PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PROZEMPIC®

semaglutide injection

2 mg/pen (1.34 mg/mL)
4 mg/pen (1.34 mg/mL)
8 mg/pen (2.68 mg/mL)

Pre-filled pen delivering doses of 0.25 mg or 0.5 mg
Pre-filled pen delivering doses of 1 mg
and
Pre-filled pen delivering doses of 2 mg

ATC code: A10BJ06
Antihyperglycemic Agent

Glucagon-like Peptide-1 (GLP-1) Receptor Agonist

Novo Nordisk Canada
101 – 2476 Argentia Road
Mississauga, Ontario
L5N 6M1

Date of Initial Authorization:
January 4, 2018

Date of Revision:
January 4, 2022

Submission Control No: 248754

RECENT MAJOR LABEL CHANGES

4.2	Recommended Dose and Dosage Adjustment	01/2022

TABLE OF CONTENTS

RECENT MAJOR LABEL CHANGES 2

TABLE OF CONTENTS 2

PART I: HEALTH PROFESSIONAL INFORMATION 4

1 INDICATIONS 4
- 1.1 Pediatrics 4
- 1.2 Geriatrics 4

2 CONTRAINDICATIONS 4

3 SERIOUS WARNINGS AND PRECAUTIONS BOX 5

4 DOSAGE AND ADMINISTRATION 5
- 4.1 Dosing Considerations 5
- 4.2 Recommended Dose and Dosage Adjustment 5
- 4.4 Administration 6
- 4.5 Missed Dose 6

5 OVERDOSAGE 6

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING 7

7 WARNINGS AND PRECAUTIONS 8
- 7.1 Special Populations 10
- 7.1.1 Pregnant Women 10
- 7.1.2 Breastfeeding 11
- 7.1.3 Pediatrics 11
- 7.1.4 Geriatrics 11
- 7.1.5 Renal Insufficiency 11
- 7.1.6 Hepatic Insufficiency 11

8 ADVERSE REACTIONS 11
- 8.1 Adverse Reaction Overview 11
- 8.2 Clinical Trial Adverse Reactions 12
- 8.3 Less Common Clinical Trial Adverse Reactions 15
- 8.5 Post-Market Adverse Reactions 15

9 DRUG INTERACTIONS 15
- 9.2 Overview 15
- 9.4 Drug-Drug Interactions 15
- 9.5 Drug-Food Interactions 16
- 9.6 Drug-Herb Interactions 16
- 9.7 Drug-Laboratory Test Interactions 16
- 9.8 Drug-Lifestyle Interactions 17

10 CLINICAL PHARMACOLOGY 17
10.1 Mechanism of Action 17
10.2 Pharmacodynamics 17
10.3 Pharmacokinetics 18
11 STORAGE, STABILITY AND DISPOSAL 19
12 SPECIAL HANDLING INSTRUCTIONS 20
PART II: SCIENTIFIC INFORMATION 21
13 PHARMACEUTICAL INFORMATION 21
14 CLINICAL TRIALS 21
14.1 Trial Design and Study Demographics 21
14.2 Study Results 24
14.4 Immunogenicity 33
15 MICROBIOLOGY 33
16 NON-CLINICAL TOXICOLOGY 34
PATIENT MEDICATION INFORMATION 36

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

OZEMPIC® is indicated for the once-weekly treatment of adult patients with type 2 diabetes mellitus to improve glycemic control, in combination with:

- diet and exercise in patients for whom metformin is inappropriate due to contraindication or intolerance.
- metformin, when diet and exercise plus maximal tolerated dose of metformin do not achieve adequate glycemic control.
- metformin and a sulfonylurea, when diet and exercise plus dual therapy with metformin and a sulfonylurea do not achieve adequate glycemic control.
- metformin or a sulfonylurea and a sodium-glucose cotransporter 2 inhibitor (SGLT2i), when diet and exercise plus metformin or a sulfonylurea, in addition to an SGLT2i, do not achieve adequate glycemic control.
- basal insulin with metformin, when diet and exercise plus basal insulin with metformin do not achieve adequate glycemic control (see 14 CLINICAL TRIALS).

OZEMPIC® has not been studied in combination with prandial insulin (short acting). OZEMPIC® is not a substitute for insulin.

OZEMPIC® should not be used in patients with type 1 diabetes mellitus (formerly known as insulin-dependent diabetes mellitus or IDDM) or for the treatment of diabetic ketoacidosis.

See DOSAGE AND ADMINISTRATION for information on adjustment of doses of concomitant medications when adding OZEMPIC® to the treatment regimen.

1.1 Pediatrics

Pediatrics (< 18 years of age): The safety and efficacy of OZEMPIC® have not been studied in pediatric populations. OZEMPIC® is not indicated for use in pediatric patients.

1.2 Geriatrics

Geriatrics (> 65 years of age): OZEMPIC® was studied in a limited number of patients 75 years of age or older.

2 CONTRAINDICATIONS

- OZEMPIC® is contraindicated in patients with a personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). See 7 WARNINGS AND PRECAUTIONS.
- OZEMPIC® is contraindicated in patients with hypersensitivity to OZEMPIC® or to any of the product components. See 7 WARNINGS AND PRECAUTIONS.
- OZEMPIC® should not be used during pregnancy or breastfeeding.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Risk of Thyroid C-cell Tumours

- Semaglutide causes treatment-dependent thyroid C-cell tumours at clinically relevant exposures in both sexes of rats and mice (see16 NON-CLINICAL TOXICOLOGY). It is unknown whether semaglutide causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be ruled out by clinical or nonclinical studies.
- OZEMPIC® is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). It is unknown whether monitoring with serum calcitonin or thyroid ultrasound will mitigate human risk of thyroid C-cell tumors. Patients should be counseled regarding the risk and symptoms of thyroid tumors (see 2 CONTRAINDICATIONS, 7 WARNINGS AND PRECAUTIONS, 8 ADVERSE REACTIONS and 16 NON-CLINICAL TOXICOLOGY).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

OZEMPIC® is to be administered once weekly, at any time of the day, with or without meals. OZEMPIC® should not be administered daily.

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).

OZEMPIC® can be used as monotherapy when metformin is not tolerated or is contraindicated, or as combination therapy with one or more antidiabetic drugs (metformin, sulfonylurea [SU], basal insulin, SGLT2i). OZEMPIC® should not be given in combination with other GLP-1 analogs. Combination with DPP-4 inhibitors has not been studied.

When OZEMPIC® is added to existing metformin therapy, the current dose of metformin can be continued unchanged.

An increased risk of hypoglycemia was seen with concomitant use of SU or basal insulin with OZEMPIC®. When OZEMPIC® is added to existing therapy of a sulfonylurea or insulin, a reduction in the dose of sulfonylurea or insulin should be considered to reduce the risk of hypoglycemia. In clinical trials, insulin dose was decreased by 20% at onset of OZEMPIC® treatment. See 7 WARNINGS AND PRECAUTIONS.

4.2 Recommended Dose and Dosage Adjustment

The recommended starting dose of OZEMPIC® is 0.25 mg once weekly. OZEMPIC® 0.25 mg is not a therapeutic dose. After 4 weeks, the dose should be increased to 0.5 mg once weekly. If additional glycemic control is needed after 4 weeks, the dose may be increased to 1 mg once weekly to further improve glycemic control. If additional glycemic control is needed after 4

weeks, the dose may be increased to 2 mg once weekly. The maximum recommended dose is 2 mg once weekly.

Geriatrics (≥ 65 years old)
Based on population PK modeling, no dose adjustment is required based on age. See 10 CLINICAL PHARMACOLOGY,.

Pediatrics (<18 years old)
The safety and efficacy of OZEMPIC® in pediatrics aged below 18 years have not been studied.. OZEMPIC® is not indicated for pediatric use.

Patients with Renal Insufficiency
No dosage adjustment is required for patients with renal insufficiency. OZEMPIC® is not recommended for use in patients with end-stage renal disease (see 7 WARNINGS AND PRECAUTIONS, and 10 CLINICAL PHARMACOLOGY, Pharmacokinetics.

Patients with hepatic insufficiency
The safety and efficacy of OZEMPIC® in patients with hepatic insufficiency has not been studied. Therefore, OZEMPIC® should be used with caution in this patient population (*See* 10 CLINICAL PHARMACOLOGY, Pharmacokinetics.)

4.4 Administration

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.

Inspect OZEMPIC® visually before use. It should appear clear and colourless. Do not use OZEMPIC® if particulate matter and colouration is seen.

When using OZEMPIC® with insulin, instruct patients to administer as separate injections and to never mix the products.

It is acceptable to inject OZEMPIC® and insulin in the same body region but the injections should not be adjacent to each other. Rotate injection sites with each dose. Do not use the same site for each injection. OZEMPIC® should not be administered intravenously or intramuscularly.

4.5 Missed Dose

If a dose is missed, it should be administered as soon as possible 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.

5 OVERDOSAGE

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 event was nausea. All patients recovered without complications.

There is no specific antidote for overdose with OZEMPIC®. 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 OZEMPIC® of approximately 1 week.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Subcutaneous	Injectable, 1.34 mg/mL or 2.68 mg/mL	Disodium phosphate dihydrate, propylene glycol, phenol, and water for injections.

OZEMPIC® is provided in a pre-filled, multi-dose, disposable pen, which contains the drug solution, semaglutide in a 1.5 mL or 3 mL cartridge.

Each 1 mL of OZEMPIC® solution contains 1.34 mg or 2.68 mg of semaglutide and the following non-medicinal ingredients disodium phosphate dihydrate, propylene glycol, phenol, and water for injections. OZEMPIC® is a clear and colourless solution with a pH of 7.4.

The primary packaging contains a 1.5 mL or 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 rubber disc (bromobutyl/polyisoprene) inserted. The cartridge is assembled into a pre-filled multi-dose disposable pen made of polypropylene, polyoxymethylene, polycarbonate and acrylonitrile butadiene styrene.

There are three variants of the pre-filled multi-dose pen for OZEMPIC®.

OZEMPIC® 0.25 mg, 0.5mg/dose contains 1.5 mL solution, equivalent to 2 mg semaglutide.
OZEMPIC® 1 mg/dose contains 3 mL solution, equivalent to 4 mg semaglutide.
OZEMPIC® 2 mg/dose contains 3 mL solution, equivalent to 8 mg semaglutide.

Patients should not administer the full volume of the pen at any time.

NovoFine® Plus needles are included in the OZEMPIC® package.

Pack sizes of:

<u>Carton of 1 Pen</u>

- Pen delivers doses of 0.25 mg or 0.5 mg
- 6 NovoFine® Plus needles
- Intended to be used for dose escalation and maintenance treatment at the 0.5 mg dose

<u>Carton of 1 Pen</u>

- Pen delivers 1 mg doses
- 4 NovoFine® Plus needles

- Intended to be used for maintenance treatment at the 1 mg dose only

Carton of 1 Pen

- Pen delivers 2 mg doses
- 4 NovoFine® Plus needles
- Intended to be used for the maintenance treatment at the 2 mg dose only.

7 WARNINGS AND PRECAUTIONS

Please see the Serious Warnings and Precautions Box at the beginning of Part I: Health Professional Information.

General

OZEMPIC® should not be used in patients with type 1 diabetes mellitus or for the treatment of patients with diabetic ketoacidosis.

OZEMPIC® should not be administered intramuscularly.

Carcinogenesis and Mutagenesis

Risk of Thyroid C-Cell Tumors

In mice and rats, semaglutide caused a treatment-duration-dependent increase in the incidence of thyroid C-cell tumors (adenomas and carcinomas) after lifetime exposure at clinically relevant plasma exposures (see 16 NON-CLINICAL TOXICOLOGY). It is unknown whether semaglutide causes thyroid C-cell tumors, including MTC, in humans as human relevance could not be determined. Thyroid C-cell tumors in rodents are a known class effect for GLP-1 receptor agonists.

In clinical trials, there were no cases of MTC observed in patients treated with OZEMPIC®.

Counsel patients regarding the potential risk for MTC with the use of OZEMPIC® and inform them of symptoms of thyroid tumors (e.g. a mass in the neck, dysphagia, dyspnea, persistent hoarseness).

It is unknown whether monitoring with serum calcitonin or thyroid ultrasound will mitigate the potential risk of MTC, and such monitoring may increase the risk of unnecessary procedures, due to low test specificity for serum calcitonin and a high background incidence of thyroid disease. Patients with thyroid nodules noted on physical examination or neck imaging obtained for other reasons should be referred to an endocrinologist for further evaluation. Although routine monitoring of serum calcitonin is of uncertain value in patients treated with OZEMPIC® if serum calcitonin is measured and found to be elevated, the patient should be referred to an endocrinologist for further evaluation. (see 8.2 Clinical Trial Adverse Reactions

OZEMPIC® is contraindicated in patients with a personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).

Cardiovascular

Heart Rate Increase

OZEMPIC® causes an increase in heart rate (see 10 CLINICAL PHARMACOLOGY). Caution should be observed in patients who have cardiac conditions that might be worsened by an increase in heart rate, such as tachyarrhythmias (see 9 DRUG INTERACTIONS).

PR Interval Prolongation
OZEMPIC® causes a prolongation of the PR interval of the electrocardiogram (see 10 CLINICAL PHARMACOLOGY). Caution should be observed in patients with pre-existing conduction system abnormalities (e.g., marked first-degree AV block or second- or third-degree AV block) or a history of rhythm disturbances (e.g., tachyarrhythmias).

Heart Failure
There is no therapeutic experience in patients with congestive heart failure New York Heart Association (NYHA) class IV.

Endocrine and Metabolism
Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin
Patients receiving OZEMPIC® in conjunction with sulfonylurea or basal insulin may have an increased risk of hypoglycemia. The risk of hypoglycemia may be lowered by a reduction in the dose of sulfonylurea (or other concomitantly administered insulin secretagogues) or insulin when initiating treatment with OZEMPIC®. See 4 DOSAGE AND ADMINISTRATION, and 8 ADVERSE REACTIONS.

Other incretin drugs
Concomitant use of OZEMPIC® with other GLP-1 analogs and DPP-4 inhibitors has not been studied. It is unknown if concomitant use of drugs acting via similar pathways affects the efficacy and safety of OZEMPIC®.

