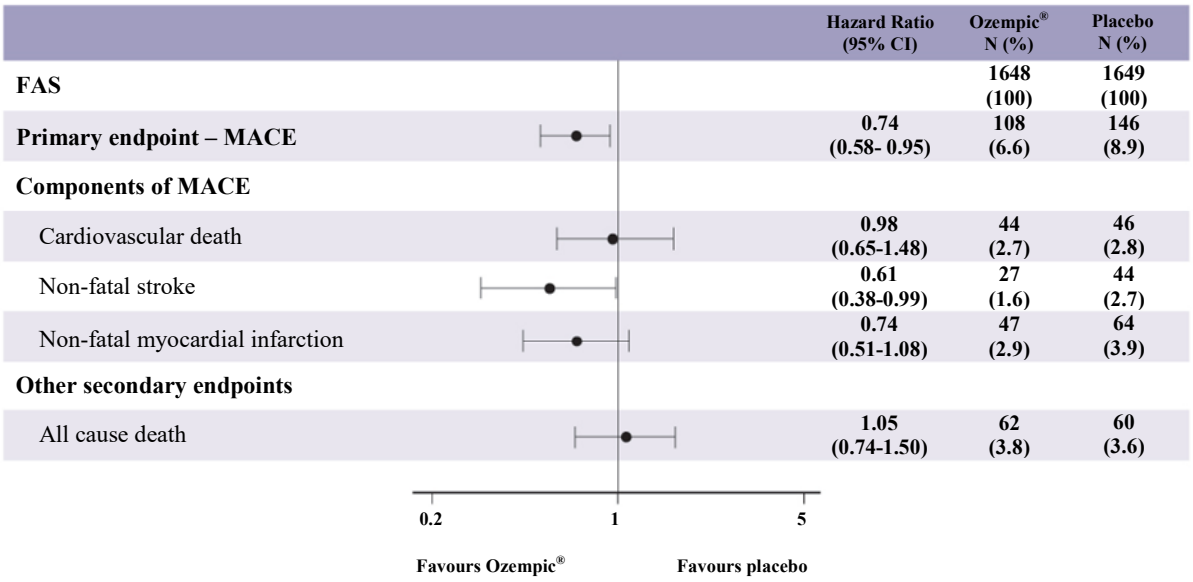


Figure 4 Forest plot: analyses of time to first occurrence of the composite outcome, its components and all cause death (SUSTAIN 6)

There were 158 events of new or worsening nephropathy. The hazard ratio [95% CI] for time to nephropathy (new onset of persistent macroalbuminuria, persistent doubling of serum creatinine, need for continuous renal replacement therapy and death due to renal disease) was 0.64 [0.46; 0.88] driven by new onset of persistent macroalbuminuria.

Body weight
After one year of treatment, a weight loss of ≥5% and ≥10% was achieved for more subjects with Ozempic® 0.5 mg (46% and 13%) and 1 mg (52–62% and 21–24%) compared with the active comparators sitagliptin (18% and 3%) and exenatide ER (17% and 4%).

In the 40-week trial vs. dulaglutide a weight loss of ≥5% and ≥10% was achieved for more subjects with Ozempic® 0.5 mg (44% and 14%) compared with dulaglutide 0.75 mg (23% and 3%) and Ozempic® 1 mg (up to 63% and 27%) compared with dulaglutide 1.5 mg (30% and 8%).

A significant and sustained reduction in body weight from baseline to week 104 was observed with Ozempic® 0.5 mg and 1 mg vs. placebo 0.5 mg and 1 mg, in addition to standard-of-care (-3.6 kg and -4.9 kg vs. -0.7 kg and -0.5 kg , respectively) in SUSTAIN 6.

Blood pressure
Significant reductions in mean systolic blood pressure were observed when Ozempic® 0.5 mg (3.5–5.1 mmHg) and 1 mg (5.4–7.3 mmHg) were used in combination with oral antidiabetic medicinal products or basal insulin. For diastolic blood pressure, there were no significant differences between semaglutide and comparators.

