ZEPBOUND- tirzepatide injection, solution
Eli Lilly and Company

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ZEPBOUND safely and effectively. See full prescribing information for ZEPBOUND.
ZEPBOUND™ (tirzepatide) Injection, for subcutaneous use
Initial U.S. Approval: 2022

WARNING: RISK OF THYROID C-CELL TUMORS

See full prescribing information for complete boxed warning.

- **In rats, tirzepatide causes thyroid C-cell tumors. It is unknown whether ZEPBOUND causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as the human relevance of tirzepatide-induced rodent thyroid C-cell tumors has not been determined (5.1, 13.1).**
- **ZEPBOUND is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk of MTC and symptoms of thyroid tumors (4, 5.1).**

INDICATIONS AND USAGE

ZEPBOUND™ is a glucose-dependent insulinotropic polypeptide (GIP) receptor and glucagon-like peptide-1 (GLP-1) receptor agonist indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of:

- 30 kg/m^2 or greater (obesity) or
- 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, dyslipidemia, type 2 diabetes mellitus, obstructive sleep apnea or cardiovascular disease). (1)

Limitations of Use:

- Coadministration with other tirzepatide-containing products or any GLP-1 receptor agonist is not recommended. (1)
- The safety and efficacy of coadministration with other products for weight management have not been established. (1)
- ZEPBOUND has not been studied in patients with a history of pancreatitis. (1)

DOSAGE AND ADMINISTRATION

- The recommended starting dosage is 2.5 mg injected subcutaneously once weekly. (2.2)
- After 4 weeks, increase to 5 mg injected subcutaneously once weekly. (2.2)
- Increase the dosage in 2.5 mg increments after at least 4 weeks on the current dose. (2.2)
- The recommended maintenance dosages are 5 mg, 10 mg, or 15 mg injected subcutaneously once weekly. (2.2)
- Consider treatment response and tolerability when selecting the maintenance dosage. (2.2)
- The maximum dosage is 15 mg subcutaneously once weekly. (2.2)
- Administer once weekly at any time of day, with or without meals. (2.4)
- Inject subcutaneously in the abdomen, thigh, or upper arm. (2.4)
- Rotate injection sites with each dose. (2.4)

DOSAGE FORMS AND STRENGTHS

Injection: 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, or 15 mg per 0.5 mL in single-dose pen (3)

CONTRAINDICATIONS

- Personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2 (4)
- Known serious hypersensitivity to tirzepatide or any of the excipients in ZEPBOUND (4)

WARNINGS AND PRECAUTIONS

- *Severe Gastrointestinal Disease:* Use has been associated with gastrointestinal adverse reactions, sometimes severe. Has not been studied in patients with severe gastrointestinal disease and is not recommended in these patients. (5.2)
- *Acute Kidney Injury:* Monitor renal function in patients reporting adverse reactions that could lead to volume depletion. (5.3)

- *Acute Gallbladder Disease:* Has been reported in clinical trials. If cholecystitis is suspected, gallbladder studies and clinical follow-up are indicated. (5.4)
- *Acute Pancreatitis:* Has been reported in clinical trials. Discontinue promptly if pancreatitis is suspected. Do not restart if pancreatitis is confirmed. (5.5)
- *Hypersensitivity Reactions:* Serious hypersensitivity reactions (e.g., anaphylaxis, angioedema) have been reported postmarketing with tirzepatide. If suspected, advise patients to promptly seek medical attention and discontinue ZEPBOUND. (5.6)
- *Hypoglycemia:* Concomitant use with an insulin secretagogue or insulin may increase the risk of hypoglycemia, including severe hypoglycemia. Reducing dose of insulin secretagogue or insulin may be necessary. Inform all patients of the risk of hypoglycemia and educate them on the signs and symptoms of hypoglycemia. (5.7)
- *Diabetic Retinopathy Complications in Patients with Type 2 Diabetes Mellitus:* Has not been studied in patients with non-proliferative diabetic retinopathy requiring acute therapy, proliferative diabetic retinopathy, or diabetic macular edema. Monitor patients with a history of diabetic retinopathy for progression. (5.8)
- *Suicidal Behavior and Ideation:* Monitor for depression or suicidal thoughts. Discontinue ZEPBOUND if symptoms develop. (5.9)

ADVERSE REACTIONS

The most common adverse reactions, reported in ≥5% of patients treated with ZEPBOUND are: nausea, diarrhea, vomiting, constipation, abdominal pain, dyspepsia, injection site reactions, fatigue, hypersensitivity reactions, eructation, hair loss, gastroesophageal reflux disease. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-LillyRx (1-800-545-5979) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

ZEPBOUND delays gastric emptying and has the potential to impact the absorption of concomitantly administered oral medications. (7.2)

USE IN SPECIFIC POPULATIONS

- *Pregnancy:* May cause fetal harm. When pregnancy is recognized, discontinue ZEPBOUND. (8.1)
- *Females of Reproductive Potential:* Advise females using oral 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. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 11/2023

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FULL PRESCRIBING INFORMATION

WARNING: RISK OF THYROID C-CELL TUMORS

- **In rats, tirzepatide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures. It is unknown whether ZEPBOUND causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as human relevance of tirzepatide-induced rodent thyroid C-cell tumors has not been determined *[see Warnings and Precautions (5.1) and Nonclinical Toxicology (13.1)]*.**
- **ZEPBOUND is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2) *[see Contraindications (4)]*. 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). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with ZEPBOUND *[see Contraindications (4) and Warnings and Precautions (5.1)]*.**

1 INDICATIONS AND USAGE

ZEPBOUND™ is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of:

- 30 kg/m^2 or greater (obesity) or
- 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, dyslipidemia, type 2 diabetes mellitus, obstructive sleep apnea, or cardiovascular disease).