Hepatic/Biliary/Pancreatic
Pancreatitis
Acute pancreatitis has been observed with the use of GLP-1 receptor agonists. In glycemic control trials (see Table 3), acute pancreatitis was confirmed by adjudication in 7 OZEMPIC®-treated patients (0.3 cases per 100 patient years) versus 3 in patients treated with another GLP-1 receptor agonist (0.2 cases per 100 patient years); no cases were seen with placebo or other drug classes. One case of chronic pancreatitis was confirmed in an OZEMPIC®-treated patient. In a 2-year trial (SUSTAIN 6), acute pancreatitis was confirmed by adjudication in 8 OZEMPIC®-treated patients (0.27 cases per 100 patient years of observation) and 10 placebo-treated patients (0.33 cases per 100 patient years of observation), both on a background of standard of care. There were no cases of chronic pancreatitis.

Patients should be informed of the characteristic symptoms of acute pancreatitis. After initiation of OZEMPIC®, observe patients for signs and symptoms of pancreatitis. If pancreatitis is suspected, OZEMPIC® should be discontinued; if confirmed, OZEMPIC® should not be restarted. Consider anti-diabetic therapies other than OZEMPIC® in patients with a history of pancreatitis.

Immune
Hypersensitivity
Severe, life-threatening, generalized allergy, including anaphylaxis, may occur with any GLP-1 receptor agonist, including OZEMPIC®. If a hypersensitivity reaction occurs, the patient should discontinue OZEMPIC® and promptly seek medical advice.

Monitoring and Laboratory Tests
Regular self-monitoring of blood glucose is not needed in order to adjust the dose of OZEMPIC®. However, when initiating treatment with OZEMPIC® in combination with a sulfonylurea or insulin, blood glucose self-monitoring may become necessary to reduce the

dose of the sulfonylurea or insulin in order to reduce the risk of hypoglycemia.

However, patients should be informed that response to all diabetic therapies should be monitored by periodic measurement of A_{1C} levels, with a goal of decreasing these levels towards the normal range. A_{1C} is especially useful for evaluating long-term glycemic control.

Ophthalmologic

Diabetic Retinopathy Complications

In a 2-year trial involving patients with type 2 diabetes and high cardiovascular risk, more events of diabetic retinopathy complications occurred in patients treated with OZEMPIC® (3.0%) compared to placebo (1.8%). The absolute risk increase for diabetic retinopathy complications was larger among patients with a history of diabetic retinopathy at baseline than among patients without a known history of diabetic retinopathy.

Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy. Long-term glycemic control may decrease the risk of diabetic retinopathy. Patients with a history of diabetic retinopathy should be monitored for progression of diabetic retinopathy.

Renal

Renal Insufficiency

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 diarrhea, may cause dehydration which could cause a deterioration of renal function. Monitor renal function in patients with renal insufficiency reporting severe adverse gastrointestinal reactions. See 8 ADVERSE REACTIONS.

In patients treated with GLP-1 receptor agonists, there have been post-marketing reports of acute renal failure and worsening of chronic renal failure, which may sometimes require hemodialysis. Some of these events were reported in patients without known underlying renal disease. A majority of reported events occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration. Because these reactions may worsen renal function, use caution when initiating or escalating doses of OZEMPIC® in patients with renal impairment. Monitor renal function in patients with renal impairment reporting severe adverse gastrointestinal reactions.

No dose adjustment of OZEMPIC® is required for patients with mild, moderate or severe renal impairment. There is limited clinical experience in patients with severe renal impairment (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m2), and caution should be used in this patient population. OZEMPIC® is not recommended for use in patients with end-stage renal disease.

7.1 Special Populations

7.1.1 Pregnant Women

Studies in animals have shown reproductive toxicity (see PART II, Toxicology). No clinical trials in pregnant women have been conducted. Therefore, semaglutide should not be used during pregnancy. Women of childbearing potential are recommended to use contraception when treated with semaglutide. If a patient wishes to become pregnant, or pregnancy occurs, semaglutide should be discontinued. Semaglutide should be discontinued at least 2 months

before a planned pregnancy due to the long half-life. See 10 CLINICAL PHARMACOLOGY, Pharmacokinetics.

7.1.2 Breastfeeding

It is not known whether OZEMPIC® is excreted in human milk. Semaglutide was present in the milk of lactating rats. Because many drugs are excreted in human milk and the effects on the infant are unknown, OZEMPIC® should not be used for the duration of breastfeeding.

7.1.3 Pediatrics

Safety and efficacy of OZEMPIC® have not been studied in pediatric patients. OZEMPIC® is not indicated for patients with Type 2 Diabetes who are under 18 years of age.

7.1.4 Geriatrics

In the pool of glycemic control trials, 1015 (24.7%) OZEMPIC®-treated patients were 65 years of age and above and 136 (3.3%) OZEMPIC®-treated patients were 75 years of age and above. In SUSTAIN 6, a long-term cardiovascular outcome trial, 788 (48.0%) OZEMPIC®-treated patients were 65 years of age and above and 157 (9.6%) OZEMPIC®-treated patients were 75 years of age and above.

No overall differences in safety or efficacy were detected between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out due to limited data in geriatric patients.

7.1.5 Renal Insufficiency

In the glycemic control trials, at baseline, 1108 (35.2%) OZEMPIC®-treated patients had mild renal impairment (eGFR ≥60 but <90 mL/min/1.73 m^2) and 83 (2.6%) OZEMPIC®-treated patients had moderate renal impairment (eGFR ≥30 but <60 mL/min/1.73 m^2). In SUSTAIN 6, 684 (41.7%) OZEMPIC®-treated patients had mild renal impairment, 420 (25.6%) OZEMPIC®-treated patients had moderate renal impairment, and 41 (2.5%) OZEMPIC®-treated patients had severe renal impairment (eGFR <30 mL/min/1.73 m^2). OZEMPIC® should not be used in patients with end stage renal impairment due to very limited clinical experience with OZEMPIC® in this population (5 patients).

7.1.6 Hepatic Insufficiency

The safety and efficacy of OZEMPIC® in patients with hepatic insufficiency has not been studied. Therefore, OZEMPIC® should be used with caution in this patient population. *(See* 10 CLINICAL PHARMACOLOGY*,* Pharmacokinetics*).*

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The most frequently reported adverse reactions in clinical trials were gastrointestinal disorders, including nausea, diarrhea and vomiting. In general, these reactions were mild or moderate in severity. More patients taking OZEMPIC® versus comparator drugs had severe or serious adverse events and/or discontinued treatment due to gastrointestinal disorders.

The following serious adverse reactions are described below or elsewhere in the Product Monograph:

- Risk of Thyroid C-cell Tumors (see 7 WARNINGS AND PRECAUTIONS)
- Pancreatitis (see 7 WARNINGS AND PRECAUTIONS)
- Diabetic Retinopathy Complications (see 7 WARNINGS AND PRECAUTIONS)
- Use with Medications Known to Cause Hypoglycemia (see 7 WARNINGS AND PRECAUTIONS)
- Renal Insufficiency (see 7 WARNINGS AND PRECAUTIONS)

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

In 8 phase 3a trials, 4792 patients were exposed to OZEMPIC® (0.5 mg or 1 mg) alone or in combination with other glucose lowering medicinal products. The duration of the treatment ranged from 30 weeks to 2 years.

In a 40-week phase 3b trial, 959 patients were exposed to OZEMPIC® 1 mg or 2 mg. The safety profile of semaglutide 2 mg was consistent with the safety profile of semaglutide seen in the phase 3a trials. Gastrointestinal disorders were reported in a slightly greater proportion of patients exposed to semaglutide 2 mg (34.0%) compared to semaglutide 1 mg (30.8%). The gastrointestinal adverse reactions led to treatment discontinuation in similar proportions in the semaglutide 1 mg (2.7 %) and 2 mg (3.3 %) treatment groups.

Common Adverse Reactions
The numbers presented in Table 1 are based on a broad pool of seven randomised, placebo- or active-controlled phase 3a trials of 30 or 52 weeks duration, designed to evaluate the efficacy and safety of semaglutide (0.5 and 1.0 mg) in a broad population of patients with type 2 diabetes, from treatment naïve patients to patients with long-standing diabetes on insulin treatment. The pooled comparator group includes placebo and different active comparators (exenatide ER 2.0 mg, sitagliptin, and insulin glargine). The proportions (%) of patients with events presented in Table 1 are Cochran-Mantel-Haenszel adjusted to account for potential confounding by trial. The numbers are for the on-treatment observation period.
In total, the phase 3a pool included 1373 patients exposed to OZEMPIC® 0.5 mg (1165 exposure years), 1777 patients exposed to OZEMPIC® 1.0 mg (1548 exposure years) and 1657 patients exposed to comparator (1467 exposure years).

Table **1** shows common adverse reactions in ≥1% of OZEMPIC®-treated patients and which occurred more frequently in OZEMPIC®-treated patients than comparator-treated (active comparator or placebo) in 7 randomised, placebo- or active-controlled phase 3a trials. This table excludes hypoglycemia, which can be seen in Table 2.

Table 1 Adverse reactions in Active Comparator or Placebo Trials Reported in ≥1% of OZEMPIC®-Treated Patients

Adverse Reaction	Comparator (N=1657) %	OZEMPIC® 0.5 mg (N=1373) %	OZEMPIC® 1 mg (N=1777) %
Gastrointestinal disorders			
Nausea	6.3	17.0	19.9
Diarrhea	5.7	12.2	13.3
Abdominal pain[1]	4.7	8.7	8.1
Vomiting	3.3	6.4	8.4
Constipation	2.7	6.9	6.2
Dyspepsia	2.1	4.1	5.2
Abdominal distension	0.8	2.3	2.9
Gastro-esophageal reflux disease	1.0	1.6	2.7
Eructation	0.2	1.3	1.8
Gastritis	0.5	1.6	1.2
Flatulence	0.5	0.5	1.5
General disorders and administration site conditions			
Fatigue[2]	1.4	2.6	3.3
Hepatobiliary disorders			
Cholelithiasis	0.5	0.7	1.1
Investigations			
Lipase increased[3]	6.4	9.0	9.0
Amylase increased[4]	2.6	3.4	3.0
Weight decreased	0.2	0.9	1.5
Metabolism and nutrition disorders			
Decreased appetite	2.0	6.3	7.2
Nervous system disorders			
Dizziness	1.7	2.8	3.1

[1]Abdominal pain, abdominal pain upper, abdominal pain lower, gastrointestinal pain, abdominal tenderness, abdominal discomfort, epigastric discomfort
[2]Fatigue, asthenia
[3]Lipase increased, lipase abnormal, hyperlipasemia, lipase
[4]Amylase increased, amylase, abnormal, hyperamylasemia, amylase

Gastrointestinal Adverse Reactions
In the pool of placebo- and active controlled trials, gastrointestinal adverse reactions occurred more frequently among patients receiving OZEMPIC® than comparators (comparator 22.0%, 0.5 mg 41.7%, 1 mg 42.1%). More patients receiving OZEMPIC® 0.5 mg (3.9%) and OZEMPIC® 1 mg (5.9%) discontinued treatment due to gastrointestinal adverse reactions than patients receiving comparator (0.9%). Investigators graded the severity of gastrointestinal adverse reactions occurring on 0.5 mg and 1 mg of OZEMPIC® as “mild” in 38.8% and 36.5% of cases, respectively, “moderate” in 9.8% and 12.5% of cases, respectively, or severe in 1.7% and 1.8% of cases, respectively. Most events were of a short duration. The majority of the nausea, vomiting and diarrhea events occurred during dose escalation. Subjects with lower body weight tended to have an increased incidence of gastrointestinal adverse events.

Hypoglycemia
Table 2 summarizes the incidence of severe, documented symptomatic (≤3.9 mmol/L glucose threshold) or severe, blood glucose confirmed symptomatic (≤3.1 mmol/L glucose threshold) hypoglycemia in the placebo-controlled trials. Hypoglycemia was more frequent in patients taking OZEMPIC® and basal insulin, despite basal insulin dose being lowered by 20% at OZEMPIC® treatment onset. Hypoglycemia was more frequent when OZEMPIC® was used in combination with a sulfonylurea. See 7 WARNINGS AND PRECAUTIONS, and 14 CLINICAL TRIALS.

Table 2 Hypoglycemia Adverse Reactions in Placebo-Controlled Trials

	Placebo	OZEMPIC® 0.5 mg	OZEMPIC® 1 mg
Add-on to Basal Insulin with or without Metformin			
(30 weeks)	**N=132**	**N=132**	**N=131**
Severe	0%	0%	1.5%
Documented symptomatic (≤3.9 mmol/L glucose threshold)	15.2%	16.7%	29.8%
Severe or Blood Glucose Confirmed Symptomatic (≤3.1 mmol/Lglucose threshold)	5.3%	8.3%	10.7%

Severe hypoglycemia occurred in 0.8%, 1.2% and 0.9% of patients when OZEMPIC® 0.5 mg, OZEMPIC® 1 mg and comparators, respectively, was co-administered with a sulfonylurea. Documented symptomatic hypoglycemia occurred in 17.3%, 24.4% and 25% of patients when OZEMPIC® 0.5 mg, OZEMPIC® 1 mg and comparators respectively, was co-administered with a sulfonylurea. Severe or blood glucose confirmed symptomatic hypoglycemia occurred in 6.5%,10.4% and 14% of patients when OZEMPIC® 0.5 mg, OZEMPIC® 1 mg and comparators, respectively, was co-administered with a sulfonylurea. Severe or blood glucose confirmed hypoglycemia occurred in 2.7% of patients (4.3 events per 100 PYE) when OZEMPIC® 1 mg was added to SGLT2i compared to none for placebo-treated patients. Documented symptomatic hypoglycemia occurred in 5.3% of patients (13.0 events per 100 PYE) when OZEMPIC® 1 mg was added to SGLT2i compared to none for placebo-treated patients.

Amylase and Lipase Increase
In placebo-controlled trials, patients exposed to OZEMPIC® had a mean increase from baseline in amylase of 13% and lipase of 22% while placebo-treated patients had no increase.

Discontinuation due to an adverse event
The incidence of discontinuation of treatment due to adverse events in placebo- and active controlled trials was 6.1% for patients treated with 0.5 mg OZEMPIC®, 8.7% for patients treated with 1 mg of OZEMPIC® and 3.0% for patients treated with comparator drugs. The most frequent adverse events leading to discontinuation from OZEMPIC® treatment were gastrointestinal.

Diabetic Retinopathy Complications
In a 2-year clinical trial involving 3,297 patients with type 2 diabetes and high cardiovascular risk, diabetic retinopathy complications were an adjudicated composite endpoint (including need for retinal photocoagulation, need for treatment with intravitreal agents, vitreous hemorrhage, and diabetes-related blindness). In this trial events of diabetic retinopathy complications occurred in more patients treated with OZEMPIC® (3.0%) compared to placebo (1.8%). More than 80% of patients with an event of diabetic retinopathy complications had a documented history of diabetic retinopathy at baseline. See 7 WARNINGS AND PRECAUTIONS. In patients that did not have a documented history of diabetic retinopathy the number of events were similar for OZEMPIC® and placebo.