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
Maximum concentration was reached 1 to 3 days post dose. Steady state exposure was achieved following 4–5 weeks of once weekly administration. In patients with type 2 diabetes, the mean steady state concentrations following subcutaneous administration of 0.5 mg and 1 mg semaglutide were approximately 16 nmol/l and 30 nmol/l, respectively. Semaglutide exposure increased in a dose proportional manner for doses of 0.5 mg and 1 mg. Similar exposure was achieved with subcutaneous administration of semaglutide in the abdomen, thigh, or upper arm. Absolute bioavailability of subcutaneous semaglutide was 89%.

Distribution
The mean volume of distribution of semaglutide following subcutaneous administration in patients with type 2 diabetes was approximately 12.5 l. Semaglutide was 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 sidechain. The enzyme neutral endopeptidase (NEP) is expected to be involved in the metabolism of semaglutide.

Elimination
In a study with a single subcutaneous dose of radiolabelled semaglutide, it was found that the primary excretion routes of semaglutide-related material were via urine and faeces; approximately 2/3 of semaglutide-related material were excreted in urine and approximately 1/3 in faeces. Approximately 3% of the dose was excreted as intact semaglutide via urine. In patients with type 2 diabetes clearance of semaglutide was approximately 0.05 l/h. With an elimination half-life of approximately 1 week, semaglutide will be present in the circulation for about 5 weeks after the last dose.

Special population

Elderly
Age had no effect on the pharmacokinetics of semaglutide based on data from phase 3a studies including patients of 20–86 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.

Body weight
Body weight has an effect on the exposure of semaglutide. Higher body weight results in lower exposure; a 20% difference in body weight between individuals will result in an approximate 16% difference in exposure. Semaglutide doses of 0.5 mg and 1 mg provide adequate systemic exposure over a body weight range of 40–198 kg.

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 subjects with normal renal function. This was also shown for subjects with type 2 diabetes and with renal impairment based on data from phase 3a studies, although the experience in patients with end-stage renal disease was limited.

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) compared with subjects with normal hepatic function in a study with a single-dose of 0.5 mg semaglutide.

Paediatric population
Semaglutide has not been studied in paediatric patients.

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.

List of excipients
Disodium phosphate dihydrate, propylene glycol, phenol, hydrochloric acid (for pH adjustment), sodium hydroxide (for pH adjustment) and water for injections.

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

Special precautions for storage
Before first use: Store in a refrigerator (2°C to 8°C). Keep away from the cooling element.
Do not freeze Ozempic® and do not use Ozempic® if it has been frozen.

After first use: After first use the medicinal product may be stored for a maximum of 6 weeks. Store below 30°C or in a refrigerator (2°C to 8°C). Do not freeze Ozempic® and do not use Ozempic® if it has been frozen.
Keep the pen cap on when the pen is not in use in order to protect it from light.

Always remove the injection needle after each injection and store the pen without a needle attached. This may prevent blocked needles, contamination, infection, leakage of solution and inaccurate dosing.

Nature and contents of container
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 size:
1 pre-filled pen and 4 disposable NovoFine® Plus needles.
Each pre-filled pen contains 3 ml of solution, delivering doses of 1 mg.

Special precautions for disposal and other handling
The patient should be advised to discard the injection needle after each injection and store the pen without an injection needle attached. This may prevent blocked needles, contamination, infection, leakage of solution and inaccurate dosing. Needles and other waste material should be disposed of in accordance with local requirements.

The pen is for use by one person only.
Ozempic® should not be used if it does not appear clear and colourless or almost colourless.
Ozempic® should not be used if it has been frozen.

Ozempic® can be administered with needles up to a length of 8 mm. The pen is designed to be used with NovoFine® or NovoTwist® disposable needles. NovoFine® Plus needles are included in the package.