Limitations of Use

- ZEPBOUND contains tirzepatide. Coadministration with other tirzepatide-containing products 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.
- ZEPBOUND has not been studied in patients with a history of pancreatitis *[see Warnings and Precautions (5.5)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select adult patients for ZEPBOUND treatment as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management based on their BMI. Table 1 presents a chart for determining BMI based on height and weight. BMI is calculated by dividing weight (in kilograms) by height (in meters) squared.

Table 1: BMI Conversion Chart

Weight	(lb)	125	130	135	140	145	150	155	160	165	170	175	180	185	190	195	200	205	210	215	220	225
	(kg)	56.8	59.1	61.4	63.6	65.9	68.2	70.5	72.7	75.0	77.3	79.5	81.8	84.1	86.4	88.6	90.9	93.2	95.5	97.7	100.0	102.3
Height																						
(in)	(cm)																					
58	147.3	26	27	28	29	30	31	32	34	35	36	37	38	39	40	41	42	43	44	45	46	47
59	149.9	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	43	44	45	46
60	152.4	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
61	154.9	24	25	26	27	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43
62	157.5	23	24	25	26	27	27	28	29	30	31	32	33	34	35	36	37	38	38	39	40	41
63	160.0	22	23	24	25	26	27	28	28	29	30	31	32	33	34	35	36	36	37	38	39	40
64	162.6	22	22	23	24	25	26	27	28	28	29	30	31	32	33	34	34	35	36	37	38	39
65	165.1	21	22	23	23	24	25	26	27	28	28	29	30	31	32	33	33	34	35	36	37	38
66	167.6	20	21	22	23	23	24	25	26	27	27	28	29	30	31	32	32	33	34	35	36	36
67	170.2	20	20	21	22	23	24	24	25	26	27	27	28	29	30	31	31	32	33	34	35	35
68	172.7	19	20	21	21	22	23	24	24	25	26	27	27	28	29	30	30	31	32	33	34	34
69	175.3	18	19	20	21	21	22	23	24	24	25	26	27	27	28	29	30	30	31	32	33	33
70	177.8	18	19	19	20	21	22	22	23	24	24	25	26	27	27	28	29	29	30	31	32	32
71	180.3	17	18	19	20	20	21	22	22	23	24	24	25	26	27	27	28	29	29	30	31	31
72	182.9	17	18	18	19	20	20	21	22	22	23	24	24	25	26	27	27	28	29	29	30	31
73	185.4	17	17	18	19	19	20	20	21	22	22	23	24	24	25	26	26	27	28	28	29	30
74	188.0	16	17	17	18	19	19	20	21	21	22	23	23	24	24	25	26	26	27	28	28	29
75	190.5	16	16	17	18	18	19	19	20	21	21	22	23	23	24	24	25	26	26	27	28	28
76	193.0	15	16	16	17	18	18	19	20	20	21	21	22	23	23	24	24	25	26	26	27	27

2.2 Recommended Dosage

- The recommended starting dosage of ZEPBOUND is 2.5 mg injected subcutaneously once weekly. The 2.5 mg dosage is for treatment initiation and is not intended for chronic weight management.
- 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 recommended maintenance dosages of ZEPBOUND in adults are 5 mg, 10 mg, or 15 mg injected subcutaneously once weekly.
- Consider treatment response and tolerability when selecting the maintenance dosage. If patients do not tolerate a maintenance dosage, consider a lower maintenance dosage.
- The maximum dosage of ZEPBOUND is 15 mg injected subcutaneously once weekly.

2.3 Recommendations Regarding 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.
- 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).

2.4 Important Administration Instructions

- Prior to initiation of ZEPBOUND, train patients and caregivers on proper injection technique. Refer to the accompanying Instructions for Use for complete administration instructions with illustrations.
- 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.
- Inject ZEPBOUND subcutaneously in the abdomen, thigh, or upper arm.
- Rotate injection sites with each dose.

3 DOSAGE FORMS AND STRENGTHS

Injection: Clear, colorless to slightly yellow solution available in pre-filled single-dose pens of the following strengths:

- 2.5 mg/0.5 mL
- 5 mg/0.5 mL
- 7.5 mg/0.5 mL
- 10 mg/0.5 mL
- 12.5 mg/0.5 mL
- 15 mg/0.5 mL

4 CONTRAINDICATIONS

ZEPBOUND is contraindicated in patients with:

- A personal or family history of MTC or in patients with MEN 2 *[see Warnings and Precautions (5.1)]*.
- Known serious hypersensitivity to tirzepatide or any of the excipients in ZEPBOUND. Serious hypersensitivity reactions, including anaphylaxis and angioedema, have been reported with tirzepatide *[see Warnings and Precautions (5.6) and Adverse Reactions (6.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Thyroid C-Cell Tumors

In rats, tirzepatide caused a dose-dependent and treatment-duration-dependent increase in the incidence of thyroid C-cell tumors (adenomas and carcinomas) in a 2-year study at clinically relevant plasma exposures *[see Nonclinical Toxicology (13.1)]*. It is unknown whether ZEPBOUND causes thyroid C-cell tumors, including MTC, in humans as human relevance of tirzepatide-induced rodent thyroid C-cell tumors has not been determined.

