--- HIGHLIGHTS OF PRESCRIBING INFORMATION ---

These highlights do not include all the information needed to use OZEMPIC® safely and effectively. See full prescribing information for OZEMPIC®.

OZEMPIC® (semaglutide) injection, for subcutaneous use

Initial U.S. Approval: 2017

--- WARNING: RISK OF THYROID C−CELL TUMORS ---

See full prescribing information for complete boxed warning.

• In rodents, semaglutide causes thyroid C-cell tumors. It is unknown whether OZEMPIC® causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as the human relevance of semaglutide-induced rodent thyroid C-cell tumors has not been determined (5.1, 13.1).

• OZEMPIC® is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk of MTC and symptoms of thyroid tumors (4, 5.1).

--- DOSAGE AND ADMINISTRATION ---

Injection: 2 mg/1.5 mL (1.34 mg/mL) available in:
• Single-patient-use pen that delivers 0.25 mg or 0.5 mg per injection (3).
• Single-patient-use pen that delivers 1 mg per injection (3).

--- CONTRAINDICATIONS ---

• Personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2 (4).
• Known hypersensitivity to OZEMPIC® or any of the product components (4).

--- WARNINGS AND PRECAUTIONS ---

• Pancreatitis: Has been reported in clinical trials. Discontinue promptly if pancreatitis is suspected. Do not restart if pancreatitis is confirmed (5.2).
• Diabetic Retinopathy Complications: Has been reported in a clinical trial. Patients with a history of diabetic retinopathy should be monitored (5.3).
• Never share an OZEMPIC® pen between patients, even if the needle is changed (5.4).
• Hypoglycemia: When OZEMPIC® is used with an insulin secretagogue or insulin, consider lowering the dose of the secretagogue or insulin to reduce the risk of hypoglycemia (5.5).
• Acute Kidney Injury: Monitor renal function in patients with renal impairment reporting severe adverse gastrointestinal reactions (5.6).
• Hypersensitivity Reactions: Discontinue OZEMPIC® if suspected and promptly seek medical advice (5.7).

--- ADVERSE REACTIONS ---

The most common adverse reactions, reported in ≥5% of patients treated with OZEMPIC® are:

• Nausea, vomiting, diarrhea, abdominal pain and constipation (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Novo Nordisk Inc., at 1-888-693-6742 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

--- DRUG INTERACTIONS ---

Oral Medications: OZEMPIC® delays gastric emptying. May impact absorption of concomitantly administered oral medications (7.2).

--- USE IN SPECIFIC POPULATIONS ---

Females and Males of Reproductive Potential: Discontinue OZEMPIC® in women at least 2 months before a planned pregnancy due to the long washout period for semaglutide (8.3).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

--- INDICATIONS AND USAGE ---

OZEMPIC® is a glucagon-like peptide 1 (GLP-1) receptor agonist indicated as:
• an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (1).
• to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease (1).

Limitations of Use:
• Has not been studied in patients with a history of pancreatitis. Consider another antidiabetic therapy (1, 5.2).
• Not indicated for use in type 1 diabetes mellitus or treatment of diabetic ketoacidosis (1).

--- RECENT MAJOR CHANGES ---

01/2020

Indications and Usage (1) 01/2020

Warnings and Precautions, Macrovascular Outcomes (5.8) Removed 01/2020

--- INSTRUCTIONS FOR PRESCRIBERS ---

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--- REVISED: 01/2020 ---
FULL PRESCRIBING INFORMATION

WARNING: RISK OF THYROID C−CELL TUMORS

• In rodents, semaglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures. It is unknown whether OZEMPIC® causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as human relevance of semaglutide-induced rodent thyroid C-cell tumors has not been determined [see Warnings and Precautions (5.1)].

• OZEMPIC® is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2. 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). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with OZEMPIC® [see Contraindications (4) and Warnings and Precautions (5.1)].

1 INDICATIONS AND USAGE

OZEMPIC® is indicated:

• as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus [see Clinical Studies (14.1)].

• to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction or non-fatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease [see Clinical Studies (14.4)].

Limitations of Use

• OZEMPIC® has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis [see Warnings and Precautions (5.2)].

• OZEMPIC® is not a substitute for insulin. OZEMPIC® is not indicated for use in patients with type 1 diabetes mellitus or for the treatment of patients with diabetic ketoacidosis, as it would not be effective in these settings.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

• Start OZEMPIC® with a 0.25 mg subcutaneous injection once weekly for 4 weeks. The 0.25 mg dose is intended for treatment initiation and is not effective for glycemic control.

• After 4 weeks on the 0.25 mg dose, increase the dosage to 0.5 mg once weekly.

• If additional glycemic control is needed after at least 4 weeks on the 0.5 mg dose, the dosage may be increased to 1 mg once weekly. The maximum recommended dosage is 1 mg once weekly.

• Administer OZEMPIC® once weekly, on the same day each week, at any time of the day, with or without meals.

• 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).

• If a dose is missed, administer OZEMPIC® as soon as possible within 5 days after the missed dose. If more than 5 days have passed, skip the missed dose and administer the next dose on the regularly scheduled day. In each case, patients can then resume their regular once weekly dosing schedule.

2.2 Important Administration Instructions

• Administer OZEMPIC® subcutaneously to the abdomen, thigh, or upper arm. Instruct patients to use a different injection site each week when injecting in the same body region.

• Inspect OZEMPIC® visually before use. It should appear clear and colorless. Do not use OZEMPIC® if particulate matter and coloration 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.

3 DOSAGE FORMS AND STRENGTHS

Injection. 2 mg/1.5 mL (1.34 mg/mL) of semaglutide as a clear, colorless solution available in:

• Pre-filled, disposable, single-patient-use pen that delivers 0.25 mg (for treatment initiation) or 0.5 mg (for maintenance treatment) per injection.

• Pre-filled, disposable, single-patient-use pen that delivers 1 mg (for maintenance treatment) per injection.

4 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 Warnings and Precautions (5.1)].

• Known hypersensitivity to semaglutide or to any of the product components [see Warnings and Precautions (5.7)].

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Thyroid C-Cell Tumors

In mice and rats, semaglutide caused a dose-dependent and treatment-duration-dependent increase in the incidence of thyroid C-cell tumors (adenomas and carcinomas) after lifelong exposure at clinically relevant plasma exposures [see Nonclinical Toxicology (13.1)]. It is unknown whether OZEMPIC® causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as human relevance of semaglutide-induced rodent thyroid C-cell tumors has not been determined.

Cases of MTC in patients treated with tiraglutide, another GLP-1 receptor agonist, have been reported in the postmarketing period; the data in these reports are insufficient to establish or exclude a causal relationship between MTC and GLP-1 receptor agonist use in humans.

OZEMPIC® is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2. 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).

Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with OZEMPIC® [see Contraindications (4) and Warnings and Precautions (5.1)].
American, and 19% were Asian; 21% identified as Hispanic or Latino ethnicity. At baseline, patients had type 2 diabetes for an average of 8.8 years and had a mean HbA\(_1c\) of 8.2%. At baseline, 8.9% of the population reported retinopathy. Baseline estimated renal function was normal (eGFR ≥90 mL/min/1.73m\(^2\)) in 57.2% and mildly impaired (eGFR 60 to 90 mL/min/1.73m\(^2\)) in 35.9% and moderately impaired (eGFR 30 to 60 mL/min/1.73m\(^2\)) in 6.9% of patients.