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

Denmark

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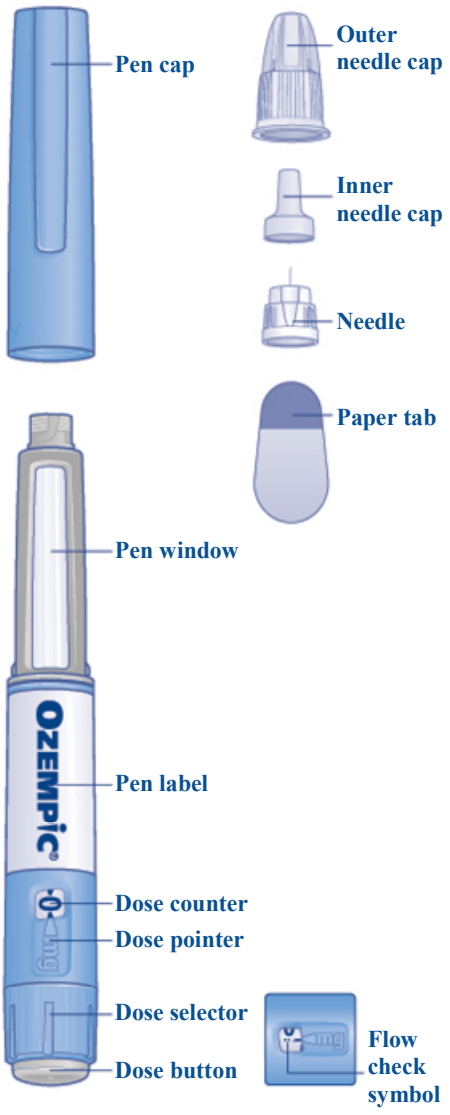
Ozempic®
1 mg/dose
solution for injection in pre-filled pen
semaglutide

Instructions on how to use Ozempic® 1 mg solution for injection in pre-filled pen

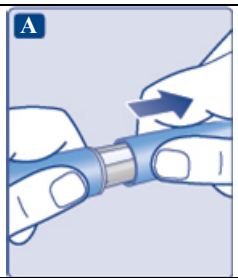
Please read these instructions carefully before using your Ozempic® pre-filled pen.
Do not use the pen without proper training from your doctor or nurse.
Start by checking your pen to **make sure that it contains Ozempic® 1 mg,** then look at the illustrations below to get to know the different parts of your pen and needle.
If you are blind or have poor eyesight and cannot read the dose counter on the pen, do not use this pen without help. Get help from a person with good eyesight who is trained to use the Ozempic® pre-filled pen.
Your pen is a pre-filled dial-a-dose pen. It contains 4 mg of semaglutide, and you can only select doses of 1 mg. Your pen is designed to be used with NovoFine® and NovoTwist® disposable needles up to a length of 8 mm.
NovoFine® Plus needles are included in the pack.

Ozempic® pre-filled pen and needle (example)

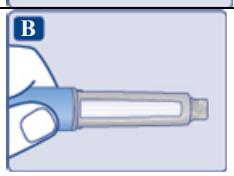


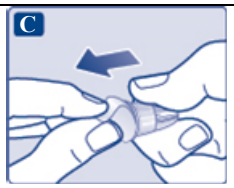
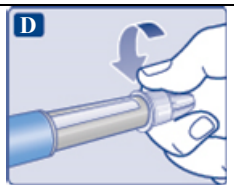
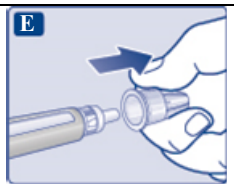
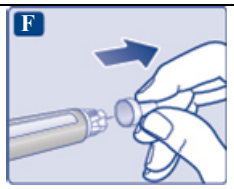
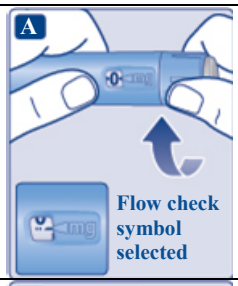
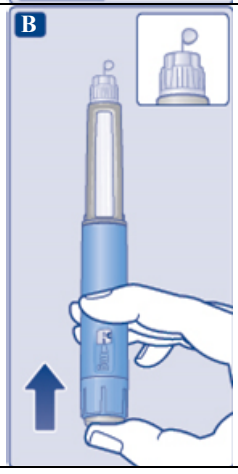
1. Prepare your pen with a new needle

- **Check the name and coloured label** of your pen, to make sure that it contains Ozempic®. This is especially important if you take more than one type of injectable medicine. Using the wrong medicine could cause severe harm to your health.
- **Pull off the pen cap.**



- **Check that the solution in your pen is clear** and colourless. Look through the pen window. If the solution looks cloudy or coloured, do not use the pen.