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).

Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with ZEPBOUND. Such monitoring may increase the risk of unnecessary procedures, due to the low test specificity for serum calcitonin and a high background incidence of thyroid disease. Significantly elevated serum calcitonin values may indicate MTC and patients with MTC usually have calcitonin values >50 ng/L. If serum calcitonin is measured and found to be elevated, the patient should be further evaluated. Patients with thyroid nodules noted on physical examination or neck imaging should also be further evaluated.

5.2 Severe Gastrointestinal Disease

Use of ZEPBOUND has been associated with gastrointestinal adverse reactions,

sometimes severe *[see Adverse Reactions 6.1]*. In clinical trials, severe gastrointestinal adverse reactions were reported more frequently among patients receiving ZEPBOUND (5 mg 1.7%, 10 mg 2.5%, 15 mg 3.1%) than placebo (1%). ZEPBOUND has not been studied in patients with severe gastrointestinal disease, including severe gastroparesis, and is therefore not recommended in these patients.

5.3 Acute Kidney Injury

Use of ZEPBOUND has been associated with acute kidney injury, which can result from dehydration due to gastrointestinal adverse reactions to ZEPBOUND; including nausea, vomiting, and diarrhea *[see Adverse Reactions (6.1)]*.

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.

5.4 Acute Gallbladder Disease

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

In clinical trials of ZEPBOUND, cholelithiasis was reported in 1.1% of ZEPBOUND-treated patients and 1% of placebo-treated patients, cholecystitis was reported in 0.7% 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. If cholecystitis is suspected, gallbladder diagnostic studies and appropriate clinical follow-up are indicated.

5.5 Acute Pancreatitis

Acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, has been observed in patients treated with GLP-1 receptor agonists or tirzepatide.

In clinical trials of tirzepatide for a different indication, 14 events of acute pancreatitis were confirmed by adjudication in 13 tirzepatide-treated patients (0.23 patients per 100 years of exposure) versus 3 events in 3 comparator-treated patients (0.11 patients per 100 years of exposure). In ZEPBOUND clinical trials, 0.2% of ZEPBOUND-treated patients had acute pancreatitis confirmed by adjudication (0.14 patients per 100 years of exposure) versus 0.2% of placebo-treated patients (0.15 patients per 100 years of exposure). ZEPBOUND has not been studied in patients with a prior history of pancreatitis. It is unknown if patients with a history of pancreatitis are at higher risk for development of pancreatitis on ZEPBOUND.

After initiation of ZEPBOUND, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting). If pancreatitis is suspected, discontinue ZEPBOUND and initiate appropriate management. If the diagnosis of pancreatitis is confirmed, ZEPBOUND should not be restarted.

5.6 Hypersensitivity Reactions

There have been postmarketing reports of serious hypersensitivity reactions (e.g., anaphylaxis, angioedema) in patients treated with tirzepatide. In ZEPBOUND clinical

trials, 0.1% of ZEPBOUND-treated patients had severe hypersensitivity reactions compared to no placebo-treated patients. If hypersensitivity reactions occur, advise patients to promptly seek medical attention and discontinue use of ZEPBOUND. Do not use in patients with a previous serious hypersensitivity reaction to tirzepatide or any of the excipients in ZEPBOUND *[see Contraindications (4) and Adverse Reactions (6.2)]*.

Serious hypersensitivity reactions, including anaphylaxis and angioedema, have been reported with GLP-1 receptor agonists. Use caution in patients with a history of angioedema or anaphylaxis with a GLP-1 receptor agonist because it is unknown whether such patients will be predisposed to these reactions with ZEPBOUND.

5.7 Hypoglycemia

ZEPBOUND lowers blood glucose and can cause hypoglycemia.

In a trial of patients with type 2 diabetes mellitus and BMI ≥27 kg/m^2, hypoglycemia (plasma glucose <54 mg/dL) was reported in 4.2% of ZEPBOUND-treated patients versus 1.3% of placebo-treated patients. In this trial, patients taking 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 tirzepatide in combination with insulin *[see Drug Interactions (7.1)]*.

Hypoglycemia has also been associated with ZEPBOUND and GLP-1 receptor agonists in adults without type 2 diabetes mellitus *[see Adverse Reactions (6.1)]*.

Inform patients of the risk of hypoglycemia and educate them on the signs and symptoms of hypoglycemia. In patients with diabetes mellitus, monitor blood glucose prior to starting ZEPBOUND and during ZEPBOUND treatment. The risk of hypoglycemia may be lowered by a reduction in the dose of sulfonylurea (or other concomitantly administered insulin secretagogue) or insulin.

5.8 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. Tirzepatide has not been studied in patients with non-proliferative diabetic retinopathy requiring acute therapy, proliferative diabetic retinopathy, or diabetic macular edema. Patients with a history of diabetic retinopathy should be monitored for progression of diabetic retinopathy.