### Pool of Placebo- and Active-Controlled Trials

The occurrence of adverse reactions was also evaluated in a larger pool of patients from type 2 diabetes participating in 7 placebo- and active-controlled glycemic control trials [see Clinical Studies (14)] including two trials in Japanese patients evaluating the use of OZEMPIC® as monotherapy and add-on therapy to oral medications or insulin. In this pool, a total of 3150 patients with type 2 diabetes were treated with OZEMPIC® for a mean duration of 44.9 weeks. Across the treatment arms, the mean age of patients was 57 years, 3.2% were 75 years or older and 57% were female. In these trials, 60% were White, 6% were Black or African American, and 31% were Asian; 16% identified as Hispanic or Latino ethnicity. At baseline, patients had type 2 diabetes for an average of 8.2 years and had a mean HbA\(_1c\) of 8.2%. At baseline, 7.8% of the population reported retinopathy. Baseline estimated renal function was normal (eGFR ≥90 mL/min/1.73m\(^2\)) in 63.1%, mildly impaired (eGFR 60 to 90 mL/min/1.73m\(^2\)) in 34.3%, and moderately impaired (eGFR 30 to 60 mL/min/1.73m\(^2\)) in 2.5% of the patients.

### Common Adverse Reactions

Table 1 shows common adverse reactions, excluding hypoglycemia, associated with the use of OZEMPIC® in the pool of placebo-controlled trials. These adverse reactions occurred more commonly on OZEMPIC® than on placebo and occurred in at least 5% of patients treated with OZEMPIC®.

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Placebo (N=262) %</th>
<th>OZEMPIC® 0.5 mg (N=260) %</th>
<th>OZEMPIC® 1 mg (N=261) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>6.1</td>
<td>15.8</td>
<td>20.3</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2.3</td>
<td>5.0</td>
<td>9.2</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1.9</td>
<td>8.5</td>
<td>8.8</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>4.6</td>
<td>7.3</td>
<td>5.7</td>
</tr>
<tr>
<td>Constipation</td>
<td>1.5</td>
<td>5.0</td>
<td>3.1</td>
</tr>
</tbody>
</table>

In the pool of placebo- and active-controlled trials and in the 2-year cardiovascular outcomes trial, the types and frequency of common adverse reactions, excluding hypoglycemia, were similar to those listed in Table 1.

### Gastrointestinal Adverse Reactions

In the pool of placebo-controlled trials, gastrointestinal adverse reactions occurred more frequently among patients receiving OZEMPIC® than placebo (placebo 15.3%, OZEMPIC® 0.5 mg 32.7%, OZEMPIC® 1 mg 36.4%). The majority of reports of nausea, vomiting, and/or diarrhea occurred during dose escalation. More patients receiving OZEMPIC® 0.5 mg (3.1%) and OZEMPIC® 1 mg (3.8%) discontinued treatment due to gastrointestinal adverse reactions than patients receiving placebo (0.4%).

In addition to the reactions in Table 1, the following gastrointestinal adverse reactions with a frequency of <5% were associated with OZEMPIC®: vomiting (0.2%, 0.2%, 0.4%), eructation (0%, 0%, 0%), flatulence (0.8%, 0%, 1.5%), gastroesophageal reflux disease (0%, 1.9%, 1.5%), and constipation (0.8%, 0.8%, 0.4%).

### Other Adverse Reactions

#### Hypoglycemia

Table 2 summarizes the incidence of events related to hypoglycemia by various definitions in the placebo-controlled trials. In these trials, patients were treated with OZEMPIC® in combination with insulin or other oral medications. The estimated background risk of major birth defects and pre-eclampsia, spontaneous abortions, preterm delivery, stillbirth, and delivery complications. There are clinical considerations regarding the risks of poorly controlled diabetes in pregnancy [see Clinical Considerations]. Based on animal reproduction studies, there may be potential risks to the fetus from exposure to semaglutide during pregnancy. OZEMPIC® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

### Oral Medications

OZEMPIC® causes a delay of gastric emptying, and thereby has the potential to impact the absorption of orally administered medications. In clinical pharmacology trials, semaglutide did not affect the absorption of orally administered medications to any clinically relevant degree [see Clinical Pharmacology (12.3)]. Nonetheless, caution should be exercised when oral medications are concomitantly administered with OZEMPIC®.

### USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy

There are limited data with semaglutide use in pregnant women to inform a drug-associated risk for adverse developmental outcomes. There are clinical considerations regarding the risks of poorly controlled diabetes in pregnancy [see Clinical Considerations]. Based on animal reproduction studies, there may be potential risks to the fetus from exposure to semaglutide during pregnancy. OZEMPIC® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In pregnant rats administered semaglutide during organogenesis, embryofetal mortality, structural abnormalities and alterations to growth occurred at maternal exposures below the maximum recommended human dose (MRHD) based on AUC. In rabbits and cynomolgus monkeys administered semaglutide during organogenesis, early pregnancy losses and structural abnormalities were observed at below the MRHD (rabbit) and ≥5-fold the MRHD (monkey). These findings coincided with a marked maternal body weight loss in both animal species [see Data].

The estimated background risk of major birth defects is 6–10% in women with pre-gestational diabetes and HbA\(_1c\) >7 and has been reported to be as high as 20–25% in women with an HbA\(_1c\) >10. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2.4% and 15-20%, respectively.

#### Clinical Considerations

**Disease associated maternal and fetal risk**

Poorly controlled diabetes during pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, stillbirth and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

**Data**

**Animal Data**

In a combined fertility and embryofetal development study in rats, subcutaneous doses of 0.01, 0.03 and 0.09 mg/kg/day (0.1–0.4, and 1.1-fold the MRHD) were administered to males for 4
weeks prior to and throughout mating and to females for 2 weeks prior to mating, and throughout organogenesis to Gestation Day 17. In parental animals, pharmacologically mediated reductions in body weight gain and food consumption were observed at all dose levels. In the offspring, reduced growth and fetuses with visceral (heart blood vessels) and skeletal (cranial bones, vertebra, ribs) abnormalities were observed at the highest dose level.

In an embryofetal development study in pregnant rabbits, subcutaneous doses of 0.0101, 0.0025 or 0.0075 mg/kg/day (0.03-, 0.3- and 2.3-fold the MRHD) were administered throughout organogenesis from Gestation Day 6 to 19. Pharmacologically mediated reductions in maternal body weight and food consumption were observed at all dose levels. Early pregnancy losses and increased incidences of minor visceral (kidney, liver) and skeletal (sternebra) fetal abnormalities were observed at ≥0.0025 mg/kg/day, at clinically relevant exposures.

In an embryofetal development study in pregnant cynomolgus monkeys, subcutaneous doses of 0.015, 0.075, and 0.15 mg/kg twice weekly (1.0-, 5.2-, and 14.9-fold the MRHD) were administered throughout organogenesis, from Gestation Day 16 to 50. Pharmacologically mediated, marked initial maternal body weight loss and reductions in body weight gain and food consumption coincided with the occurrence of sporadic abnormalities (vertebra, sternebra, ribs) at ≥0.075 mg/kg twice weekly (≥3X human exposure).

In a pre- and postnatal development study in pregnant cynomolgus monkeys, subcutaneous doses of 0.015, 0.075, and 0.15 mg/kg twice weekly (0.7-, 3.3-, and 7.2-fold the MRHD) were administered from Gestation Day 16 to 140. Pharmacologically mediated marked initial maternal body weight loss and reductions in body weight gain and food consumption coincided with an increase in early pregnancy losses and led to delivery of slightly smaller offspring at ≥0.075 mg/kg twice weekly (≥3X human exposure).

