Product Monograph

Including Patient Medication Information

PrZEPBOUND®

tirzepatide injection

Solution, 2.5 mg/0.6 mL, 5 mg/0.6 mL, 7.5 mg/0.6 mL, 10 mg/0.6 mL, 12.5 mg/0.6 mL, and 15 mg/0.6 mL, in a multi-dose prefilled pen (KwikPen®) for subcutaneous use

Glucose-Dependent Insulinotropic Polypeptide (GIP) and Glucagon-Like Peptide-1 (GLP-1) Receptor Agonist

Obesity Management Medication

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Recent Major Label Changes

1 Indications	2026-06
1 Indications, 1.2 Geriatrics	2026-06
2 Contraindications	2026-04
4 Dosage and Administration, 4.1 Dosing Considerations	2026-06
4 Dosage and Administration, 4.2 Recommended Dose and Dosage Adjustment	2026-06
7 Warnings and Precautions, Non-arteritic anterior ischemic optic neuropathy (NAION)	2026-06
7 Warnings and Precautions, 7.1.2 Breastfeeding	2026-04

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Part 1: Healthcare Professional Information

1. Indications

ZEPBOUND (tirzepatide injection) is indicated for once-weekly administration as an adjunct to a reduced-calorie diet and increased physical activity:

- for chronic weight management, including weight loss and weight maintenance in adults with an initial body mass index (BMI) of:
  - 30 kg/m^2 or greater (obesity) or
  - 27 kg/m^2 to less than 30 kg/m^2 (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, dyslipidemia, prediabetes, type 2 diabetes mellitus, obstructive sleep apnea, or cardiovascular disease).
- to treat moderate to severe obstructive sleep apnea (OSA) in adults with obesity (BMI 30 kg/m^2 or greater).

Limitations of Use

- ZEPBOUND contains tirzepatide. Coadministration with other tirzepatide-containing products (e.g., Mounjaro®) or with any glucagon-like peptide-1 (GLP-1) receptor agonist is not recommended.
- The safety and efficacy of ZEPBOUND in combination with other products intended for weight management, including prescription drugs, over-the-counter drugs, and herbal preparations, have not been established.

1.1. Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2. Geriatrics

Geriatrics (≥65 years of age): In weight management clinical trials, 246 (8.8%) ZEPBOUND-treated patients were 65 years of age or older, and 15 (0.5%) ZEPBOUND-treated patients were 75 years of age or older at baseline.

No overall differences in safety or efficacy have been observed in clinical trial patients ≥65 years of age compared to younger patients (see 4 Dosage and Administration, 7.1.4 Geriatrics, and 10.3 Pharmacokinetics).

Clinical studies in OSA did not include sufficient numbers of patients aged 65 years or older to determine whether they respond differently from younger adult patients. Other reported clinical experience with tirzepatide has not identified differences in responses between patients ≥65 years of age and younger patients (7.1.4 Geriatrics).

2. Contraindications

ZEPBOUND is contraindicated:

- In patients who are hypersensitive to tirzepatide or to any ingredient in the formulation, including any nonmedicinal ingredient (e.g., benzyl alcohol), or component of the container (see 7 Warnings and Precautions). (For a complete listing of the ingredients, see 6 Dosage Forms, Strengths, Composition, and Packaging).

- 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).
- During pregnancy (see 7.1.1 Pregnancy).

3. Serious Warnings and Precautions Box

RISK OF THYROID C-CELL TUMORS

- Tirzepatide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors (adenomas and carcinomas) at clinically relevant exposures in male and female rats. It is unknown whether ZEPBOUND causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC) in humans. The human relevance of tirzepatide-induced rodent thyroid C-cell tumors has not been determined (see 7 Warnings and Precautions and 16 Non-Clinical Toxicology).
- ZEPBOUND 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

- Coadministration with other tirzepatide-containing products (e.g., Mounjaro) or with any glucagon-like peptide-1 (GLP-1) receptor agonist is not recommended.
- In patients with type 2 diabetes, an increased risk of hypoglycemia was seen with concomitant use of a sulfonylurea with ZEPBOUND. ZEPBOUND lowers blood glucose. When initiating ZEPBOUND, consider reducing the dose of concomitantly administered insulin secretagogues (e.g., sulfonylureas) or insulin to reduce the risk of hypoglycemia (see 7 Warnings and Precautions).
- Obstructive Sleep Apnea (OSA): Some patients with moderate to severe obstructive sleep apnea may require positive airway pressure (PAP) therapy. ZEPBOUND is not a replacement for PAP therapy in patients who require it, and decisions regarding initiation, continuation, or modification of PAP should be directed by the healthcare provider.

4.2. Recommended Dose and Dosage Adjustment

- The recommended starting dosage of ZEPBOUND is 2.5 mg injected subcutaneously once weekly. The 2.5 mg dosage is for treatment initiation.
- After 4 weeks, increase the dosage to 5 mg injected subcutaneously once weekly.
- The dosage may be increased in 2.5 mg increments, after at least 4 weeks on the current dose.
- The maximum dosage of ZEPBOUND is 15 mg injected subcutaneously once weekly.

Chronic Weight Management

- The recommended maintenance dosages in adults are 5 mg, 10 mg, or 15 mg injected

subcutaneously once weekly.

Obstructive Sleep Apnea

- The recommended maintenance dosages in adults are 10 mg or 15 mg injected subcutaneously once weekly.

Special Populations

- Renal Insufficiency: No dose adjustment is required in patients with renal impairment (see 10.3 Pharmacokinetics).
- Hepatic Insufficiency: No dose adjustment is recommended in patients with hepatic insufficiency (see 10.3 Pharmacokinetics).
- Geriatrics (≥65 years): No dose adjustment is required in patients over 65 years of age (see 7.1.4 Geriatrics and 10.3 Pharmacokinetics).
- Pediatrics (<18 years): The safety and effectiveness of ZEPBOUND have not been studied in patients under 18 years of age. ZEPBOUND is not indicated for pediatric use (see 7.1.3 Pediatrics).

4.4. Administration

- Prior to initiation of ZEPBOUND, train patients and caregivers on proper injection technique. Advise the patient to carefully read the Instructions for Use included with the Patient Medication Information, and to watch the instructional videos, before administering the medicinal product.
- Inspect ZEPBOUND visually before use. It should appear clear and colorless to slightly yellow. Do not use ZEPBOUND if particulate matter or discoloration is seen.
- Administer ZEPBOUND once weekly at any time of day, with or without meals. ZEPBOUND should not be administered daily.
- Inject ZEPBOUND subcutaneously in the abdomen, thigh, or upper arm.
- Rotate injection sites with each dose.
- ZEPBOUND should not be administered intramuscularly or intravenously.
- Patients using ZEPBOUND go through one pen per month as each pen delivers 4 doses of tirzepatide.
- The day of weekly administration can be changed, if necessary, as long as the time between the two doses is at least 3 days (72 hours).

4.5. Missed Dose

If a dose is missed, instruct patients to administer ZEPBOUND as soon as possible within 4 days (96 hours) after the missed dose. If more than 4 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.

5. Overdose

Potential symptoms from an overdose could be gastrointestinal related (e.g., nausea). In the event of overdose, appropriate supportive care (including frequent blood glucose monitoring)

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 tirzepatide.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6. Dosage Forms, Strengths, Composition, and Packaging

ZEPBOUND is a clear and colourless to slightly yellow solution that is free of particles.

Table 1 – Dosage Forms, Strengths, and Composition

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Subcutaneous	Sterile solution of tirzepatide for injection in a multi-dose prefilled pen (KwikPen®) 4 doses of 2.5 mg/0.6 mL (10 mg in 2.4 mL) 4 doses of 5 mg/0.6 mL (20 mg in 2.4 mL) 4 doses of 7.5 mg/0.6 mL (30 mg in 2.4 mL) 4 doses of 10 mg/0.6 mL (40 mg in 2.4 mL) 4 doses of 12.5 mg/0.6 mL (50 mg in 2.4 mL) 4 doses of 15 mg/0.6 mL (60 mg in 2.4 mL)	Benzyl alcohol (preservative), glycerin, hydrochloric acid solution, phenol (preservative), sodium chloride, sodium hydroxide solution, sodium phosphate dibasic heptahydrate, water for injection (preserved formulation)

ZEPBOUND is packaged in a cardboard outer carton and is available as an individual multi-dose prefilled pen.

7. Warnings and Precautions

See 3 Serious Warnings and Precautions Box.

General

The ZEPBOUND multi-dose prefilled pen (KwikPen) contains 5.4 mg benzyl alcohol in each 0.6 mL dose. Patients with hepatic or renal impairment should be informed of the potential risk of metabolic acidosis due to accumulation of benzyl alcohol over time. Benzyl alcohol may cause allergic reactions (see 2 Contraindications).

Carcinogenesis and Genotoxicity

Risk of Thyroid C-Cell Tumors

Tirzepatide caused a dose-dependent and treatment-duration-dependent increase in the incidence of thyroid C-cell tumors (adenomas and carcinomas) in both sexes of rats in a two-year study at clinically relevant plasma exposures (see 16 Non-Clinical Toxicology). It is unknown whether ZEPBOUND 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 effect for GLP-1 receptor agonists.

ZEPBOUND 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 ZEPBOUND and inform them of symptoms of thyroid tumors (e.g., a mass in the neck, dysphagia, dyspnea, persistent hoarseness).

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

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 of serum calcitonin and a high background incidence of thyroid disease. However, if serum calcitonin is measured and found to be elevated, the patient should be referred to an endocrinologist for further evaluation. Similarly, patients with thyroid nodules noted on physical examination or neck imaging obtained for other reasons should be referred to an endocrinologist for further evaluation.

Cardiovascular

Heart Rate Increase

ZEPBOUND causes an increase in heart rate. Caution should be observed in patients who have cardiac conditions that might be worsened by an increase in heart rate (see 9.4 Drug-Drug Interactions).

Heart Failure

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

Driving and Operating Machinery

No studies on the effects of the ability to drive and use machines have been performed. Patients with obesity/overweight and T2DM taking ZEPBOUND in combination with a sulfonylurea or insulin should be advised to take precautions to avoid hypoglycemia while driving and using machines.

Endocrine and Metabolism

Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin in Patients with Type 2 Diabetes Mellitus

Patients with type 2 diabetes mellitus (T2DM) receiving ZEPBOUND for weight management in combination with an insulin secretagogue (e.g., a sulfonylurea) or insulin may have an increased risk of hypoglycemia. The risk of hypoglycemia may be lowered by a reduction in the

dose of the insulin secretagogue or insulin (see 8.2 Clinical Trial Adverse Reactions and 9.2 Drug Interactions Overview).

Inform patients of the risk of hypoglycemia and educate them on the signs and symptoms of hypoglycemia. In patients with T2DM, monitor blood glucose prior to starting ZEPBOUND and during ZEPBOUND treatment.

Other Incretin Drugs

The use of ZEPBOUND in combination with other incretin drugs (e.g., GLP-1 receptor agonists or DPP-4 inhibitors) or with other tirzepatide-containing drugs (i.e., Mounjaro) has not been studied and ZEPBOUND should not be used in combination with those drugs. It is unknown if concomitant use of drugs acting via similar pathways affects the efficacy and safety of ZEPBOUND.

Gastrointestinal

Use of ZEPBOUND (tirzepatide injection) has been associated with gastrointestinal adverse reactions, sometimes severe (see 8.2 Clinical Trial Adverse Reactions). In clinical trials for weight reduction, severe gastrointestinal adverse reactions were reported more frequently among patients receiving ZEPBOUND (2.7%) than placebo (1.2%). Similar rates of severe gastrointestinal adverse reactions were seen in the clinical trials for OSA.

ZEPBOUND has not been studied in patients with severe gastrointestinal disease, including severe gastroparesis, and is therefore not recommended in these patients. Events related to impaired gastric emptying, including severe gastroparesis, have been reported. Monitor and consider dose modification or discontinuation in patients who develop severe gastrointestinal symptoms while on treatment.

Malnutrition

Events related to malnutrition have been reported, including severe, in patients receiving ZEPBOUND. Risks associated with malnutrition include, but are not limited to, vitamin and mineral deficiency, protein deficiency, and low body weight. Nutritional guidance and, as needed, supplementation or support, should be considered. Discontinuation should be considered for severe or persistent cases.

Hepatic/Biliary/Pancreatic

Acute Gallbladder Disease

Treatment with ZEPBOUND and GLP-1 receptor agonists is associated with an increased occurrence of acute gallbladder disease.

In a pool of 3 placebo-controlled clinical trials of ZEPBOUND for weight reduction, cholelithiasis was reported in 1.1% of ZEPBOUND-treated patients and 1.0% of placebo-treated patients, cholecystitis was reported in 0.6% of ZEPBOUND-treated patients and 0.2% of placebo-treated patients, and cholecystectomy was reported in 0.2% of ZEPBOUND-treated patients and no placebo-treated patients. Acute gallbladder events were associated with weight reduction. Similar rates of cholelithiasis were reported in the 2 clinical trials for OSA. If cholecystitis is suspected, gallbladder diagnostic studies and appropriate clinical follow-up are indicated.

Acute Pancreatitis

Acute pancreatitis has been observed in patients treated with GLP-1 receptor agonists. In clinical trials of tirzepatide for T2D, 14 events of acute pancreatitis were confirmed by

adjudication in 13 (0.2%) tirzepatide-treated patients (0.23 patients per 100 years of exposure) versus 3 events in 3 (0.1%) comparator-treated patients (0.11 patients per 100 years of exposure). In ZEPBOUND placebo-controlled trials for weight reduction, 6 events of acute pancreatitis were confirmed by adjudication in 6 (0.2%) ZEPBOUND-treated patients (0.15 patients per 100 patient years of exposure) versus 3 events in 3 (0.2%) placebo-treated patients (0.18 patients per 100 patient years of exposure). The exposure-adjusted incidence rate for treatment-emergent adjudication-confirmed pancreatitis in the pooled clinical studies for OSA (SURMOUNT-OSA-1 and -2) was 0.84 patients per 100 years of exposure for tirzepatide-treated patients and 0 for placebo-treated patients.

After initiation of ZEPBOUND, observe patients carefully for signs and symptoms of pancreatitis. Patients should be informed of the characteristic symptoms of acute pancreatitis. In the absence of other signs and symptoms of pancreatitis, elevations in pancreatic enzymes alone are not predictive of pancreatitis. If pancreatitis is suspected, ZEPBOUND should be discontinued and appropriate management initiated; if confirmed, ZEPBOUND should not be restarted. ZEPBOUND has not been evaluated in patients with a prior history of pancreatitis and should be used with caution in these patients.

Immune

Hypersensitivity Reactions

Hypersensitivity reactions have been reported with ZEPBOUND in clinical trials. There have been postmarketing reports of serious hypersensitivity reactions (e.g. anaphylactic reactions and angioedema) in patients treated with tirzepatide. If hypersensitivity reactions occur, discontinue use of ZEPBOUND; treat promptly per standard of care, and monitor until signs and symptoms resolve. Do not use in patients with a previous hypersensitivity to tirzepatide or any of the excipients in ZEPBOUND, or component of the container (see 2 Contraindications).

Anaphylaxis and angioedema have been reported with GLP-1 receptor agonists. Use ZEPBOUND with caution in patients with a history of angioedema or anaphylaxis with a GLP-1 receptor agonist or related products because it is unknown whether such patients will be predisposed to anaphylaxis with ZEPBOUND.

Ophthalmologic

Diabetic Retinopathy Complications in Patients with Type 2 Diabetes Mellitus

Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy. ZEPBOUND has not been studied in patients with non-proliferative diabetic retinopathy requiring acute therapy, proliferative diabetic retinopathy, or diabetic macular edema, and should be used with caution in these patients, with appropriate monitoring.

Non-arteritic anterior ischemic optic neuropathy (NAION)

Events of non-arteritic anterior ischemic optic neuropathy (NAION) have been reported in patients treated with GLP-1 receptor agonist products. There is no identified time interval for when NAION may develop following treatment start. Patients reporting a sudden loss of vision (including partial loss) should be urgently referred for ophthalmological examination and treatment with tirzepatide should be discontinued if NAION is confirmed.

Perioperative Considerations

Aspiration during General Anesthesia or Deep Sedation

There have been rare postmarketing reports of pulmonary aspiration in patients receiving GLP-1 receptor agonists undergoing elective surgeries or procedures requiring general anesthesia or deep sedation who had residual gastric contents despite reported adherence to preoperative fasting recommendations.

Available data are insufficient to inform recommendations to mitigate the risk of pulmonary aspiration during general anesthesia or deep sedation in patients using ZEPBOUND, including whether modifying preoperative fasting recommendations or temporarily discontinuing ZEPBOUND could reduce the incidence of retained gastric contents. Instruct patients to inform healthcare providers prior to any planned surgeries or procedures if they are using ZEPBOUND.

Psychiatric

Suicidal Ideation and Behaviour

Suicidal ideation and behaviour have been reported with products which induce weight loss (chronic weight management). Monitor patients treated with ZEPBOUND for the emergence or worsening of depression, suicidal thoughts or behaviours, and/or any unusual changes in mood or behaviour. Discontinue ZEPBOUND in patients who experience suicidal thoughts or behaviours. Avoid ZEPBOUND in patients with a history of suicidal attempts or active suicidal ideation.

Renal

Acute Kidney Injury

Tirzepatide has been associated with gastrointestinal adverse reactions, which include nausea, vomiting, and diarrhea (see 8 Adverse Reactions). These events may lead to dehydration, which could cause a deterioration in renal function, including acute renal failure.

In patients treated with GLP-1 receptor agonists, there have been postmarketing reports of acute kidney injury and worsening of chronic renal failure, which may sometimes require hemodialysis. Some of these events have been reported in patients without known underlying renal disease. A majority of the reported events occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration. Monitor renal function in patients reporting adverse reactions to ZEPBOUND that could lead to volume depletion.

Reproductive Health

Women of childbearing potential are recommended to use contraception when treated with tirzepatide. ZEPBOUND is contraindicated during pregnancy (see 2 Contraindications, 7.1.1 Pregnancy, and 16 Non-Clinical Toxicology).

Advise patients using oral hormonal contraceptives to switch to a non-oral contraceptive method, or add a barrier method of contraception for 4 weeks after initiation and for 4 weeks after each dose escalation with ZEPBOUND (see 9.4 Drug-Drug Interactions).