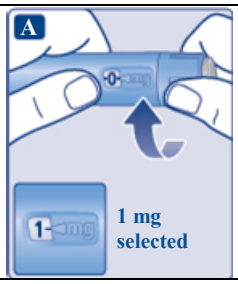
• **Take a new needle** tear off the paper tab. Check the paper tab and the outer needle cap for damages that could affect sterility. If any damage is seen use a new needle. • **Tear off the paper tab.**	
• **Push the needle straight onto the pen. Turn until it is on tight.**	
• **Pull off the outer needle cap and keep it for later.** You will need it after the injection, to safely remove the needle from the pen.	
• **Pull off the inner needle cap and throw it away.** If you try to put it back on, you may accidentally stick yourself with the needle. A drop of solution may appear at the needle tip. This is normal, but you must still check the flow, if you use a new pen for the first time. See step 2 'Check the flow'. **Do not attach a new needle** to your pen until you are ready to take your injection.	
⚠ **Always use a new needle for each injection.** This reduces the risk of blocked needles, contamination, infection and inaccurate dosing.	
⚠ **Never use a bent or damaged needle.**	
2. Check the flow	
• **Before your first injection with each new pen, check the flow.** If your pen is already in use, go to step 3 'Select your dose'. • Turn the dose selector **until the dose counter shows the flow check symbol** (▪▪ ▬).	
• Hold the pen with the needle pointing up. **Press and hold in the dose button** until the dose counter returns to 0. The 0 must line up with the dose pointer. A drop of solution should appear at the needle tip.	

A small drop may remain at the needle tip, but it will not be injected.
If no drop appears, repeat step 2 'Check the flow' up to 6 times. If there is still no drop, change the needle and repeat step 2 'Check the flow' once more.
If a drop still does not appear, dispose of the pen and use a new one.

⚠ **Always make sure that a drop appears** at the needle tip before you use a new pen for the first time. This makes sure that the solution flows.
If no drop appears, you will **not** inject any medicine even though the dose counter may move. **This may indicate a blocked or damaged needle.**
If you do not check the flow before your first injection with each new pen, you may not get the prescribed dose and the intended effect of Ozempic®.

3. Select your dose

- **Turn the dose selector to select 1 mg.**
  Keep turning until the dose counter stops and shows 1 mg.



Only the dose counter and dose pointer will show that 1 mg has been selected.
The dose selector clicks differently when turned forwards, backwards or past 1 mg. Do not count the pen clicks.

⚠ **Always use the dose counter and the dose pointer to see that 1 mg has been selected before injecting this medicine.**
Do not count the pen clicks.
1 mg in the dose counter must line up precisely with the dose pointer to ensure that you get a correct dose.

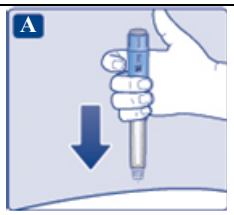
How much solution is left

- **To see how much solution is left,** use the dose counter: Turn the dose selector until the **dose counter stops.** If it shows 1, **at least 1 mg** is left in your pen.
  If the **dose counter stops before 1 mg,** there is not enough solution left for a full dose of 1 mg.

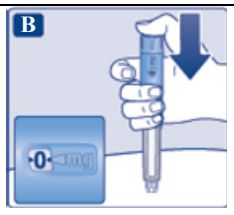
⚠ If there is not enough solution left in your pen for a full dose, do not use it. Use a new Ozempic® pen.