In clinical trials up to 1 year involving 4,807 patients with type 2 diabetes patients, adverse events related to diabetic retinopathy were reported in similar proportions of subjects treated

with OZEMPIC® (1.7%) and comparators (2.0%).

Heart Rate Increase
In placebo- and active-controlled trials, OZEMPIC® 0.5 mg and 1 mg resulted in a mean increase in heart rate of 1-6 beats per minute. There was a mean decrease in heart rate of 0.3 beats per minute in placebo-treated patients. In a 2-year trial in patients with cardiovascular risk factors, 28.8% of OZEMPIC®-treated subjects had an increase in pulse rate of >5 bpm compared to 22.1% on placebo.

8.3 Less Common Clinical Trial Adverse Reactions

Cardiovascular: Increased heart rate (tachycardia, heart rate increased, sinus tachycardia)
Gastrointestinal: Abdominal distension, dyspepsia, and gastritis.
General: Injection site reactions, weight decreased
Immune-system: Anaphylactic reaction (anaphylactic reaction, anaphylactic shock)
Nervous system: Dysgeusia

Injection Site Reactions
In placebo-controlled trials, injection site reactions (e.g. injection-site discomfort, erythema) were reported in 0.2% of OZEMPIC® -treated patients and 0.8% of placebo-treated patients.

8.5 Post-Market Adverse Reactions

The following additional adverse reactions have been reported during post-approval use of OZEMPIC®. Because these events are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Metabolism and nutrition disorders: dehydration, diabetic ketoacidosis and ketosis
Renal and urinary disorders: acute kidney injury, renal impairment and renal failure
Skin and subcutaneous tissue disorders: angioedema
Nervous system disorders: hypoglycemic unconsciousness
Gastrointestinal disorders: pancreatitis
Hepatobiliary disorders: cholecystitis

9 DRUG INTERACTIONS

9.2 Overview

The delay of gastric emptying with semaglutide may influence the absorption of concomitantly administered oral medicinal products. In clinical pharmacology trials assessing the effect of semaglutide 1 mg on the absorption of co-administered oral medications at steady state no clinically relevant drug-drug interactions with semaglutide was observed based on the evaluated medications.

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 3 Established or Potential Drug-Drug Interactions

Semaglutide	Source of Evidence	Effect	Clinical comment
Atorvastatin	CT	No clinically relevant change in AUC or C_{max}	None
Oral Contraceptives (containing ethinylestradiol and levonorgestrel)			
Digoxin	CT	Semaglutide did not change AUC or C_{max}	None
Metformin			
Warfarin (S-warfarin and R-warfarin)			

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

No dose adjustment is required for these oral medications when co-administered with semaglutide.

Drugs that Increase Heart Rate
OZEMPIC® causes an increase in heart rate (see 7 WARNINGS AND PRECAUTIONS & 10 CLINICAL PHARMACOLOGY). The impact on heart rate of co-administration of OZEMPIC® with other drugs that increase heart rate (e.g., sympathomimetic drugs) has not been evaluated in drug-drug interaction studies. As a result, co-administration of OZEMPIC® with these drugs should be undertaken with caution.

Drugs that Cause PR Interval Prolongation
OZEMPIC® causes an increase in the PR interval (see 7 WARNINGS AND PRECAUTIONS & 10 CLINICAL PHARMACOLOGY). The impact on the PR interval of co-administration of OZEMPIC® with other drugs that prolong the PR interval (including, but not limited to, antiarrhythmics, calcium channel blockers, beta-adrenoceptor blockers, digitalis glycosides, HIV protease inhibitors) has not been evaluated. As a result, co-administration of OZEMPIC® with these drugs should be undertaken with caution.

9.5 Drug-Food Interactions

Interactions with food have not been studied.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been studied.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been studied.

9.8 Drug-Lifestyle Interactions

OZEMPIC® 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 hypoglycemia while driving and using machines.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Semaglutide is a GLP-1 analogue with 94% sequence homology to human GLP-1. Semaglutide acts as a GLP-1 receptor agonist that selectively binds to and activates the GLP-1 receptor. The GLP-1 receptor is the target for native GLP-1, an endogenous incretin hormone that potentiates glucose-dependent insulin secretion from the pancreatic beta cells. Unlike native GLP-1, semaglutide has a pharmacokinetic profile in humans suitable for once weekly administration. Following subcutaneous administration, the protracted action profile is based on binding to albumin which reduces the renal clearance and increased enzymatic stability towards the dipeptidyl peptidase (DPPIV) enzyme resulting in a long plasma half-life of approximately one week.

Semaglutide action is mediated via a specific interaction with GLP-1 receptors, leading to an increase in cyclic adenosine monophosphate (cAMP). Semaglutide stimulates insulin secretion in a glucose-dependent manner. Simultaneously, semaglutide lowers glucagon secretion, also in a glucose-dependent manner. Thus, when blood glucose is high, insulin secretion is stimulated and glucagon secretion is inhibited. Conversely, when blood glucose is low semaglutide diminishes insulin secretion and does not impair glucagon secretion. The mechanism of blood glucose lowering also involves a delay in gastric emptying.

10.2 Pharmacodynamics

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

<u>Fasting and Postprandial Glucose</u>
Semaglutide reduced 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%), 2 hour postprandial glucose (4.1 mmol/L) (37%), mean 24 hour glucose concentration (1.7 mmol/L) (22%), and postprandial glucose excursions over (3 meals) (0.6-1.1 mmol/L) compared to placebo.

Semaglutide lowered fasting glucose after the first dose.

<u>First and Second Phase Insulin Secretion</u>
Both first and second phase insulin secretion were increased in patients with type 2 diabetes treated with OZEMPIC® compared to placebo.

<u>Glucagon Secretion</u>
Semaglutide lowered the fasting and postprandial glucagon concentrations. In patients with type 2 diabetes, treatment with 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 hypoglycemia, 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.

Cardiac electrophysiology (QTc)
Semaglutide did not prolong QTc intervals at dose levels up to 1.5 mg at steady state dosing up to 16 weeks in 83 healthy patients in a QTc trial. The effect of 2 mg subcutaneous semaglutide on cardiac repolarization has not been directly tested in a QTc trial.

Heart Rate: In clinical trials, semaglutide treatment was associated with an increase in heart rate at all dose levels. (see 7 WARNINGS AND PRECAUTIONS, 8 ADVERSE REACTIONS and 9 DRUG INTERACTIONS).

PR Interval: Semaglutide causes PR interval prolongation, with no evidence of dose-dependency over the 0.5 to 1.5 mg dose range studied. (see 7 WARNINGS AND PRECAUTIONS and 9 DRUG INTERACTIONS).

QTcI Interval: Semaglutide at doses of 0.5, 1.0, and 1.5 mg was associated with a QTcI-shortening effect over the 0-48 h time frame studied, with no evidence of dose-dependency.

10.3 Pharmacokinetics

Table 4 – Summary of semaglutide pharmacokinetic parameters in patients with Type 2 Diabetes at dose levels of 1 mg and 2 mg derived from population PK modelling

	C_{max}	t_{max}	$t_{1/2}$	AUC_{0-168h}	CL/F	Vss/F
Steady state 1 mg	30	48	Approximately 1 week	4516	0.05	12.5
Steady state 2 mg	62	40	Approximately 1 week	9031	0.05	12.5

Absorption: Absolute bioavailability of s.c semaglutide was 89%. Maximum concentration was reached 1 to 3 days post dose. Semaglutide exposure increased in a dose proportional manner for doses of 0.5 mg, 1 mg and 2 mg.

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 s.c. administration of 0.5 mg and 1 mg semaglutide were approximately 16 nmol/L and 30 nmol/L, respectively. In the trial comparing semaglutide 1 mg and 2 mg, the mean steady state concentrations were 27

nmol/l and 54 nmol/l, respectively.

Similar exposure was achieved with s.c. administration of semaglutide in the abdomen, thigh, or upper arm.

Distribution: The mean volume of distribution of semaglutide following s.c. administration in patients with type 2 diabetes was approximately 12.5 L. Semaglutide was extensively bound to plasma albumin (>99%).

Metabolism: Semaglutide is metabolised through proteolytic cleavage of the peptide backbone and sequential beta-oxidation of the fatty acid sidechain.

Elimination: The primary excretion routes of semaglutide related material were via the urine and faeces. Approximately 3% of the dose was excreted as intact semaglutide via urine.

Clearance of semaglutide in patients with type 2 diabetes 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 Populations and Conditions
Based on a population pharmacokinetic analysis, age, sex, race, ethnicity, renal impairment (mild or moderate), and glycemic status do not have a clinically meaningful effect on the pharmacokinetics of semaglutide. The exposure of semaglutide increases with decreasing body weight and is associated with an increase in gastrointestinal adverse events. Semaglutide doses of 0.5 mg, 1 mg and 2 mg provide adequate systemic exposure over a body weight range of 40-198 kg.

Hepatic Insufficiency: Hepatic insufficiency did not have any impact on the exposure of semaglutide in a single-dose 0.5mg study. The pharmacokinetics of semaglutide were evaluated in patients with different degrees of hepatic insufficiency (mild, moderate, severe) compared with subjects with normal hepatic function in a study. No Phase 3 trials were conducted with subjects with hepatic insufficiency and type 2 diabetes.

Renal Insufficiency: Renal insufficiency did not impact the pharmacokinetics of a single dose of semaglutide in a clinically relevant manner. This was shown in a study with a single dose of 0.5 mg semaglutide in patients with different degree of renal insufficiency (mild, moderate, severe, ESRD) compared with subjects with normal renal function. This was also shown for subjects with type 2 diabetes and with mild, moderate or severe renal insufficiency based on data from phase 3 studies.

11 STORAGE, STABILITY AND DISPOSAL

Keep away from the cooling element. Protect from excessive heat and light. Do not freeze OZEMPIC® and do not use OZEMPIC® if it has been frozen.

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

Recommended Storage Conditions for OZEMPIC®

Prior to first use	After first use	
Refrigerated 2°C to 8°C	Room Temperature below 30°C	Refrigerated 2°C to 8°C
Until expiration date	8 weeks	

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

12 SPECIAL HANDLING INSTRUCTIONS

Each OZEMPIC® pen is for use by a single patient. A OZEMPIC® pen must never be shared between patients, even if the needle is changed.

Substances added to OZEMPIC® may cause degradation of semaglutide. OZEMPIC® must not be mixed with other medicinal products, e.g. infusion fluids.

The patient should be advised to discard the injection needle after each injection in accordance with local requirements.

OZEMPIC® should not be used if it does not appear clear and colourless.

OZEMPIC® can be administered with needles up to a length of 8 mm. The pen is designed to be used with NovoFine® and NovoTwist® disposable needles.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

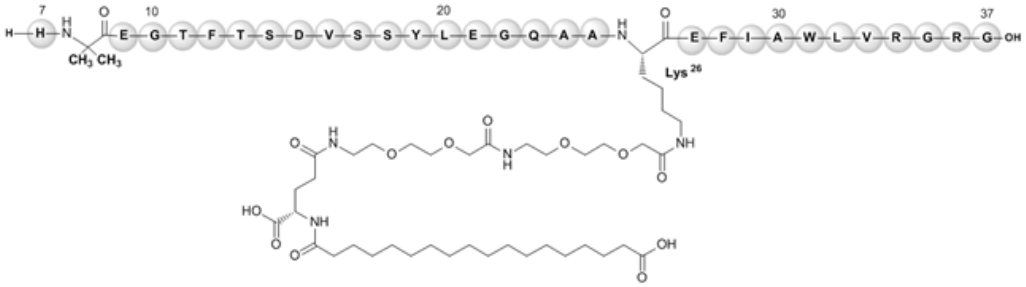
Drug Substance

Proper name: OZEMPIC®

Chemical name: semaglutide

Molecular formula and molecular mass: $C_{187}H_{291}N_{45}O_{59}$ and 4113.6 Dalton

Structural formula:



Physicochemical properties: Each 1 mL of OZEMPIC® solution contains 1.34 mg of semaglutide. Each pre-filled pen contains either 1.5 mL or 3 mL solution of OZEMPIC® equivalent to 2 mg or 4 mg semaglutide.

Product Characteristics
OZEMPIC® (semaglutide) is a clear and colourless solution.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

The efficacy and safety of OZEMPIC® 0.5 mg and 1 mg once-weekly were evaluated in six randomized controlled phase 3a trials. Of these, four trials [3626, 3624, 3625, and 3627 (SUSTAIN 2-5)] were combination trials that had glycemic efficacy assessment as the primary objective, while one 2-year trial 3744 (SUSTAIN 6) had safety (cardiovascular risk assessment) as the primary objective. Two additional Phase 3b trials have been conducted. The first included 1201 patients and was conducted to compare the efficacy and safety of OZEMPIC® 0.5mg and 1mg once weekly versus dulaglutide 0.75 mg and 1.5 mg once weekly (SUSTAIN 7). The second included 302 patients and was conducted to compare the efficacy and safety of OZEMPIC® 1.0 mg once weekly versus placebo in combination with an SGLT2i (SUSTAIN 9).

The efficacy and safety of OZEMPIC® 2 mg once weekly was evaluated in a phase 3b trial (SUSTAIN FORTE) including 961 patients.

Table 4 summarises the trial designs and study demographics of the four pivotal Phase 3a combination trials and the three Phase 3b comparative safety and efficacy trials (SUSTAIN 7, SUSTAIN 9 and SUSTAIN FORTE).

Table 5 summarises the trial designs and study demographics for the cardiovascular safety study (SUSTAIN 6).