7.1. Special Populations

7.1.1. Pregnancy

No clinical trials have been conducted in pregnancy. Studies in animals (i.e., rats and rabbits) have shown reproductive and developmental toxicity, including harm to fetal development and maternal weight loss (see 16 Non-Clinical Toxicology). The extent of exposure in pregnancy during clinical trials is very limited and has been reported in individual cases only.

ZEPBOUND is contraindicated during pregnancy (see 2 Contraindications). If a patient wishes to become pregnant, ZEPBOUND should be discontinued at least 1 month before a planned pregnancy due to the long half-life of tirzepatide.

7.1.2. Breastfeeding

In a 5 mg single-dose clinical lactation study, the concentration of tirzepatide in breast milk was found to be either undetectable (limit of detection in breastmilk 4 ng/mL) to very low compared to maternal administered dose and maternal plasma concentrations (see 10.3 Pharmacokinetics). There are no available data on the effects of tirzepatide on the breastfed infant or on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZEPBOUND and any potential adverse effects on the breastfed infant from ZEPBOUND or from the underlying maternal condition.

7.1.3. Pediatrics

The safety and effectiveness of ZEPBOUND have not been established in pediatric patients less than 18 years of age. ZEPBOUND is not indicated for use in pediatric patients.

7.1.4. Geriatrics

No dose adjustment is required in patients over 65 years of age (see 10.3 Pharmacokinetics).

In clinical trials for weight management, 246 (8.8%) ZEPBOUND-treated patients were 65 years of age or older and 15 (0.5%) ZEPBOUND-treated patients were 75 years of age or older at baseline.

No overall differences in safety or efficacy in the weight management clinical trials were detected between these patients and younger patients.

In the two clinical trials for OSA in adults with obesity, 20 (4.3%) ZEPBOUND-treated patients were 65 years of age and older and 4 (0.9%) ZEPBOUND-treated patients were aged 75 through 84 years of age, with no patients aged 85 years or older. Therefore, the clinical studies for OSA did not include sufficient numbers of patients 65 years and older to determine whether they respond differently from younger adult patients with moderate to severe OSA and obesity. Other reported clinical experience with tirzepatide has not identified differences in responses between patients ≥65 years of age and younger patients.

7.1.5. Hepatic Impairment

In a clinical pharmacology study in subjects with varying degrees of hepatic impairment, no change in tirzepatide pharmacokinetics (PK) was observed (see 10.3 Pharmacokinetics). However, there is limited clinical experience in patients with mild, moderate, or severe hepatic

impairment; therefore, use ZEPBOUND with caution in these patient populations.

7.1.6. Renal Impairment

In the clinical trials for weight management, 850 (30.3%) of ZEPBOUND-treated patients had mild renal impairment (eGFR ≥60 and <90 mL/min/1.73 m^2), 59 (2.1%) had moderate renal impairment (eGFR ≥30 and <60 mL/min/1.73 m^2) and 0 (0.0%) had severe renal impairment (eGFR <30 mL/min/1.73 m^2) at baseline. ZEPBOUND is not recommended in patients with end stage renal impairment due to very limited clinical experience with ZEPBOUND in this population (see 10.3 Pharmacokinetics).

8. Adverse Reactions

8.1. Adverse Reaction Overview

In a pool of 3 placebo-controlled trials for weight management, the most frequently reported adverse reactions were gastrointestinal disorders, including nausea, diarrhea, constipation and vomiting. In general, these reactions were mild or moderate in severity. Gastrointestinal adverse reactions led to 3.8% of patients discontinuing tirzepatide treatment.

The following serious adverse reactions are described below or elsewhere in the product monograph (see 7 Warnings and Precautions):

- Risk of Thyroid C-Cell Tumors
- Gastrointestinal Adverse Reactions
- Malnutrition
- Acute Kidney Injury
- Acute Gallbladder Disease
- Acute Pancreatitis
- Hypersensitivity Reactions
- Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin in Patients with T2DM
- Diabetic Retinopathy Complications in Patients with T2DM
- Suicidal Ideation and Behaviour
- Aspiration during General Anesthesia or Deep Sedation

8.2. Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, 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 may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Adverse Reactions in Weight Management Clinical Trials

The safety of ZEPBOUND was evaluated in a pool of 2 randomized, double-blind, placebo-controlled trials that included 2519 adult patients with overweight or obesity treated with ZEPBOUND 5 mg (SURMOUNT-1 only), 10 mg, or 15 mg for up to 72 weeks and a 4-week off drug safety follow-up period (SURMOUNT-1 and -2) (see 14.1 Clinical Trials by Indication). For

patients treated with ZEPBOUND, the mean age was 47 years and 37% were male. The population was 72% White, 12% Asian, 8% Black or African American, and 7% American Indian or Alaska Native; 51% identified as Hispanic or Latino ethnicity. Baseline characteristics included an average BMI of 37.4 kg/m^2, 29% with a BMI ≥40 kg/m^2, 41% with hypertension, 37% with dyslipidemia, 25% with T2DM (SURMOUNT-2 only), 7% with obstructive sleep apnea, and 4% with cardiovascular disease.

Across both trials, 4.8%, 6.3%, and 6.7% of patients treated with 5 mg, 10 mg, and 15 mg of ZEPBOUND, respectively, permanently discontinued treatment as a result of adverse reactions compared to 3.4% of patients treated with placebo. The majority of patients who discontinued ZEPBOUND treatment due to adverse reactions did so during the first few months of treatment due to gastrointestinal adverse reactions.

Common Adverse Reactions

Table 2 shows common adverse reactions associated with the use of ZEPBOUND in 2 placebo-controlled trials. These adverse reactions occurred more commonly with ZEPBOUND than with placebo and occurred in at least 1% of patients treated with ZEPBOUND.

Table 2 – Adverse Reactions (≥1% and Greater than Placebo) in Adults with Obesity or Overweight Treated with ZEPBOUND for Chronic Weight Management in Two 72-week, Placebo-Controlled Studies (SURMOUNT-1 and -2)

Adverse Reaction	ZEPBOUND 5 mg n (%)	ZEPBOUND 10 mg n (%)	ZEPBOUND 15 mg n (%)	Placebo n (%)
Gastrointestinal Disorders				
Nausea	155 (24.6)	275 (29.0)	263 (28.0)	81 (8.5)
Diarrhea[a]	118 (18.7)	197 (20.8)	212 (22.5)	75 (7.8)
Constipation[b]	106 (16.8)	134 (14.1)	102 (10.8)	50 (5.2)
Vomiting	52 (8.3)	102 (10.8)	118 (12.5)	21 (2.2)
Abdominal Pain[c]	56 (8.9)	88 (9.3)	98 (10.4)	49 (5.1)
Dyspepsia	56 (8.9)	85 (9.0)	93 (9.9)	37(3.9)
Gastroesophageal Reflux Disease	27 (4.3)	37 (3.9)	43 (4.6)	20 (2.1)
Eructation	24 (3.8)	52. (5.5)	48 (5.1)	6 (0.6)
Flatulence	21 (3.3)	30 (3.2)	38 (4.0)	15 (1.6)
Abdominal Distension	22 (3.5)	32 (3.4)	38 (4.0)	21 (2.2)
Dry Mouth	5 (0.8)	11 (1.2)	7 (0.7)	1 (0.1)
General Disorders and Administration Site Conditions				
Injection Site Reactions[d]	36 (5.7)	77 (8.1)	77 (8.2)	17 (1.8)
Fatigue[e]	29 (4.6)	54 (5.7)	64 (6.8)	30 (3.1)
Immune System Disorders				
Hypersensitivity Reactions	31 (4.9)	47 (5.0)	51 (5.4)	30 (3.1)
Nervous System Disorders				

Dizziness	26 (4.1)	52 (5.5)	34 (3.6)	20 (2.1)
Skin and Subcutaneous Tissue Disorders				
Hair Loss	32 (5.1)	40 (4.2)	46 (4.9)	8 (0.8)
Vascular Disorders				
Hypotension[f]	4 (0.6)	9 (1.0)	15 (1.6)	1 (0.1)

[a] Includes diarrhea, frequent bowel movements.

[b] Includes constipation, feces hard.

[c] Includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness, gastrointestinal pain.

[d] Includes multiple related adverse event terms, such as injection site bruising, injection site erythema, injection site haematoma, injection site haemorrhage, injection site hypersensitivity, injection site induration, injection site inflammation, injection site irritation, injection site oedema, injection site pain, injection site paraesthesia, injection site pruritus, injection site rash, injection site reaction, injection site swelling.

[e] Includes asthenia, fatigue, lethargy, malaise.

[f] Includes blood pressure decreased, hypotension, orthostatic hypotension.

In a clinical trial for chronic weight management that included an intensive lifestyle intervention lead-in period (Study SURMOUNT-3), 287 patients were treated with ZEPBOUND for up to 72 weeks. In a randomized withdrawal trial (Study SURMOUNT-4), 783 patients were treated with ZEPBOUND for up to 36 weeks, and 335 of these patients were treated for up to 88 weeks (see 14.1 Clinical Trials by Indication). In Study SURMOUNT-3, 10% of ZEPBOUND-treated patients and 2% of placebo-treated patients discontinued drug due to adverse reactions. In Study SURMOUNT-4, 7% of patients discontinued ZEPBOUND before randomized withdrawal at Week 36 due to adverse reactions. In Studies SURMOUNT-3 and SURMOUNT-4, adverse reactions were similar to those reported in the two pooled clinical trials, Studies SURMOUNT-1 and SURMOUNT-2.

Gastrointestinal Adverse Reactions

In a pool of 2 ZEPBOUND placebo-controlled clinical trials (SURMOUNT-1 and SURMOUNT-2), gastrointestinal adverse reactions occurred more frequently among patients receiving ZEPBOUND (5 mg 55.6%, 10 mg 55.8%, 15 mg 55.6%) than placebo (29.7%). More patients receiving ZEPBOUND (5 mg 1.9%, 10 mg 3.3%, 15 mg 4.3%) discontinued treatment due to gastrointestinal adverse reactions than patients receiving placebo (0.5%). The majority of nausea, vomiting, and/or diarrhea events occurred during dose escalation and decreased over time.

Hypotension

Pooled data from the 2 placebo-controlled clinical trials, SURMOUNT-1 and SURMOUNT-2 showed that hypotension occurred more frequently among patients receiving ZEPBOUND (5 mg 1.1%, 10 mg 1.4%, 15 mg 2.1%) than patients receiving placebo (0.1%). Hypotension was more frequently seen in ZEPBOUND-treated patients on concomitant antihypertensive therapy (5 mg 0.5%, 10 mg 1.8%, 15 mg 3.4%) compared to ZEPBOUND-treated patients not on antihypertensive therapy (5 mg 1.4%, 10 mg 1.1%, 15 mg 1.3%). Hypotension also occurred in association with gastrointestinal adverse events and dehydration.

Hypersensitivity Reactions

In the pooled results from the 2 placebo-controlled clinical trials, SURMOUNT-1 and SURMOUNT-2, the percentage of participants reporting immediate hypersensitivity reactions (reactions that occurred within 24 hours of study drug administration) was higher in the

ZEPBOUND-treated patients (5 mg 1.8%, 10 mg 2.4%, 15 mg 2.1%) compared to placebo-treated patients (0.4%). The percentage of participants reporting non-immediate hypersensitivity reactions (reactions that occurred more than 24 hours after study drug administration, but prior to the next administration of study drug) was (5 mg 3.5%, 10 mg 3.2%, 15 mg 3.8%) in ZEPBOUND-treated patients compared to 2.7% of placebo-treated patients. In a pool of 4 clinical trials (SURMOUNT-1, -2, -3, and -4), hypersensitivity reactions were more frequent in those with anti-tirzepatide antibodies (5.5%) compared to those who did not develop anti-tirzepatide antibodies (3.0%) (see 10 Clinical Pharmacology). The majority of the hypersensitivity reactions in trials were skin reactions (e.g., rash, itching).

Injection Site Reactions

In a pool of 3 placebo-controlled clinical trials (SURMOUNT-1, -2, and -3), the percentage of participants reporting at least 1 injection-site reaction was higher in the participants treated with ZEPBOUND compared to placebo (8.0% vs. 1.8%, respectively). In a pool of 4 clinical trials (SURMOUNT-1, -2, -3, and -4), injection site reactions occurred in 13.6% of ZEPBOUND-treated patients with anti-tirzepatide antibodies and in 1.8% of ZEPBOUND-treated patients who did not develop anti-tirzepatide antibodies.

Hair Loss

All hair loss events reported with ZEPBOUND in clinical trials were mild or moderate in severity. No ZEPBOUND-treated patients and one placebo-treated patient discontinued study treatment due to hair loss.

Other Adverse Reactions

Acute Kidney Injury

In a pool of 3 placebo-controlled clinical trials (SURMOUNT-1, -2, and -3), acute kidney injury was reported in 0.5% of ZEPBOUND-treated patients compared to 0.2% of placebo-treated patients.

Acute Gallbladder Disease

In a pool of 3 placebo-controlled clinical trials of ZEPBOUND (SURMOUNT-1, -2, and -3), cholelithiasis was reported in 1.1% of ZEPBOUND-treated patients and 1.0% of placebo-treated patients, cholecystitis was reported in 0.6% of ZEPBOUND-treated patients and 0.2% of placebo-treated patients, and cholecystectomy was reported in 0.2% of ZEPBOUND-treated patients and no placebo-treated patients. Acute gallbladder events were associated with weight reduction.

Hypoglycemia

In a trial of patients with T2DM and BMI ≥27 kg/m^2 (SURMOUNT-2), hypoglycemia (plasma glucose <3.0 mmol/L) was reported in 4.2% of ZEPBOUND-treated patients versus 1.3% of placebo-treated patients. In this trial, patients receiving ZEPBOUND in combination with an insulin secretagogue (e.g., sulfonylurea) had increased risk of hypoglycemia (10.3%) compared to ZEPBOUND-treated patients not taking a sulfonylurea (2.1%). There is also increased risk of hypoglycemia in patients treated with ZEPBOUND in combination with insulin (see 9.2 Drug Interactions Overview).

In clinical trials, in adults with obesity/overweight without T2DM, there was no systematic capturing of hypoglycemia.

Heart Rate Increase

Based on a pool of 3 placebo-controlled trials (SURMOUNT-1, -2, and -3), treatment across

ZEPBOUND doses resulted in a mean increase in heart rate of 3 beats per minute compared to no increase in placebo-treated patients.

Adverse Reactions in Obstructive Sleep Apnea Clinical Trials

Tirzepatide was evaluated in 2 randomized, double-blind, placebo-controlled trials (SURMOUNT-OSA-1 and -2) that included a total of 467 adults with moderate to severe OSA and obesity of which 233 patients were treated with tirzepatide injection 10 mg or 15 mg once-weekly for up to 52 weeks (see 14.1. Clinical Trials by Indication). SURMOUNT-OSA-1 enrolled 234 patients who were unable or unwilling to use Positive Airway Pressure (PAP) therapy and SURMOUNT-OSA-2 enrolled 235 patients who were on PAP therapy. The adverse reactions observed with tirzepatide 10 mg or 15 mg administered subcutaneously once weekly were similar to those reported in the two pooled placebo controlled clinical trials for weight reduction (SURMOUNT-1 and -2).

8.3. Less Common Clinical Trial Adverse Reactions

Nervous System Disorders: dysgeusia

Pancreatic disorders: pancreatitis

8.4. Abnormal Laboratory Findings: Hematologic, Clinical Chemistry, and Other Quantitative Data

Clinical Trial Findings

Pancreatic Enzymes

Amylase and lipase were measured in the clinical trials for weight management. Treatment with ZEPBOUND resulted in mean increases from baseline in pancreatic amylase of 23% and lipase of 34%. The percentage of patients with values above 3 times the upper limit of normal for amylase or lipase at any timepoint on-treatment after baseline are presented below. The clinical significance of elevations of amylase or lipase in patients without other signs and symptoms of pancreatitis is unknown (see 7 Warnings and Precautions).

Table 3 – Amylase and Lipase

	Placebo N=1250 n (%)	**ZEPBOUND N=2806 n (%)**
Amylase > 3X ULN	10 (0.8)	39 (1.4)
Lipase > 3X ULN	12 (1.0)	43 (1.5)

N: number of patients; n: number of patients with event; %: percentage of patients; ULN: upper limit of normal.

8.5. Post-Market Adverse Reactions

The following adverse reactions have been reported during post-marketing use of tirzepatide, the active ingredient in ZEPBOUND. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or to establish a causal relationship to drug exposure.

Gastrointestinal disorders: ileus

Immune system disorders: anaphylactic reaction

Skin and subcutaneous tissue disorders: angioedema

Nervous system disorders: dysesthesia

Pulmonary: Pulmonary aspiration has been reported in patients receiving GLP-1 receptor agonists undergoing elective surgeries or procedures requiring general anesthesia or deep sedation.

Renal: acute kidney injury

Eye disorders: Non-arteritic anterior ischemic optic neuropathy (NAION).

9. Drug Interactions

9.2. Drug Interactions Overview

ZEPBOUND delays gastric emptying, and thereby has the potential to impact the absorption of concomitantly administered oral medications. The impact of tirzepatide on gastric emptying was greatest after a single dose of 5 mg and diminished after subsequent doses.

Dose adjustments with concomitant use of insulin secretagogues (e.g., sulfonylurea) or insulin may be necessary (see 7 Warnings and Precautions and 8.2 Clinical Trial Adverse Reactions).

9.4. Drug-Drug Interactions

The drugs listed in Table 4 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 4 – Established or Potential Drug-Drug Interactions

Proper/Common Name	Source of Evidence	Effect	Clinical Comment
Acetaminophen	Clinical Trial	Administration of acetaminophen in the presence of tirzepatide 5 mg resulted in a reduction of acetaminophen C_{max} by approximately 55% and a delay in t_{max} of 1 hour. The effect on C_{max} and t_{max} diminished with repeated dosing over time. Overall acetaminophen exposure (AUC_{0-24hr}) was not influenced.	No dose adjustment of acetaminophen is necessary when administered with tirzepatide.
Oral Contraceptives	Clinical Trial	Administration of a combination oral contraceptive (0.035 mg ethinyl estradiol plus 0.25 mg norgestimate) in the presence of a single dose of tirzepatide (5 mg) resulted in a reduction of oral contraceptive C_{max} by 55 to 66%, with a 16 to 23% reduction in AUC and a delay in t_{max} of 2.5 to 4.5 hours. These effects may be due to the impact of ZEPBOUND on gastric	Advise patients using oral hormonal contraceptives to switch to a non-oral contraceptive method, or to add a barrier method of contraception for 4 weeks after initiation and for 4 weeks after each dose escalation

		emptying.	with ZEPBOUND.
Drugs that Increase Heart Rate	Clinical Trial	ZEPBOUND resulted in a mean increase in heart rate of 3 beats per minute. There was a mean increase in heart rate of 0 beats per minute in placebo-treated patients.	Caution should be observed if ZEPBOUND is administered with other drugs that also increase heart rate, such as drugs with sympathomimetic or anticholinergic activity (see 7 Warnings and Precautions).