5.9 Suicidal Behavior and Ideation

Suicidal behavior and ideation have been reported in clinical trials with other chronic weight management products. Monitor patients treated with ZEPBOUND for the emergence or worsening of depression, suicidal thoughts or behaviors, and/or any unusual changes in mood or behavior. Discontinue ZEPBOUND in patients who experience suicidal thoughts or behaviors. Avoid ZEPBOUND in patients with a history of suicidal attempts or active suicidal ideation.

6 ADVERSE REACTIONS

The following serious adverse reactions are described below or elsewhere in the prescribing information:

- Risk of Thyroid C-cell Tumors *[see Warnings and Precautions (5.1)]*
- Severe Gastrointestinal Disease *[see Warnings and Precautions (5.2)]*

- Acute Kidney Injury *[see Warnings and Precautions (5.3)]*
- Acute Gallbladder Disease *[see Warnings and Precautions (5.4)]*
- Acute Pancreatitis *[see Warnings and Precautions (5.5)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.6)]*
- Hypoglycemia *[see Warnings and Precautions (5.7)]*
- Diabetic Retinopathy Complications in Patients with Type 2 Diabetes Mellitus *[see Warnings and Precautions (5.8)]*
- Suicidal Behavior and Ideation *[see Warnings and Precautions (5.9)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

ZEPBOUND was evaluated for safety in 2 randomized, double-blind, placebo-controlled trials that included 2519 adult patients with overweight or obesity treated with ZEPBOUND for up to 72 weeks and a 4-week off drug follow-up period *[see Clinical Studies (14.1)]*. The mean age of patients 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 type 2 diabetes mellitus, 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 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 the placebo-controlled trials for chronic weight management. These adverse reactions occurred more commonly with ZEPBOUND than with placebo and occurred in at least 2% of patients treated with ZEPBOUND.

Table 2: Adverse Reactions (≥2% and Greater than Placebo) in ZEPBOUND-Treated Adults with Obesity or Overweight for Chronic Weight Management

Adverse Reaction	**Placebo (N=958) %**	**ZEPBOUND 5 mg (N=630) %**	**ZEPBOUND 10 mg (N=948) %**	**ZEPBOUND 15 mg (N=941) %**
Nausea	8	25	29	28
Diarrhea[a]	8	19	21	23
Vomiting	2	8	11	13
Constipation[b]	5	17	14	11
Abdominal Pain[c]	5	9	9	10
Dyspepsia	4	9	9	10
Injection Site Reactions[d]	2	6	8	8
Fatigue[e]	3	5	6	7
Hypersensitivity Reactions	3	5	5	5
Eructation	1	4	5	5

Hair Loss	1	5	4	5
Gastroesophageal Reflux Disease	2	4	4	5
Flatulence	2	3	3	4
Abdominal Distension	2	3	3	4
Dizziness	2	4	5	4
Hypotension[f]	0	1	1	2

[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.
[d] Includes multiple related adverse event terms, such as injection site bruising, injection site erythema, injection site pruritus, injection site pain, injection site rash, injection site reaction.
[e] Includes asthenia, fatigue, lethargy, malaise.
[f] Includes blood pressure decreased, hypotension, orthostatic hypotension.

Gastrointestinal Adverse Reactions

In ZEPBOUND clinical trials, gastrointestinal adverse reactions occurred more frequently among patients receiving ZEPBOUND (5 mg 56%, 10 mg 56%, 15 mg 56%) than placebo (30%). More patients receiving ZEPBOUND 5 mg (1.9%), ZEPBOUND 10 mg (3.3%), and ZEPBOUND 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

In ZEPBOUND clinical trials, hypotension occurred more frequently among patients taking ZEPBOUND (1.6%) than patients taking placebo (0.1%). Hypotension was more frequently seen in ZEPBOUND-treated patients on concomitant antihypertensive therapy (2.2%) compared to ZEPBOUND-treated patients not on antihypertensive therapy (1.2%). Hypotension also occurred in association with gastrointestinal adverse events and dehydration.

Hypersensitivity Reactions

In ZEPBOUND clinical trials, immediate hypersensitivity reactions (within one day after drug administration) occurred in 2.1% of ZEPBOUND-treated patients compared to 0.4% of placebo-treated patients, while non-immediate hypersensitivity reactions occurred in 3.5% of ZEPBOUND-treated patients compared to 2.7% of placebo-treated patients. Among ZEPBOUND-treated patients, hypersensitivity reactions were more frequent in those with anti-tirzepatide antibodies (6.2%) compared to those who did not develop anti-tirzepatide antibodies (3%) *[see Clinical Pharmacology (12.6)]*. The majority of the hypersensitivity reactions in trials were skin reactions (e.g., rash, itching).

Injection Site Reactions

In ZEPBOUND-treated patients in clinical trials, injection site reactions were more frequent in those with anti-tirzepatide antibodies (11.3%) compared to those who did not develop anti-tirzepatide antibodies (1%) *[see Clinical Pharmacology (12.6)]*.

Hair Loss

Hair loss adverse reactions in ZEPBOUND-treated patients were associated with weight reduction. In ZEPBOUND clinical trials, hair loss was reported more frequently in female than male patients in the ZEPBOUND (7.1% female versus 0.5% male) and placebo

(1.3% female versus 0% male) treatment groups. No ZEPBOUND-treated patients and one placebo-treated patient discontinued study treatment due to hair loss.