8.2 Lactation
Risk Summary

There are no data on the presence of semaglutide in human milk, the effects on the breastfed infant, or the effects on milk production. Semaglutide was present in the milk of lactating rats, however, due to species-specific differences in lactation physiology, the clinical relevance of these data are not clear (see Data). The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for OZEMPIC® and any potential adverse effects on the breastfed infant from OZEMPIC® or from the underlying maternal condition.

Data

In lactating rats, semaglutide was detected in milk at levels 3-12 fold lower than in maternal plasma.

8.3 Females and Males of Reproductive Potential
Discontinue OZEMPIC® in women at least 2 months before a planned pregnancy due to the long washout period for semaglutide (see Use in Specific Populations (8.1)).

8.4 Pediatric Use
Safety and efficacy of OZEMPIC® have not been established in pediatric patients (younger than 18 years).

8.5 Geriatric Use
In the pool of placebo- and active-controlled glycemic control trials, 744 (23.6%) OZEMPIC®-treated patients were 65 years of age and over and 102 OZEMPIC®-treated patients (3.2%) patients were 75 years of age and over. In SUSTAIN 6, the cardiovascular outcome trial, 788 (49.0%) OZEMPIC®-treated patients were 65 years of age and over and 157 OZEMPIC®-treated patients (9.6%) patients were 75 years of age and over.

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.

8.6 Renal Impairment
No dose adjustment of OZEMPIC® is recommended for patients with renal impairment. In subjects with renal impairment including end-stage renal disease (ESRD), no clinically relevant change in semaglutide pharmacokinetics (PK) was observed (see Clinical Pharmacology (12.3)).

8.7 Hepatic Impairment
No dose adjustment of OZEMPIC® is recommended for patients with hepatic impairment. In a study in subjects with different degrees of hepatic impairment, no clinically relevant change in semaglutide pharmacokinetics (PK) was observed (see Clinical Pharmacology (12.3)).

10 OVERDOSAGE
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.

11 DESCRIPTION
OZEMPIC® (semaglutide) injection, for subcutaneous use, contains semaglutide, a human GLP-1 receptor agonist (or GLP-1 analog). The peptide backbone is produced by yeast fermentation. Furthermore, semaglutide is stabilized against degradation by the DPP-4 enzyme.

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

GLP-1 is a physiological hormone that has multiple actions on glucose, mediated by the GLP-1 receptors. The principal mechanism of protraction resulting in the long half-life of semaglutide is albumin binding, which results in decreased renal clearance and protection from metabolic degradation. Furthermore, semaglutide is stabilized against degradation by the DPP-4 enzyme.

Semaglutide reduces blood glucose through a mechanism where it stimulates insulin secretion and lowers glucagon secretion, both in a glucose-dependent manner. Thus, when blood glucose is high, insulin secretion is stimulated, and glucagon secretion is inhibited. The mechanism of blood glucose lowering also involves a minor delay in gastric emptying in the early postprandial phase.

12 CLINICAL PHARMACOLOGY

12.1 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 target for native GLP-1.

GLP-1 is a physiological hormone that has multiple actions on glucose, mediated by the GLP-1 receptors. The principal mechanism of protraction resulting in the long half-life of semaglutide is albumin binding, which results in decreased renal clearance and protection from metabolic degradation. Furthermore, semaglutide is stabilized against degradation by the DPP-4 enzyme.

Semaglutide reduces blood glucose through a mechanism where it stimulates insulin secretion and lowers glucagon secretion, both in a glucose-dependent manner. Thus, when blood glucose is high, insulin secretion is stimulated, and glucagon secretion is inhibited. The mechanism of blood glucose lowering also involves a minor delay in gastric emptying in the early postprandial phase.

12.2 Pharmacodynamics
Semaglutide lowers fasting and postprandial blood glucose and reduces body weight. All pharmacodynamic evaluations were performed after 12 weeks of treatment (including dose escalation) at steady state with semaglutide 1 mg.

Fasting and Postprandial Glucose
Semaglutide reduces fasting and postprandial glucose concentrations. In patients with type 2 diabetes, treatment with semaglutide 1 mg resulted in reductions in glucose in terms of absolute change from baseline and relative reduction compared to placebo of 29 mg/dL (22%) for fasting glucose, 74 mg/dL (36%) for 2-hour postprandial glucose, and 30 mg/dL (22%) for mean 24-hour glucose concentration (see Figure 1).

Figure 1. Mean 24-hour plasma glucose profiles (standardized meals) in patients with type 2 diabetes before (baseline) and after 12 weeks of treatment with semaglutide or placebo
During induced hypoglycemia, semaglutide did not alter the counter regulatory responses of increased glucagon compared to placebo and did not impair the decrease of C-peptide in patients with type 2 diabetes.

Gastric emptying

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

Cardiac electrophysiology (QTc)

The effect of semaglutide on cardiac repolarization was tested in a thorough QTc trial. At a dose of 1.5 times the maximum recommended dose, semaglutide does not prolong QTc intervals to any clinically relevant extent.

12.3 Pharmacokinetics

Absorption

Absolute bioavailability of semaglutide is 89%. Maximum concentration of semaglutide is reached 1 to 3 days post dose.

Similar exposure is achieved with subcutaneous administration of semaglutide in the abdomen, thigh, or upper arm.

In patients with type 2 diabetes, semaglutide exposure increases in a dose-proportional manner for once-weekly doses of 0.5 mg and 1 mg. Steady-state exposure is achieved following 4-5 weeks of once-weekly administration. In patients with type 2 diabetes, the mean population-PK estimated steady-state concentrations following once weekly subcutaneous administration of 0.5 mg and 1 mg semaglutide were approximately 65.0 ng/mL and 123.0 ng/mL, respectively.

Distribution

The mean apparent volume of distribution of semaglutide following subcutaneous administration in patients with type 2 diabetes is approximately 12.5 L. Semaglutide is extensively bound to plasma albumin (≤99%).

Elimination

The apparent clearance of semaglutide in patients with type 2 diabetes is 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.

Metabolism

The primary route of elimination for semaglutide is metabolism following proteolytic cleavage of the peptide backbone and sequential beta-oxidation of the fatty acid sidechain.

Excretion

The primary excretion routes of semaglutide-related material are via the urine and feces. Approximately 3% of the dose is excreted in the urine as intact semaglutide.

Specific Populations

Based on a population pharmacokinetic analysis, age, sex, race, and ethnicity, and renal impairment do not have a clinically meaningful effect on the pharmacokinetics of semaglutide. The exposure of semaglutide decreases with an increase in body weight. However, semaglutide doses of 0.5 mg and 1 mg provide adequate systemic exposure over the body weight range of 40-198 kg evaluated in the clinical trials. The effects of intrinsic factors on the pharmacokinetics of semaglutide are shown in Figure 3.
In a combined fertility and embryo-fetal development study in rats, subcutaneous doses of 0.01, 0.03 and 0.09 mg/kg/day (0.1-, 0.4-, and 1.1-fold the MRHD) 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 17. No effects were observed on male fertility. In females, an increase in oestrus cycle length was observed at all dose levels, together with a small reduction in numbers of corpora lutea at 0.03 mg/kg/day. These effects were likely an adaptive response secondary to the pharmacological effect of semaglutide on food consumption and body weight.