Drugs that Cause PR Interval or QTc Interval Prolongation

In phase 3 clinical studies, no clinically meaningful treatment-emergent differences in PR interval or QTc duration were noted between placebo, tirzepatide, or comparators.

A dedicated thorough QT study has not been conducted with ZEPBOUND.

9.5. Drug-Food Interactions

Interactions with food have not been established.

9.6. Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7. Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10. Clinical Pharmacology

10.1. Mechanism of Action

Tirzepatide is a glucose-dependent insulinotropic polypeptide (GIP) receptor agonist and GLP-1 receptor agonist. It is an amino acid sequence including a C20 fatty diacid moiety that enables albumin binding and prolongs the half-life. Tirzepatide selectively binds to and activates both the GIP and GLP-1 receptors, the targets for native GIP and GLP-1.

GLP-1 is a physiological regulator of appetite and caloric intake. Nonclinical studies suggest the addition of GIP may further contribute to the regulation of food intake.

Both GIP receptors and GLP-1 receptors are found in areas of the brain important for appetite regulation. Animal studies show that tirzepatide distributes to and activates neurons in brain regions involved in regulation of appetite and food intake.

In human adipocytes, tirzepatide binds to and activates GIP receptors to regulate glucose uptake and modulate lipid uptake and lipolysis. Tirzepatide modulates fat utilization through the GIP receptor.

10.2. Pharmacodynamics

Tirzepatide lowers body weight with greater fat mass loss than lean mass loss. Tirzepatide modulates carbohydrate and lipid metabolism.

Tirzepatide decreases calorie intake and appetite by increasing feelings of satiety and fullness,

and by decreasing feelings of hunger. Tirzepatide reduces food cravings and preferences for high sugar and high fat foods and reduces the brain response that is related to these types of foods.

Tirzepatide stimulates insulin secretion in a glucose-dependent manner and reduces glucagon secretion. Tirzepatide increases insulin sensitivity, as demonstrated in a hyperinsulinemic euglycemic clamp study in patients with T2DM after 28 weeks of treatment. These effects can lead to a reduction of blood glucose.

Tirzepatide delays gastric emptying. The delay is largest after the first dose and this effect diminishes over time.

Cardiac Electrophysiology

In phase 3 clinical studies, no clinically meaningful treatment-emergent differences in PR interval or QTc duration were noted between placebo, tirzepatide, or comparators. A dedicated thorough QT study has not been conducted with ZEPBOUND.

QTc and PR interval were evaluated using a population pharmacokinetic model-based analyses utilizing all data from healthy participants and patients with T2DM who were given either placebo or tirzepatide in one phase 1 study and two phase 2 studies. Concentration-QTc analysis and concentration-PR interval analysis based upon these three studies did not suggest an association between tirzepatide and QTc prolongation or PR interval duration.

10.3. Pharmacokinetics

The pharmacokinetics of tirzepatide is similar between healthy subjects and patients with overweight or obesity, and patients with OSA and obesity. Steady-state plasma tirzepatide concentrations were achieved following 4 weeks of once weekly administration. Tirzepatide exposure increases in a dose-proportional manner.

Absorption

Following subcutaneous administration, the median time (range) to maximum plasma concentration of tirzepatide is 24 hours (8 to 72 hours). The mean absolute bioavailability of tirzepatide following subcutaneous administration is 80%. Similar exposure was achieved with subcutaneous administration of tirzepatide in the abdomen, thigh, or upper arm.

Distribution

The mean [coefficient of variation (CV) %] apparent steady-state volume of distribution of tirzepatide following subcutaneous administration in patients with overweight or obesity, and patients with OSA and obesity is approximately 9.7 L (29%) and 11.8 L (37%), respectively. Tirzepatide is highly bound to plasma albumin (99%).

Elimination

The primary excretion routes of tirzepatide metabolites are via urine and feces. Intact tirzepatide is not observed in urine or feces. The apparent population mean clearance (CV%) of tirzepatide in patients with overweight or obesity, and patients with OSA and obesity is approximately 0.06 L/h (~20%) with an elimination half-life of approximately 5-6 days.

Metabolism

Tirzepatide is metabolized by proteolytic cleavage of the peptide backbone, beta-oxidation of the C20 fatty diacid moiety, and amide hydrolysis.

Special populations and conditions

The intrinsic factors of age, sex, race, ethnicity, and body weight do not have a clinically

relevant effect on the PK of tirzepatide.

- **Pediatrics:** tirzepatide has not been studied in pediatric patients.
- **Sex:** sex had no effect on the pharmacokinetics of tirzepatide.
- **Pregnancy and breastfeeding:** studies characterizing the pharmacokinetics of tirzepatide in pregnant patients have not been performed.

  Following subcutaneous administration of a single 5 mg dose to 11 healthy lactating adult females, the concentration of tirzepatide in breastmilk was found to be undetectable (limit of detection in breastmilk 4 ng/mL) in 164/171 samples assayed. Very low concentrations of tirzepatide (4.6 to 7.2 ng/mL) were detected in 7 breast milk samples and the cumulative amount of tirzepatide detected in the 7 breast milk samples over the 28-day sampling window was equivalent to less than 0.02% of the maternal administered dose, with the last measurable concentrations occurring 5 days post-dose. The AUC of tirzepatide in breastmilk could not be calculated, due to insufficient quantifiable concentrations.
- **Ethnic origin:** race had no clinically meaningful effect on the pharmacokinetics of tirzepatide.
- **Hepatic Insufficiency:** Hepatic impairment does not impact the pharmacokinetics of tirzepatide. The pharmacokinetics of tirzepatide after a single 5 mg dose were evaluated in patients with different degrees of hepatic impairment (mild, moderate, severe) compared with subjects with normal hepatic function (see 4 Dosage and Administration and 7.1 Special Populations).
- **Renal Insufficiency:** Renal impairment does not impact the pharmacokinetics of tirzepatide. The pharmacokinetics of tirzepatide after a single 5 mg dose were evaluated in patients with different degrees of renal impairment (mild, moderate, severe, ESRD) compared with subjects with normal renal function. Data from clinical studies have also shown that renal impairment in patients with overweight or obesity does not impact the pharmacokinetics of tirzepatide (see 4 Dosage and Administration and 7.1 Special Populations).
- **Obesity:** pharmacokinetic analyses have demonstrated an observed inverse relationship between body weight and tirzepatide exposure.

10.4. Immunogenicity

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity (including neutralizing antibody) 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 tirzepatide cannot be directly compared with the incidence of antibodies of other products.

In a pool of four placebo-controlled clinical trials (SURMOUNT-1, SURMOUNT-2, and SURMOUNT-3 with treatment phase durations of 72 weeks, and SURMOUNT-4 with a treatment phase duration of 88 weeks), there were 3484 (97.1%) treatment emergent anti-drug antibodies (TE ADA) -evaluable participants from 3588 ZEPBOUND-treated participants with overweight or obesity in the safety population. In these trials, 2268 (65.1%) ZEPBOUND-treated patients developed anti-tirzepatide antibodies. The anti-tirzepatide antibody formation in 1473 (42.6%) and 635 (18.3%) of ZEPBOUND-treated patients showed cross-reactivity to native GIP or native GLP-1, respectively.

Of the patients receiving ZEPBOUND, 80 (2.3%) and 79 (2.3%) developed neutralizing antibodies against tirzepatide activity on the GIP or GLP-1 receptors, respectively and 25 (0.7%)

and 3 (0.1%) developed neutralizing antibodies against native GIP or GLP-1, respectively.

In the Phase 3 clinical trials in OSA (SURMOUNT-OSA-1 and SURMOUNT-OSA-2 with treatment phase durations of 52 weeks) there were 226 (97.0%) TE ADA-evaluable patients from 233 ZEPBOUND-treated patients with OSA and obesity in the safety population. In these trials, 137 (60.6%) developed anti-tirzepatide antibody. The anti-tirzepatide antibody formation in 84 (37.2%) and 44 (19.5%) of ZEPBOUND-treated patients showed cross-reactivity to native GIP and native GLP-1, respectively. No ZEPBOUND-treated patients with OSA and obesity had neutralizing antibodies against tirzepatide, native GIP or native GLP-1.

There was no identified clinically significant effect of anti-tirzepatide antibodies on pharmacokinetics or effectiveness of ZEPBOUND. More ZEPBOUND-treated patients who developed anti-tirzepatide antibodies experienced hypersensitivity reactions or injection site reactions than those who did not develop these antibodies (see 8 Adverse Reactions).

11. Storage, Stability, and Disposal

Store ZEPBOUND in a refrigerator at 2°C to 8°C up to the expiration date. Do not use ZEPBOUND beyond the expiration date.

Do not freeze ZEPBOUND. Do not use ZEPBOUND if frozen.

Protect ZEPBOUND from light.

If needed, each multi-dose pen can be stored unrefrigerated at temperatures not to exceed 30°C for up to 30 days.

The ZEPBOUND multi-dose KwikPen contains 4 doses. The pen must be discarded in a puncture-resistant container, or in accordance with local requirements after the four weekly doses of ZEPBOUND have been used.

12. Special Handling Instructions

Each ZEPBOUND multi-dose KwikPen delivers four doses.

ZEPBOUND should not be used if the pen is damaged.

ZEPBOUND should not be used if the solution does not appear clear, free of particles, and colourless to slightly yellow.

If the KwikPen is dropped on a hard surface, it should not be used.

Part 2: Scientific Information

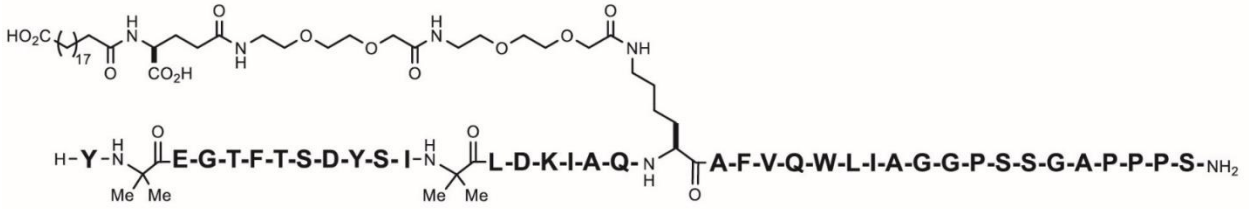
13. Pharmaceutical Information

Drug Substance

Non-proprietary name of the drug substance: tirzepatide

Molecular formula and molecular mass: $C_{225}H_{348}N_{48}O_{68}$ and 4813 Dalton

Structural formula:



Physicochemical properties: White to practically white amorphous solid

Table 5 – Tirzepatide Substance Solubility Profile

Solvent	Solubility of Tirzepatide (mg/mL)	Part of Solvent Required for 1 Part of Solute (g of Solute per Volume of Solvent)	Solubility Description[a]
5-mM Phosphate Buffer pH 7.0	Not less than 120 at 25°C	8.33 mL to dissolve 1 g	Freely Soluble

[a] Solubility descriptions are consistent with the USP, Ph.Eur., and Japanese Pharmacopoeias.

Product Characteristics:

ZEPBOUND (tirzepatide injection), for subcutaneous use, contains tirzepatide, a long-acting once-weekly GIP and GLP-1 receptor agonist. Tirzepatide is based on the GIP sequence and contains aminoisobutyric acid (Aib) in positions 2 and 13, a C-terminal amide, and Lys residue at position 20 that is attached to 1,20-eicosanedioic acid via a linker. ZEPBOUND has a pH of 6.5 - 7.5.

14. Clinical Trials

14.1. Clinical Trials by Indication

Chronic Weight Management in Adults with Overweight or Obesity

Table 6 – Summary of Patient Demographics for Clinical Trials in Adult Patients with Either Obesity (BMI ≥30 kg/m^2), or Overweight (BMI ≥27 to <30 kg/m^2) and at Least One Weight-Related Comorbidity

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex n (%)
SURMOUNT-1	Phase 3, 72-week randomized, double-blind, placebo-controlled	ZEPBOUND: 5 mg 10 mg 15 mg SC, weekly Placebo: SC, weekly	2539	45 years (18 – 84)	Female: 1714 (68%) Male: 825 (32%)
SURMOUNT-2	Phase 3, 72-week randomized, double-blind, placebo-controlled, in patients with T2DM	ZEPBOUND: 10 mg 15 mg SC, weekly Placebo: SC, weekly	938	54 years (18 – 85)	Female: 476 (51%) Male: 462 (49%)
SURMOUNT-3	Phase 3, 12-week intensive lifestyle intervention lead-in, followed by 72-week randomized, double-blind, placebo-controlled	ZEPBOUND: MTD (10 or 15 mg) SC, weekly Placebo: SC, weekly	806 enrolled 579 randomized	46 years (18 – 77)	Female: 364 (63%) Male: 215 (37%)
SURMOUNT-4	Phase 3, 36-week open-label lead-in, followed by 52-week randomized, double-blind, placebo-controlled	<u>Open-label lead-in period</u> ZEPBOUND: MTD (10 or 15 mg) SC, weekly <u>Double-blind period</u> ZEPBOUND: MTD (10 or 15 mg) SC, weekly Placebo: SC, weekly	783 enrolled 670 randomized	48 years (18 – 80)	Female: 546 (70%) Male: 236 (30%)

Abbreviations: MTD = maximum tolerated dose, SC= subcutaneous, T2DM = Type 2 Diabetes Mellitus.

Note: All clinical trials for the approval of ZEPBOUND were conducted using a single dose prefilled pen (see 14.2 Comparative Bioavailability Studies).

Weight Reduction and Weight Maintenance Studies

The efficacy of ZEPBOUND for chronic weight management (weight reduction and maintenance) in conjunction with a reduced-calorie diet and increased physical activity was studied in two randomized, double-blind, placebo-controlled trials, SURMOUNT-1 and SURMOUNT-2.

SURMOUNT-1

SURMOUNT-1 was a 72-week trial that enrolled 2539 adult patients with obesity (BMI ≥30 kg/m^2), or with overweight (BMI 27 to <30 kg/m^2) and at least one weight-related comorbid condition, such as dyslipidemia, hypertension, obstructive sleep apnea, or cardiovascular disease; patients with T2DM were excluded. Patients were randomized in a 1:1:1:1 ratio to once weekly ZEPBOUND 5 mg, ZEPBOUND 10 mg, ZEPBOUND 15 mg, or placebo, with an escalation period of up to 20 weeks followed by the maintenance period. All patients received a standard lifestyle intervention which included instruction on a reduced-calorie diet (approximately 500 kcal/day deficit) and increased physical activity counseling (recommended minimum of 150 min/week) that began with the first dose of study medication or placebo and continued throughout the trial. Patients also received counseling on behaviour modification strategies to adhere to diet and exercise recommendations. Weight reduction was assessed after 72 weeks of treatment (at least 52 weeks at maintenance dose).

At baseline, mean age was 45 years (range 18-84 years), 68% of the participants were women, 71% were White, 11% were Asian, 9% were American Indian/Alaska Native, and 8% were Black or African American. A total of 48% were Hispanic or Latino ethnicity. Mean baseline body weight was 104.8 kg and mean BMI was 38 kg/m^2. Baseline characteristics included 40.6% of participants with prediabetes, 32% with hypertension, 30% with dyslipidemia, 8% with obstructive sleep apnea, and 3% with cardiovascular disease.

The proportions of patients who discontinued study drug in SURMOUNT-1 were 14.3%, 16.4%, and 15.1% for the 5 mg, 10 mg, and 15 mg ZEPBOUND-treated groups, respectively, and 26.4% for the placebo-treated group.

SURMOUNT-2

SURMOUNT-2 was a 72-week trial that enrolled 938 adult patients with BMI ≥27 kg/m^2 and T2DM. Patients included in the trial had HbA1c between 7% and 10% and were treated with either diet and exercise alone, or any oral anti-hyperglycemic agent except dipeptidyl peptidase-4 (DPP-4) inhibitors or GLP-1 receptor agonists. Patients who were taking insulin or injectable GLP-1 receptor agonists were excluded. Patients were randomized in a 1:1:1 ratio to once weekly ZEPBOUND 10 mg, ZEPBOUND 15 mg, or placebo with an escalation period of up to 20 weeks followed by the maintenance period. All patients received a standard lifestyle intervention similar to that, described for SURMOUNT-1. Weight reduction was assessed after 72 weeks of treatment (at least 52 weeks at maintenance dose).

At baseline, mean age was 54 years (range 18-85 years), 51% were women, 76% were White, 13% were Asian, and 8% were Black or African American. A total of 60% were Hispanic or Latino. Mean baseline body weight was 100.7 kg, mean BMI was 36.1 kg/m^2, and mean HbA1c was 8.0%. Baseline characteristics included 66% of participants with hypertension, 61% with dyslipidemia, 8% with obstructive sleep apnea, and 10% with cardiovascular disease.

The proportions of patients who discontinued study drug in SURMOUNT-2 were 9.3% and 13.8% for the 10 mg and 15 mg ZEPBOUND-treated groups, respectively, and 14.9% for the placebo-treated group.

Study Results

Effect of ZEPBOUND on Body Weight and Waist Circumference

For SURMOUNT-1 and -2, the co-primary efficacy end-points were the mean percent change in body weight and the percentage of patients achieving ≥5% weight reduction from baseline to Week 72 for ZEPBOUND 10 mg and/or ZEPBOUND 15 mg.

After 72 weeks of treatment, ZEPBOUND 10 mg and ZEPBOUND 15 mg resulted in a statistically significant reduction in body weight compared with placebo, and in greater proportions of patients who achieved at least 5% weight reduction compared to placebo (Table 7).