Other Adverse Reactions

Acute Kidney Injury

In clinical trials, acute kidney injury was reported in 0.5% of ZEPBOUND-treated patients compared to 0.2% of placebo-treated patients.

Acute Gallbladder Disease

In clinical trials of ZEPBOUND, cholelithiasis was reported in 1.1% of ZEPBOUND-treated patients and 1% of placebo-treated patients, cholecystitis was reported in 0.7% 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.

Hypoglycemia

In a trial of patients with type 2 diabetes mellitus and BMI ≥27 kg/m^2, hypoglycemia (plasma glucose <54 mg/dL) was reported in 4.2% of ZEPBOUND-treated patients versus 1.3% of placebo-treated patients.

In a trial of ZEPBOUND in adults with obesity/overweight without type 2 diabetes mellitus, there was no systematic capturing of hypoglycemia, but plasma glucose <54 mg/dL was reported in 0.3% of ZEPBOUND-treated patients versus no placebo-treated patients.

Heart Rate Increase

In ZEPBOUND clinical trials, treatment with ZEPBOUND resulted in a mean increase in heart rate of 1 to 3 beats per minute compared to no increase in placebo-treated patients.

Laboratory Abnormalities

Amylase and Lipase Increase

In clinical trials, treatment with ZEPBOUND resulted in mean increases from baseline in serum pancreatic amylase concentrations of 20% to 25% and serum lipase concentrations of 28% to 35%, compared to mean increases from baseline in pancreatic amylase of 2.1% and serum lipase of 5.8% in placebo-treated patients. The clinical significance of elevations in amylase or lipase with ZEPBOUND is unknown in the absence of other signs and symptoms of pancreatitis.

6.2 Postmarketing Experience

The following adverse reactions have been reported during post-approval 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.

Hypersensitivity: anaphylaxis, angioedema

Gastrointestinal: ileus

7 DRUG INTERACTIONS

7.1 Concomitant Use with an Insulin Secretagogue (e.g., Sulfonylurea) or with Insulin

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 Warnings and Precautions (5.7)]*.

7.2 Oral Medications

ZEPBOUND delays gastric emptying and thereby has the potential to impact the absorption of concomitantly administered oral medications. Caution should be exercised when oral medications are concomitantly administered with ZEPBOUND.

Monitor patients on oral medications dependent on threshold concentrations for efficacy and those with a narrow therapeutic index (e.g., warfarin) when concomitantly administered with ZEPBOUND.

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 with ZEPBOUND and for 4 weeks after each dose escalation. Hormonal contraceptives that are not administered orally should not be affected *[see Use in Specific Populations (8.3) and Clinical Pharmacology (12.2, 12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There will be a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ZEPBOUND (tirzepatide) during pregnancy. Pregnant patients exposed to ZEPBOUND and healthcare providers are encouraged to contact Eli Lilly and Company at 1-800-LillyRx (1-800-545-5979).

Risk Summary

Weight loss offers no benefit to a pregnant patient and may cause fetal harm. Advise pregnant patients that weight loss is not recommended during pregnancy and to discontinue ZEPBOUND when a pregnancy is recognized *(see Clinical Considerations)*. Available data with tirzepatide in pregnant patients are insufficient to evaluate for a drug-related risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Based on animal reproduction studies, there may be risks to the fetus from exposure to tirzepatide during pregnancy.

In pregnant rats administered tirzepatide during organogenesis, fetal growth reductions and fetal abnormalities occurred at clinical exposure in maternal rats based on AUC. In rabbits administered tirzepatide during organogenesis, fetal growth reductions were observed at clinically relevant exposures based on AUC. These adverse embryo/fetal effects in animals coincided with pharmacological effects on maternal weight and food consumption *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is increased when compared to the general population. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Appropriate weight gain based on pre-pregnancy weight is currently recommended for

all pregnant patients, including those with obesity or overweight, due to the obligatory weight gain that occurs in maternal tissues during pregnancy.

Data

Animal Data

In pregnant rats given twice weekly subcutaneous doses of 0.02, 0.1, and 0.5 mg/kg tirzepatide (0.03-, 0.07-, and 0.5-fold the maximum recommended human dose (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 decreased fetal weights coincided with pharmacologically-mediated reductions in maternal body weights and food consumption at 0.5 mg/kg. In pregnant rabbits given once weekly subcutaneous doses of 0.01, 0.03, or 0.1 mg/kg tirzepatide (0.01-, 0.06-, and 0.2-fold the MRHD) during organogenesis, pharmacologically mediated effects on the gastrointestinal system resulting in maternal mortality or abortion in a few rabbits occurred at all dose levels. Reduced fetal weights associated with decreased maternal food consumption and body weights were observed at 0.1 mg/kg. In a pre- and post-natal study in rats administered subcutaneous doses of 0.02, 0.10, or 0.25 mg/kg tirzepatide twice weekly from implantation through lactation, F_1 pups from F_0 maternal rats given 0.25 mg/kg tirzepatide had statistically significant lower mean body weight when compared to controls from post-natal day 7 through post-natal day 126 for males and post-natal day 56 for females.