Table 5 Summary of patient demographics for clinical trials in specific indication – Type 2 Diabetes

Study #	Trial design and duration	Dosage and route of administration	Background therapy	Study subjects (n = number)[a]	Mean age (Range)	Gender N (%)
3626 (SUSTAIN 2)	Multicentre, multinational, 56-week, randomised, double-blind, double-dummy, parallel-group active-controlled trial	OZEMPIC® 0.5 mg SC once-weekly + sitagliptin placebo once-daily Or OZEMPIC® 1 mg SC once-weekly + sitagliptin placebo once-daily Or sitagliptin 100 mg once-daily + OZEMPIC® placebo 0.5mg SC once-weekly Or sitagliptin 100 mg once-daily + OZEMPIC® placebo 1mg SC once-weekly	Metformin, thiazolidinedione or Metformin + thiazolidinedione	1225	Mean (SD) 55.1 (10.0) Range 23-83	Female: 605 (49.4) Male: 620 (50.6)
3624 (SUSTAIN 3)	Multicentre, multinational, 56-week, randomised, open-label, parallel-group, active-controlled trial	OZEMPIC® 1 mg SC once-weekly Or exenatide ER 2 mg once-weekly	1-2 OADs (metformin, thiazolidinedione or sulphonylurea)	809	Mean (SD) 56.6 (10.7) Range 20-83	Female: 362 (44.7) Male: 447 (55.3)

Study #	Trial design and duration	Dosage and route of administration	Background therapy	Study subjects (n = number)[a]	Mean age (Range)	Gender N (%)
3625 (SUSTAIN 4)	Multicentre, multinational, 30-week, randomised, open-label, parallel-group, active-controlled trial	OZEMPIC® 0.5 mg SC once-weekly Or OZEMPIC® 1 mg SC once-weekly Or Insulin glargine started at 10 IU SC, thereafter titrated to target once-daily	Metformin with or without sulphonylurea	1082	Mean (SD) 56.5 (10.4) Range 22-82	Female: 508 (47.0) Male: 574 (53.0)
3627 (SUSTAIN 5)	Multicentre, multinational, 30-week, randomised, double-blind, parallel-group, placebo-controlled trial	OZEMPIC® 0.5 mg SC once-weekly Or OZEMPIC® 1 mg SC once-weekly Or placebo 0.5 mg SC once-weekly Or placebo 1 mg SC once-weekly	Basal insulin with or without metformin	396	Mean (SD) 58.8 (10.1) Range 19-86	Female: 174 (43.9) Male: 222 (56.1)
4216 (SUSTAIN 7)	Multicentre, multinational, 40-week, randomised, open-label, parallel-group, active-controlled trial	OZEMPIC® 0.5 mg SC once-weekly Or OZEMPIC® 1.0 mg SC once-weekly Or Dulaglutide 0.75 mg SC once-weekly Or Dulaglutide 1.5 mg SC once-weekly	Metformin	1201	Mean (SD) 56 (10.6) Range 22 - 84	Female: 537 (44.8) Male: 662 (55.2)
4269 (SUSTAIN 9)	Multicentre, multinational 30-week randomised, double-blind, placebo-controlled, two arm, parallel-group trial	OZEMPIC® 1.0 mg SC once-weekly Or Placebo	SGLT2 either with or without Metformin or Sulfonylurea	302	Mean (SD) 57 (9.5) Range 25 – 83	Female: 126 (41.7) Male: 176 (58.3)

Study #	Trial design and duration	Dosage and route of administration	Background therapy	Study subjects (n = number)[a]	Mean age (Range)	Gender N (%)
4506 (SUSTAIN FORTE)	Multicentre, multinational, 40 week randomised, double-blind, active-controlled trial	OZEMPIC® 1.0 mg SC once-weekly + OZEMPIC® 1.0 mg SC once-weekly OR OZEMPIC® 1.0 mg SC once-weekly + placebo 1 mg SC once-weekly	Metformin with or without Sulfonylurea	959	Mean (SD) 58 (10.0) Range 27 - 85	Female: 398 (41.4) Male: 563 (58.6)

[a]Randomized subjects exposed to at least one dose of semaglutide. For SUSTAIN 9 this includes all randomized subjects including one un-exposed subject
OAD = Oral anti-diabetic
SD = Standard Deviation
SC = subcutaneous
SGLT2i = sodium-glucose cotransporter 2 inhibitor

Table 6 Summary of patient demographics for clinical trials - Cardiovascular Safety

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
3744 (SUSTAIN 6)	Multicentre, multinational, 104-week, randomised, double-blind, parallel-group, placebo-controlled cardiovascular outcomes trial	OZEMPIC® 0.5 mg SC once-weekly + standard of care Or OZEMPIC® 1 mg SC once-weekly + standard of care Or placebo 0.5 mg SC once-weekly + standard of care Or placebo 1 mg SC once-weekly + standard of care	3297[a]	Mean (SD) 64.6 (7.4) Range 50-89	Female: 1295 (39.3) Male: 2002 (60.7)

[a]All Randomized subjects.

14.2 Study Results

Combination with metformin and/or thiazolidinediones - SUSTAIN 2

In a 56-week randomized, double-blind double-dummy, active-controlled, parallel-group trial, 1231 patients were randomized 2:2:1:1 to OZEMPIC® 0.5 mg/sitagliptin placebo, OZEMPIC® 1 mg/sitagliptin placebo, sitagliptin/OZEMPIC® 0.5 mg placebo or sitagliptin/OZEMPIC® 1.0 mg placebo, all in combination with metformin (94%) and/or TZD (6%). Subjects continued pre-trial background medication throughout the entire trial. The primary objective was to compare the effect of once weekly dosing of 2 dose levels of semaglutide vs sitagliptin 100 mg once-daily on

glycemic control after 56 weeks of treatment.

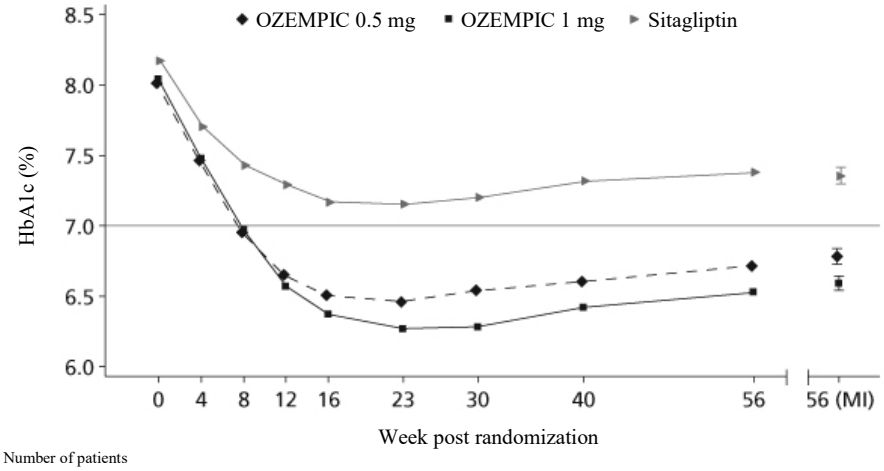
Patients had a mean age of 55 years and a mean duration of type 2 diabetes of 6.6 years, race: 68% White, 5% Black or African-American and 25% Asian, ethnicity: 17% were Hispanic or Latino (n=209). 51% were males and the mean BMI was 32 kg/m2.

Treatment with OZEMPIC® 0.5 mg and 1 mg once-weekly for 56 weeks resulted in a statistically superior reduction in HbA1c compared to sitagliptin (see Table 7 and Figure 1).

Table 7 Results at Week 56 in a Trial of OZEMPIC® Compared to Sitagliptin-Combination with metformin and/or thiazolidinediones

	OZEMPIC® 0.5 mg	**OZEMPIC® 1 mg**	**Sitagliptin 100mg**
Intent-to-Treat (ITT) Population (N)[a]	409	409	407
HbA_{1c} (%)			
Baseline (mean)	8.0	8.0	8.2
Change from baseline at week 56[b]	-1.3	-1.5	-0.7
Difference from sitagliptin[b] [95% Confidence Interval]	-0.6 [-0.7; -0.4]	-0.8 [-0.9; -0.6]	-
p-value[c]	<0.0001	<0.0001	-
Patients (%) achieving HbA_{1c} <7%	66	73	40
Fasting Plasma Glucose (mmol/L)			
Baseline (mean)	9.3	9.3	9.6
Change from baseline at week 56[b]	-1.95	-2.41	-1.25
Body weight (kg)			
Baseline (mean)	89.9	89.2	89.3
Change from baseline at week 56[b]	-4.2	-5.5	-1.7

[a]The intent-to-treat population includes all randomized and exposed patients. At week 56 the primary HbA1c endpoint was missing for 7%, 5% and 6% of patients and during the trial rescue medication was initiated by 5%, 2% and 19% of patients randomized to OZEMPIC® 0.5 mg, OZEMPIC® 1 mg and sitagliptin, respectively. Missing data were imputed using multiple imputation based on retrieved dropouts.
[b]Intent-to treat analysis using ANCOVA adjusted for baseline value and country.
[c] 2-sided p-value for non-inferiority (margin 0.3%) and superiority, tested hierarchically



Number of patients				
OZEMPIC 0.5 mg	409	383	382	409
OZEMPIC 1 mg	409	378	387	409
Sitagliptin	407	387	384	407

Observed mean HbA1c at scheduled visits and retrieved dropout multiple imputation (MI) based estimate at week 56 with standard error

Figure 1 Mean HbA1c (%) over time - baseline to week 56 (SUSTAIN 2)

Combination with metformin or metformin with sulfonylurea - SUSTAIN 3
In a 56-week randomized open-label active-controlled trial, 813 patients on metformin alone (49%), metformin with sulfonylurea (45%) or thiazolidinediones (6%) were randomized 1:1 to OZEMPIC® 1 mg once-weekly or exenatide ER 2 mg once-weekly. Subjects were to continue pre-trial background medication throughout the entire trial.

The primary objective was to compare the effect of semaglutide 1.0 mg once-weekly vs exenatide ER 2.0 mg once-weekly on glycemic control after 56 weeks of treatment.

Patients had a mean age of 57 years and a mean duration of type 2 diabetes of 9 years, race: 84% White, 7% Black or African-American and 2% Asian, ethnicity: 24% (n=197) Hispanic or Latino. 55% were males and the mean BMI was 34 kg/m^2.

Treatment with OZEMPIC® 1 mg once-weekly for 56 weeks resulted in a statistically superior reductions in HbA_{1c} compared to exenatide ER 2 mg once-weekly (see Table 8).

Table 8 Results at Week 56 in a Trial of OZEMPIC® Compared to Exenatide 2 mg once-weekly - Combination with metformin or metformin with sulfonylurea

	OZEMPIC® 1 mg	Exenatide ER 2 mg
Intent-to-Treat (ITT) Population (N)[a]	404	405
HbA_{1c} (%)		
Baseline (mean)	8.4	8.3
Change at baseline week 56[b]	-1.4	-0.9
Difference from exenatide ER[b] [95% Confidence Interval]	-0.5 [-0.7; -0.3]	-
p-value[c]	<0.0001	
Patients (%) achieving HbA_{1c} <7%	62	40
Fasting Plasma Glucose (mmol/L)		
Baseline (mean)	10.6	10.4
Change from baseline at week 56[b]	-2.47	-1.87
Body weight (kg)		
Baseline (mean)	96.2	95.4
Change at baseline week 56[b]	-4.8	-2.0

[a]The intent-to-treat population includes all randomized and exposed patients. At week 56 the primary HbA1c endpoint was missing for 9% and 11% of patients and during the trial rescue medication was initiated by 5% and 10% of patients randomized to OZEMPIC® 1 mg and exenatide ER 2 mg, respectively. Missing data were imputed using multiple imputation based on retrieved dropouts.
[b]Intent-to-treat analysis using ANCOVA adjusted for baseline value and country.
[c]2-sided p-value for non-inferiority (margin 0.3%) and superiority, tested hierarchically

Combination with 1-2 oral antidiabetic drugs: metformin monotherapy or metformin and sulfonylurea- SUSTAIN 4

In a 30-week open-label active-controlled, parallel-group trial, 1089 patients were randomised 1:1:1 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%). Subjects were to continue pre-trial background medication throughout the entire trial. Patients on insulin glargine started on 10 U injected once-daily. The insulin dose adjustment aimed to reach a pre-breakfast FPG of 4.0 to <5.5 mmol/L (71- <100 mg/dL), with no maximum dose specified. The mean daily insulin dose at the end of the trial was 29 U per day.

The primary objective was to compare the effect of once-weekly dosing of 2 dose levels of semaglutide vs insulin glargine once-daily on glycemic control after 30 weeks of treatment.

Patients had a mean age of 57 years and a mean duration of type 2 diabetes of 8.6 years, race: 77% White, 9% Black or African-Americans and 11% Asian, ethnicity: 20% (n=213) Hispanic or Latino. 53% were male and the mean BMI was 33 kg/m^2.

Treatment with OZEMPIC® 0.5 mg and 1 mg once-weekly for 30 weeks resulted in a statistically superior reduction- in HbA_{1c} compared to insulin glargine (see Table 9).

Table 9 Results at Week 30 in a Trial of OZEMPIC® Compared to Insulin Glargine - Combination with 1-2 oral antidiabetic drugs: metformin monotherapy or metformin and sulfonylurea

	OZEMPIC® 0.5 mg	OZEMPIC® 1 mg	Insulin Glargine
Intent-to-Treat (ITT) Population (N)[a]	362	360	360
HbA_{1c} (%)			
Baseline (mean)	8.1	8.2	8.1
Change from baseline at week 30[b]	-1.2	-1.5	-0.9
Difference from insulin glargine[b] [95% Confidence Interval]	-0.3 [-0.5; -0.1]	-0.6 [-0.8; -0.4]	-
p-value[c]	<0.0047	<0.0001	
Patients (%) achieving HbA_{1c} <7%[c]	55	66	40
Fasting Plasma Glucose (mmol/L)			
Baseline (mean)	9.6	9.9	9.7
Change from baseline at week 30[b]	-1.93	-2.56	-2.06
Body weight (kg)			
Baseline (mean)	93.7	94.0	92.6
Change from baseline at week 30[b]	-3.2	-4.7	0.9

[a]The intent-to-treat population includes all randomized and exposed patients. At week 30 the primary HbA1c endpoint was missing for 8%, 6% and 6% of patients and during the trial rescue medication was initiated by 4%, 3% and 1% of patients randomized to OZEMPIC® 0.5 mg, OZEMPIC® 1 mg and insulin glargine, respectively. Missing data were imputed using multiple imputation based on retrieved dropouts.
[b]Intent-to-treat analysis using ANCOVA adjusted for baseline value, country and stratification factors.
[c]2-sided p-value for non-inferiority (margin 0.3%) and superiority, tested hierarchically

Combination with basal insulin - SUSTAIN 5

In a 30-week randomized double-blind parallel-group trial, 397 patients inadequately controlled with basal insulin with or without metformin were randomized 2:2:1:1 to OZEMPIC® 0.5 mg once-weekly, OZEMPIC® 1 mg once-weekly or placebo 0.5 mg or placebo 1.0 mg once-weekly as add-on to the pre-trial background medication. Patients with HbA_{1c} ≤ 8.0% at screening reduced the insulin dose by 20% at start of the trial to reduce the risk of hypoglycemia.