Among patients treated with ZEPBOUND 10 mg and 15 mg, greater proportions of patients achieved at least 10%, 15%, and 20% weight reduction compared to placebo (see Table 7). The reduction in body weight was observed with ZEPBOUND irrespective of age, sex, race, ethnicity, baseline BMI, and glycemic status.

ZEPBOUND 10 mg and 15 mg achieved superiority compared to placebo for mean change in waist circumference.

Table 7 – Changes in Body Weight and Waist Circumference at Week 72 in participants with Overweight or Obesity without T2DM SURMOUNT-1 and participants with Overweight or Obesity with T2DM (SURMOUNT-2)

	SURMOUNT-1				SURMOUNT-2		
Intention-to-Treat (ITT) Population[a]	**Placebo N = 643**	**ZEPBOUND 5 mg N = 630**	**ZEPBOUND 10 mg N = 636**	**ZEPBOUND 15 mg N = 630**	**Placebo N = 315**	**ZEPBOUND 10 mg N = 312**	**ZEPBOUND 15 mg N = 311**
Co-primary End-points							
Baseline Mean Body Weight (kg)	104.8	102.9	105.8	105.6	101.7	100.9	99.6
% Change from baseline[b]	-3.1	-15.0	-19.5	-20.9	-3.2	-12.8	-14.7
Relative difference from placebo[b] (95% CI)		-11.9 (-13.4, -10.4)[d,e]	-16.4 (-17.9, -14.8)[d]	-17.8 (-19.3, -16.3)[d]		-9.6 (-11.1, -8.1)[d]	-11.6 (-13.0, -10.1)[d]
% of Patients losing ≥5% body weight	34.5	85.1	88.9	90.9	32.5	79.2	82.8
Relative difference from placebo (95% CI)		50.3 (44.3, 56.2)[c,d,e]	54.6 (49.1, 60.0)[c,d]	56.4 (50.9, 62.0)[c,d]		46.8 (39.5, 54.1)[c,d]	50.4 (43.1, 57.8)[c,d]
Key Secondary End-points							
% of Patients losing ≥10% body weight	18.8		78.1	83.5	9.5	60.5	64.8
Relative difference from placebo (95% CI)			59.5 (54.2, 64.9)[c,d]	64.8 (59.6, 70.1)[c,d]		51.0 (44.4, 57.7)[c,d]	55.3 (48.6, 62.0)[c,d]
% of Patients losing ≥15% body weight	8.8		66.6	70.6	2.7	39.7	48.0
Relative difference from placebo (95% CI)			58.1 (53.2, 63.0)[c,d]	62.0 (57.2, 66.8)[c,d]		37.0 (31.1, 42.9)[c,d]	45.4 (39.4, 51.4)[c,d]
% of Patients losing ≥20% body weight	3.1		50.1	56.7	1.0	21.5	30.8
Relative difference from placebo (95% CI)			47.3 (42.7, 51.9)[c,d]	53.8 (49.3, 58.3)[c,d]		20.5 (15.7, 25.4)[c,d]	29.7 (24.3, 35.0)[c,d]

Waist Circumference							
Baseline mean (cm)	114.0		114.8	114.4	116.0	114.2	114.6
Change from baseline[b]	-4.0		-17.7	-18.5	-3.3	-10.8	-13.1
Difference from placebo[b] (95% CI)			-13.8 (-15.2, -12.3)[d]	-14.5 (-15.9, -13.0)[d]		-7.4 (-9.0, -5.9)[d]	-9.8 (-11.2, -8.3)[d]

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; N = number of patients randomly assigned to study drug.

[a] The intention-to-treat population includes all randomly assigned patients. For SURMOUNT-1 at Week 72, body weight was missing for 21.6%, 10.2%, 10.5%, and 9.4% of patients randomly assigned to placebo, ZEPBOUND 5 mg, 10 mg, and 15 mg, respectively. For SURMOUNT-2 at Week 72, body weight was missing for 11.1%, 4.8%, and 8.4% of patients randomly assigned to placebo, ZEPBOUND 10 mg, and 15 mg, respectively. The missing values were imputed by a hybrid approach using retrieved dropouts from the same treatment group (if missing not due to COVID-19) or using all non-missing data assuming missing at random (for missing solely due to COVID-19).

[b] Least-squares mean from ANCOVA adjusted for baseline value and other stratification factors.

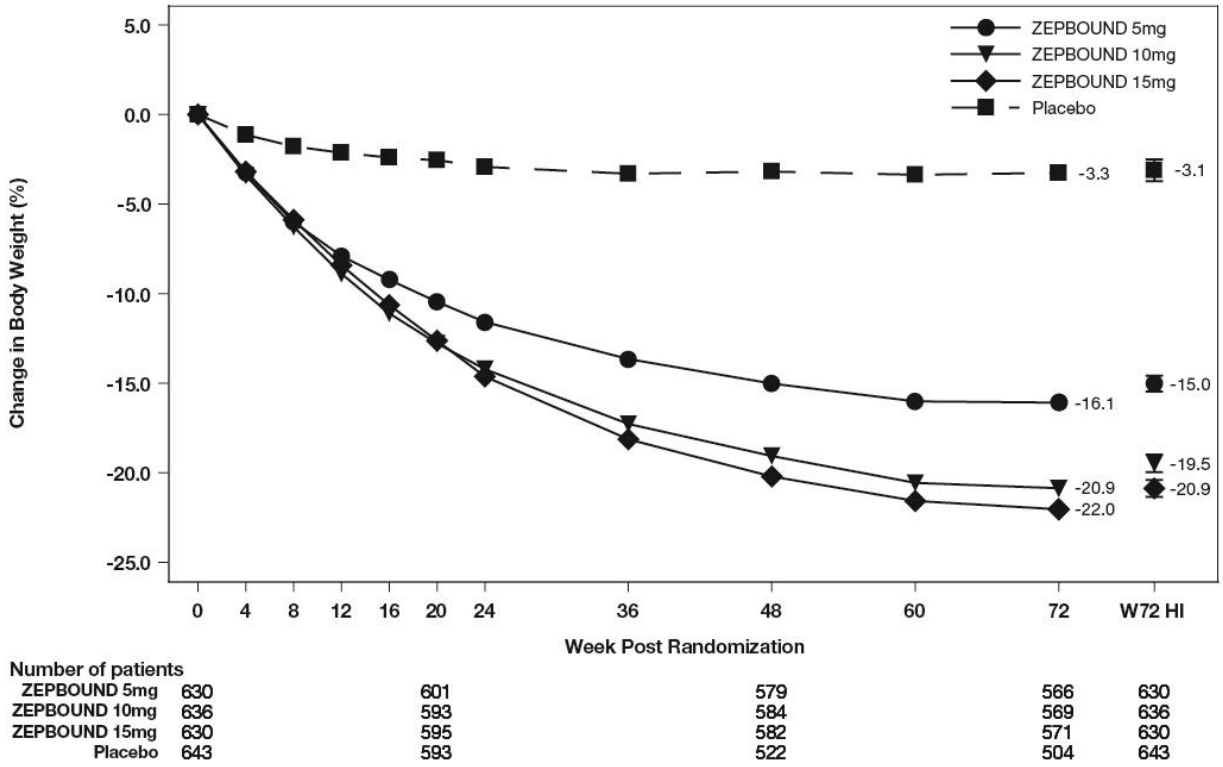
[c] Analyzed using logistic regression adjusted for baseline value.

[d] p-value<0.001 (unadjusted 2-sided) for superiority, controlled for type I error rate.

[e] Data provided for 5 mg was a key secondary endpoint, controlled for type I error rate.

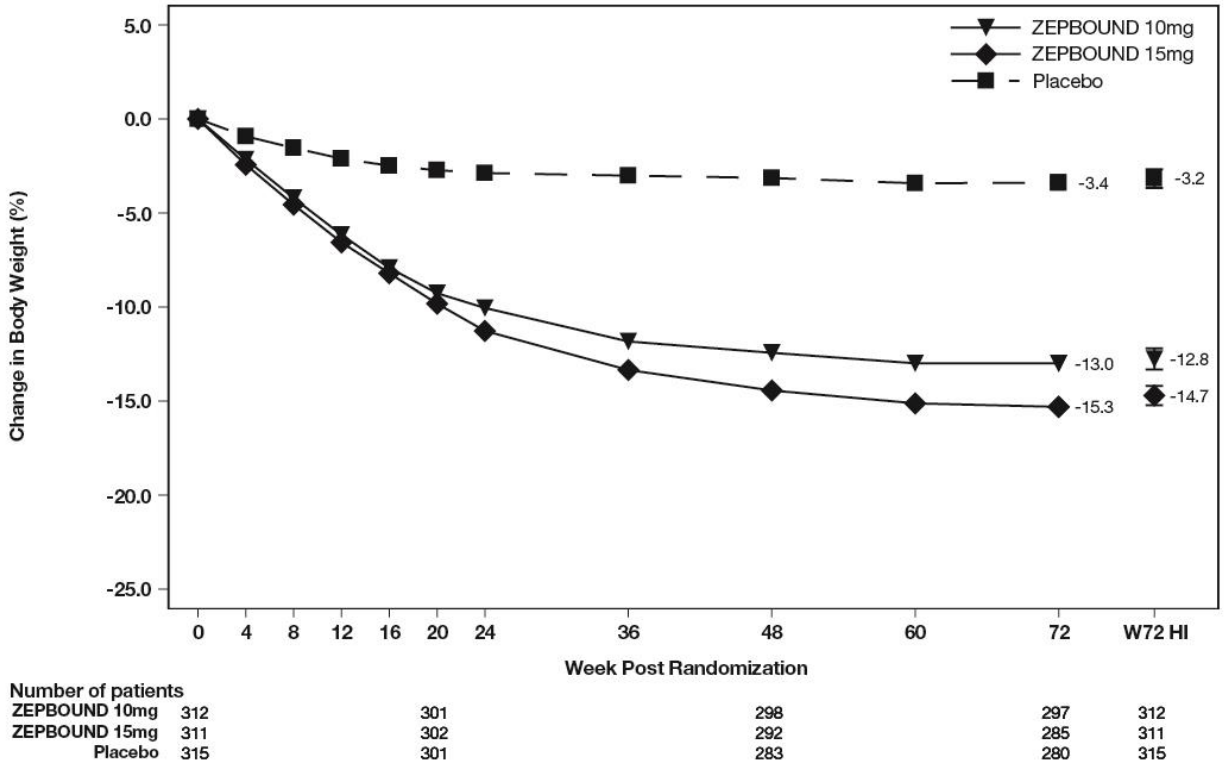
The time courses of weight reduction with ZEPBOUND and placebo from baseline through Week 72 are depicted in Figure 1 for SURMOUNT-1 and Figure 2 for SURMOUNT-2.

Figure 1 – Change from Baseline (%) in Body Weight in Patients with Obesity or Overweight (without Type 2 Diabetes) in Study SURMOUNT-1



Note: Displayed results are from the Intent-to-Treat Population. (1) Observed mean value from Week 0 to Week 72, and (2) least-squares mean ± standard error at Week 72 hybrid imputation (HI).

Figure 2 – Change from Baseline (%) in Body Weight in Patients with Obesity or Overweight (with Type 2 Diabetes) in Study SURMOUNT-2



Note: Displayed results are from the Intent-to-Treat Population. (1) Observed mean value from Week 0 to Week 72, and (2) least squares mean ± standard error at Week 72 hybrid imputation (HI).

Effect of ZEPBOUND on Cardiometabolic Parameters

Cardiometabolic parameters are shown in Table 8 for SURMOUNT-1 and SURMOUNT-2.

Table 8 – Changes in Cardiometabolic Parameters at Week 72 in participants with Overweight or Obesity without T2DM (SURMOUNT-1) and participants with Overweight or Obesity with T2DM (SURMOUNT-2)

	SURMOUNT-1		SURMOUNT-2	
Intention-to-Treat (ITT) Population[a]	**Placebo (N=643)**	**Pooled ZEPBOUND 5/10/15 mg (N=1896)**	**Placebo (N=315)**	**Pooled ZEPBOUND 10/15 mg (N=623)**
Systolic Blood Pressure (mmHg)				
Baseline mean	122.9	123.5	131.0	130.3
Change from baseline[b]	-1.0	-7.2	-1.2	-6.3
Difference from placebo[b] (95% CI)		-6.2 (-7.7, -4.8)[d]		-5.2 (-7.2, -3.1)[d]

HDL (mmol/L)				
Baseline mean[e]	1.2	1.2	1.1	1.1
% change from baseline[c]	-0.7	8.0	0.2	9.0
Relative difference from placebo[c] (95% CI)		8.8 (6.1, 11.5)[d]		8.7 (5.3, 12.2)[d]
Non-HDL (mmol/L)				
Baseline mean[e]	3.6	3.6	3.4	3.2
% change from baseline[c]	-2.3	-9.7	3.7	-5.9
Relative difference from placebo[c] (95% CI)		-7.5 (-10.1, -4.9)[d]		-9.2 (-13.0, -5.3)[d]
Triglycerides (mmol/L)				
Baseline mean[e]	1.5	1.4	1.9	1.8
% change from baseline[c]	-5.6	-24.8	-3.3	-27.2
Relative difference from placebo[c] (95% CI)		-20.3 (-24.3, -16.1)[d]		-24.7 (-29.5, -19.5)[d]
Fasting Insulin (pmol/L)				
Baseline mean[e]	83.2	81.4		
% change from baseline[c]	-6.6	-42.9		
Relative difference from placebo[c] (95% CI)		-38.9 (-44.8, -32.4)[d]		

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; N = number of patients randomly assigned to study drug.

[a] The intention-to-treat population includes all randomly assigned patients. The missing values were imputed by a hybrid approach using retrieved dropouts from the same treatment group (if missing not due to COVID-19) or using all non-missing data assuming missing at random (for missing solely due to COVID-19).

[b] Least-squares mean from ANCOVA adjusted for baseline value and other stratification factors.

[c] Analyzed using log-transformed data.

[d] p-value<0.001 (unadjusted 2-sided) for superiority, controlled for type I error rate.

[e] Baseline value is the geometric mean.

Table 9 – Changes in Key Secondary End-points at Week 72 in Patients with Obesity or Overweight with Type 2 Diabetes in Study SURMOUNT-2

Intention-to-Treat (ITT) Population[a]	**Placebo N = 315**	**ZEPBOUND 10 mg N = 312**	**ZEPBOUND 15 mg N = 311**
HbA1c (%)			
Baseline mean	8.0	8.0	8.1
Change from baseline[b]	-0.5	-2.1	-2.1
Difference from placebo[b] (95% CI)		-1.6 (-1.7, -1.4)[d]	-1.6 (-1.8, -1.4)[d]
Patients (%) achieving HbA1c[c]			
< 7%	36.2	86.9	84.2
≤ 6.5%	20.0	79.7	79.4
< 5.7%	3.9	46.0	48.6
Fasting Serum Glucose (mmol/L)			
Baseline mean	8.8	8.8	9.0
Change from baseline[b]	-0.6	-2.7	-2.7

Difference from placebo (95% CI)[b]		-2.1 (-2.5, -1.8)[d]	-2.1 (-2.5, -1.7)[d]

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; N = number of patients randomly assigned to study drug.

[a] The intention-to-treat population includes all randomly assigned patients. The missing values were imputed by a hybrid approach using retrieved dropouts from the same treatment group (if missing not due to COVID-19) or using all non-missing data assuming missing at random (for missing solely due to COVID-19).

[b] Least-squares mean from ANCOVA adjusted for baseline value and other stratification factors.

[c] Analyzed using logistic regression adjusted for baseline value.

[d] p-value<0.001 (unadjusted 2-sided) for superiority, controlled for type I error rate.

Patient-reported outcomes

In SURMOUNT-1 pooled ZEPBOUND 10 and 15 mg achieved superiority to placebo on the key secondary objective of mean change in SF-36v2 acute form Physical Functioning domain score at Week 72, which is a patient reported outcome that assesses health functioning at the time of assessment. By dose, greater proportions of patients achieved clinically meaningful improvements in the SF-36v2 physical functioning domain (improvement in score of at least 5.76) with ZEPBOUND than with placebo; 36.6% (10 mg), 38.2% (15 mg) vs. 24.5% (placebo).

Weight Reduction Following Intensive Lifestyle Intervention in Adults with Obesity or Overweight (Study SURMOUNT-3)

SURMOUNT-3 was an 84-week trial that enrolled 806 adult patients with obesity (BMI ≥30 kg/m^2), or with overweight (BMI 27 to <30 kg/m^2) and at least one weight-related comorbid condition, such as dyslipidemia, hypertension, obstructive sleep apnea, or cardiovascular disease; patients with T2DM were excluded. Mean body weight for the enrolled patients at the start of the study was 109.7 kg and mean BMI was 38.8 kg/m^2. Participants underwent a 12-week intensive lifestyle intervention lead-in period (reduced caloric intake to approximately 1200 kcal/day for women and 1500 kcal/day for men and exercise for at least 150 minutes per week). At the end of the lead-in period, 579 patients who achieved ≥5.0% weight reduction were randomized in a 1:1 ratio to ZEPBOUND or placebo. The mean age of patients randomized to treatment was 46 years (range 18-77 years), 63% were women, 86% were White, 1% were Asian, and 11% were Black or African American. A total of 54% were Hispanic or Latino. Mean body weight at randomization was 101.9 kg and mean BMI at randomization was 35.9 kg/m^2. Baseline characteristics for the 579 randomized patients included 34% of participants with hypertension, 26% with dyslipidemia, 10% with obstructive sleep apnea, and 2% with cardiovascular disease.

ZEPBOUND dosages were escalated over a period of up to 20 weeks to a maximum tolerated dose (MTD) of 10 mg or 15 mg subcutaneous once weekly. During the randomized treatment period, patients received a standard lifestyle instruction every 12 weeks on reduced-calorie diet (approximately 500 kcal/day deficit) and increased physical activity (recommended minimum of 150 min/week) that began with the first dose of ZEPBOUND or placebo and continued throughout the 72-week treatment period; behaviour modification strategies were recommended as needed. Weight reduction was assessed after 72 weeks of treatment (at least 52 weeks at the MTD).

Study Results

The proportions of patients who discontinued study drug after randomization in SURMOUNT-3 were 21.3% for the ZEPBOUND-treated group and 30.5% for the placebo-treated group.

At the end of the 12-week intensive lifestyle intervention the average body weight loss was 6.9% for patients who were subsequently randomized (Week 0).