8.2 Lactation

Risk Summary

There are no data on the presence of tirzepatide or its metabolites in animal or human milk, the effects on the breastfed infant, or the effects 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.

8.3 Females and Males of Reproductive Potential

Contraception

Use of ZEPBOUND may reduce the efficacy of oral hormonal contraceptives due to delayed gastric emptying. This delay is largest after the first dose and diminishes over time. 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 with ZEPBOUND and for 4 weeks after each dose escalation *[see Drug Interactions (7.2) and Clinical Pharmacology (12.2, 12.3)]*.

8.4 Pediatric Use

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

8.5 Geriatric Use

In ZEPBOUND clinical trials, 226 (9%) ZEPBOUND-treated patients were 65 years of age or older, and 13 (0.5%) ZEPBOUND-treated patients were 75 years of age or older at baseline.

No overall differences in safety or effectiveness of ZEPBOUND have been observed between patients 65 years of age and older and younger adult patients.

8.6 Renal Impairment

No dosage adjustment of ZEPBOUND is recommended for patients with renal impairment. In subjects with renal impairment including end-stage renal disease (ESRD), no change in tirzepatide pharmacokinetics (PK) was observed *[see Clinical Pharmacology (12.3)]*. Monitor renal function in patients reporting adverse reactions to ZEPBOUND that could lead to volume depletion *[see Warnings and Precautions (5.3)]*.

8.7 Hepatic Impairment

No dosage adjustment of ZEPBOUND is recommended for patients with hepatic impairment. In a clinical pharmacology study in subjects with varying degrees of hepatic impairment, no change in tirzepatide PK was observed *[see Clinical Pharmacology (12.3)]*.

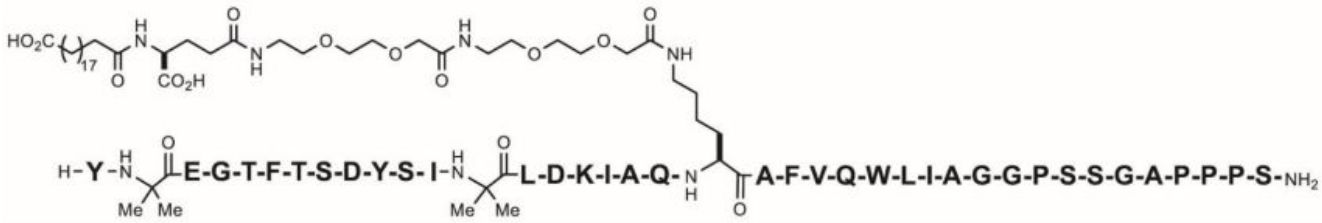
10 OVERDOSAGE

In the event of an overdosage, contact the Poison Help Line (1-800-222-1222) or a medical toxicologist for additional overdosage management recommendations. Appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms. A period of observation and treatment for these symptoms may be necessary, taking into account the half-life of tirzepatide of approximately 5 days.

11 DESCRIPTION

ZEPBOUND (tirzepatide) injection, for subcutaneous use, contains tirzepatide, a GIP receptor and GLP-1 receptor agonist. Tirzepatide is based on the GIP sequence and contains 2 non-coded amino acids (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. The molecular weight is 4813.53 Da and the empirical formula is $C_{225}H_{348}N_{48}O_{68}$.

Structural formula:



ZEPBOUND is a clear, colorless to slightly yellow, sterile, preservative-free solution for subcutaneous use. Each single-dose pen contains 0.5 mL solution of 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, or 15 mg of tirzepatide and the following excipients: sodium chloride (4.1 mg), sodium phosphate dibasic heptahydrate (0.7 mg), and water for injection. Hydrochloric acid solution and/or sodium hydroxide solution may have been added to adjust the pH. ZEPBOUND has a pH of 6.5 – 7.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tirzepatide is a GIP receptor 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.

12.2 Pharmacodynamics

Tirzepatide lowers body weight with greater fat mass loss than lean mass loss. Tirzepatide decreases calorie intake, and the effects are likely mediated by affecting appetite.

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 type 2 diabetes mellitus 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.

12.3 Pharmacokinetics

The pharmacokinetics of tirzepatide is similar between healthy subjects and patients with overweight or 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 is approximately 9.7 L (28.5%). Tirzepatide is highly bound to plasma albumin (99%).

Elimination

The apparent population mean clearance (CV%) of tirzepatide in patients with overweight or obesity is 0.056 L/h (20.9%) with an elimination half-life of approximately 5 days.

Metabolism

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

Excretion

The primary excretion routes of tirzepatide metabolites are via urine and feces. Intact tirzepatide is not observed in urine or feces.

Specific Populations

The intrinsic factors of age (18 to 84 years), sex, race (71% White, 11% Asian, 9%

American Indian or Alaska Native, and 8% Black or African American), ethnicity, or body weight do not have a clinically relevant effect on the PK of tirzepatide.

Patients with Renal Impairment

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 Use in Specific Populations (8.6)]*.

Patients with Hepatic Impairment

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 Use in Specific Populations (8.7)]*.

Drug Interaction Studies

Potential for Tirzepatide to Influence the Pharmacokinetics of Other Drugs

In vitro studies have shown low potential for tirzepatide to inhibit or induce CYP enzymes, and to inhibit drug transporters.