14 CLINICAL STUDIES

14.1 Overview of Clinical Studies

OZEMPIC® has been studied as monotherapy and in combination with metformin, metformin and sulfonylureas, metformin and/or thiazolidinediones, and basal insulin in patients with type 2 diabetes mellitus. The efficacy of OZEMPIC® was compared with placebo, sitagliptin, exenatide extended-release (ER), and insulin glargine.

Most trials evaluated the use of OZEMPIC® 0.5 mg, and 1 mg, with the exception of the trial comparing OZEMPIC® and exenatide ER where only the 1 mg dose was studied.

In patients with type 2 diabetes mellitus, OZEMPIC® produced clinically relevant reduction from baseline in HbA1c compared with placebo. The efficacy of OZEMPIC® was not impacted by age, gender, race, ethnicity, BMI at baseline, body weight (kg) at baseline, diabetes duration and level of renal function impairment.

14.2 Monotherapy Use of OZEMPIC® in Patients with Type 2 Diabetes Mellitus

In a 30-week double-blind trial (NCT02054897), 388 patients with type 2 diabetes mellitus inadequately controlled with diet and exercise were randomized to OZEMPIC® 0.5 mg or OZEMPIC® 1 mg once weekly or placebo. Patients had a mean age of 54 years and 54% were men. The mean duration of type 2 diabetes was 6.6 years, and the mean BMI was 33 kg/m². Overall, 64% were White, 8% were Black or African American, and 21% were Asian; 30% identified as Hispanic or Latino ethnicity.

Most patients were randomized to OZEMPIC® 0.5 mg and 1 mg once weekly for 30 weeks resulting in a statistically significant reduction in HbA1c compared with placebo (see Table 3).

Table 3. Results at Week 30 in a Trial of OZEMPIC® as Monotherapy in Adult Patients with Type 2 Diabetes Mellitus Inadequately Controlled with Diet and Exercise

<table>
<thead>
<tr>
<th>Placebo</th>
<th>OZEMPIC® 0.5 mg</th>
<th>OZEMPIC® 1 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intent-to-Treat (ITT) Population (N)</td>
<td>129</td>
<td>128</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.0</td>
<td>8.1</td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>8.0</td>
<td>8.1</td>
</tr>
<tr>
<td>Change at week 30</td>
<td>-0.1</td>
<td>-1.4</td>
</tr>
<tr>
<td>Difference from placebob [95% CI]</td>
<td>-1.2 [-1.5, -0.9]c</td>
<td>-1.4 [-1.7, -1.1]c</td>
</tr>
<tr>
<td>Patients (%) achieving HbA1c&lt;7%</td>
<td>28</td>
<td>73</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>174</td>
<td>174</td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>15</td>
<td>-41</td>
</tr>
<tr>
<td>Change at week 30</td>
<td>15</td>
<td>-41</td>
</tr>
</tbody>
</table>

The intent-to-treat population includes all randomized and exposed patients. At week 30 the primary HbA1c endpoint was missing for 10%, 7% and 7% of patients and during the trial rescue medication was initiated by 10%, 5% and 4% of patients randomized to placebo, OZEMPIC® 0.5 mg and OZEMPIC® 1 mg, respectively. Missing data were imputed using multiple imputation based on all dose levels, together with a small reduction in numbers of corpora lutea at 0.03 mg/kg/day. These effects were likely an adaptive response secondary to the pharmacological effect of semaglutide on food consumption and body weight.

Table 4. Results at Week 56 in a Trial of OZEMPIC® Compared to Sitagliptin in Adult Patients with Type 2 Diabetes Mellitus in Combination with Metformin and/or Thiazolidinediones

<table>
<thead>
<tr>
<th>Intent-to-Treat (ITT) Population (N)</th>
<th>OZEMPIC® 0.5 mg</th>
<th>OZEMPIC® 1 mg</th>
<th>Sitagliptin</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%)</td>
<td>409</td>
<td>409</td>
<td>407</td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>8.0</td>
<td>8.2</td>
<td>8.2</td>
</tr>
<tr>
<td>Change at week 56</td>
<td>-1.3</td>
<td>-1.5</td>
<td>-0.7</td>
</tr>
<tr>
<td>Difference from sitagliptinb [95% CI]</td>
<td>-0.6 [-0.9, -0.3]</td>
<td>-0.6 [-0.9, -0.3]</td>
<td>-0.6 [-0.9, -0.3]</td>
</tr>
<tr>
<td>Patients (%) achieving HbA1c&lt;7%</td>
<td>66</td>
<td>73</td>
<td>40</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>166</td>
<td>171</td>
<td>173</td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>-35</td>
<td>-43</td>
<td>-23</td>
</tr>
<tr>
<td>Change at week 56</td>
<td>-35</td>
<td>-43</td>
<td>-23</td>
</tr>
</tbody>
</table>

The intent-to-treat population includes all randomized and exposed patients. At week 56 the primary HbA1c endpoint was missing for 5%, 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 all dose levels, together with a small reduction in numbers of corpora lutea at 0.03 mg/kg/day. These effects were likely an adaptive response secondary to the pharmacological effect of semaglutide on food consumption and body weight.

Combination with metformin or metformin with sulfonylurea

In a 56-week, open-label trial (NCT01885208), 813 patients with type 2 diabetes mellitus on metformin alone (49%), metformin with sulfonylurea (45%), or other (6%) were randomized to OZEMPIC® 0.5 mg once weekly or exenatide 2 mg once weekly. The mean baseline body weight was 89.9 kg, 89.2 kg, 89.3 kg in the OZEMPIC® 0.5 mg, OZEMPIC® 1 mg, and sitagliptin arms, respectively. The mean changes from baseline to week 56 were -4.2 kg, -5.5 kg, and -1.7 kg for the OZEMPIC® 0.5 mg, OZEMPIC® 1 mg, and sitagliptin arms, respectively. The difference from sitagliptin (95% CI) for OZEMPIC® 0.5 mg was -2.5 kg (-3.2, -1.8), and for OZEMPIC® 1 mg was -3.6 kg (-4.5, -3.1).

Figure 5. Mean HbA1c (%) over time - baseline to week 56

Combination with metformin or metformin with sulfonylurea

In a 56-week, open-label trial (NCT01885208), 813 patients with type 2 diabetes mellitus on metformin alone (49%), metformin with sulfonylurea (45%), or other (6%) were randomized to OZEMPIC® 0.5 mg once weekly or exenatide 2 mg once weekly. The mean baseline body weight was 89.9 kg, 89.2 kg, 89.3 kg in the OZEMPIC® 0.5 mg, OZEMPIC® 1 mg, and sitagliptin arms, respectively. The mean changes from baseline to week 56 were -4.2 kg, -5.5 kg, and -1.7 kg for the OZEMPIC® 0.5 mg, OZEMPIC® 1 mg, and sitagliptin arms, respectively. The difference from sitagliptin (95% CI) for OZEMPIC® 0.5 mg was -2.5 kg (-3.2, -1.8), and for OZEMPIC® 1 mg was -3.6 kg (-4.5, -3.1).