The co-primary efficacy parameters were mean percent change in body weight and the percentage of patients achieving ≥5% weight reduction from randomization (Week 0) to Week 72. ZEPBOUND treatment resulted in a statistically significant reduction in body weight compared to placebo, and a greater proportion of patients treated with ZEPBOUND achieved at least 5%, 10%, 15% and 20% weight reduction compared to placebo (see Table 10). At the end of the treatment period, 94% of patients in the ZEPBOUND group maintained ≥80% of the body weight reductions achieved during the 12-week lead-in period, compared to 43.8% of patients in the placebo group.

Table 10 – Changes in Body Weight at Week 72 in SURMOUNT-3 (after 12-week intensive lifestyle intervention leading to ≥5% weight loss)

Intention-to-Treat (ITT) Population[a,b]	**Placebo N = 292**	**ZEPBOUND MTD N = 287**	**% Difference from Placebo (95% CI)**
Baseline Weight [mean (kg)]	101.3	102.5	
Co-primary Endpoints			
Percent Change in Body Weight from randomization[c]	2.5	-18.4	-20.8 (-23.2, -18.5)[e]
Percent of Patients with ≥5% body weight reduction	16.5	87.5	71.1 (63.6, 78.5)[d,e]
Key Secondary Endpoints			
Patients (%) achieving body weight reduction from Week 0 to Week 72			
≥10% body weight reduction	8.9	76.7	67.9 (60.7, 75.1)[d,e]
≥15% body weight reduction	4.2	65.4	61.3 (54.5, 68.1)[d,e]
≥20% body weight reduction	2.2	44.7	42.6 (36.0, 49.1)[d,e]

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; MTD = maximum tolerated dose (10 mg or 15 mg); N = number of patients randomly assigned to study drug.

[a] The intent-to-treat population included only randomized patients with ≥5% weight reduction at Week 0 after 12 weeks of intensive lifestyle intervention. During the 12-week lead-in period, 227 of 806 patients (28.2%) discontinued from the study. Of these 141 (17.5%) discontinued due to not achieving the randomization criteria of ≥5% weight reduction.

[b] The intent-to-treat population includes all randomly assigned patients. For SURMOUNT-3 at Week 72, body weight was missing for 23.6% and 8.7% of patients randomly assigned to placebo and ZEPBOUND MTD (10 or 15 mg), respectively. The missing values were imputed by a hybrid approach using retrieved dropouts from the same treatment group (if missing not due to COVID-19) or using all non-missing data assuming missing at random (for missing solely due to COVID-19).

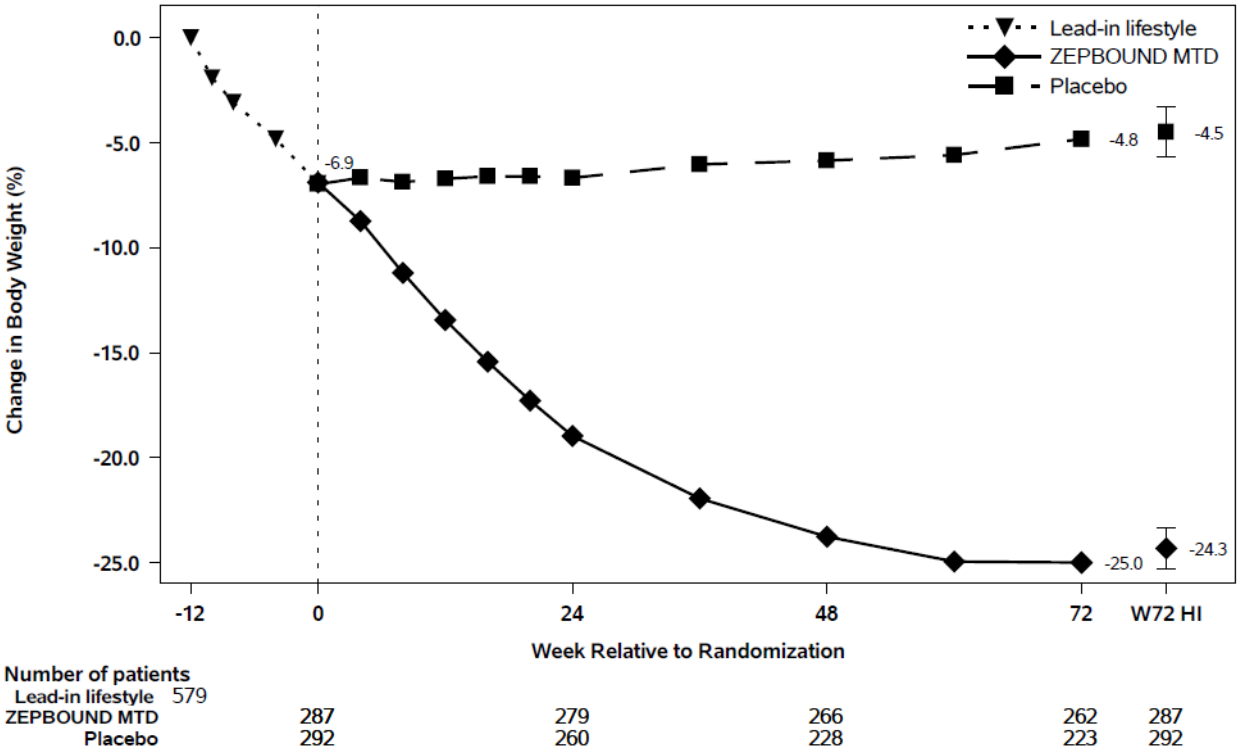
[c] Least-squares mean from ANCOVA adjusted for baseline value and other stratification factors.

[d] Analyzed using logistic regression adjusted for baseline value.

[e] p-value<0.001 (unadjusted 2-sided) for superiority, controlled for type I error rate.

The time course of weight reduction during the 12-week intensive lifestyle intervention lead-in and from Week 0 through 72 weeks with ZEPBOUND and placebo are depicted in Figure 3 for SURMOUNT-3.

Figure 3 – Change in Body Weight (%) in SURMOUNT-3



Note: Displayed results are from the randomized Population. (1) Observed mean value from Week -12 to Week 72, and (2) least squares mean ± standard error at Week 72 hybrid imputation (HI). Change from Week -12 is not a primary endpoint in SURMOUNT-3.

Changes in Cardiometabolic Parameters from Randomization to Week 72 in SURMOUNT-3 (After the Intensive Lifestyle Intervention Lead in Period)

Treatment with maximum tolerated dose of tirzepatide enhanced the improvements in cardiometabolic risk factors that were achieved in the lead-in period. Systolic and diastolic blood pressure improved by an additional -5.1 mmHg and -3.2 mmHg, respectively, lipid parameters improved by an additional -3% to -26% and fasting insulin further declined by 39%.

Weight Reduction Following Randomized Withdrawal in Adults with Obesity or Overweight (Study SURMOUNT-4)

SURMOUNT-4 was an 88-week trial that enrolled 783 adult patients with obesity (BMI ≥30 kg/m^2), or with overweight (BMI 27 to <30 kg/m^2) and at least one weight-related comorbid condition, such as dyslipidemia, hypertension, obstructive sleep apnea, or cardiovascular disease; patients with T2DM were excluded.

All patients received ZEPBOUND subcutaneously once weekly during the 36-week lead-in period that included a 20-week dose escalation. Mean body weight at study entry for these patients was 107.0 kg and mean BMI was 38.3 kg/m^2. A total of 113 patients (14.4%) discontinued treatment before randomization. The most common reason was adverse event (n=53, 6.8%).

A total of 670 patients were randomized in a 1:1 ratio to ZEPBOUND MTD or placebo for an additional 52 weeks. Among the randomized patients, the mean age was 49 years (range 19-

81 years), 71% were women, 80% were White, 11% were Black or African American and 7% were Asian. A total of 44% were Hispanic or Latino. Mean body weight at randomization (Week 36) was 85.2 kg and mean BMI at randomization (Week 36) was 30.5 kg/m^2. Baseline characteristics for the 670 randomized patients included 35% with hypertension, 32% with dyslipidemia, 12% with obstructive sleep apnea, and 6% with cardiovascular disease. All patients received instruction on a reduced-calorie diet (approximately 500 kcal/day deficit) and increased physical activity counseling (recommended to a minimum of 150 min/week) that began with the first dose of study medication or placebo and continued throughout the trial. Patients also received counseling on behaviour modification strategies to adhere to diet and exercise recommendations.

The proportions of patients who discontinued study drug between randomization at Week 36, and end of study at Week 88 was 10.4% for the ZEPBOUND-treated group and 17.9% for the placebo-treated group.

Study Results

The primary efficacy parameter was mean percent change in body weight from randomization (Week 36) to Week 88. Treatment with ZEPBOUND resulted in a statistically significant reduction in body weight compared with body weight regain in the placebo group from randomization (Week 36) to Week 88 (see Table 11).

Table 11 – Changes in Body Weight at Week 88 in SURMOUNT-4 (After 36-week Open-label Tirzepatide Lead-in)

	SURMOUNT-4 N = 670[a]		
Body weight (only randomized patients)			
Mean at Week 0 (kg)	107.30		
	Placebo N = 335	**ZEPBOUND MTD[e] N = 335**	**% Difference from Placebo (95% CI)**
Primary Endpoint			
Body Weight			
Mean at Week 36 (kg)	85.8	84.6	
% change from Week 36 at Week 88[b]	14.0	-5.5	-19.4 (-21.2, -17.7)[d]
Key Secondary Endpoints			
Patients (%) achieving body weight reduction from Week 0 to Week 88			
≥5% body weight reduction	70.3	97.3	27.0 (21.0, 33.0)[c,d]
≥10% body weight reduction	46.2	92.1	45.7 (38.6, 52.8)[c,d]
≥15% body weight reduction	25.9	84.1	58.1 (50.6, 65.6)[c,d]
≥20% body weight reduction	12.6	69.5	56.8 (49.8, 63.9)[c,d]

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; MTD = maximum tolerated dose; N = number of patients randomly assigned to study drug.

[a] The intent-to-treat population includes all randomly assigned patients. At Week 88, body weight was missing for 13.7% and 7.5% of patients randomly assigned to placebo and tirzepatide MTD (10 mg or 15 mg), respectively. The missing values were imputed by a hybrid approach using retrieved dropouts from the same treatment group (if missing not due to COVID-19) or using all non-missing data assuming missing at random (for missing solely due to COVID-19).

[b] Least-squares mean from ANCOVA adjusted for baseline value and other stratification factors.

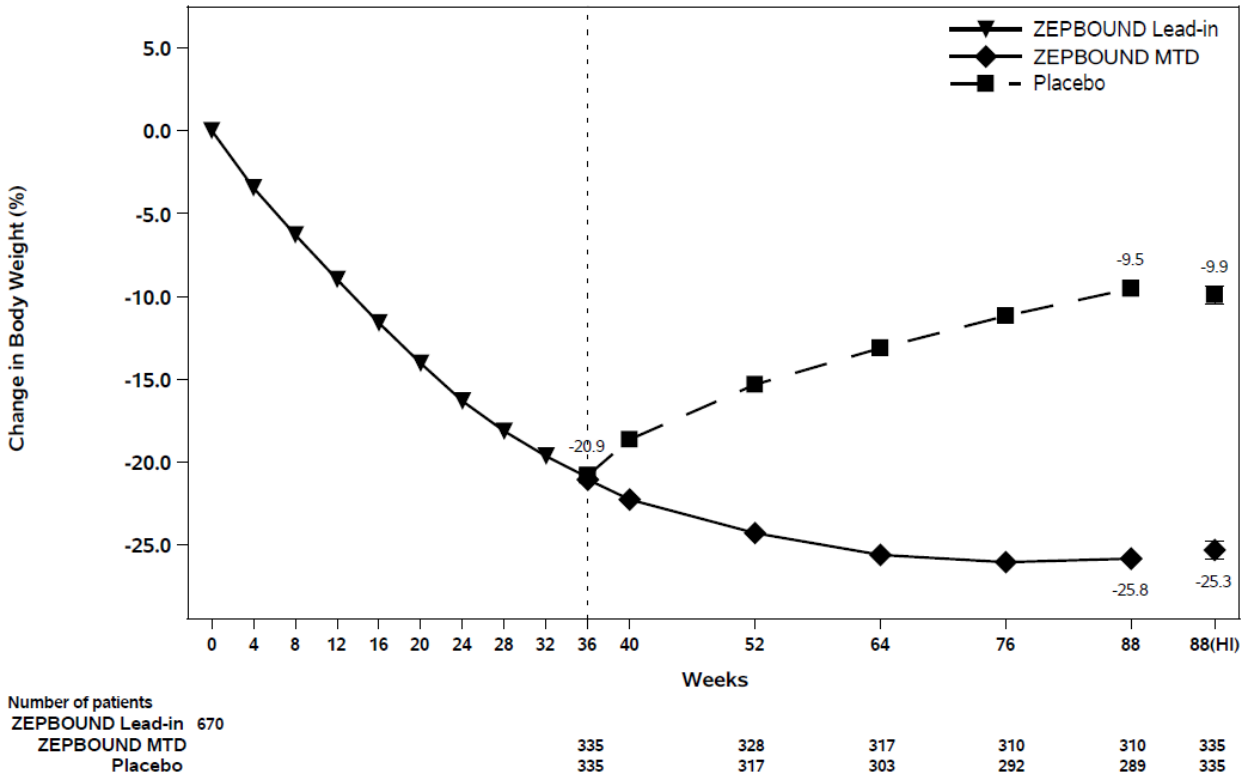
[c] Analyzed using logistic regression adjusted for baseline value.

[d] p-value<0.001 (unadjusted 2-sided) for superiority, controlled for type I error rate.

[e] A total of 91.0% of patients had an MTD of 15 mg based on their final dose during the double-blind treatment period.

The time course of weight reduction with ZEPBOUND and placebo from Week 0 through 88 weeks is depicted in Figure 4 for SURMOUNT-4.

Figure 4 – Change in Body Weight (%) in SURMOUNT-4



Note: Displayed results are from the randomized Population. (1) Displayed results are observed mean value from Week 0 to Week 88 and (2) least squares mean ± standard error at Week 88 hybrid imputation (HI). Change from Week 0 was not a primary endpoint in SURMOUNT-4.

<u>Changes in Cardiometabolic Parameters from Week 36 to Week 88 in SURMOUNT-4 (After 36-week Open-label Tirzepatide Lead-in)</u>

During the 36-week open-label period, decreases in blood pressure, lipids and glycemia were observed. Participants who switched to placebo at randomization ended the study with a substantial body weight reduction (9.9%); however much of their initial improvement in cardiometabolic risk factors had been reversed.

Improvements in the Physical Functioning domain score were also observed for patients treated with ZEPBOUND in SURMOUNT-2, -3, and -4.

Moderate to Severe Obstructive Sleep Apnea in Adults with Obesity

Table 12 – Summary of Patient Demographics for Clinical Trials in Adults with Obstructive Sleep Apnea and Obesity

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex n (%)
SURMOUNT-OSA-1	Phase 3, 52-week randomized, double-blind, placebo-controlled study in patients with moderate to severe OSA and obesity who were unable or unwilling to use PAP therapy	ZEPBOUND: MTD (10 or 15 mg) SC, weekly Placebo: SC, weekly	234	48 years (20 – 76)	Female: 77 (33%) Male: 157 (67%)
SURMOUNT-OSA-2	Phase 3, 52-week randomized, double-blind, placebo-controlled study in patients with moderate to severe OSA and obesity who were on PAP therapy	ZEPBOUND: MTD (10 or 15 mg) SC, weekly Placebo: SC, weekly	235	52 years (26 – 79)	Female: 65 (28%) Male: 170 (72%)

Abbreviations: MTD = maximum tolerated dose, PAP = Positive Airway Pressure, SC= subcutaneous.

Overview of SURMOUNT-OSA-1 and SURMOUNT-OSA-2

The efficacy of ZEPBOUND in combination with a reduced-calorie diet and increased physical activity for moderate to severe obstructive sleep apnea (OSA) (apnea-hypopnea index [AHI] ≥15 events/hour) in adults with obesity (BMI ≥30 kg/m^2) was evaluated in two randomized, double-blind, placebo-controlled, 52-week Phase 3 clinical trials (SURMOUNT-OSA-1 and -2). The two trials enrolled a total of 469 adult patients with moderate (AHI 15 to <30 events/hour) to severe (≥30 events/hour) OSA and obesity. Patients had a history of at least 1 self-reported unsuccessful dietary effort to lose body weight. Patients with type 2 diabetes mellitus were excluded.

In studies SURMOUNT-OSA-1 and -2, patients were randomized in a 1:1 ratio to receive ZEPBOUND (234 patients) or placebo (235 patients) for 52 weeks. The ZEPBOUND dosages were the maximum tolerated doses of 10 mg or 15 mg subcutaneous once-weekly with an escalation period of up to 20 weeks followed by a maintenance period. All patients received instruction on a reduced-calorie diet (approximately 500 kcal/day deficit) and increased physical activity counseling (recommended minimum of 150 min/week) throughout the study.

SURMOUNT-OSA-1 enrolled patients unable or unwilling to use Positive Airway Pressure (PAP) therapy. Patients enrolled in SURMOUNT-OSA-2 were on PAP therapy and were instructed to suspend PAP for 7 days prior to assessment of the primary endpoint. The clinical studies for OSA did not evaluate the timing or appropriateness of PAP discontinuation in patients who were previously compliant with PAP.

In SURMOUNT-OSA-1, at baseline, the mean age of patients was 48 years (range 20-76 years), 33% of the patients were female, 66% were White, 20% were Asian, 8% were American

Indian/Alaska Native, and 6% were Black or African American. A total of 42% were Hispanic or Latino ethnicity. Mean baseline body weight was 115 kg and mean BMI was 39 kg/m^2. Baseline characteristics included a mean baseline AHI of 52 events/hour, and 35% of patients had moderate OSA and 63% had severe OSA.

In SURMOUNT-OSA-2, at baseline, the mean age of patients was 52 years (range 26-79 years), 28% of the patients were female, 73% were White, 14% were Asian, 8% were American Indian/Alaska Native, and 5% were Black or African American. A total of 32% were Hispanic or Latino ethnicity. Mean baseline body weight was 116 kg and mean BMI was 39 kg/m^2. Baseline characteristics included a mean baseline AHI of 50 events/hour, and 31% of patients had moderate OSA and 68% had severe OSA.