ZEPBOUND delays gastric emptying and thereby has the potential to impact the absorption of concomitantly administered oral medications *[see Drug Interactions (7.2)]*.

The impact of tirzepatide on gastric emptying was greatest after a single dose of 5 mg and diminished after subsequent doses.

Following a first dose of tirzepatide 5 mg, acetaminophen maximum concentration (C_{max}) was reduced by 55%, and the median peak plasma concentration (t_{max}) occurred 1 hour later. After coadministration at Week 6 with tirzepatide 15 mg, there was no meaningful impact on acetaminophen C_{max} and t_{max}. Overall acetaminophen exposure ($AUC_{0\text{-}24hr}$) was not influenced.

Following administration of a combined oral contraceptive (0.035 mg ethinyl estradiol and 0.25 mg norgestimate) in the presence of a single dose of tirzepatide 5 mg, mean C_{max} of ethinyl estradiol, norgestimate, and norelgestromin was reduced by 59%, 66%, and 55%, while mean AUC was reduced by 20%, 21%, and 23%, respectively. A delay in t_{max} of 2.5 to 4.5 hours was observed.

12.6 Immunogenicity

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the trials described below with the incidence of anti-drug antibodies in other trials.

During the 72-week treatment period with anti-drug antibodies (ADA) sampling in the chronic weight management studies *[see Clinical Studies (14)]*, 64.5% (1591/2467) of ZEPBOUND-treated patients developed anti-tirzepatide antibodies. In these trials, anti-tirzepatide antibody formation in 40% and 16.5% of ZEPBOUND-treated patients showed cross-reactivity to native GIP or native GLP-1, respectively.

Of the ZEPBOUND-treated patients, 2.8% and 2.7% developed neutralizing antibodies against tirzepatide activity on the GIP or GLP-1 receptors, respectively, and 0.8% and 0.1% developed neutralizing antibodies against native GIP or GLP-1, respectively.

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 Adverse Reactions (6.1)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

A 2-year carcinogenicity study was conducted with tirzepatide in male and female rats at doses of 0.15, 0.50, and 1.5 mg/kg (0.1-, 0.4-, and 1-fold the MRHD of 15 mg once weekly based on AUC) administered by subcutaneous injection twice weekly. A statistically significant increase in thyroid C-cell adenomas was observed in male rats (≥0.5 mg/kg) and female rats (≥0.15 mg/kg), and a statistically significant increase in thyroid C-cell adenomas and carcinomas combined was observed in male and female rats at all doses examined. In a 6-month carcinogenicity study in rasH2 transgenic mice, tirzepatide at doses of 1, 3, and 10 mg/kg administered by subcutaneous injection twice weekly was not tumorigenic.

Tirzepatide was not genotoxic in a rat bone marrow micronucleus assay.

In fertility and early embryonic development studies, male and female rats were administered twice weekly subcutaneous 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. 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.

14 CLINICAL STUDIES

14.1 Weight Management Studies in Adults with Overweight or Obesity

Overview of Clinical 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 (Study 1 and Study 2), in which weight reduction was assessed after 72 weeks of treatment (at least 52 weeks at maintenance dose). In Study 1, the dose of ZEPBOUND or matching placebo was escalated to 5 mg, 10 mg, or 15 mg subcutaneously once weekly during a 20-week titration period followed by the maintenance period. In Study 2, the dose of ZEPBOUND or matching placebo was escalated to 10 mg or 15 mg subcutaneously once weekly during a 20-week titration period followed by the maintenance period.

In Studies 1 and 2, 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.

Study 1 (NCT04184622) 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 type 2 diabetes mellitus were excluded. Patients were randomized in a 1:1:1:1 ratio to ZEPBOUND 5 mg, ZEPBOUND 10 mg, ZEPBOUND 15 mg, or placebo once weekly. At baseline, mean age was 45 years (range 18-84 years), 68% 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. Mean baseline body weight was 104.8 kg and mean BMI was 38 kg/m^2. Baseline characteristics included 32% with hypertension, 30% with dyslipidemia, 8% with obstructive sleep apnea, and 3% with cardiovascular disease.

Study 2 (NCT04657003) was a 72-week trial that enrolled 938 adult patients with BMI ≥27 kg/m^2 and type 2 diabetes mellitus. Patients included in the trial had HbA1c 7-10% 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 for type 2 diabetes mellitus were excluded. Patients were randomized in a 1:1:1 ratio to ZEPBOUND 10 mg, ZEPBOUND 15 mg, or placebo once weekly. 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 and mean BMI was 36.1 kg/m^2. Baseline characteristics included 66% with hypertension, 61% with dyslipidemia, 8% with obstructive sleep apnea, and 10% with cardiovascular disease.

Results

The proportions of patients who discontinued study drug in Study 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. The proportions of patients who discontinued study drug in Study 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.

For Studies 1 and 2, the primary efficacy parameters were mean percent change in body weight and the percentage of patients achieving ≥5% weight reduction from baseline to Week 72 (see Table 3).

After 72 weeks of treatment, ZEPBOUND resulted in a statistically significant reduction in body weight compared with placebo, and greater proportions of patients treated with ZEPBOUND 5 mg, 10 mg, and 15 mg achieved at least 5% weight reduction compared to placebo. 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 3). A reduction in body weight was observed with ZEPBOUND irrespective of age, sex, race, ethnicity, baseline BMI, and glycemic status.