The primary objective was to demonstrate superiority of once-weekly dosing of 2 dose levels of semaglutide vs placebo on glycemic control in subjects with T2D on basal insulin.

Patients had a mean age of 59 years and a mean duration of type 2 diabetes of 13 years, race: 78% White, 5% Black or African-American, 17% Asian, ethnicity: 12% (n=46) Hispanic or Latino. 56% were male and the mean BMI was 32 kg/m^2.

Treatment with OZEMPIC® 0.5 mg and 1 mg resulted in a statistically superior reduction in HbA_{1c} after 30 weeks of treatment compared to placebo (see Table 10).

Table 10 Results at Week 30 in a Trial of OZEMPIC® in Combination with Basal Insulin With or Without Metformin

	OZEMPIC® 0.5 mg	OZEMPIC® 1 mg	Placebo
Intent-to-Treat (ITT) Population (N)[a]	132	131	133
HbA_{1c} (%)			
Baseline (mean)	8.4	8.3	8.4
Change from baseline at week 30[b]	-1.3	-1.7	-0.2
Difference from placebo[b] [95% Confidence Interval]	-1.1 [-1.4; -0.8]	-1.6 [-1.8; -1.3]	-
p-value[c]	<0.0001	<0.0001	
Patients (%) achieving HbA_{1c} <7%	56	73	13
Fasting Plasma Glucose (mmol/L)			
Baseline (mean)	8.9	8.5	8.6
Change from baseline at week 30[b]	-1.55	-2.17	-0.45
Body weight (kg)			
Baseline (mean)	92.7	92.5	89.9
Change from baseline at week 30[b]	-3.5	-6.0	-1.2

[a]The intent-to-treat population includes all randomized and exposed patients. At week 30 the primary HbA1c endpoint was missing for 7%, 5% and 5% of patients and during the trial rescue medication was initiated by 14%, 2% and 1% of patients randomized to placebo, OZEMPIC® 0.5 mg and OZEMPIC® 1 mg, respectively. Missing data were imputed using multiple imputation based on retrieved dropouts.
[b]Intent-to-treat analysis using ANCOVA adjusted for baseline value, country and stratification factors.
[c]2-sided p-value for superiority, tested hierarchically

Cardiovascular Outcomes in Patients with Type 2 Diabetes and High Cardiovascular Risk

SUSTAIN 6

SUSTAIN 6 was a 104-week, double-blind trial in which 3,297 patients with type 2 diabetes and high risk of cardiovascular events were randomized to OZEMPIC® 0.5 mg once weekly, OZEMPIC® 1 mg once weekly, or placebo in addition to standard-of-care. The primary objective of the trial was to confirm that treatment with semaglutide does not result in any unacceptable increase in cardiovascular risk as compared to placebo in adults with type 2 diabetes. This was done by demonstrating that the upper limit of the two-sided 95% confidence interval (CI) of the hazard ratio for semaglutide versus placebo is less than 1.8 when comparing time to first occurrence of a major adverse cardiovascular event (MACE).

In total, 2,735 (83%) of the patients had a history of cardiovascular disease and 562 (17%) were at high risk but without known cardiovascular disease. The mean age at baseline was 65 years, and 61% were men. The mean duration of diabetes was 13.9 years, and mean BMI was 33 kg/m2. Overall, 83% were White, 7% were Black or African American, and 8% were Asian; 16% identified as Hispanic or Latino ethnicity. Concomitant diseases of patients in this trial included, but were not limited to, heart failure (24%), hypertension (93%), history of ischemic stroke (12%) and history of a myocardial infarction (33%).

In total, 98.0% of the patients completed the trial and the vital status was known at the end of the trial for 99.6%. The primary composite endpoint was the time from randomisation to first occurrence of a major adverse cardiovascular event (MACE): cardiovascular death, non-fatal myocardial infarction or non-fatal stroke. The total number of primary component MACE endpoints was 254 (108 [6.6%] with OZEMPIC® and 146 [8.9%] with placebo). The estimated hazard ratio of MACE associated with OZEMPIC® relative to placebo was 0.74 with a 95% confidence interval of (0.58, 0.95). No increased risk for MACE was observed with OZEMPIC®.

In the SUSTAIN 6 study, based on a post-hoc test for superiority once non-inferiority had been demonstrated, treatment with OZEMPIC® showed a statistically significant reduction in the occurrence of MACE. The overall MACE reduction was driven by the non-fatal stroke and non-fatal myocardial infarction components of MACE.

The results of SUSTAIN 6, including the contribution of each component to the primary composite endpoint, are shown in Figure 2.

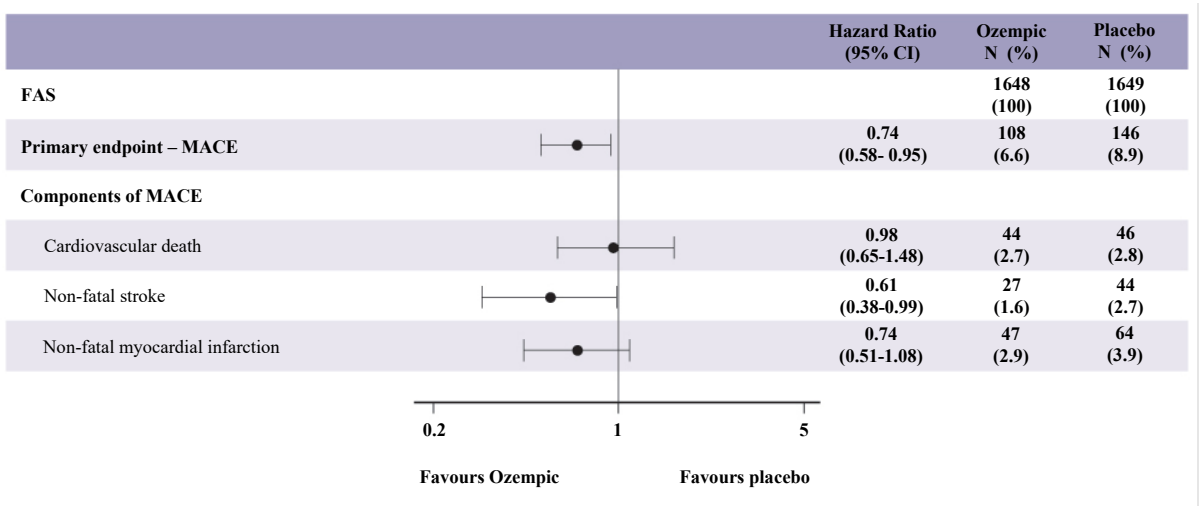


Figure 2 Forest plot: analyses of each individual cardiovascular event (SUSTAIN 6)

OZEMPIC® vs. dulaglutide both in combination with Metformin - SUSTAIN 7
In a 40-week, open-label trial, 1201 patients were randomized 1:1:1:1 to once-weekly OZEMPIC® 0.5mg, dulaglutide 0.75mg, OZEMPIC® 1.0mg, or dulaglutide 1.5 mg. Subjects continued pre-trial background medication of daily metformin throughout the entire trial.

The primary objective was to compare the effect of once-weekly dosing of two dose levels of OZEMPIC® versus once-weekly dosing of each of the two dose levels of dulaglutide on glycemic control in subjects on a background treatment with metformin.

Patients had a mean duration of type 2 diabetes of 7.4 years and a mean BMI of 33.5 kg/m^2. Patients were 77% White, 6% Black or African-American, 16% Asian ethnicity, 11% (n=138) were Hispanic or Latino.

Treatment with OZEMPIC® 0.5 mg and 1 mg resulted in a statistically superior reduction in HbA_{1c} after 40 weeks of treatment compared to dulaglutide (see Table 11).

Table 11 Results at Week 40 in a Trial of OZEMPIC® compared to dulaglutide in Combination with Metformin

	OZEMPIC® 0.5 mg	Dulaglutide 0.75 mg	OZEMPIC® 1 mg	Dulaglutide 1.5 mg
Intent-to-Treat (ITT) Population (N)[a]	**301**	**299**	**300**	**299**
HbA_{1c} (%)[d]				
Baseline (mean)	8.3	8.2	8.2	8.2
Change from baseline at week 40[b]	-1.4	-1.1	-1.6	-1.3
Difference from dulaglutide [95% CI][b]	-0.3 [-0.4; -0.1]	-	-0.3 [-0.5; -0.1]	-
p-value[b]	0.0017		0.0004	
Patients (%) achieving HbA_{1c} <7%	65[c]	51	73[c]	63
FPG (mmol/l)				
Baseline (mean)	9.8	9.7	9.8	9.6
Change from baseline at week 40[b]	-2.0	-2.0	-2.6	-2.0
Body weight (kg)				
Baseline (mean)	96.4	95.6	95.5	93.4
Change from baseline at week 40[b]	-4.2	-2.1	-5.8	-2.8
Difference from dulaglutide [95% CI][b]	-2.1 [-3.0; -1.3]	-	-3.1 [-3.9; -2.3]	-

[a]The intent-to-treat population includes all randomized and exposed patients. At week 40 the primary HbA1c endpoint was missing for 8%, 9%, 5% and 6% of patients and during the trial rescue medication was initiated by 1%, 2%, 5% and 2% of patients randomized to OZEMPIC® 0.5 mg, OZEMPIC® 1.0 mg, dulaglutide 0.75 mg and dulaglutide 1.5 mg, respectively. Missing data were imputed using multiple imputation based on retrieved drop outs.
[b]Intent-to-treat analysis using ANCOVA adjusted for baseline value and country.
[c]2-sided p-value < 0.01, logistic regression analysis adjusted for baseline value and region.
[d]2-sided p-value <0.0001 for non-inferiority (margin 0.4%) and superiority, tested hierarchically within dose level in the primary mixed model of repeated measurement analysis.

OZEMPIC® vs. placebo as an add on to SGLT2i with or without metformin or sulfonylurea - SUSTAIN 9

In a 30-week randomized, double-blind, placebo-controlled, multicentre, multinational, two-arm, parallel-group trial, 302 patients were randomized 1:1 to OZEMPIC® 1.0 mg or placebo both in combination with an SGLT2i. Subjects continued pre-trial background medication of metformin or a sulfonylurea throughout the entire trial. The randomization was stratified based on anti-diabetic background medication at screening (subject using SU or not using SU) and country (Japan/other). The primary objective was to compare the effect of once weekly dosing of OZEMPIC® in combination with an SGLT2i on glycemic control after 30 weeks of treatment.

Patients had a mean age of 57 years and a mean duration of type 2 diabetes of 9.7 years, race: 69% White, 4% Black or African-American and 24% Asian, ethnicity: 7% were Hispanic or Latino (n = 22). 58% were males and the mean body weight and mean BMI were 89.6 kg and 31.1 kg/m^2 respectively in the semaglutide group and 93.8 kg and 32.7 kg/m^2 in the placebo group.

In this trial, 99.7% of subjects were on SGLT-2 inhibitors, 71.5% were on metformin and 12.9%

were on SU. The most commonly used SGLT-2 inhibitors in this trial were empagliflozin (33.8%), dapagliflozin (35.1%) and canagliflozin (22.5%).

Treatment with OZEMPIC® 1 mg once-weekly in combination with an SGTL2i for 30 weeks resulted in a statistically superior reduction in HbA1c compared to placebo.

Table 12 Results at Week 30 in a Trial of OZEMPIC® vs. placebo as an add on to SGLT2i with or without metformin or sulfonylurea

	OZEMPIC® 1 mg	Placebo
Intent-to-Treat (ITT) Population (N)[a]	**151**	**151**
HbA_{1c} (%)		
Baseline (mean)	8.0	8.1
Change at baseline week 30[b]	-1.3	-0.2
Difference from Placebo[b] [95% Confidence Interval]	-1.14 [-1.37; -0.92]	
p-value[b]	<0.0001	
Patients (%) achieving HbA_{1c} <7%	70	20
Fasting Plasma Glucose (mmol/L)		
Baseline (mean)	9.11	8.94
Change from baseline at week 30[b]	-1.69	-0.08
Body weight (kg)		
Baseline (mean)	89.6	93.8
Change at baseline week 30[b]	-4.1	-1.0

[a]The intent-to-treat population includes all randomized patients. At week 30 the primary HbA1c endpoint was missing for 5.3% and 6.6% of patients and during the trial rescue medication was initiated by 0.7% and 5.3% of patients randomized to OZEMPIC® 1.0 mg and placebo, respectively. Missing data were imputed using multiple imputation based on retrieved drop outs.
[b]Intent-to-treat analysis using ANCOVA adjusted for baseline value, stratification (diabetic background medication at screening: using SU or not using SU) and region.

OZEMPIC® 2.0 mg vs. OZEMPIC® 1.0 mg as add on to metformin with or without a sulfonylurea – SUSTAIN FORTE

In a 40-week double-blind trial, 961 patients inadequately controlled with metformin with or without sulfonylurea were randomised to OZEMPIC® 1 mg once weekly or OZEMPIC® 2 mg.

Patients had a mean age of 58 years and a mean duration of type 2 diabetes of 9.5 years, 88.1% were White, 4.5% were Black or African-American and 7.2% were Asian. For ethnicity, 11.5% of patients (n = 111) were Hispanic or Latino. Mean BMI was 34.6 kg/m^2.

Treatment with OZEMPIC® 2 mg resulted in a statistically superior reduction in HbA1c after 40 weeks of treatment compared to OZEMPIC® 1 mg.

Table 13 Results at Week 40 in a Trial of OZEMPIC® 2 mg vs. OZEMPIC® 1 mg in combination with metformin, with or without sulfonylurea

	OZEMPIC® 1 mg	OZEMPIC® 2 mg
Intent-to-Treat (ITT) Population (N)[a]	481	480
HbA_{1c} (%)		
Baseline (mean)	8.8	8.9
Change at baseline week 40[b]	-1.9	-2.1
Difference from 1 mg[b] [95% Confidence Interval]		-0.18 [-0.31 ; -0.04]
p-value[b]		0.0098
Patients (%) achieving HbA_{1c} <7%	57.5	67.6
Fasting Plasma Glucose (mmol/L)		
Baseline (mean)	10.9	10.7
Change from baseline at week 40[b]	-3.07	-3.39
Body weight (kg)		
Baseline (mean)	98.6	100.1
Change at baseline week 40[b]	-5.6	-6.4

[a]The intent-to-treat population includes all randomized patients. At week 40 the primary HbA1c endpoint was missing for 5.0% and 3.1% of patients and during the trial rescue medication was initiated by 1.7% and 4.2% of patients randomized to OZEMPIC® 2.0 mg and OZEMPIC® 1.0 mg, respectively. Missing data were imputed using multiple imputation based on retrieved drop outs.
[b]Intent-to-treat analysis using ANCOVA adjusted for baseline value, country and stratification factors.
[c]2-sided p-value for superiority.