The proportion of patients who discontinued study drug in SURMOUNT-OSA-1 was 15%, for the ZEPBOUND-treated group, and 30% for the placebo-treated group. In SURMOUNT-OSA-2, the proportion of patients who discontinued study drug was 10% for the ZEPBOUND-treated group, and 26% for the placebo-treated group.

Table 13 describes the baseline disease characteristics of participants in SURMOUNT-OSA-1 and -OSA-2.

Table 13 – Baseline Disease Characteristics of Participants with OSA and Obesity in SURMOUNT-OSA-1 and SURMOUNT-OSA-2

	SURMOUNT-OSA-1 (N=234)	SURMOUNT-OSA-2 (N=235)
Baseline AHI (events/hour), mean (SD)	51.5 (31.0)	49.5 (26.7)
Moderate OSA,%[a]	35.2	30.9
Severe OSA,%[b]	63.1	68.2
ESS Total, mean (SD)	10.5 (5.2)	10.0 (4.6)
Total Hypoxic Burden (% min/hour), mean (SD)	208.4 (189.1)	193.0 (174.6)
BMI (kg/m^2), mean (SD)	39.1 (7.0)	38.7 (6.0)
Pre-diabetes,%	65.0	56.6
Hypertension,%	75.6	77.4
Cardiac disorders,%	10.3	11.1
Dyslipidemia,%	80.8	83.8

Abbreviations: AHI = Apnea-Hypopnea Index; BMI = body-mass index; ESS = Epworth Sleepiness Score; OSA = obstructive sleep apnea; SD = standard deviation.

[a] Moderate OSA was defined as an AHI ≥15 – 30 events/hour on polysomnogram at baseline.

[b] Severe OSA was defined as an AHI ≥30 events/hour on polysomnogram at baseline.

Results for SURMOUNT-OSA-1 and SURMOUNT-OSA-2

The primary endpoint for SURMOUNT-OSA-1 and -OSA-2 was the change from baseline in the apnea-hypopnea index (AHI) at Week 52, as assessed by polysomnography (PSG).

In SURMOUNT-OSA-1 and -OSA-2, treatment with ZEPBOUND for 52 weeks resulted in a statistically significant reduction in AHI compared with placebo, and greater proportions of participants treated with ZEPBOUND achieved remission or mild non-symptomatic OSA and at

least a 50% reduction in AHI compared to placebo. Table 14 provides the efficacy results for SURMOUNT-OSA-1 and -OSA-2. In both SURMOUNT-OSA-1 and -OSA-2, participants treated with ZEPBOUND achieved a greater reduction in systolic blood pressure and high-sensitivity C-reactive protein levels compared to placebo.

Table 14 – Changes in Apnea-Hypopnea Index (AHI), Hypoxic Burden, and Body Weight at Week 52 in SURMOUNT-OSA-1 and SURMOUNT-OSA-2

Modified Intent-to-Treat (mITT) Population[a]	SURMOUNT-OSA-1		SURMOUNT-OSA-2	
	Placebo N = 120	ZEPBOUND MTD[g] (10 mg or 15 mg) N = 114	Placebo N = 114	ZEPBOUND MTD[g] (10 mg or 15 mg) N = 119
AHI (events/hr)				
Baseline mean	50.1	52.9	53.1	46.1
Change from baseline[b]	-5.3	-25.3	-5.5	-29.3
Difference from placebo[b] (95% CI)	-20.0 (-25.8, -14.2)[e]		-23.8 (-29.6, -17.9)[e]	
% change in AHI				
% change from baseline[b]	-3.0	-50.7	-2.5	-58.7
% difference from placebo[b] (95% CI)	-47.7 (-65.8, -29.6)[e]		-56.2 (-73.7, -38.7)[e]	
Patients (%) achieving ≥50% reduction in AHI				
% of patients with ≥50% reduction[d]	19.0	61.2	23.3	72.4
% difference from placebo (95% CI)	42.8 (30.8, 54.8)[e]		48.6 (36.6, 60.7)[e]	
Remission or mild non-symptomatic OSA				
% of Patients with AHI <5 or AHI 5-14 and ESS≤10[d]	15.9	42.2	14.3	50.2
% difference from placebo (95% CI)	28.7 (18.3, 39.2)[e]		33.2 (22.1, 44.3)[e]	
Sleep apnea-specific hypoxic burden (% min/h)				
Baseline mean[f]	137.8	153.6	142.1	132.2
Change from baseline[b]	-25.1	-95.2	-41.7	-103.0
Difference from placebo[b] (95% CI)	-70.1 (-90.9, -49.3)[c,e]		-61.3 (-84.7, -37.9)[c,e]	
Body weight (kg)				
Baseline mean	112.8	116.7	115.1	115.8
% change from baseline[b]	-1.6	-17.7	-2.3	-19.6

% difference from placebo[b] (95% CI)	-16.1 (-18.0, -14.2)[e]	-17.3 (-19.3, -15.3)[e]

Abbreviations: AHI = Apnea-Hypopnea Index; ANCOVA = analysis of covariance; CI = confidence interval; ESS = Epworth Sleepiness Scale; h = hour; MTD = maximum tolerated dose; N = number of participants randomly assigned and received at least 1 dose of study drug.

[a] Analyses were based on the modified intent-to-treat population which was defined as randomly assigned participants who were exposed to at least 1 dose of study intervention; two participants in SURMOUNT-OSA-2 were randomized but did not receive study drug.

[b] Least-squares mean from ANCOVA adjusted for baseline values and stratification factors, with multiple imputation for missing data at Week 52.

[c] Analyzed using log transformed data.

[d] Calculated by combining proportion of participants achieving target in imputed datasets.

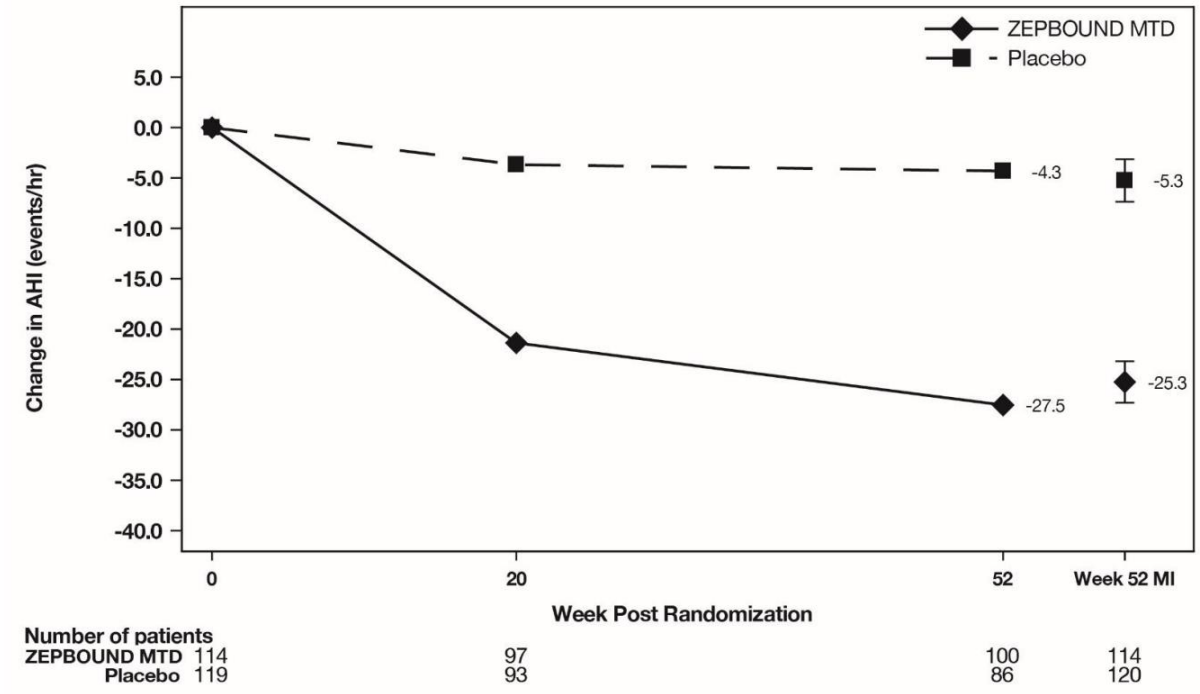
[e] p-value <0.001 (unadjusted 2-sided) for superiority, controlled for multiplicity.

[f] Baseline value is the geometric mean.

[g] A total of 84% of patients in SURMOUNT-OSA-1 and 94% of patients in SURMOUNT-OSA-2 had an MTD of 15 mg based on their final dose during the double-blind treatment period.

The time course of change in AHI with tirzepatide and placebo from baseline through Week 52 are shown in Figure 5 for SURMOUNT-OSA-1 and in Figure 6 for SURMOUNT-OSA-2.

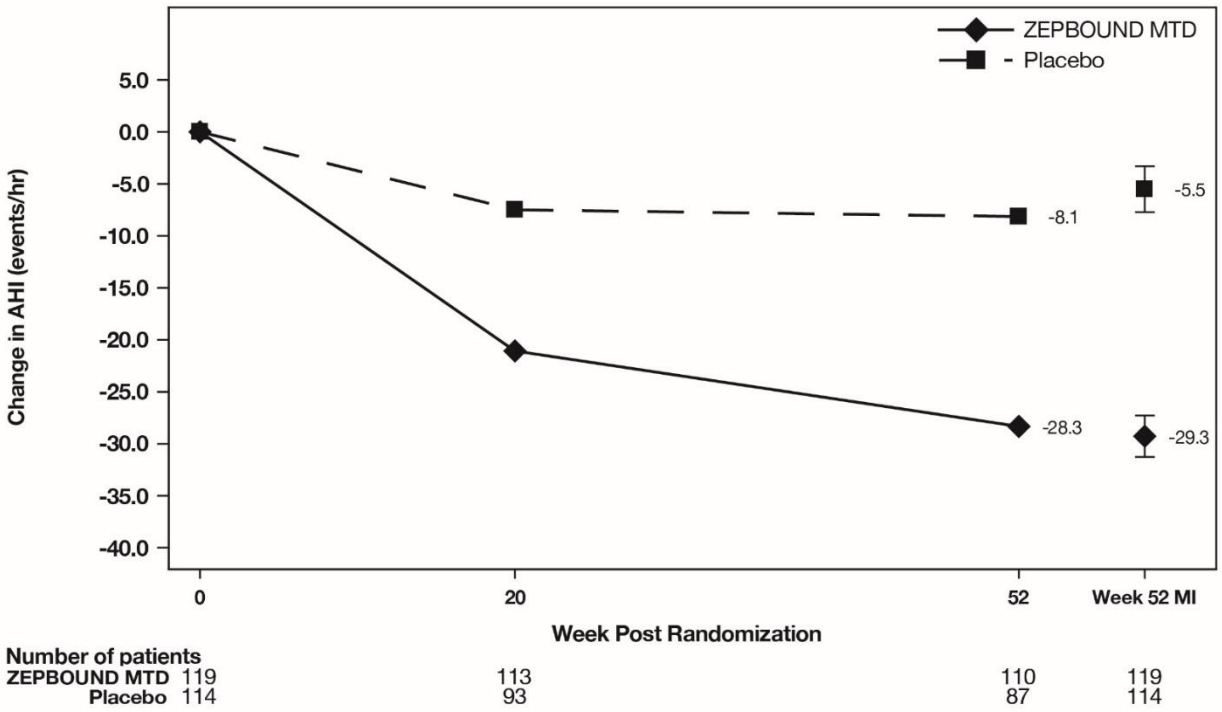
Figure 5 – Change from Baseline in Apnea-Hypopnea Index (AHI) Through Week 52 (SURMOUNT-OSA-1)



Abbreviations: AHI = Apnea-Hypopnea Index; ANCOVA = analysis of covariance; MTD = maximum tolerated dose.

Note: Displayed results are from modified Intent-to-Treat Population. (1) Observed mean value from Week 0 through Week 52, and (2) least squares mean ± standard error at Week 52 from ANCOVA adjusted for baseline values and stratification factors, with multiple imputation of missing data.

Figure 6 – Change from Baseline in Apnea-Hypopnea Index (AHI) Through Week 52 (SURMOUNT-OSA-2)



Abbreviations: AHI = Apnea-Hypopnea Index; ANCOVA = analysis of covariance; MTD = maximum tolerated dose.

Note: Displayed results are from modified Intent-to-Treat Population. (1) Observed mean value from Week 0 through Week 52, and (2) least squares mean ± standard error at Week 52 from ANCOVA adjusted for baseline values and stratification factors, with multiple imputation of missing data. PAP use was stopped 7 days prior to AHI measurements.

In SURMOUNT-OSA-1 and SURMOUNT-OSA-2, treatment with ZEPBOUND showed improvements in sleep-related impairment and sleep disturbance compared to placebo at Week 52, as assessed using the Patient-Reported Outcomes Measurement Information System (PROMIS) Short Form Sleep-Related Impairment 8a (PROMIS SRI) and the PROMIS sleep disturbance short form 8b (PROMIS SD).

14.2. Comparative Bioavailability Studies

A randomized, multicenter, open-label, two-way, single-dose, crossover comparative bioavailability study of ZEPBOUND (tirzepatide injection in a multi-dose prefilled KwikPen) and tirzepatide injection in a single-dose prefilled pen, administered as 0.6 mL x 5 mg/0.6 mL for ZEPBOUND in a multi-dose prefilled KwikPen and as 0.5 mL x 5 mg/0.5 mL for tirzepatide injection in a single-dose prefilled pen, was conducted in healthy, adult, female and male subjects. Comparative bioavailability data from 62 subjects that were included in the statistical analysis are presented in Table 15.

Table 15 – Summary Table of the Comparative Bioavailability Data

Tirzepatide (1 x 5 mg) Geometric Mean (CV%)				
Parameter	**Test[a]**	**Reference[b]**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_T (ng·h/mL)	118000 (22%)	125000 (23%)	94.3	92.6 – 96.0
AUC_I (ng·h/mL)	119000 (22%)	127000 (22%)	94.8	93.1 – 96.5
C_{max} (ng/mL)	524 (27%)	649 (31%)	80.8	78.0 – 83.8
T_{max}[c] (h)	36.0 (8.00 – 144)	12.0 (7.97 – 168)		
$T_{1/2}$[d] (h)	126 (81.5 – 186)	122 (39.0 – 178)		

[a] ZEPBOUND (tirzepatide injection in a multi-dose prefilled KwikPen) Solution, 5 mg/0.6 mL.

[b] Tirzepatide injection in a single-dose prefilled pen Solution, 5 mg/0.5 mL.

[c] Expressed as the median (range).

[d] Expressed as the geometric mean (range).

15. Microbiology

No microbiological information is required for this drug product.

16. Non-Clinical Toxicology

General Toxicology: Tirzepatide was administered twice weekly by subcutaneous injection to rats and cynomolgus monkeys, at doses up to 3 mg/kg (1.96x human exposure based on AUC) and 0.5 mg/kg (1.35x human exposure based on AUC), respectively. Primary findings were consistent with the activity of incretins, including GLP-1 receptor agonists, and included significantly decreased food consumption and body weight loss.

Genotoxicity: Tirzepatide was not genotoxic in a rat bone marrow micronucleus assay at single SC administered doses up to 3 mg/kg.

Carcinogenicity: A 2-year carcinogenicity study (lifetime exposure) was conducted with tirzepatide in male and female rats, administered twice weekly by subcutaneous injection, at doses of 0.15, 0.5, and 1.5 mg/kg (0.1-, 0.4-, and 1-fold the maximum recommended human dose (MRHD) of 15 mg once weekly based on AUC). Tirzepatide caused an increase in thyroid C-cell tumors (adenomas and carcinomas combined) in both sexes at all dose levels.

In a 6-month carcinogenicity study in rasH2 transgenic mice, tirzepatide at doses of 1, 3, and 10 mg/kg administered twice weekly by subcutaneous injection was not tumorigenic.

Reproductive and Developmental Toxicology: In fertility and early embryonic development studies, male and female rats were administered tirzepatide twice weekly by subcutaneous

injection at doses of 0.5, 1.5, or 3 mg/kg (0.3-, 1-, and 2-fold and 0.3-, 0.9-, and 2-fold, respectively, the MRHD of 15 mg once weekly based on AUC). No effects of tirzepatide were observed on sperm morphology, mating, fertility, and conception. However, in female rats, an increase in the number of females with prolonged diestrus and a decrease in the mean number of corpora lutea resulting in a decrease in the mean number of implantation sites and viable embryos was observed at all dose levels. These effects were considered secondary to the pharmacological effects of tirzepatide on food consumption and body weight.

Pregnant rats were given twice weekly subcutaneous doses of 0.02, 0.1, and 0.5 mg/kg tirzepatide (0.03-, 0.1-, and 0.5-fold the MRHD of 15 mg once weekly based on AUC) during organogenesis. Increased incidences of external, visceral, and skeletal malformations, increased incidences of visceral and skeletal developmental variations, and reduced fetal weights were observed, in addition to decreases in maternal body weights and food consumption, at 0.5 mg/kg.

Pregnant rabbits were given tirzepatide once weekly subcutaneous doses of 0.01, 0.03, or 0.1 mg/kg (0.01-, 0.1-, and 0.23-fold the MRHD of 15 mg once weekly based on AUC) during organogenesis. Adverse effects on the gastrointestinal system resulting in maternal mortality or abortion in a few rabbits were observed at all dose levels. Reduced fetal weights, decreased maternal food consumption and decreased maternal body weights were observed at 0.1 mg/kg.

In a prenatal-postnatal study in F_0 maternal rats administered tirzepatide twice weekly by subcutaneous injection at doses of 0.02, 0.10, or 0.25 mg/kg from implantation through lactation, F_1 pups from F_0 maternal rats given 0.25 mg/kg tirzepatide had lower mean body weight from birth through the end of the study for males and postnatal day 56 for females.

Juvenile Toxicity: Consistent with adult rats, in a juvenile toxicity study in rats, effects were limited to pharmacological effects of tirzepatide on body weight and food consumption and other reversible effects secondary to tirzepatide pharmacology. Tirzepatide led to a delay in sexual maturity in male and female rats, which was attributed to the reduced body weight gain during treatment. These data indicate that tirzepatide does not have specific toxicities in juvenile animals.