Table 5. Results at Week 56 in a Trial of OZEMPIC® Compared to Exenatide 2 mg Once Weekly in Adult Patients with Type 2 Diabetes Mellitus in Combination with Metformin or Metformin with Sulfonylurea

<table>
<thead>
<tr>
<th>Intent-to-Treat (ITT) Population (N)</th>
<th>OZEMPIC® 1 mg</th>
<th>Exenatide ER 2 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%)</td>
<td>404</td>
<td>405</td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>8.4</td>
<td>8.3</td>
</tr>
<tr>
<td>Change at week 56</td>
<td>-1.4</td>
<td>-0.9</td>
</tr>
<tr>
<td>Difference from exenatideb [95% CI]</td>
<td>-0.5 [-0.7, -0.3]</td>
<td>-0.5 [-0.7, -0.3]</td>
</tr>
<tr>
<td>Patients (%) achieving HbA1c&lt;7%</td>
<td>62</td>
<td>40</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>191</td>
<td>188</td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>-44</td>
<td>-34</td>
</tr>
<tr>
<td>Change at week 56</td>
<td>-44</td>
<td>-34</td>
</tr>
</tbody>
</table>

The intent-to-treat population includes all randomized and exposed patients. At week 56 the primary HbA1c endpoint was missing for 5% 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 all dose levels, together with a small reduction in numbers of corpora lutea at 0.03 mg/kg/day. These effects were likely an adaptive response secondary to the pharmacological effect of semaglutide on food consumption and body weight.
14. Cardiovascular Outcomes Trial of OZEMPIC® in Patients with Type 2 Diabetes Mellitus and Cardiovascular Disease

SUSTAIN 6 (NCT0120446) was a multi-center, multi-national, placebo-controlled, double-blind cardiovascular outcomes trial. In this trial, 3,297 patients with inadequately controlled type 2 diabetes and atherosclerotic cardiovascular disease were randomized to OZEMPIC® (0.5 mg or 1 mg) once weekly or placebo for a minimum observation time of 2 years. The trial compared the risk of Major Adverse Cardiovascular Event (MACE) between semaglutide and placebo when these were added to and used concomitantly with standard of care treatments for diabetes and cardiovascular disease. The primary endpoint, MACE, was the time to first occurrence of a three-part composite outcome which included cardiovascular death, non-fatal myocardial infarction and non-fatal stroke.

Patients eligible to enter the trial were: 50 years of age or older and had established, stable, cardiovascular, cerebrovascular, peripheral artery disease, chronic kidney disease or NYHA class II and III heart failure or were 60 years of age or older and had other specified risk factors for cardiovascular disease. In total, 1,940 patients (58.8%) had established cardiovascular disease without chronic kidney disease, 353 (10.7%) had chronic kidney disease only, and 442 (13.4%) had both cardiovascular disease and kidney disease. In the trial 453 patients (13.7%) had peripheral artery 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, 96.0% of the patients completed the trial and the vital status was known at the end of the trial for 99.6%.

For the primary analysis, a Cox proportional hazards model was used to test for non-inferiority of OZEMPIC® to placebo for time to first MACE using a risk margin of 1.3. The statistical analysis plan pre-specified that the 0.5 mg and 1 mg doses would be combined. Type-1 error was controlled across multiple tests using a hierarchical testing strategy.

OZEMPIC® significantly reduced the occurrence of MACE. The estimated hazard ratio for time to first MACE was 0.74 (95% CI: 0.58, 0.95). Refer to Figure 6 and Table 8.

Figure 6. Kaplan-Meier: Time to First Occurrence of a MACE in the SUSTAIN 6 Trial

The treatment effect for the primary composite endpoint and its components in the SUSTAIN 6 trial is shown in Table 7.

Table 7. Treatment Effect for MACE and its Components, Median Study Observation Time of 2.1 Years

<table>
<thead>
<tr>
<th>Patients at risk</th>
<th>Placebo</th>
<th>OZEMPIC®</th>
<th>Hazard ratio vs Placebo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE %</td>
<td>1648</td>
<td>1619</td>
<td>1601</td>
</tr>
<tr>
<td>Non-fatal Stroke</td>
<td>1544</td>
<td>1568</td>
<td>1543</td>
</tr>
<tr>
<td>Cardiovascular Death</td>
<td>1508</td>
<td>1534</td>
<td>1503</td>
</tr>
<tr>
<td>Fatal of Non-fatal Myocardial Infarction</td>
<td>1479</td>
<td>1460</td>
<td></td>
</tr>
<tr>
<td>Fatal of Non-fatal Stroke</td>
<td>1460</td>
<td>1460</td>
<td></td>
</tr>
</tbody>
</table>

The treatment effect for the primary composite endpoint and its components in the SUSTAIN 6 trial is shown in Table 8.

Table 8. Treatment Effect for MACE and its Components, Median Study Observation Time of 2.1 Years

<table>
<thead>
<tr>
<th>Placebo N=1649 (%)</th>
<th>OZEMPIC® N=1614 (%)</th>
<th>Hazard ratio vs Placebo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke (time to first occurrence)</td>
<td>146 (8.9)</td>
<td>108 (6.6)</td>
</tr>
<tr>
<td>Non-fatal Myocardial Infarction</td>
<td>64 (3.9)</td>
<td>47 (2.9)</td>
</tr>
<tr>
<td>Non-fatal Stroke</td>
<td>44 (2.7)</td>
<td>27 (1.6)</td>
</tr>
<tr>
<td>Cardiovascular Death</td>
<td>46 (2.6)</td>
<td>44 (2.7)</td>
</tr>
<tr>
<td>Fatal of Non-fatal Myocardial Infarction</td>
<td>67 (4.1)</td>
<td>54 (3.3)</td>
</tr>
<tr>
<td>Fatal of Non-fatal Stroke</td>
<td>46 (2.6)</td>
<td>30 (1.8)</td>
</tr>
</tbody>
</table>

The mean baseline body weight was 93.7 kg, 94.0 kg, and 92.6 kg in the OZEMPIC® 0.5 mg, OZEMPIC® 1 mg, and insulin glargine arms, respectively. The mean changes from baseline to week 30 were -3.2 kg, -4.7 kg and 0.9 kg in the OZEMPIC® 0.5 mg, OZEMPIC® 1 mg, and insulin glargine arms, respectively. The difference from insulin glargine (95% CI) for OZEMPIC® 0.5 mg was -2.6 kg (-3.7, -1.5) and for OZEMPIC® 1 mg was -4.7 kg (-5.8, -3.6).

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 the rescue medication was initiated by 14%, 2% 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.
• Intended for treatment initiation at the 0.25 mg dose and maintenance treatment at the 0.5 mg dose

Carton of 2 Pens (NDC 0169-4136-02)

• Pen delivers doses of 1 mg per injection

• 4 NovoFine® Plus needles

• Intended for maintenance treatment at the 1 mg dose only

Each OZEMPIC® pen is for use by a single patient. An OZEMPIC® pen must never be shared between patients, even if the needle is changed [see Warnings and Precautions (5.4)].

Recommended Storage

Prior to first use, OZEMPIC® should be stored in a refrigerator between 36°F to 46°F (2°C to 8°C) (Table 9). Do not store in the freezer or directly adjacent to the refrigerator cooling element. Do not freeze OZEMPIC® and do not use OZEMPIC® if it has been frozen.

After first use of the OZEMPIC® pen, the pen can be stored for 56 days at controlled room temperature (59°F to 86°F; 15°C to 30°C) or in a refrigerator (36°F to 46°F; 2°C to 8°C). Do not freeze. Keep the pen cap on when not in use. OZEMPIC® should be protected from excessive heat and sunlight. Always remove and safely discard the needle after each injection and store the OZEMPIC® pen without an injection needle attached. Always use a new needle for each injection.