14.4 Immunogenicity

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, the incidence of antibodies to semaglutide cannot be directly compared with the incidence of antibodies of other products.

Across the glycemic control trials in which patients were administered up to 1 mg OZEMPIC®, 32 (1%) OZEMPIC®-treated patients developed anti-drug antibodies (ADAs) to the active ingredient in OZEMPIC® (i.e., semaglutide). Of these, 19 patients (0.6% of the overall population) developed antibodies cross-reacting with native GLP-1 and none developed semaglutide-neutralizing antibodies or semaglutide ADAs with endogenous GLP-1 neutralizing effect.

The presence of semaglutide ADAs did not correlate with reduced efficacy or safety of OZEMPIC® in this limited patient population

15 MICROBIOLOGY

Not Applicable.

16 NON-CLINICAL TOXICOLOGY

Safety Pharmacology

Acute effects of semaglutide on vital organ function (central nervous system, cardiovascular system and respiration) and renal function were evaluated following subcutaneous dosing in rats or telemetered conscious unrestrained cynomolgus monkeys. Semaglutide was generally well tolerated, but displayed pharmacologically-mediated effects of abnormal gait (walking on toes), decreased touch response, passivity, dirty muzzle, lethargy, piloerection, and increased acute transient diuresis in the rat, at doses below the human Cmax exposure at the maximal recommended human dose (MRHD). In the monkey, no adverse effects were identified on acute cardiovascular function, at doses up to 7-fold the Cmax exposure at the MRHD. *In vitro* investigations (hERG ion channel assay and isolated rabbit Purkinje fibres) indicated no effects on cardiac repolarisation.

General Toxicology

Repeat dose toxicity studies were conducted in mice, rats and monkeys. Generally, decreased food consumption was observed in all studies and was accompanied by reduced body weight gain and body weights. Secondary to these effects, non-adverse clinical pathology and organ weight changes were observed across species. Clinical signs of decreased activity, hunched posture, and piloerection were also observed, during the first few weeks of dosing at the highest doses.

In a 13-week repeat-dose toxicity study, mice were dosed subcutaneously with 1, 3 and 10 mg/kg/day (9, 30 and 90-fold the human exposure at the MRHD based on animal AUC, respectively). Thyroid C-cell hyperplasia was observed at all dose levels and consequently, a NOAEL could not be identified for this study.

In a 26-week repeat-dose toxicity study, rats were dosed subcutaneously with 0.03, 0.13, and 0.6 mg/kg/day (below, 3-, and 14-fold the human exposure at the MRHD based on AUC, respectively). In the absence of any adverse findings, the NOAEL was determined to be 0.6 mg/kg/day.

In a 52-week repeat-dose toxicity study, cynomolgus monkeys were dosed subcutaneously with 0.01, 0.06, and 0.36 mg/kg/day (below, 2-, and 14-fold the human exposure at the MRHD based on AUC, respectively). Electrocardiography (ECG) recordings revealed a continuous left-bundle-branch-block ECG recording in Weeks 26 and 52 in one high-dose female. In addition, hisopathology revealed multifocal myocardial vacuolation, with karyomegaly, in the left ventricle of one high-dose male. As it could not be excluded that these findings were treatment related, 0.06 mg/kg twice-weekly was determined to be the NOAEL.

Carcinogenicity

Non-lethal thyroid C-cell tumours observed in rodents are a class effect for GLP-1 receptor agonists. In a 2-year carcinogenicity study in CD-1 mice, subcutaneous doses of 0.3, 1 and 3 mg/kg/day (2-, 9-, and 31-fold the human exposure at the MRHD based on AUC, respectively) was administered to the males, and 0.1, 0.3 and 1 mg/kg/day (below, 2-, and 9-fold the human exposure at the MRHD based on AUC, respectively) was administered to the females. High incidence rates of focal/multifocal C-cell hyperplasia and C-cell adenoma were observed in both sexes at all doses. In control animals, the incidence rate of C-cell hyperplasia was very low and no incidences of C-cell adenoma were observed. The increase in thyroid C-cell adenomas was statistically significant in both sexes at all doses. A numerical increase in C-cell carcinomas was observed in males and females at all doses, while no incidences of C-cell carcinomas were

observed in control animals. A NOAEL could not be identified for this study.

In a 2-year carcinogenicity study in Sprague Dawley rats, subcutaneous doses of 0.0025, 0.01, 0.025 and 0.1 mg/kg/day were administered (below, below, below, and 3-fold the human exposure at the MRHD based on AUC, respectively). An increase in incidence of focal C-cell hyperplasia of the thyroid was observed in males at all doses. A statistically significant increase in thyroid C-cell adenomas was observed in males and females at all doses, and a statistically significant increase in thyroid C-cell carcinomas was observed in males at ≥0.01 mg/kg/day, and in females at 0.1 mg/kg/day. The increases in the incidences of thyroid C-cell adenomas and carcinomas were largely dose-dependent. A NOAEL could not be identified for this study.

In both studies, the increased incidences of thyroid C-cell hyperplasia, adenoma, and carcinoma were determined to be treatment-related. Thyroid C-cell tumours are rare findings during carcinogenicity testing in mice and rats. The human relevance of thyroid C-cell tumors in these rodent species is unknown and could not be determined based on the results of the clinical or nonclinical studies (see WARNINGS AND PRECAUTIONS, Carcinogenesis and Mutagenesis).

No other treatment-related tumours were observed in the carcinogenicity studies.

Genotoxicity
Semaglutide was not mutagenic or clastogenic in a standard battery of genotoxicity tests (bacterial reverse mutation test, *in vitro* chromosomal aberration test in human peripheral blood lymphocytes, and *in vivo* rat bone marrow micronucleus test).

Reproductive and Developmental Toxicology
In a combined fertility and embryo-fetal developmental toxicity study in rats, subcutaneous doses of 0.01, 0.03 and 0.09 mg/kg/day (all below the human exposure at the MRHD based on AUC, respectively) were administered to male and female rats. Males were dosed for 4 weeks prior to mating, and females were dosed for 2 weeks prior to mating and throughout organogenesis until Gestation Day (GD) 17. No effects were observed on mating performance or male fertility. In females, an increase in estrus cycle length was observed at all dose levels, together with a small reduction in numbers of corpora lutea (ovulations) at ≥0.03 mg/kg/day. Semaglutide caused embryotoxicity below clinically relevant exposures. Semaglutide caused reductions in maternal body weight, and reduction in number of corpora lutea, leading to fewer implantations and reduced fetal growth. In fetuses, increased incidences of skeletal and visceral malformations were observed at the mid and high dose, consisting of short tibia/malrotated hindlimb at the high dose and retro-oesophageal aortic arch (cardiovascular malformation) in combination with variation in the origin of the right subclavian artery observed at the two highest doses. Increased incidences of minor abnormalities were also observed at the high-dose, including skeletal variations (partially fused, misaligned, or reduced ossification of skeletal components) and dilated lateral brain ventricles. Thus, the NOAEL for the embryo-fetal toxicity of semaglutide in rats was determined to be 0.01 mg/kg/day.

In an embryo-fetal developmental toxicity study in rabbits, subcutaneous doses of 0.001, 0.0025 and 0.0075 mg/kg/day (below, below, and equal to the human exposure at the MRHD based on AUC, respectively) were administered to female rabbits throughout organogenesis i.e. from GD6 to GD19. Semaglutide markedly reduced maternal body weight gain and food and water consumption. Semaglutide caused increased post-implantation losses and an increased incidence of incomplete ossification of metacarpals (skeletal variation) at the mid and the high dose, and increased incidences of other minor, non-adverse skeletal abnormalities at all dose levels. There was also an increased incidence of minor visceral abnormalities, consisting of

dilated renal pelvis at the high dose, and increased incidences of forelimb/paw flexure at the mid and high doses. An increased number of visceral malformations were also observed at the mid and high dose that were not observed in controls, and consisted of multiple folded retina: absent vitreous humour, misshapen heart: dilated pulmonary trunk, absent kidney/ureter, absent adrenals, and bent scapula: hyperextension of the forelimb. Thus, the NOAEL for the embryo-fetal toxicity of semaglutide in rabbits was determined to be 0.001 mg/kg/day.

In an embryo-fetal developmental toxicity study in cynomolgus monkeys, subcutaneous doses of 0.015, 0.075, and 0.15mg/kg (below, 3-, and 8-fold the human exposure at the MRHD based on AUC, respectively) were administered to pregnant monkeys from GD 20 to 50 every 3 days. Marked maternal body weight loss and reduced food consumption was observed at all doses during the dosing period. A slightly increased incidence of fetal malformations was observed at the mid- and high-dose. The fetal abnormalities included skeletal abnormalities, consisting of shifts in the alignment of the vertebrae, ribs, and sternebrae at the cervico-thoracic border observed in one fetus of each of the mid- and high-dose groups, a misshapen right brain hemisphere, which was due to accumulation of blood between the dura mater and the brain, in a high-dose fetus, fused kidneys in a mid-dose fetus, and liver cysts in another mid-dose fetus. Thus, the NOAEL for the embryo-fetal toxicity of semaglutide in cynomolgus monkeys was determined to be 0.015 mg/kg administered every 3 days.

In a combined embryo-fetal and pre- and postnatal developmental toxicity study in cynomolgus monkeys, subcutaneous doses of 0.015, 0.075, and 0.15mg/kg (below, 2-, and 4-fold the human exposure at the MRHD based on AUC, respectively) were administered to pregnant monkeys from GD 20 to 140 every 3 days. A higher incidence of pre-natal loss was observed in the mid- and high-dose groups. The incidence of pre-natal loss was 5/24 (21%), 5/22 (23%), 7/22 (32%), and 10/24 (42%) in the control, low-, mid-, and high-dose groups, respectively, with the most losses occurring between GD 20 and 50; early pre-natal loss was 2/24 (8.3%), 1/22 (4.5%), 5/22 (23%), and 8/24 (33%) in the control, low-, mid-, and high-dose groups, respectively. A higher incidence of post-natal loss was also observed at all doses. The incidence of post-natal loss was 0/19 (0%), 5/17(29%), 3/15(20%), and 3/14(21%) in the control, low-, mid-, and high-dose groups, respectively. Infants were also slightly smaller at delivery in the two highest dose groups, but recovered during the lactation period. The NOAEL for the developmental toxicity of semaglutide in cynomolgus monkeys was determined to be 0.015 mg/kg administered every 3 days.

Juvenile Toxicity

In a juvenile toxicity study in rats, subcutaneous doses of 0.02, 0.13 and 0.6 mg/kg/day (below, 3-, and 12-fold the human exposure at the MRHD based on AUC, respectively) were administered to young rats from Postnatal Day 21 to 98. As in other studies, lower body weight gain, body weights, and food consumption were observed in animals administered semaglutide when compared to control animals. Semaglutide also caused a delay in sexual maturation in both males and females. There were no consequential effects on estrus cycle length, the reproductive organs of either sex, the reproductive capacity of either sex, or on the ability of the females to maintain pregnancy.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrOZEMPIC®

(semaglutide injection)

Read this carefully before you start taking **OZEMPIC®** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **OZEMPIC®**.

What is OZEMPIC® used for?

- OZEMPIC® contains the active substance semaglutide. It is used to lower blood sugar (glucose) in adults with type 2 diabetes.

- OZEMPIC® is used on its own if your blood sugar level is not properly controlled by diet and exercise alone and you cannot use metformin.

- OZEMPIC® is used in combination with one or more other medicines for diabetes when they are not enough to control your blood sugar levels. These other medicines may include: oral antidiabetics (such as metformin, sulfonylurea, or sodium glucose co-transporter 2 inhibitor medicines) or insulin.

- It is important that you keep following any diet and lifestyle advice from your doctor, pharmacist or nurse while using OZEMPIC®.

- OZEMPIC® is not a substitute for insulin. OZEMPIC® should not be used in patients with Type 1 diabetes mellitus (formerly known as insulin-dependent diabetes mellitus or IDDM), or for treatment of diabetic ketoacidosis.

How does OZEMPIC® work?

OZEMPIC® belongs to a class of medicines called GLP-1 receptor agonists (glucagon-like peptide-1 receptor agonists). OZEMPIC® helps your body make more insulin when your blood sugar is high.

What are the ingredients in OZEMPIC®?

Medicinal ingredients: semaglutide. One mL solution for injection contains 1.34 mg or 2.68 mg semaglutide.

Non-medicinal ingredients: disodium phosphate dihydrate, propylene glycol, phenol, and water for injections.

OZEMPIC® comes in the following dosage forms:

OZEMPIC® is supplied as a clear and colourless solution for injection in a pre-filled pen.

OZEMPIC® is available in a carton of 1 disposable, pre-filled, multi-dose pen delivering doses of 0.25 mg or 0.5 mg, including 6 NovoFine® Plus needles. This pack size is intended to be used for dose escalation and maintenance treatment at the 0.5 mg dose. The pen contains 1.5 mL solution.

OZEMPIC® is available in a carton of 1 disposable, pre-filled, multi-dose pen delivering only doses of 1 mg, including 4 NovoFine® Plus needles. This pack size is intended to be used for maintenance treatment at the 1 mg dose only. The pen contains 3 mL solution.

Ozempic® is available in a carton of 1 disposable, pre-filled, multi-dose pen delivering only doses of 2 mg, including 4 NovoFine® Plus needles. This pack size is intended to be used for maintenance treatment at the 2 mg dose only. The pen contains 3 mL solution.

Do not use OZEMPIC® if:

- You are allergic to semaglutide or any of the other ingredients of this medicine.
- You or a member of your family has ever had medullary thyroid cancer (MTC).
- You have Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).
- You are pregnant or breastfeeding.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take OZEMPIC®. Talk about any health conditions or problems you may have, including if you:

- or a member of your family has or has had medullary thyroid carcinoma (MTC), or if you have Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).
- Have type 1 diabetes.
- Have ever had diabetic ketoacidosis (increased ketones in the blood or urine).
- Have ever had an allergic reaction to OZEMPIC®.
- Have a high heart rate (fast pulse).
- Have ever had pancreatitis.
- Are breastfeeding or plan to breastfeed.
- Are pregnant or plan to become pregnant.
- Have end stage renal disease.
- Have gastrointestinal (digestive) problems, including severe vomiting, diarrhea and/or dehydration.
- Have hepatic (liver) disease.
- Have diabetic retinopathy.