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrZEPBOUND®

tirzepatide injection

This Patient Medication Information is written for the person who will be using **ZEPBOUND**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have questions or want more information about **ZEPBOUND**, talk to a healthcare professional.

Serious warnings and precautions box

- Tirzepatide, the medicinal ingredient in ZEPBOUND, increased the risk of developing thyroid C-cell tumors in rats. It is not known if the risk seen in rats applies to humans. It is uncertain if ZEPBOUND may increase your risk for developing thyroid C-cell tumors, including medullary thyroid carcinoma.
- Do not use ZEPBOUND if you:
  - have a personal or family history of Medullary Thyroid Cancer (MTC);
  - have Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).
- Your healthcare professional will speak to you about the risk and symptoms of thyroid tumors.

What ZEPBOUND is used for:

ZEPBOUND is used together with a low calorie diet and exercise :

- to help lose weight and keep the weight off over a long term. It is used in adults who have a body mass index (BMI) that is:
  - 30 kg/m^2 or higher (obesity), or
  - between 27 kg/m^2 and 30 kg/m^2 (overweight). These patients will also have at least one other health problem related to weight such as:
    - high blood pressure,
    - high levels of fats in the blood,
    - pre-diabetes,
    - diabetes,
    - obstructive sleep apnea, or
    - heart disease
- to treat obstructive sleep apnea (OSA) in adults with moderate to severe OSA and obesity.

How ZEPBOUND works:

Tirzepatide, the medicinal ingredient in ZEPBOUND acts on two different receptors (GIP and GLP-1) in the body to increase feelings of fullness, and decrease feelings of hunger. This leads to less appetite and lower intake of calories. ZEPBOUND also reduces food cravings for high sugar and high fat foods and reduces the brain response that is related to these types of foods.

The ingredients in ZEPBOUND are:

Medicinal ingredient: tirzepatide

Non-medicinal ingredients: benzyl alcohol (preservative), glycerin, hydrochloric acid solution, phenol (preservative), sodium chloride, sodium hydroxide solution, sodium phosphate dibasic heptahydrate, and water for injection.

ZEPBOUND comes in the following dosage form:

Solution in a multi-dose prefilled pen (KwikPen) containing 4 doses: 2.5 mg/0.6 mL, 5 mg/0.6 mL, 7.5 mg/0.6 mL, 10 mg/0.6 mL, 12.5 mg/0.6 mL, and 15 mg/0.6 mL

Do not use ZEPBOUND if:

- you are allergic to tirzepatide or to any ingredient in ZEPBOUND or component of its container. This includes benzyl alcohol, which is used as a preservative.
- 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.

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

- have a heart condition that causes an increase in heart rate
- experienced severe allergic reactions and swelling when taking GLP-1 receptor agonist medicines like liraglutide or semaglutide
- have severe problems with your stomach (gastroparesis) or food digestion
- have liver problems
- have serious kidney problems
- use insulin or medicines that stimulate the pancreas to make insulin
- have previously attempted to take your own life or have had thoughts of suicide

Other warnings you should know about:

Gastrointestinal (stomach and intestine) problems

- ZEPBOUND slows stomach emptying so food passes more slowly through your stomach.
- Gastrointestinal problems including nausea, vomiting and diarrhea have been reported in people who use ZEPBOUND. These symptoms are sometimes severe. Tell your healthcare professional if you have stomach problems that are severe or will not go away.

Gallbladder Disease

- You may suddenly develop symptoms of gallbladder disease while using ZEPBOUND.
- Gallbladder disease can include inflammation of the gallbladder (cholecystitis), or gallstones blocking the bile duct (biliary colic).

- Symptoms may include sudden and intensifying pain in your abdomen, your right shoulder, or between your shoulder blades. Seek immediate medical attention if you experience severe abdominal pain, yellowing of your skin, or high fever with chills. If you think you might have a problem with your gallbladder, consult your healthcare professional.

Benzyl alcohol

- Benzyl alcohol is a preservative used in ZEPBOUND multi-dose prefilled pen (KwikPen). Benzyl alcohol can cause you to develop metabolic acidosis (acid in the blood). Metabolic acidosis can develop when large amounts of benzyl alcohol build-up in your body. Talk to your healthcare professional if you:
  - are taking other medications containing benzyl alcohol.
  - have liver or kidney problems.

Children and Adolescents

ZEPBOUND is not recommended in children and adolescents under 18 years.

Pregnancy

- If you are pregnant, able to get pregnant or think you are pregnant, there are specific risks you should discuss with your healthcare professional.
- Using ZEPBOUND while you are pregnant may harm your unborn baby.
- Avoid becoming pregnant while you are using ZEPBOUND.
- Use effective birth control during treatment.
- If you are already using a birth control that is taken by mouth:
  - Switch to a different type of birth control medicine, or
  - Add a barrier method of birth control (e.g., condoms). Use this method for 4 weeks when beginning treatment with ZEPBOUND and for 4 weeks after each time your dose is increased.
- If you wish to become pregnant, you should stop using ZEPBOUND at least 1 month before trying to get pregnant.

Breastfeeding

- ZEPBOUND may pass into your breast milk. Talk to your healthcare professional about the potential risks of breastfeeding your baby while taking ZEPBOUND.

Driving and Using Machines

- Low blood sugar (hypoglycemia) may affect your ability to concentrate. Avoid driving or using machines if you have any signs of low blood sugar.

Pancreas Problems

- Using ZEPBOUND can cause an inflamed pancreas (acute pancreatitis).
- Tell your healthcare professional if you have or have had pancreas problems such as inflammation of the pancreas.
- Your healthcare professional will monitor you for symptoms of acute pancreatitis. Speak to your healthcare professional immediately if you have severe pain in the stomach area or back which does not go away.

Serious Allergic Reactions

- Stop using ZEPBOUND and get medical help right away if you have any symptoms of a serious allergic reaction. This can include itching, rash, or difficulty breathing. See “What are possible side effects from using ZEPBOUND” for more symptoms of an allergic reaction.

Blood Tests

- Your blood sugar levels should be monitored at the start of treatment if you are taking ZEPBOUND with anti-diabetic medicines known as sulfonylurea or insulin. Monitoring your blood sugar levels will help reduce the risk of developing hypoglycemia (low blood sugar).
- Your healthcare professional will monitor your blood sugar levels periodically during your treatment with ZEPBOUND.

Kidney Problems

- During treatment with ZEPBOUND, you may experience feeling sick (nausea) or being sick (vomiting), and diarrhea. These side effects can cause dehydration (loss of fluids). Dehydration can lead to problems with your kidneys, such as sudden kidney failure.
- It is therefore important to drink plenty of fluids to prevent dehydration.
- Talk to your healthcare professional if you have any questions or concerns.

Eye problems

- *Diabetic Eye Disease (Retinopathy) in Patients with Type 2 Diabetes Mellitus:*
  - Quick improvements in blood sugar control may cause a temporary worsening of diabetic eye disease. You may need medical treatment. It could also lead to a loss of vision.
  - Tell your healthcare professional if you have diabetic eye disease (retinopathy) or if you experience vision problems during treatment with ZEPBOUND.
- *Non-arteritic anterior ischaemic optic neuropathy (NAION):*
  - If you experience a sudden loss of vision or rapidly worsening eyesight during treatment with ZEPBOUND, urgently contact your healthcare professional. This may be caused by NAION. Your healthcare professional will refer you for an eye examination by an ophthalmologist and you may have to stop your treatment with ZEPBOUND.

Malnutrition

- Nutrition problems, sometimes severe, have been reported in people who use ZEPBOUND. This can cause you to lose too much weight and have low vitamin, mineral and/or protein levels.
- While you are using ZEPBOUND, your healthcare professional may give you guidance on nutrition and/or recommend you take vitamins or supplements.

Food or Liquid Getting into Lungs During Anesthesia

- Some patients using medicines like ZEPBOUND have had problems with food or liquid from their stomach getting into their lungs while under general anesthesia or deep sedation. Tell your healthcare professional that you are using ZEPBOUND before you have a procedure that requires general anesthesia or deep sedation.

Depression or Thoughts of Suicide

- Pay attention to changes in your mood, behaviours, feelings, or thoughts. Call your healthcare professional right away if you have any:

- thoughts or behaviours of harming or killing yourself
- changes to your mental health that are new, worse, or worry you.

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

The following may interact with ZEPBOUND:

- birth control medicines that are taken by mouth. If you take these medicines while you are using ZEPBOUND, the birth control may not work as well.
- diabetes medicines known as a sulfonylurea (e.g., glyburide, gliclazide, glimepiride) or insulin. Combining these medicines with ZEPBOUND might increase the risk of getting low blood sugar. Your healthcare professional may tell you to lower your regular dose of these drugs when adding ZEPBOUND treatment.
- medicines that may increase your heart rate.
- other incretin medicines. The use of ZEPBOUND in combination with other GLP-1 receptor agonists or with DPP-4 inhibitors has not been studied and ZEPBOUND should not be used in combination with those drugs.

How to inject ZEPBOUND:

- ZEPBOUND is an injection that is given subcutaneously. Do not inject it into a vein or muscle.
- Inject ZEPBOUND once per week at any time of the day, with or without food; however, always inject on the same day each week. Set a reminder on a calendar to remind yourself of your weekly injection.
- Each month you will use: 1 multi-dose prefilled pen (KwikPen). Each KwikPen contains enough medication for 4 doses.
- Read the Instructions for Use and watch the instructional video before injecting ZEPBOUND. These provide directions on how to inject ZEPBOUND correctly.
- Before using ZEPBOUND, your healthcare professional will train you on how to properly inject the medication. Do not use ZEPBOUND without having received this training. If you do not understand the instructions or have any questions, talk with your healthcare professional.
- Use ZEPBOUND exactly as your healthcare professional has told you. Do not change your dose or stop using ZEPBOUND without talking to your healthcare professional.
- While you are using ZEPBOUND, you should eat about 500 calories less than you normally do. You should also do at least 150 minutes of moderate exercise each week.
- The KwikPen has glass parts. Handle it carefully. If you drop the KwikPen on a hard surface, do not use the medicine. Use a new KwikPen for your injection.
- The best places to give yourself the injection are your stomach area (abdomen) or upper leg (thigh). Another person should give you the injection in the back of your upper arm.
- Do not use the same site for each injection. **Change (rotate)** your injection site with each injection to avoid skin problems like thinning, thickening, or lumps. **Do not** inject:
    - where the skin has pits, is thickened or has lumps
    - where the skin is tender, bruised, scaly or hard

- into scars or damaged skin
- into the same injection site used for other medicines.

You may use the same area of the body but be sure to choose a different site in that area.

- Changing the day of the week for your injection:
  - If necessary, you can change the day of the week that you inject ZEPBOUND. If you need to do this, wait at least 3 days after your last injection.

Usual Adult Dose:

- Your healthcare professional will decide the dose that is right for you. You may receive a different dose depending on:
  - whether you are taking medications for diabetes
  - your physical health (e.g., weight, other illnesses, physical activity)
  - your diet

Usual Adult Dose for Chronic Weight Management:

- The recommended starting dose is 2.5 mg injected subcutaneously once per week for 4 weeks.
- After 4 weeks, your dose will go up to 5 mg injected subcutaneously once per week.
- If your dose is increased, it will go up by 2.5 mg at a time after using your current dose for at least 4 weeks until you reach your maintenance dose.
- The recommended maintenance dosage for Chronic Weight Management in adults is 5 mg, 10 mg, or 15 mg injected subcutaneously once per week.
- The maximum recommended dose is 15 mg once per week injected subcutaneously.

Usual Adult Dose for Obstructive Sleep Apnea:

- The recommended starting dose is 2.5 mg injected subcutaneously once per week for 4 weeks.
- After 4 weeks, your dose will go up to 5 mg injected subcutaneously once per week.
- If your dose is increased, it will go up by 2.5 mg at a time after using your current dose for at least 4 weeks until you reach your maintenance dose.
- The recommended maintenance dosage for Obstructive Sleep Apnea in adults is 10 mg, or 15 mg injected subcutaneously once per week.
- The maximum recommended dose is 15 mg once per week injected subcutaneously.

If you have moderate to severe obstructive sleep apnea (OSA): Some people with moderate to severe OSA need to use a positive airway pressure (PAP) machine to help them breathe during sleep. ZEPBOUND is not a replacement for a PAP machine if you need one. If you use a PAP machine, do not stop, or change how you use it on your own. Your healthcare professional will decide whether you should start, continue, or change your PAP therapy while you are using ZEPBOUND.

Overdose:

If you use too much tirzepatide (the medicinal ingredient in ZEPBOUND) you may have gastrointestinal side effects including nausea.

If you think you, or a person you are caring for, have injected too much ZEPBOUND, contact a healthcare professional, hospital emergency department, regional poison control centre or

Health Canada's toll-free number, 1-844-POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed Dose:

If you miss a dose and it has been:

- 4 days (96 hours) or less since you should have used ZEPBOUND, use it as soon as you remember. Then inject your next dose on your usual day.
- more than 4 days (96 hours) since you should have used ZEPBOUND, skip the missed dose. Then inject your next dose on your usual day.

Possible side effects from using ZEPBOUND:

These are not all the possible side effects you may have when using ZEPBOUND. If you experience any side effects not listed here, tell your healthcare professional.

- Belching
- Bloating of the stomach
- Change in taste
- Constipation
- Decreased appetite
- Diarrhea
- Dizziness
- Dry mouth
- Feeling tired
- Gas (flatulence)
- Hair loss
- Indigestion
- Increased heart rate
- Injection site reactions (bruising, pain, irritation, itching, and rash)
- Low blood pressure
- Nausea
- Reflux or heart burn – also called gastro-esophageal reflux
- Stomach pain
- Unusual skin sensations - such as burning, tingling or pricking
- Vomiting

ZEPBOUND can cause abnormal blood test results. Your healthcare professional will do blood tests during your treatment and will interpret the results.

Serious side effects and what to do about them

Frequency / Side Effect / Symptom	Talk to your healthcare professional		Stop using this drug and get immediate medical help
	Only if severe	In all cases	
Very common			
Gastrointestinal problems: diarrhea, nausea, vomiting, abdominal pain, feeling full		✓	
Common			
Diabetic retinopathy (diabetic eye disease): blurred vision, lines in vision		✓	
Uncommon			
Hypoglycemia (severe low blood sugar): disorientation, loss of consciousness, or seizure		✓	
Rare			
Acute pancreatitis (sudden inflammation of the pancreas): prolonged severe abdominal pain with or without vomiting		✓	✓
Dehydration that can cause sudden kidney failure: dark yellow and strong-smelling pee, feeling extremely thirsty, feeling dizzy or lightheaded		✓	✓
Sudden gallbladder problems: severe abdominal pain, yellowing of your skin, or high fever with chills		✓	✓
Unknown			
Anaphylactic reaction, angioedema (serious allergic reaction): breathing problems, swelling of the throat and face, fast heartbeat		✓	✓
Malnutrition (when the body does not get enough nutrients to		✓	

function): weight loss, weakness, feeling faint, fatigue, dry skin, irritability, unable to pay attention			
Thyroid cancer: lump or swelling in the neck, voice changes, trouble swallowing		✓	
Gastroparesis (slow stomach emptying): pain, severe nausea and vomiting, prolonged belching, and prolonged bloating		✓	✓
Suicidal ideation (thoughts of suicide): worsening depression, suicidal thoughts and behaviours, unusual changes in mood		✓	✓
Ileus (loss of muscle contraction in the intestine): bloating, abdominal pain and cramping, gas, nausea, vomiting, constipation, loss of appetite		✓	✓
Pulmonary aspiration (food or liquid from stomach getting into lungs) during general anesthesia or deep sedation: choking, cough		✓	
Non-arteritic anterior ischemic optic neuropathy (NAION, eye condition): sudden decreased vision (blurring or cloudiness) or permanent loss of vision		✓	✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell 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 (www.canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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

Storage:

Store ZEPBOUND in a refrigerator at 2°C to 8°C up to the expiration date. Do not use ZEPBOUND beyond the expiration date.

If needed, each multi-dose prefilled pen can be stored unrefrigerated at temperatures below 30°C for up to 30 days.

Do not freeze ZEPBOUND. Do not use ZEPBOUND if frozen.

Protect ZEPBOUND from light.

Each ZEPBOUND multi-dose prefilled pen (KwikPen) contains 4 doses. Discard your KwikPen after using it once per week for 4 weeks (4 doses). Put all used KwikPens into a puncture-resistant (sharps) container, or discard them in accordance with local requirements, once all the doses have been used. There may be some medicine still left in the KwikPen after the 4 weekly doses were given.

Keep out of reach and sight of children.

If you want more information about ZEPBOUND:

- 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 Drug Product Database website: (https://health-products.canada.ca/dpd-bdpp/); the manufacturer's website www.lilly.ca, or by calling 1-888-545-5972.

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INSTRUCTIONS FOR USE

PrZEPBOUND®

tirzepatide injection

multi-dose prefilled pen (KwikPen®) for subcutaneous use

Each pen contains 4 fixed doses, one dose taken weekly.

2.5 mg/0.6 mL multi-dose prefilled pen

5 mg/0.6 mL multi-dose prefilled pen

7.5 mg/0.6 mL multi-dose prefilled pen

10 mg/0.6 mL multi-dose prefilled pen

12.5 mg/0.6 mL multi-dose prefilled pen

15 mg/0.6 mL multi-dose prefilled pen

Important information you need to know before injecting ZEPBOUND

Talk to your healthcare provider about how to inject ZEPBOUND the right way. This INSTRUCTIONS FOR USE is written for the person who will be using ZEPBOUND. This may be you or a person you are caring for. After training from a healthcare professional, ZEPBOUND may be self injected or given by a caregiver.