The storage conditions are summarized in Table 9:

Table 9. Recommended Storage Conditions for the OZEMPIC® Pen

<table>
<thead>
<tr>
<th>Prior to first use</th>
<th>After first use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refrigerated</td>
<td>Room Temperature</td>
</tr>
<tr>
<td>36°F to 46°F (2°C to 8°C)</td>
<td>59°F to 86°F (15°C to 30°C)</td>
</tr>
<tr>
<td>Until expiration date</td>
<td>56 days</td>
</tr>
</tbody>
</table>

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Risk of Thyroid C-cell Tumors

Inform patients that semaglutide causes thyroid C-cell tumors in rodents and that the human relevance of this finding has not been determined. Counsel patients to report symptoms of thyroid tumors (e.g., a lump in the neck, hoarseness, dysphagia, or dyspnea) to their physician [see Boxed Warning and Warnings and Precautions (5.1)].

Pancreatitis

Inform patients of the potential risk for pancreatitis. Instruct patients to discontinue OZEMPIC® promptly and contact their physician if pancreatitis is suspected (severe abdominal pain that may radiate to the back, and which may or may not be accompanied by vomiting) [see Warnings and Precautions (5.2)].

Diabetic Retinopathy Complications

Inform patients to contact their physician if changes in vision are experienced during treatment with OZEMPIC® [see Warnings and Precautions (5.3)].

Never Share an OZEMPIC® Pen Between Patients

Advise patients that they must never share an OZEMPIC® pen with another person, even if the needle is changed, because doing so carries a risk for transmission of blood-borne pathogens [see Warnings and Precautions (5.4)].

Dehydration and Renal Failure

Advise patients treated with OZEMPIC® of the potential risk of dehydration due to gastrointestinal adverse reactions and take precautions to avoid fluid depletion. Inform patients of the potential risk for worsening renal function and explain the associated signs and symptoms of renal impairment, as well as the possibility of dialysis as a medical intervention if renal failure occurs [see Warnings and Precautions (5.6)].

Hypersensitivity Reactions

Inform patients to stop taking OZEMPIC® and seek medical advice promptly if symptoms of hypersensitivity reactions occur [see Warnings and Precautions (5.7)].

Pregnancy

Advise a pregnant woman of the potential risk to a fetus. Advise women to inform their healthcare provider if they are pregnant or intend to become pregnant [see Use in Specific Populations (8.1), (8.3)].

Inform patients 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, inform patients to resume their regular once weekly dosing schedule [see Dosage and Administration (2.1)].
Do not share your OZEMPIC® pen with other people, even if the needle has been changed. You may give other people a serious infection, or get a serious infection from them.

Read this Medication Guide before you start using OZEMPIC® and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about OZEMPIC®?

OZEMPIC® may cause serious side effects, including:
• Possible thyroid tumors, including cancer. Tell your healthcare provider if you get a lump or swelling in your neck, hoarseness, trouble swallowing, or shortness of breath. These may be symptoms of thyroid cancer. In studies with rodents, OZEMPIC® and medicines that work like OZEMPIC® caused thyroid tumors, including thyroid cancer. It is not known if OZEMPIC® will cause thyroid tumors or a type of thyroid cancer called medullary thyroid carcinoma (MTC) in people.
• Do not use OZEMPIC® if you or any of your family have ever had a type of thyroid cancer called medullary thyroid carcinoma (MTC), or if you have an endocrine system condition called Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).

What is OZEMPIC®?

OZEMPIC® is an injectable prescription medicine used:
• along with diet and exercise to improve blood sugar (glucose) in adults with type 2 diabetes mellitus.
• to reduce the risk of major cardiovascular events such as heart attack, stroke or death in adults with type 2 diabetes mellitus with known heart disease.
It is not known if OZEMPIC® can be used in people who have had pancreatitis.
OZEMPIC® is not a substitute for insulin and is not for use in people with type 1 diabetes or people with diabetic ketoacidosis.
It is not known if OZEMPIC® is safe and effective for use in children under 18 years of age.

Do not use OZEMPIC® it:
• you or any of your family have ever had a type of thyroid cancer called medullary thyroid carcinoma (MTC) or if you have an endocrine system condition called Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).
• you are allergic to semaglutide or any of the ingredients in OZEMPIC®. See the end of this Medication Guide for a complete list of ingredients in OZEMPIC®.

Before using OZEMPIC®, tell your healthcare provider if you have any other medical conditions, including if you:
• have or have had problems with your pancreas or kidneys.
• have a history of diabetic retinopathy.
• are pregnant or plan to become pregnant. It is not known if OZEMPIC® will harm your unborn baby. You should stop using OZEMPIC® 2 months before you plan to become pregnant. Talk to your healthcare provider about the best way to control your blood sugar if you plan to become pregnant or while you are pregnant.
• are breastfeeding or plan to breastfeed. It is not known if OZEMPIC® passes into your breast milk. You should talk with your healthcare provider about the best way to feed your baby while using OZEMPIC®.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. OZEMPIC® may affect the way some medicines work and some medicines may affect the way OZEMPIC® works.

Before using OZEMPIC®, talk to your healthcare provider about low blood sugar and how to manage it. Tell your healthcare provider if you are taking other medicines to treat diabetes, including insulin or sulfonylureas.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I use OZEMPIC®?
• Read the Instructions for Use that comes with OZEMPIC®.
• Use OZEMPIC® exactly as your healthcare provider tells you to.
• Your healthcare provider should show you how to use OZEMPIC® before you use it for the first time.
• OZEMPIC® is injected under the skin (subcutaneously) of your stomach (abdomen), thigh, or upper arm. Do not inject OZEMPIC® into a muscle (intramuscularly) or vein (intravenously).
• Use OZEMPIC® 1 time each week, on the same day each week, at any time of the day.

Do not use OZEMPIC®
• with diabetic ketoacidosis.
It is not known if OZEMPIC® will cause thyroid tumors or a type of thyroid cancer called medullary thyroid carcinoma (MTC) in people.
• Do not use OZEMPIC® if you or any of your family have ever had a type of thyroid cancer called medullary thyroid carcinoma (MTC), or if you have an endocrine system condition called Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).

What are the possible side effects of OZEMPIC®?
OZEMPIC® may cause serious side effects, including:
• See “What is the most important information I should know about OZEMPIC®?”
• inflammation of your pancreas (pancreatitis). Stop using OZEMPIC® and call your healthcare provider right away if you have severe pain in your stomach area (abdomen) that will not go away, with or without vomiting. You may feel the pain from your abdomen to your back.
• changes in vision. Tell your healthcare provider if you have changes in vision during treatment with OZEMPIC®.
• low blood sugar (hypoglycemia). Your risk for getting low blood sugar may be higher if you use OZEMPIC® with another medicine that can cause low blood sugar, such as a sulfonylurea or insulin. Signs and symptoms of low blood sugar may include:
  • dizziness or light-headedness
  • blurred vision
  • anxiety, irritability, or mood changes
  • sweating
  • slurred speech
  • hunger
  • confusion or drowsiness
  • shakiness
  • weakness
  • headache
  • fast heartbeat
  • feeling jittery
• kidney problems (kidney failure). In people who have kidney problems, diarrhea, nausea, and vomiting may cause a loss of fluids (dehydration) which may cause kidney problems to get worse. It is important for you to drink fluids to help reduce your chance of dehydration.
• serious allergic reactions. Stop using OZEMPIC® and get medical help right away, if you have any symptoms of a serious allergic reaction including itching, rash, or difficulty breathing.