Other warnings you should know about:

Children and adolescents

OZEMPIC® is not recommended in children and adolescents under 18 years as the safety and efficacy in this age group have not yet been established.

Pregnancy and breastfeeding

Tell your doctor if you are pregnant, think you might be pregnant, or are planning to become pregnant. OZEMPIC® should not be used during pregnancy and for at least two months before a planned pregnancy because it is not known if it may affect your unborn child.

If you could become pregnant while using OZEMPIC®, it is recommended to use contraception.

Do not use this medicine if you are breast-feeding. This is because it is not known if OZEMPIC® passes into breast milk.

Driving and using machines

Low blood sugar (hypoglycemia) may affect your ability to concentrate. Avoid driving or using machines if you get any signs of low blood sugar. See *What are possible side effects from using OZEMPIC®* for the warning signs of low blood sugar. Talk to your doctor for further information.

Severe and on-going stomach pain which could be due to acute pancreatitis

If you have severe and on-going pain in the stomach area – see a doctor straight away as this

could be a sign of acute pancreatitis (inflamed pancreas).

Dehydration
During treatment with OZEMPIC®, you may experience feeling sick (nausea) or being sick (vomiting), and diarrhea. These side effects can cause dehydration (loss of fluids). It is therefore important to drink plenty of fluids to prevent dehydration. Talk to your doctor if you have any questions or concerns.

Diabetic eye disease (retinopathy)
Fast improvements in blood sugar control may lead to a temporary worsening of diabetic eye disease. This may require treatment or lead to a loss of vision. You should inform your doctor if you have diabetic eye disease (retinopathy) or if you experience eye problems during treatment with OZEMPIC®.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

In particular, tell your doctor, pharmacist or nurse if you are using medicines containing any of the following:
- Sulfonylurea
- Insulin

Combining these medicines with OZEMPIC® might increase the risk of getting low blood sugar (hypoglycemia). Please see *What are possible side effects from using OZEMPIC®* for the warning signs of low blood sugar. Your doctor may tell you to lower your regular dose levels of these drugs when adding OZEMPIC® treatment.

The following may interact with OZEMPIC®:
The following list includes some, but not all, of the drugs that may increase your heart rate. You should check with your doctor or pharmacist before taking any other medication with OZEMPIC®:
- Drugs to treat hypertension.
- Drugs to treat heart failure.
- Drugs to treat HIV infection.
- Drugs to treat attention deficit-hyperactivity disorder.
- Drugs to suppress appetite/cause weight loss.
- Decongestants.
- Drugs to treat asthma.

How to take OZEMPIC®:
OZEMPIC® is given as an injection under the skin (subcutaneous injection). Do not inject it into a vein or muscle. The best places to give the injection are the front of your thighs, the front of your waist (abdomen), or your upper arm.

Before you use the pen for the first time, your doctor or Diabetes Nurse Educator will show you how to use it.

Detailed instructions for use are on the other side of this leaflet.

Always use this medicine exactly as your doctor has told you. Check with your doctor,

pharmacist or nurse if you are not sure.

You should use OZEMPIC® once a week on the same day each week if possible. You can give yourself the injection at any time of the day – regardless of meals. To help you remember to inject OZEMPIC® once a week only, it is recommended to note the chosen weekday (e.g. Wednesday) on the carton. You can also write the date on the carton every time you have injected OZEMPIC®.

If necessary you can change the day of your weekly injection of OZEMPIC® as long as it has been at least 2 days since your last injection of OZEMPIC®.

Do not stop using OZEMPIC® without talking to your doctor. If you stop using it, your blood sugar levels may increase.

Usual dose:
When you first start using OZEMPIC®, the starting dose is 0.25 mg once a week for four weeks. After four weeks you should increase your dose to 0.5 mg once a week. Talk to your doctor before increasing your dose.

Your doctor may increase your dose to 1 mg once a week if your blood sugar is not controlled well enough with a dose of 0.5 mg.

Your doctor may increase your dose to 2 mg once a week if your blood sugar is not controlled well enough with a dose of 1 mg.

Do not change your dose unless your doctor has told you to.

Overdose:
If you use more OZEMPIC® than you should, talk to your doctor straight away. You may get side effects such as feeling sick (nausea) or being sick (vomiting), or diarrhea.

If you think you have taken too much OZEMPIC®, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
If you forgot to inject a dose and:

- It is 5 days or less since you should have used OZEMPIC®, use it as soon as you remember. Then inject your next dose as usual on your scheduled day.
- It is more than 5 days since you should have used OZEMPIC®, skip the missed dose. Then inject your next dose as usual on your scheduled day.

Do not take an extra dose or increase the dose to make up for a missed dose.

What are possible side effects from using OZEMPIC®?

These are not all the possible side effects you may feel when taking OZEMPIC®. If you experience any side effects not listed here, contact your healthcare professional.

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Very common: may affect more than 1 in 10 people

- Feeling sick (nausea) – this usually goes away over time
- Diarrhea – this usually goes away over time
- Low blood sugar (hypoglycemia) when OZEMPIC® is used with a sulfonylurea or insulin.

The warning signs of low blood sugar may come on suddenly. They can include: cold sweat, cool pale skin, headache, fast heartbeat, feeling sick (nausea) or very hungry, changes in vision, feeling sleepy or weak, feeling nervous, anxious or confused, difficulty concentrating or shaking.

Your doctor will tell you how to treat low blood sugar and what to do if you notice these warning signs.

Common: may affect up to 1 in 10 people

- Being sick (vomiting)
- Low blood sugar (hypoglycemia) when OZEMPIC® is used with an oral antidiabetic other than a sulfonylurea
- Indigestion
- Inflamed stomach ('gastritis') - the signs also include stomach ache, feeling sick (nausea), or being sick (vomiting)
- Reflux or heartburn – also called 'gastro-esophageal reflux disease' (GERD)
- Stomach pain
- Bloating of the stomach
- Constipation
- Burping
- Gall stones
- Feeling dizzy
- Feeling tired
- Weight loss
- Less appetite
- Gas (flatulence)
- Increase of pancreatic enzymes (such as lipase and amylase)
- Complications of diabetic eye disease (retinopathy)

Uncommon: may affect up to 1 in 100 people

- Change in the way food or drink tastes
- Fast pulse
- Injection site reactions – such as bruising, pain, irritation, itching and rash
- Allergic reactions like rash, itching or hives

Rare: may affect up to 1 in 1,000 people
Severe allergic reactions (anaphylactic reactions, angioedema). You should seek immediate medical help and inform your doctor straight away if you get symptoms such as breathing problems, swelling of face, lips, tongue and/or throat with difficulty swallowing and a fast heartbeat.

Serious side effects and what to do about them		
Symptom / effect	Talk to your healthcare professional	

	Only if severe	In all cases	Stop taking drug and get immediate medical help
COMMON Diabetic retinopathy complications – complications of diabetic eye disease/diabetic eye problems		√	
UNCOMMON Pancreatitis (severe and ongoing pain in the stomach area which could be a sign of inflamed pancreas)		√	√
Severe hypoglycemia* (low blood sugar) symptoms: feeling confused, fits and passing out		√	√
RARE Severe allergic reaction (anaphylactic reaction, angioedema) symptoms: breathing problems, swelling of face, lips, tongue and/or throat with difficulty swallowing and a fast heartbeat		√	√

*The risk of severe hypoglycemia may be higher when you also take other diabetes medications.

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the pen label and carton after 'EXP'. The expiry date refers to the last day of that month.

Before opening:
Store in a refrigerator (2°C – 8°C). Do not freeze. Keep away from the cooling element.

During use:
• You can keep the pen for 8 weeks when stored at a temperature below 30°C or in a refrigerator (2°C – 8°C). Do not freeze.
• When you are not using the pen, keep the pen cap on in order to protect it from light.

Do not use this medicine if the solution is not clear and colourless.

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

If you want more information about OZEMPIC®:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (www.novonordisk.ca), or by calling 1-800-465-4334.

This leaflet was prepared by Novo Nordisk Canada Inc.

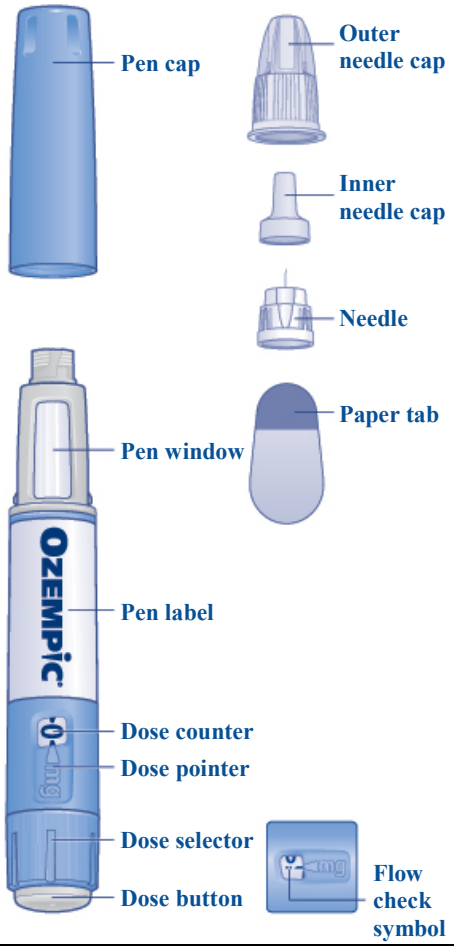
Last Revised 2022

OZEMPIC®, NovoFine® and NovoTwist® are trademarks of Novo Nordisk A/S and used under license by Novo Nordisk Canada Inc.

© 2022
Novo Nordisk Canada Inc.

Instructions on how to use OZEMPIC® solution for injection in pre-filled pen 0.25 mg or 0.5 mg doses

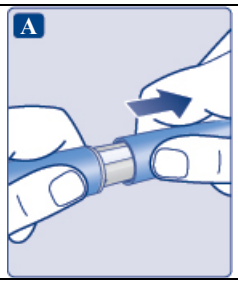
Please read these instructions carefully before using your OZEMPIC® pre-filled pen.
Do not use the pen without proper training from your doctor or nurse.
Start by checking your pen to **make sure that it contains OZEMPIC® 0.25 mg or 0.5 mg doses,** then look at the illustrations below to get to know 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.

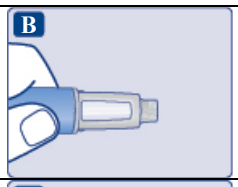
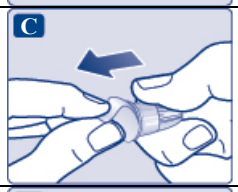
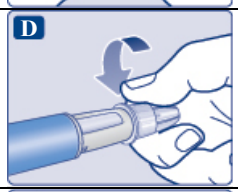
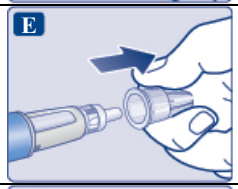
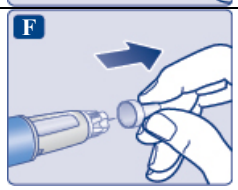
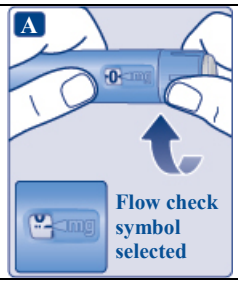


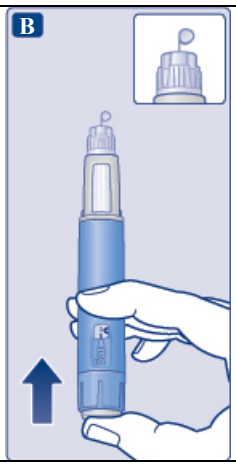
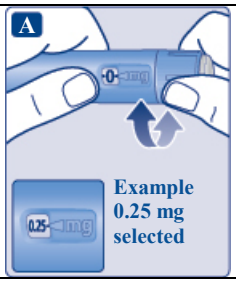
⚠
Pay special attention to these notes, as they are important for safe use of the pen.

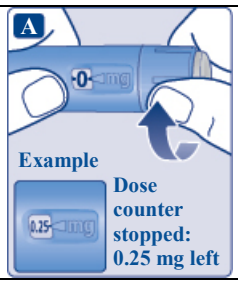
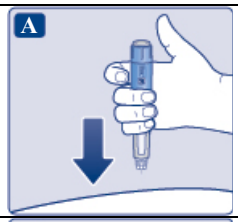
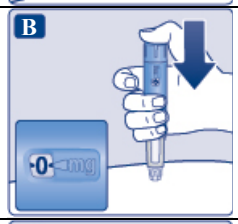
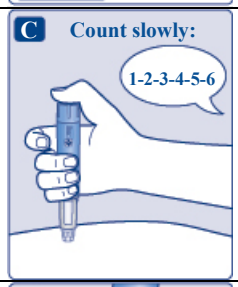
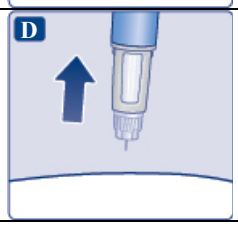
1. Prepare your pen with a new needle

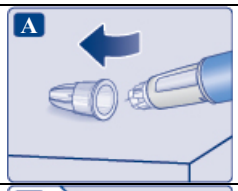
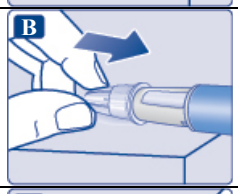
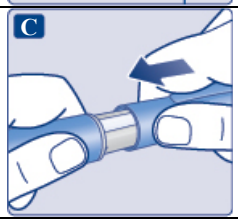
- **Check the name and coloured label** of your pen to make sure that it contains OZEMPIC® 0.25 or 0.5 mg doses. This is especially important if you take more than one type of injectable medicine. Using the wrong medicine could be harmful to your health.
- **Pull off the pen cap.**



• **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** and tear off the paper tab. If the paper tab is broken, do not use the needle, as sterility is not guaranteed.	
• **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. **Do not attach a new needle** to your pen until you are ready to take your injection.	
⚠ This may prevent blocked needles, contamination, infection and inaccurate dosing.	
⚠	
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'.	