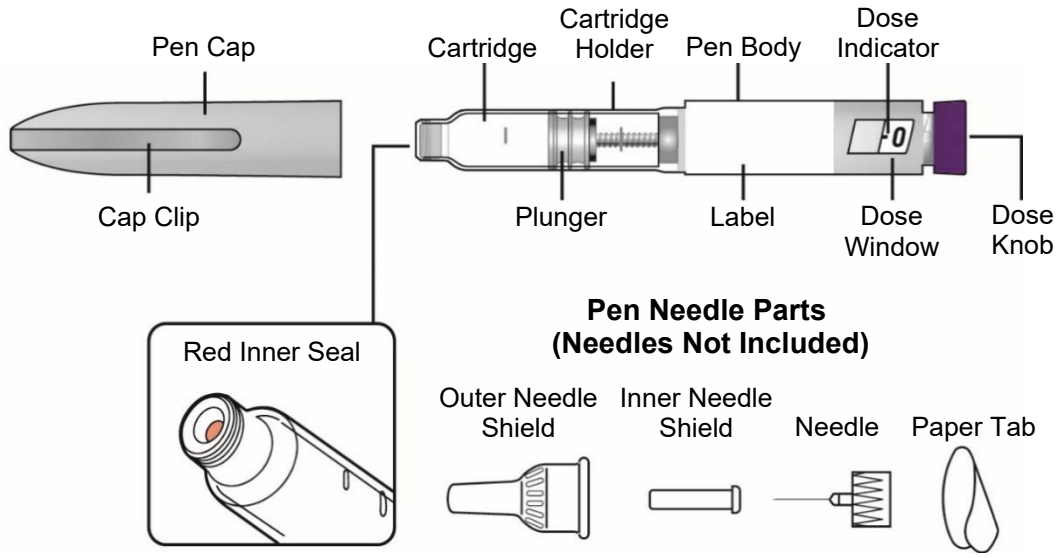
Read this "INSTRUCTIONS FOR USE" and the Patient Medication Information each time you use your ZEPBOUND multi-dose prefilled pen (KwikPen) and each time you get a new KwikPen. There may be new information. This information does not take the place of talking to your healthcare professional about your medical condition or your treatment.

- ZEPBOUND comes in a multi-dose single-patient-use prefilled pen (KwikPen).
- **One KwikPen contains 4 doses of 0.6 mL each. One dose is taken each week.**
- Inject one dose each week under the skin (subcutaneously) only.
- After you have taken the 4th dose (a month's treatment), you will see leftover medicine in the KwikPen. This is normal. The leftover medicine ensures that the KwikPen works correctly. Even though the KwikPen still has medicine in it, **do not use it. Throw it away in a sharps disposal container.** The KwikPen will prevent you from dialing a full dose after you have given yourself the 4th dose. You will not be able to turn the knob after you have given yourself the 4th dose.

- **Do not** transfer the medicine from your KwikPen into a syringe.
- **Do not** inject the leftover medication.
- **Do not** share your KwikPen with other people, even if the pen needle has been changed. You may give other people a serious infection or get a serious infection from them.
- People who are blind or have vision problems should not use the KwikPen without help from a person trained to use the KwikPen.

Guide to parts

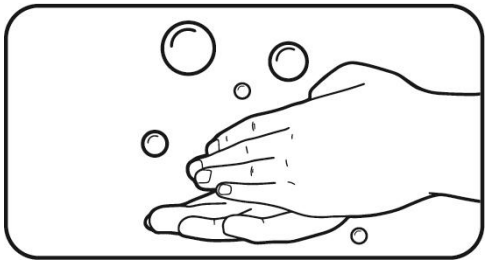
Parts of the ZEPBOUND multi-dose prefilled pen (KwikPen)



Supplies needed to give your injection

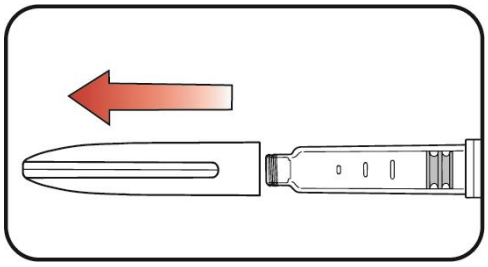
- 1 ZEPBOUND multi-dose prefilled pen (KwikPen)
- 1 pen needle (as recommended by your healthcare professional)
- Alcohol swab
- Gauze or cotton ball
- Sharps disposal container or household container

Preparing to inject ZEPBOUND



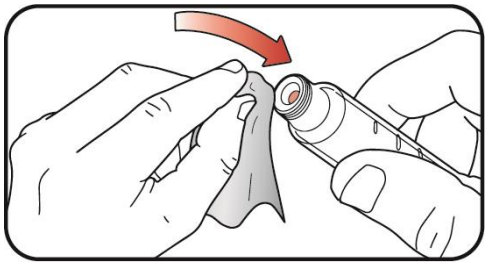
Step 1:

- Wash your hands with soap and water.



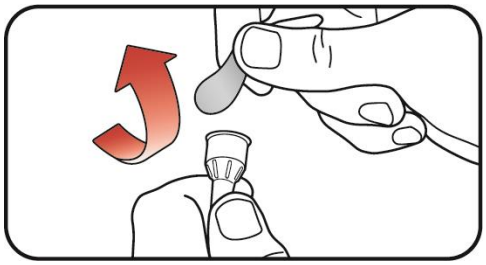
Step 2:

- Pull the KwikPen cap straight off.
- Inspect the KwikPen and label. **Do not** use if:
  - the medication name or dose strength does not match your prescription.
  - the KwikPen is expired (EXP) or looks damaged.
  - the medication has been frozen, has particles, is cloudy, or is discolored. Make sure the medicine in the KwikPen is colourless to slightly yellow.



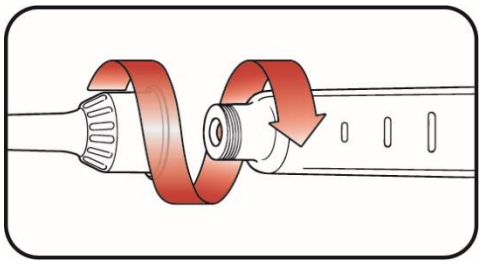
Step 3:

- Wipe the red inner seal with an alcohol swab.



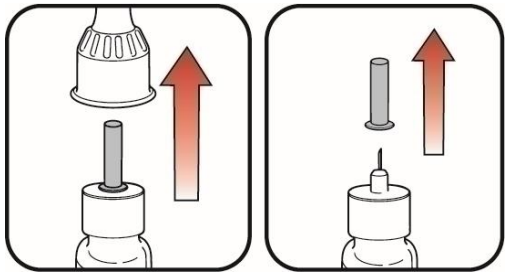
Step 4:

- **Select a new pen needle.** Always use a new pen needle for each injection to help prevent infections and blocked needles.
- Pull off the paper tab from the outer needle shield.



Step 5:

- Push the capped pen needle straight onto the KwikPen and twist the pen needle on until it is tight.

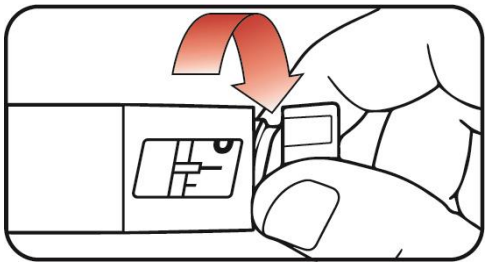


a. **Outer needle shield** b. **Inner needle shield**

Step 6:

a. Pull off the outer needle shield and keep it. This will be reused.

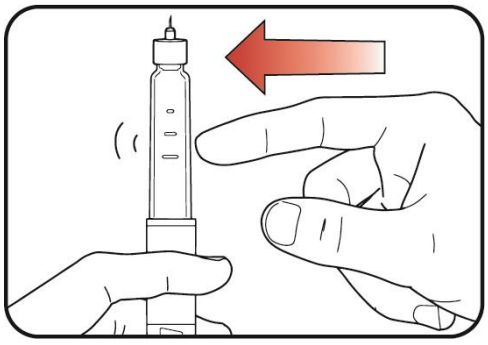
b. Pull off the inner needle shield. Put it in your household trash.



Step 7:

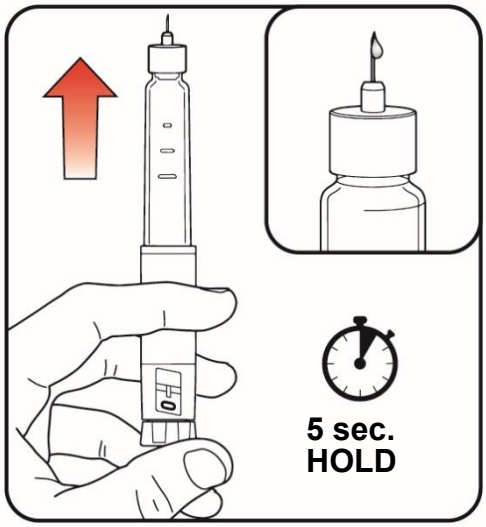
- **Slowly turn** the dose knob until you hear **2 clicks** and the extended line shown in the dose window aligns with the dose indicator.

  This is the **prime position**. It can be corrected by turning the dose knob in either direction until the prime position is achieved.



Step 8:

- Hold your KwikPen with the needle pointing up.
- Tap the cartridge holder gently to collect air bubbles at the top.



Step 9:

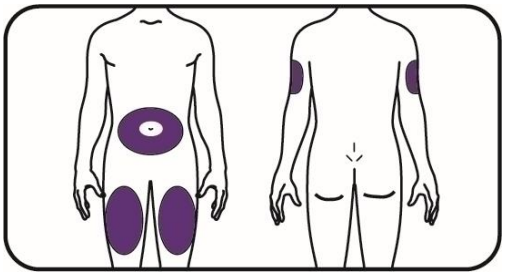
- Release some medicine into the air by **pushing the dose knob in** until it stops, then **slowly count to 5 while holding the dose knob**. The 0 icon must be shown in the dose window. **Do not** inject into your body.

Priming removes air from the cartridge and makes sure that your KwikPen is working correctly. Your KwikPen has been primed if a small amount of medicine comes out of the tip of the pen needle.

- If you do not see medicine at the tip of the needle, repeat **steps 7-9**, no more than 2 additional times.
- If you still do not see medicine, then change the pen needle and repeat **steps 7-9**, no more than 1 additional time.

– If you still do not see medicine, contact Lilly at 1-888-545-5972.

Injecting ZEPBOUND



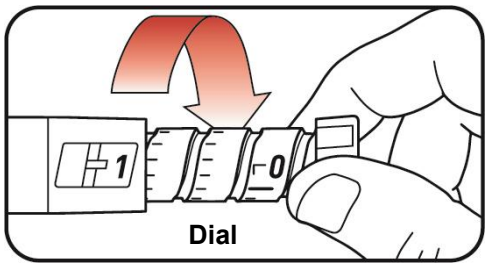
a. Front b. Back

Step 10:

- Choose an injection site.
  - **a.** You or another person can inject the medicine in your **thigh** or **stomach** (abdomen) at least 5 centimeters from the belly button (see the image).
  - **b.** Another person should give you the injection in the **back of your upper arm**.
- **Change (rotate)** your injection site each week. You may use the same area of your body but be sure to choose a different injection site in that area.

Do not inject:

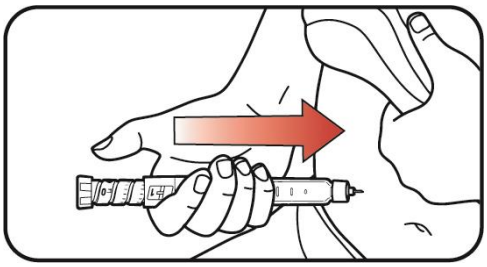
- where the skin has pits, is thickened or has lumps
- where the skin is tender, bruised, scaly or hard
- into scars or damaged skin
- into the same injection site used for other medicines.



Dial

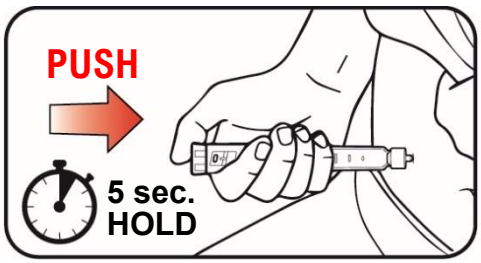
Step 11:

- Turn the dose knob until it stops and the 1 icon is shown in the dose window. **The 1 icon is equal to a full dose (0.6 mL).**

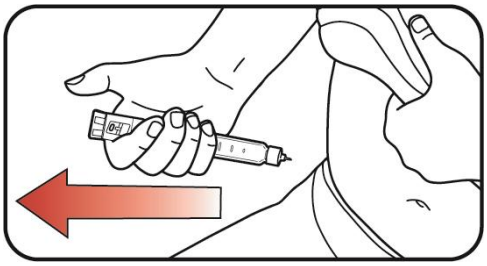


Step 12:

a. Insert the needle into your skin.



b. Inject the medicine by **pushing the dose knob in** until it stops. **Hold the dose knob in and slowly count to 5.** The 0 icon must be shown in the dose window before removing the needle.



Step 13:

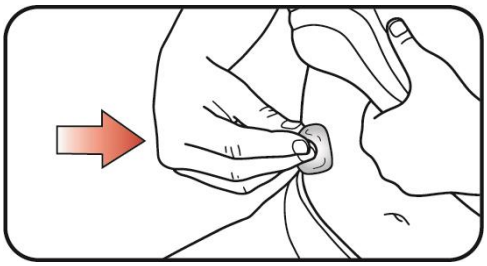
- Pull the needle out of your skin. A drop of medicine on the needle tip is normal. It will not affect your dose.
- Confirm the 0 icon is in the dose window.

  If you see the 0 icon in the dose window, you have received the full dose.

  If you do not see the 0 icon in the dose window, insert the needle back into your skin and finish your injection. **Do not** redial the dose.

  If you still do not think you received the full dose, **do not** start over or repeat the injection. See “Troubleshooting” section for more information or call 1-888-545-5972.

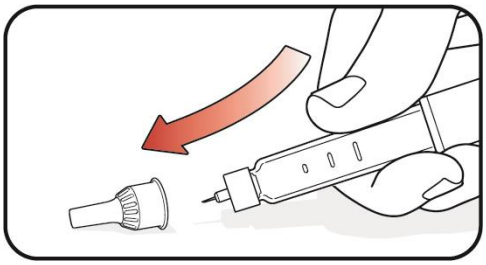
After your ZEPBOUND injection



Step 14:

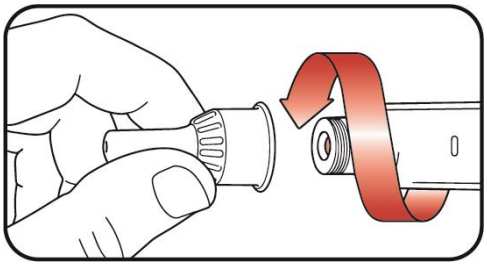
- If you see blood after you pull the needle out of your skin, lightly press the injection site with gauze or a cotton ball.

  Do not rub the injection site.



Step 15:

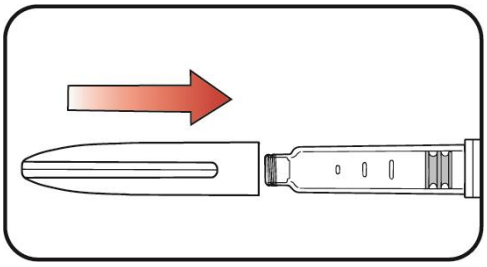
- Carefully replace the outer needle shield.



Step 16:

- Unscrew the capped needle and put the needle in a sharps container (see “Disposing of ZEPBOUND multi-dose prefilled pen (KwikPen) and needles” section).

  Do not store the KwikPen with the needle attached to prevent leaking, blocking the needle, and air from entering the KwikPen.



Step 17:

- Replace the KwikPen cap.

  Do not store the KwikPen without the pen cap attached.

Storage and handling

Unused KwikPens:

- Store your **unused KwikPen** in the **refrigerator** between 2°C and 8°C.
- KwikPens may be used until the expiration date printed on the label if the unused KwikPen has been stored in the refrigerator.
- **Do not** freeze your KwikPen. Throw away the KwikPen in a sharps disposal container if it has been frozen.

Used KwikPens:

- You may store your **used KwikPen** at **room temperature** up to 30°C for up to 30 days.
- Keep away from heat and light.
- Throw away the KwikPen 30 days after first use in a sharps disposal container even if the KwikPen has medication left in it.
- Throw away the KwikPen after receiving the 4 weekly doses contained in the pen in a sharps disposal container. Attempting to inject any leftover medicine could result in an incomplete dose even though the KwikPen still has medication left in it.

Keep your KwikPen, needles, sharps container and all medicines out of the sight and reach of children.

Disposing of ZEPBOUND multi-dose prefilled pen (KwikPen) and needles

- Put your used pen needles in a sharps disposal container right away after use.
- **Do not** throw away loose pen needles in your household trash.
- ZEPBOUND multi-dose prefilled pen (KwikPen) contains 4 doses. Discard your KwikPen in a sharps disposal container after using all 4 doses – one dose per week for 4 weeks. Put all used KwikPens into a puncture-resistant (sharps) container once all the doses have been used. There may be some medicine still left in the pen after the 4 weekly doses were given.
- If you do not have a 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, and
  - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, follow your community guidelines for the right way to dispose of it. There may be local laws about how you should throw away used needles and syringes. Talk to your healthcare professional about how to dispose of your sharps container.
- **Do not** recycle your used sharps disposal container.

Troubleshooting

- If you cannot remove the KwikPen cap, gently twist the KwikPen cap back and forth, and then pull the KwikPen cap straight off.
- If the dose knob is hard to push:
  - pushing the dose knob slower will make it easier to inject.
  - your needle may be blocked. Put on a new pen needle and prime the KwikPen.
  - you may have dust, food, or liquid inside the KwikPen. Throw the KwikPen away in a sharps disposal container and get a new KwikPen.
- If the KwikPen prevents you from turning the dose knob until the 1 is in the dose window:
  - Throw away the KwikPen, including the unused medicine, in a sharps disposal container. There may not be enough medicine left in the KwikPen to give a full dose. **Do not** attempt to inject the leftover medicine.

Additional Information:

Scan this QR code or visit www.zepbound.ca for more information on how to use ZEPBOUND including an instructional video.

For more information, please contact Eli Lilly Canada Incorporated at 1-888-545-5972 or visit the website at www.lilly.ca.

Eli Lilly Canada Inc.
P.O. Box 73
Toronto, ON M5X 1B1

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Date of Authorization:

B4.0-NL-ZEPKP-0003-CA-IFU-20260604

Medication Calendar

Use ZEPBOUND 1 time a week.	I inject my weekly 0.6 mL dose on the dates below.			
Write the day of the week you choose to inject. Inject on this day each week (Example: Monday).	(Month/Day)	(Month/Day)	(Month/Day)	(Month/Day)