The most common side effects of OZEMPIC® may include:
• nausea, vomiting, diarrhea, stomach (abdominal) pain and constipation.

Talk to your healthcare provider about any side effect that bothers you or does not go away. These are not all the possible side effects of OZEMPIC®.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of OZEMPIC®.
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use OZEMPIC® for a condition for which it was not prescribed. Do not give OZEMPIC® to other people, even if they have the same symptoms that you have. It may harm them.

You can ask your pharmacist or healthcare provider for information about OZEMPIC® that is written for health professionals.
For more information, go to OZEMPIC.com or call 1-888-693-6742.

What are the ingredients in OZEMPIC®?
Active Ingredient: semaglutide
Inactive Ingredients: disodium phosphate dihydrate, propylene glycol, phenol and water for injection

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 01/2020
**Instructions for Use**

**OZEMPIC® (oh-ZEM-pick)**

( semiclassicalide) injection

0.25 mg or 0.5 mg doses

(pen delivers doses of 0.25 mg or 0.5 mg)

- Read these instructions carefully before using your OZEMPIC® pen.
- Do not use your pen without proper training from your healthcare provider. Make sure that you know how to give yourself an injection with the pen before you start your treatment.
- Do not share your OZEMPIC® pen with other people, even if the needle has been changed. You may give other people a serious infection, or get a serious infection from them.

**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® pen.

- Start by checking your pen to make sure that it contains OZEMPIC®, then look at the pictures below to get to know the different parts of your pen and needle.
- Your pen is a prefilled, single-patient-use, 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 made to be used with NovoFine® Plus or NovoFine® disposable needles up to a length of 8 mm.
- NovoFine® Plus 32G 4 mm disposable needles are included with your OZEMPIC® pen.
- Always use a new needle for each injection.

Supplies you will need to give your OZEMPIC® injection:

- OZEMPIC® pen
- a new NovoFine® Plus or NovoFine® needle
- 1 alcohol swab
- 1 gauze pad or cotton ball
- 1 sharps disposal container for throwing away used OZEMPIC® pens and needles. See “Disposing of used OZEMPIC® pens and needles” at the end of these instructions.

**OZEMPIC® pen and NovoFine® Plus needle (example)**

- Check the OZEMPIC® medicine in your pen is clear and colorless. Look through the pen window. If OZEMPIC® looks cloudy or contains particles, do not use the pen.
- Take a new needle, and tear off the paper tab. Do not attach a new needle to your pen until you are ready to give your injection.
- Push the needle straight onto the pen. Turn until it is on tight.
- Pull off the outer needle cap. Do not throw it away.
- Pull off the inner needle cap and throw it away. A drop of OZEMPIC® may appear at the needle tip. This is normal, but you must still check the OZEMPIC® flow if you use a new pen for the first time.

**Always use a new needle for each injection.** This will reduce the risk of contamination, infection, leakage of OZEMPIC®, and blocked needles leading to the wrong dose. Do not reuse or share your needles with other people. You may give other people a serious infection, or get a serious infection from them.

Never use a bent or damaged needle.

**Step 2.**

Check the OZEMPIC® flow with each new pen

- Check the OZEMPIC® flow before your first injection with each new pen.
  - If your OZEMPIC® 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 (√).

**Always use the dose counter and the dose pointer to see how many mg you select.** You will hear a “click” every time you turn the dose selector. Do not set the dose by counting the number of clicks you hear.

Only doses of 0.25 mg or 0.5 mg can be selected with the dose selector. The selected dose must line up exactly with the dose pointer to make sure that you get a correct dose. The dose selector changes the dose. Only the dose counter and dose pointer will show how many mg you select for each dose.

You can select 0.25 mg or 0.5 mg for each dose. When your pen contains less than 0.5 mg or 0.25 mg, the dose counter stops at a dose of 0.25 mg or 0.5 mg.

The dose selector clicks differently when turned forward or backward. Do not count the pen clicks.
How much OZEMPIC® is left?

- To see how much OZEMPIC® is left in your pen, 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 OZEMPIC® left for a full dose of 0.5 mg.
  
  - If it stops at 0.25, then 0.25 mg is left in your pen. If the dose counter stops before 0.25 mg, there is not enough OZEMPIC® left for a full dose of 0.25 mg.

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

Step 4. Inject your dose

- Choose your injection site and wipe the skin with an alcohol swab. Let the injection site dry before you inject your dose (See Figure K).

- Insert the needle into your skin as your healthcare provider has shown you.

- Make sure you can see the dose counter. Do not cover it with your fingers. This could stop 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 OZEMPIC® coming from the needle tip. If this happens, the full dose will not be delivered.

- Remove the needle from your skin.

  If blood appears at the injection site, press lightly with a gauze pad or cotton ball. Do not rub the area.

  Always watch the dose counter to make sure you have injected your complete dose. Hold the dose button down until the dose counter shows 0.

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

- Place the needle in a sharps disposal container right away to reduce the risk of needle sticks. See "Disposing of used OZEMPIC® pens and needles" below for more information about how to dispose of used pens and needles the right way.

  - If you do not have a sharps disposal container, follow a 1-handed needle recapping method. Carefully slip the needle into the outer needle cap. Dispose of the needle in a sharps disposal container as soon as possible.

- If you do not have a sharps disposal container, follow a 1-handed needle recapping method. Carefully slip the needle into the outer needle cap. Dispose of the needle in a sharps disposal container as soon as possible.

- 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. This will reduce the risk of contamination, infection, leakage of OZEMPIC®, and blocked needles leading to the wrong dose. If the needle is blocked, you will not inject any OZEMPIC®.

  Always dispose of the needle after each injection.

Disposing of used OZEMPIC® pens and needles:

- Put your used OZEMPIC® pen and needle in a FDA-cleared sharps disposal container right away after use.

- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
  
  - made of a heavy-duty plastic
  
  - can be closed with a light-fitting, puncture-resistant lid, without sharps being able to come out
  
  - upright and stable during use
  
  - leak-resistant
  
  - properly labeled to warn of hazardous waste inside the container

- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about the safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA’s website at: http://www.fda.gov/safesharpsdisposal

- Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.

- Safely dispose of OZEMPIC® that is out of date or no longer needed.

Important

- Caregivers must be very careful when handling used needles to prevent accidental needle stick injuries and prevent passing (transmission) of infection.

- Never use a syringe to withdraw OZEMPIC® from your pen.

- Always carry an extra pen and new needles with you, in case of loss or damage.

- Always keep your pen and needles out of reach of others, especially children.

- Always keep your pen with you. Do not leave it in a car or other place where it can get too hot or too cold.

Caring for your pen

- 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 OZEMPIC® how before you inject.

- Do not try to repair your pen or pull it apart.

- Do not expose your pen to dust, dirt or liquid.

- Do not wash, soak, or lubricate your pen. If necessary, clean it with mild detergent on a moistened cloth.

How should I store my OZEMPIC® pen?

- Store your new, unused OZEMPIC® pens in the refrigerator between 36°F to 46°F (2°C to 8°C).

- Store your pen in use for 56 days at room temperature between 59°F to 86°F (15°C to 30°C) or in a refrigerator between 36°F to 46°F (2°C to 8°C).

- The OZEMPIC® pen you are using should be disposed of (thrown away) after 56 days, even if it still has OZEMPIC® left in it. Write the disposal date on your calendar.