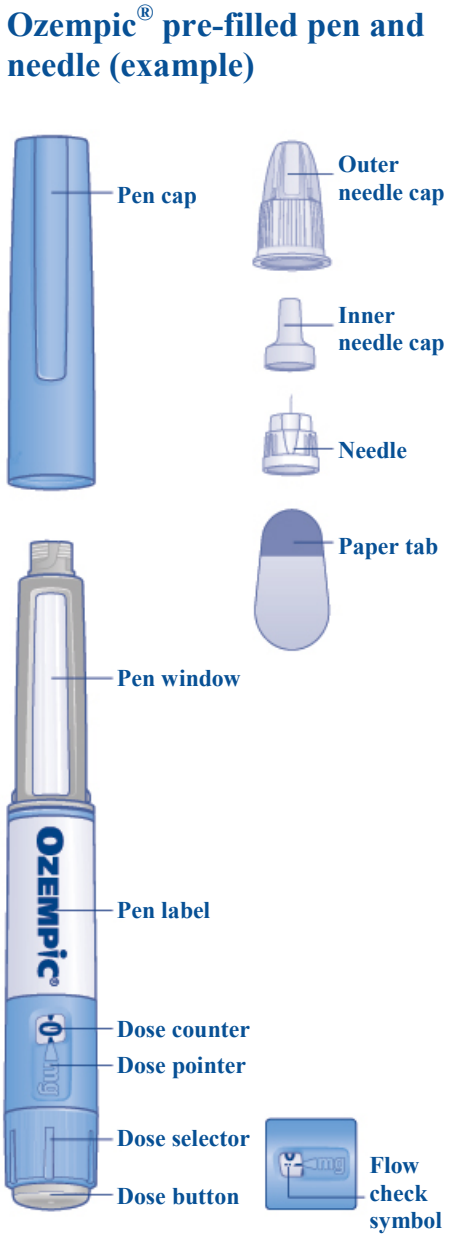
• Hold the pen with the needle pointing up. **Press and hold in the dose button** until the dose counter returns to 0. The 0 must line up with the dose pointer. A drop of solution should appear at the needle tip.	
A small drop may remain at the needle tip, but it will not be injected. **If no drop appears**, 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.	
⚠ 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 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 pen can dial up to a maximum of 0.5 mg.	
The dose selector changes the dose. Only the dose counter and dose pointer will show how many mg you select per dose. You can select up to 0.5 mg per dose. When your pen contains less than 0.5 mg, the dose counter stops before 0.5 is shown. The dose selector clicks differently when turned forwards, backwards or past the number of mg left. Do not count the pen clicks.	
⚠ **Do not count the pen clicks**. **Only doses of 0.25 mg or 0.5 mg must be selected with the dose selector**. The selected dose 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.	
	
• **Keep the needle in your skin** after the dose counter has returned to 0 and **count slowly to 6.** • 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**	

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.	
• **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 may prevent 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, which may lead to high blood sugar levels or abdominal discomfort such as nausea or vomiting.	
OZEMPIC® which has been frozen. If you do that, your blood sugar level may get too high or you might feel abdominal discomfort such as nausea or vomiting. • **Do not inject OZEMPIC® which has been exposed to direct sunlight**. If you do that, your blood sugar level may get too high. • **Do not expose your pen to dust, dirt or liquid.** • **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.	

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

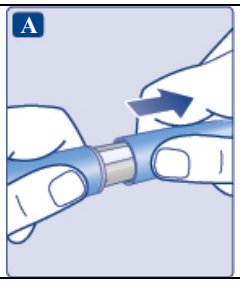
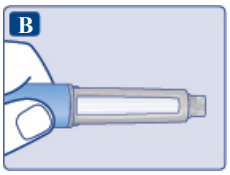
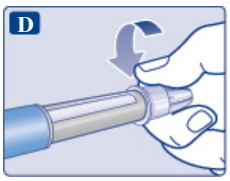
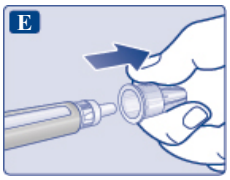
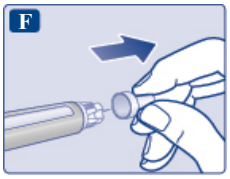
Please read these instructions carefully before using your OZEMPIC® pre-filled pen.
Do not use the pen without proper training from your doctor or nurse.
Start by checking your pen to **make sure that it contains OZEMPIC® 1 mg,** then look at the illustrations below to get to know the different parts 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.

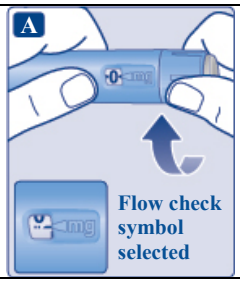
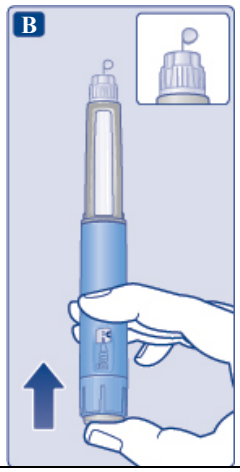
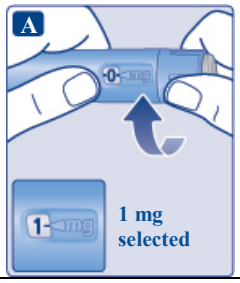


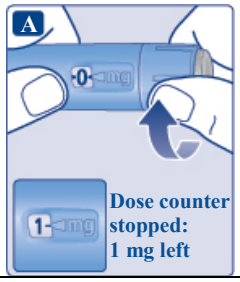
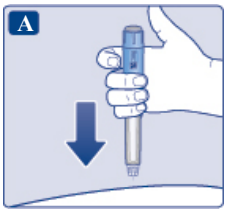
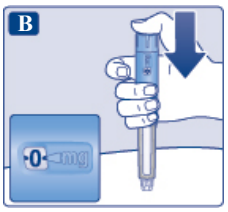
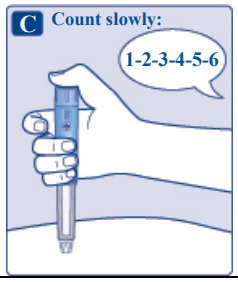
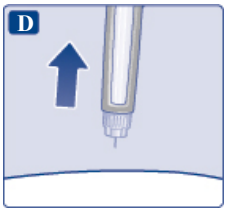
⚠
Pay special attention to these notes, as they are important for safe use of the pen.

1. Prepare your pen with a new needle

- **Check the name and coloured label** of your pen, to make sure that it contains OZEMPIC® 1 mg. This is especially important if you take more than one type of injectable medicine. Using the wrong medicine could be harmful 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** and tear off the paper tab. If the paper tab is broken, do not use the needle, as sterility is not guaranteed.	
• **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. **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 may prevent blocked needles, contamination, infection and inaccurate dosing.	
⚠ **Never use a bent or damaged needle.**	
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. You can only select 1 mg per dose. When your pen contains less than 1 mg, the dose counter stops before 1 is shown. 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.** **Only doses of 1 mg must be selected with the dose selector.** 1 mg 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.** • 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**	

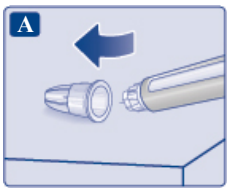
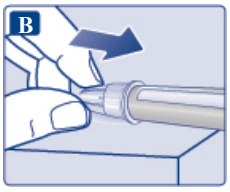
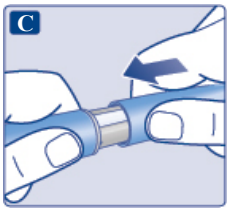
- If 0 does not appear in the dose counter after continuously pressing the dose button, you may have used a blocked or damaged needle.
- In this case, you have **not** received any medicine – even though the dose counter has moved from the original dose that you have set.

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.	
• **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 may prevent 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

Do not leave the pen in a car or another place where it can get too hot or too cold.

- **Do not inject OZEMPIC® which has been frozen.** If you do that, your blood sugar level may get too high or you might feel abdominal discomfort such as nausea or vomiting.
- **Do not inject OZEMPIC® which has been exposed to direct sunlight.** If you do that, your blood

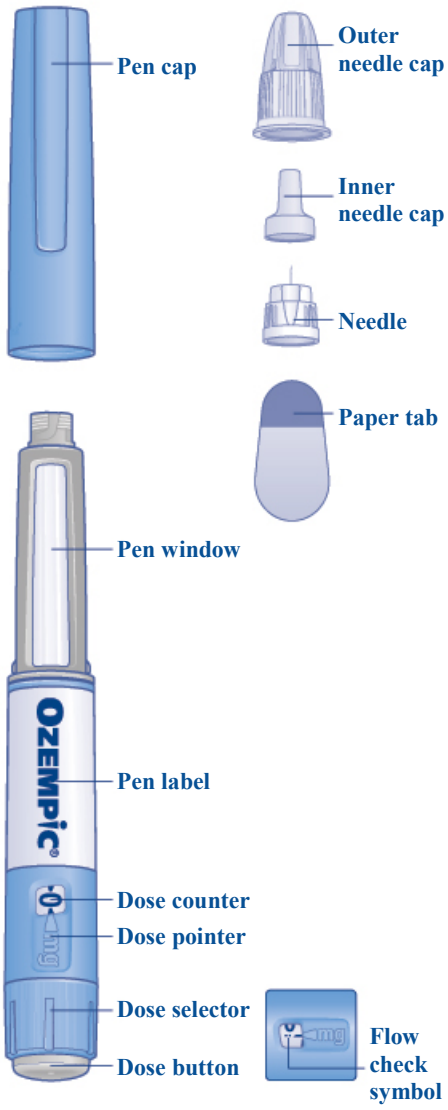
sugar level may get too high.

- **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.

Instructions on how to use OZEMPIC® solution for injection in pre-filled pen
2 mg doses

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® 2 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 8 mg of semaglutide, and you can only select doses of 2 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.

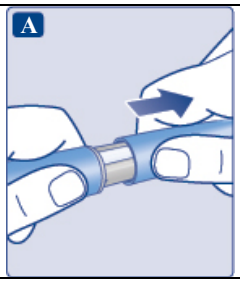
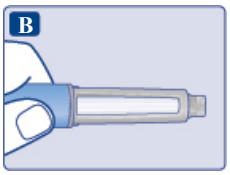
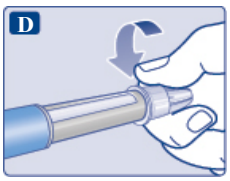
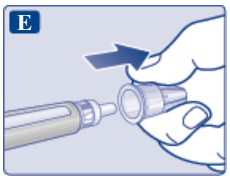
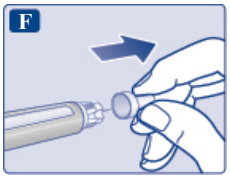
Ozempic® pre-filled pen and needle (example)

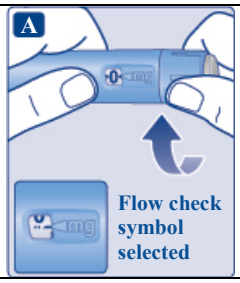
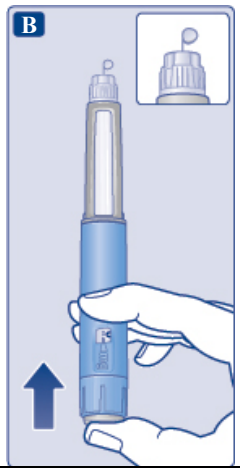


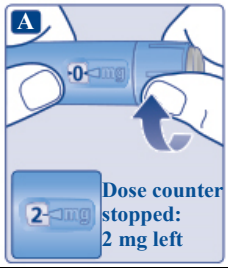
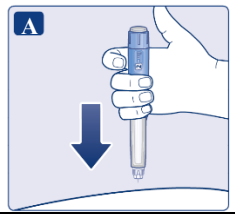
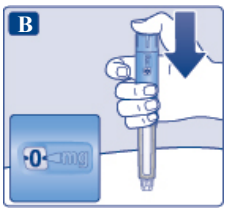
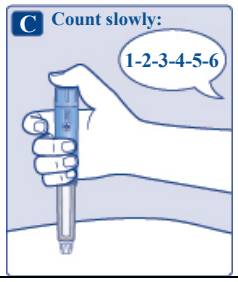
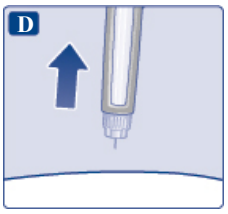
⚠
Pay special attention to these notes, as they are important for safe use of the pen.

1. Prepare your pen with a new needle

- **Check the name and coloured label** of your pen, to make sure that it contains OZEMPIC® 2 mg. This is especially important if you take more than one type of injectable medicine. Using the wrong medicine could be harmful 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** and tear off the paper tab. If the paper tab is broken, do not use the needle, as sterility is not guaranteed.	
• **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. **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 may prevent blocked needles, contamination, infection and inaccurate dosing.	
⚠ **Never use a bent or damaged needle.**	
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 2 mg. Keep turning until the dose counter stops and shows 2 mg.	
Only the dose counter and dose pointer will show that 2 mg has been selected. You can only select 2 mg per dose. When your pen contains less than 2 mg, the dose counter stops before 2 is shown. The dose selector clicks differently when turned forwards, backwards or past 2 mg. Do not count the pen clicks.	
⚠ **Always use the dose counter and the dose pointer to see that 2 mg has been selected before injecting this medicine.** **Do not count the pen clicks.** **Only doses of 2 mg must be selected with the dose selector.** 2 mg 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 2, **at least 2 mg** is left in your pen. If the **dose counter stops before 2 mg,** there is not enough solution left for a full dose of 2 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.** • 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.	

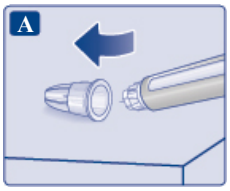
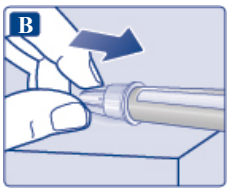
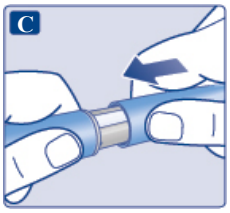
- In this case, you have **not** received any medicine – even though the dose counter has moved from the original dose that you have set.

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.	
• **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 may prevent 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.

- **Do not leave the pen in a car** or another place where it can get too hot or too cold.
- **Do not inject OZEMPIC® which has been frozen.** If you do that, your blood sugar level may get too high or you might feel abdominal discomfort such as nausea or vomiting.
- **Do not inject OZEMPIC® which has been exposed to direct sunlight.** If you do that, your blood sugar level may get too high.
- **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.