4. Inject your dose

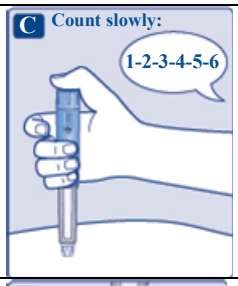
- **Insert the needle into your skin** as your doctor or nurse has shown you.
- **Make sure you can see the dose counter.** Do not cover it with your fingers. This could interrupt the injection.



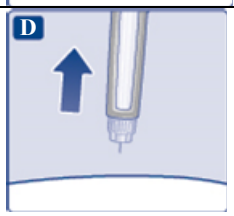
- **Press and hold down the dose button until the dose counter shows 0.** The 0 must line up with the dose pointer. You may then hear or feel a click.



- **Keep the needle in your skin** after the dose counter has returned to 0 and **count slowly to 6.** This is to make sure that you get your full dose.
- If the needle is removed earlier, you may see a stream of solution coming from the needle tip. If so, the full dose will not be delivered.



- **Remove the needle from your skin.** If blood appears at the injection site, press lightly. Do not rub the area.



You may see a drop of solution at the needle tip after injecting. This is normal and does not affect your dose.

⚠ **Always watch the dose counter to know how many mg you inject.** Hold the dose button down until the dose counter shows 0.

How to identify a blocked or damaged needle

– If 0 does not appear in the dose counter after continuously pressing the dose button, you may have used a blocked or damaged needle.
– In this case, you have **not** received any medicine – even though the dose counter has moved from the original dose that you have set.

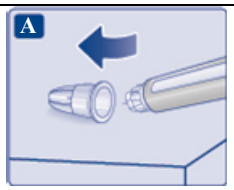
How to handle a blocked needle

Change the needle as described in step 5 'After your injection' and repeat all steps starting with step 1 'Prepare your pen with a new needle'. Make sure you select the full dose you need.

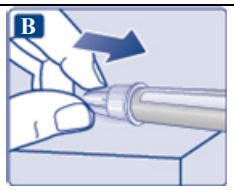
Never touch the dose counter when you inject. This can interrupt the injection.

5. After your injection

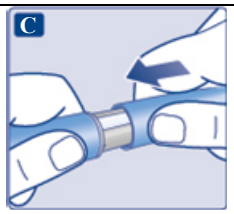
- **Lead the needle tip into the outer needle cap** on a flat surface without touching the needle or the outer needle cap.



- Once the needle is covered, **carefully push the outer needle cap completely on.**
- **Unscrew the needle** and dispose of it carefully in accordance with local guidelines. Ask your doctor, nurse or pharmacist about sharps disposal.



- **Put the pen cap on** your pen after each use to protect the solution from light.



Always dispose of the needle after each injection to ensure convenient injections and prevent blocked needles. If the needle is blocked, you will **not** inject **any** medicine.
When the pen is empty, throw it away **without** a needle on as instructed by your doctor, nurse, pharmacist or local authorities.

⚠ **Never try to put the inner needle cap back on the needle.** You may stick yourself with the needle.
⚠ **Always remove the needle from your pen immediately after each injection.**

This reduces the risk of blocked needles, contamination, infection, leakage of solution and inaccurate dosing.

Further important information

- Always keep your pen and needles **out of the sight and reach of others,** especially children.
- **Never share** your pen or your needles with other people.
- Caregivers must **be very careful when handling used needles** to prevent needle injury and cross-infection.

Caring for your pen

Treat your pen with care. Rough handling or misuse may cause inaccurate dosing. If this happens you might not get the intended effect of this medicine.

- **Do not inject Ozempic® which has been frozen.** If you do that, you might not get the intended effect of this medicine.
- **Do not inject Ozempic® which has been exposed to direct sunlight.** If you do that, you might not get the intended effect of this medicine.
- **Do not expose your pen to dust, dirt or liquid.**
- **Do not wash, soak or lubricate your pen.** If necessary, clean it with a mild detergent on a moistened cloth.
- **Do not drop your pen** or knock it against hard surfaces. If you drop it or suspect a problem, attach a new needle and check the flow before you inject.
- **Do not try to refill your pen.** Once empty, it must be disposed of.
- **Do not try to repair your pen** or pull it apart.