- Do not freeze OZEMPIC®. Do not use OZEMPIC® if it has been frozen.

- Unused OZEMPIC® pens may be used until the expiration date (“EXP”) printed on the label, if kept in the refrigerator.

- When stored in the refrigerator, do not store OZEMPIC® pens directly next to the cooling element.

- Keep OZEMPIC® away from heat and out of the light.

- Keep the pen cap on when not in use.

- Keep OZEMPIC® and all medicines out of the reach of children.

For more information go to www.OZEMPIC.com

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This Instructions for Use has been approved by the U.S. Food and Drug Administration.

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Instructions for Use

OZEMPIC® (oh-ZEM-pick) (semaglutide) injection

1 mg dose
(each pen delivers doses of 1 mg only)

• Read these instructions carefully before using your OZEMPIC® pen.
• Do not use your pen without proper training from your healthcare provider. Make sure that you know how to give yourself an injection with the pen before you start your treatment.
• Do not share your OZEMPIC® pen with other people, even if the needle has been changed. You may give other people a serious infection, or get a serious infection from them.

△ 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® pen.

• Start by checking your pen to make sure that it contains OZEMPIC®, then look at the pictures below to get to know the different parts of your pen and needle.
• Your pen is a prefilled, single-patient-use, dial-a-dose pen. It contains 2 mg of semaglutide, and you can only select doses of 1 mg. Your pen is made to be used with OZEMPIC® Plus or NovoFine® disposable needles up to a length of 8 mm.
• NovoFine® Plus 32G 4 mm disposable needles are included with your OZEMPIC® pen.
• Always use a new needle for each injection.

Supplies you will need to give your OZEMPIC® injection:
• OZEMPIC® pen 1 mg dose
• a new NovoFine® Plus or NovoFine® needle
• 1 alcohol swab
• 1 gauze pad or cotton ball
• 1 sharps disposal container for throwing away used OZEMPIC® pens and needles. See “Disposing of used OZEMPIC® pens and needles” at the end of these instructions.

OZEMPIC® pen and NovoFine® Plus needle (example)

Pen window

Dose counter

Dose selector

Expiration date (EXP)
on back of pen label

Flow check symbol

Dashed line (used to guide to your dose)

Pen cap

Outer needle cap

Inner needle cap

Needle

Paper tab

Step 1.
Prepare your pen with a new needle

• Wash your hands with soap and water.
• Check the name and colored label of your pen, to make sure that it contains OZEMPIC®.
  This is especially important if you take more than 1 type of medicine.
• Pull off the pen cap.

Step 2.
Check the OZEMPIC® flow with each new pen

• Check the OZEMPIC® flow before your first injection with each new pen.
  If your OZEMPIC® 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 (• • • •)

Step 3.
Select your dose

• Turn the dose selector until the dose counter stops and shows your 1 mg dose.
  The dashed line in the dose counter (1) will guide you to 1 mg.

△ Always use a new needle for each injection. This will reduce the risk of contamination, infection, leakage of OZEMPIC®, and blocked needles leading to the wrong dose.

Do not reuse or share your needles with other people. You may give other people a serious infection, or get a serious infection from them.

Never use a bent or damaged needle.

△ Always use the dose counter and the dose pointer to see that 1 mg has been selected.

You will hear a “click” every time you turn the dose selector. Do not set the dose by counting the number of clicks you hear.

Only doses of 1 mg can be selected with the dose selector. 1 mg must line up exactly with the dose pointer to make sure that you get a correct dose.

The dose selector changes the dose. Only the dose counter and dose pointer will show that 1 mg has been selected.

You can only select 1 mg for each dose. When your pen contains less than 1 mg, the dose counter stops before 1 mg is shown.

The dose selector clicks differently when turned forward or backward. Do not count the pen clicks.

△ 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 OZEMPIC® flows.

If no drop appears, you will not inject any OZEMPIC®, even though the dose counter may move. This may mean that there is a blocked or damaged needle.

A small drop may remain at the needle tip, but it will not be injected.

Only check the OZEMPIC® flow before your first injection with each new pen.
How much OZEMPIC® is left?

• To see how much OZEMPIC® is left in your pen, 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 OZEMPIC® left for a full dose of 1 mg.

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

Step 4. Inject your dose

Choose your injection site and wipe the skin with an alcohol swab. Let the injection site dry before you inject your dose (See Figure K).

Insert the needle into your skin as your healthcare provider has shown you.

Make sure you can see the dose counter. Do not cover it with your fingers. This could stop 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 OZEMPIC® coming from the needle tip. If this happens, the full dose will not be delivered.

Remove the needle from your skin.

If blood appears at the injection site, press lightly with a gauze pad or cotton ball. Do not rub the area.

Always watch the dose counter to make sure you have injected your complete dose. 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.

• If this happens you have not received any OZEMPIC® 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, and repeat all steps starting with Step 1: “Prepare your pen with a new needle”.

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

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

Step 5. After your injection

• Carefully remove the needle from the pen.
  Do not put the needle caps back on the needle to avoid needle sticks.

• Place the needle in a sharps disposal container right away to reduce the risk of needle sticks. See “Disposing of used OZEMPIC® pens and needles” below for more information about how to dispose of used pens and needles the right way.

• Put the pen cap on your pen after each use to protect OZEMPIC® from light.

• If you do not have a sharps disposal container, follow a 1-handed needle recap method. Carefully slip the needle into the outer needle cap. Dispose of the needle in a sharps disposal container as soon as possible.

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. This will reduce the risk of contamination, infection, leakage of OZEMPIC®, and blocked needles leading to the wrong dose. If the needle is blocked, you will not inject any OZEMPIC®.

Always dispose of the needle after each injection.

Disposing of used OZEMPIC® pens and needles:

• Put your used OZEMPIC® pen and needle in a FDA-cleared sharps disposal container right away after use.

• If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
  • made of a heavy-duty plastic
  • can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out
  • upright and stable during use
  • leak-resistant
  • properly labeled to warn of hazardous waste inside the container

• When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about the safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA’s website at: http://www.fda.gov/safesharpsdisposal

• Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this.

• Do not recycle your used sharps disposal container.

• Safely dispose of OZEMPIC® that is out of date or no longer needed.

Important

Caregivers must be very careful when handling used needles to prevent accidental needle stick injuries and prevent passing (transmission) of infection.

Never use a syringe to withdraw OZEMPIC® from your pen.

Always carry an extra pen and new needles with you, in case of loss or damage.

Always keep your pen and needles out of reach of others, especially children.

Always keep your pen with you. Do not leave it in a car or other place where it can get too hot or too cold.

Caring for your pen

• 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 OZEMPIC® flow before you inject.

• Do not try to repair your pen or pull it apart.

• Do not expose your pen to dust, dirt, or liquid.

• Do not wash, soak, or lubricate your pen. If necessary, clean it with mild detergent on a moistened cloth.

How should I store my OZEMPIC® pen?

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• The OZEMPIC®® pen you are using should be disposed of (thrown away) after 56 days, even if it still has OZEMPIC® left in it. Write the disposal date on your calendar.

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• Unused OZEMPIC® pens may be used until the expiration date ("EXP") printed on the label, if kept in the refrigerator.

• When stored in the refrigerator, do not store OZEMPIC® pens directly next to the cooling element.

• Keep OZEMPIC®® away from heat and out of the light.

• Keep the pen cap on when not in use.

• Keep OZEMPIC®® and all medicines out of the reach of children.

For more information go to www.OZEMPIC.com

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