Table 3: Changes in Body Weight at Week 72 in Studies 1 and 2

Intention-to-Treat (ITT) Population[a]	**Study 1**				**Study 2**		
	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**
Body Weight							
Baseline mean (kg)	104.8	102.9	105.8	105.6	101.7	100.9	99.6
% Change	-3.1	-15.0	-19.5	-20.9	-3.2	-12.8	-14.7

from baseline[b]							
% Difference from placebo[b] (95% CI)		-11.9 (-13.4, –10.4)[d]	-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
% Difference from placebo (95% CI)		50.3 (44.3, 56.2)[c,d]	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]
% of Patients losing ≥10% body weight	18.8	68.5	78.1	83.5	9.5	60.5	64.8
% Difference from placebo (95% CI)		49.3 (43.6, 54.9)[c,e]	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	48.0	66.6	70.6	2.7	39.7	48.0
% Difference from placebo (95% CI)		38.7 (33.6, 43.7)[c,e]	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	30.0	50.1	56.7	1.0	21.5	30.8
% Difference from placebo (95% CI)		26.6 (22.4, 30.7)[c,e]	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]

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 Study 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 Study 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.

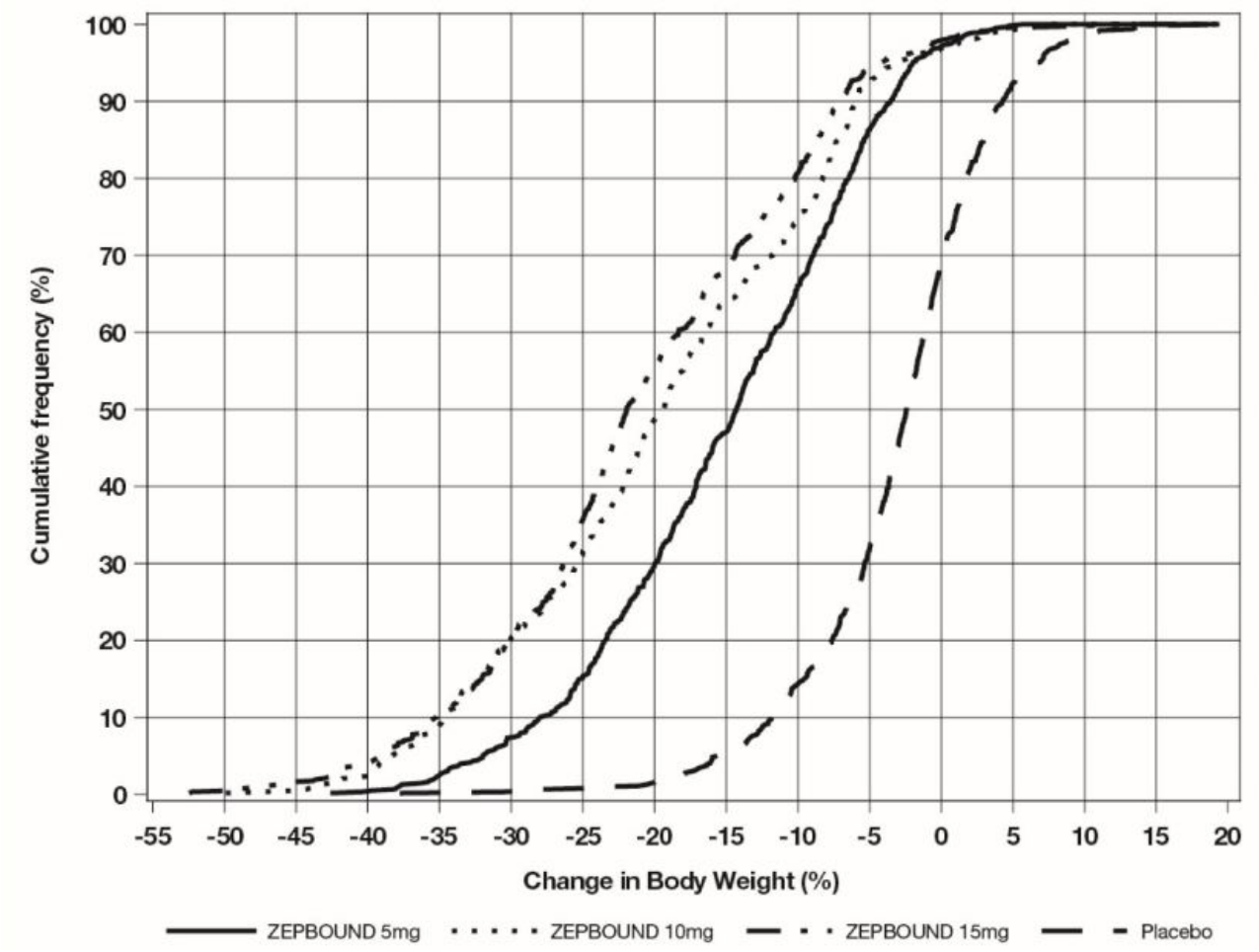
[c] Analyzed using logistic regression adjusted for baseline value.

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

[e] Not controlled for type I error rate.

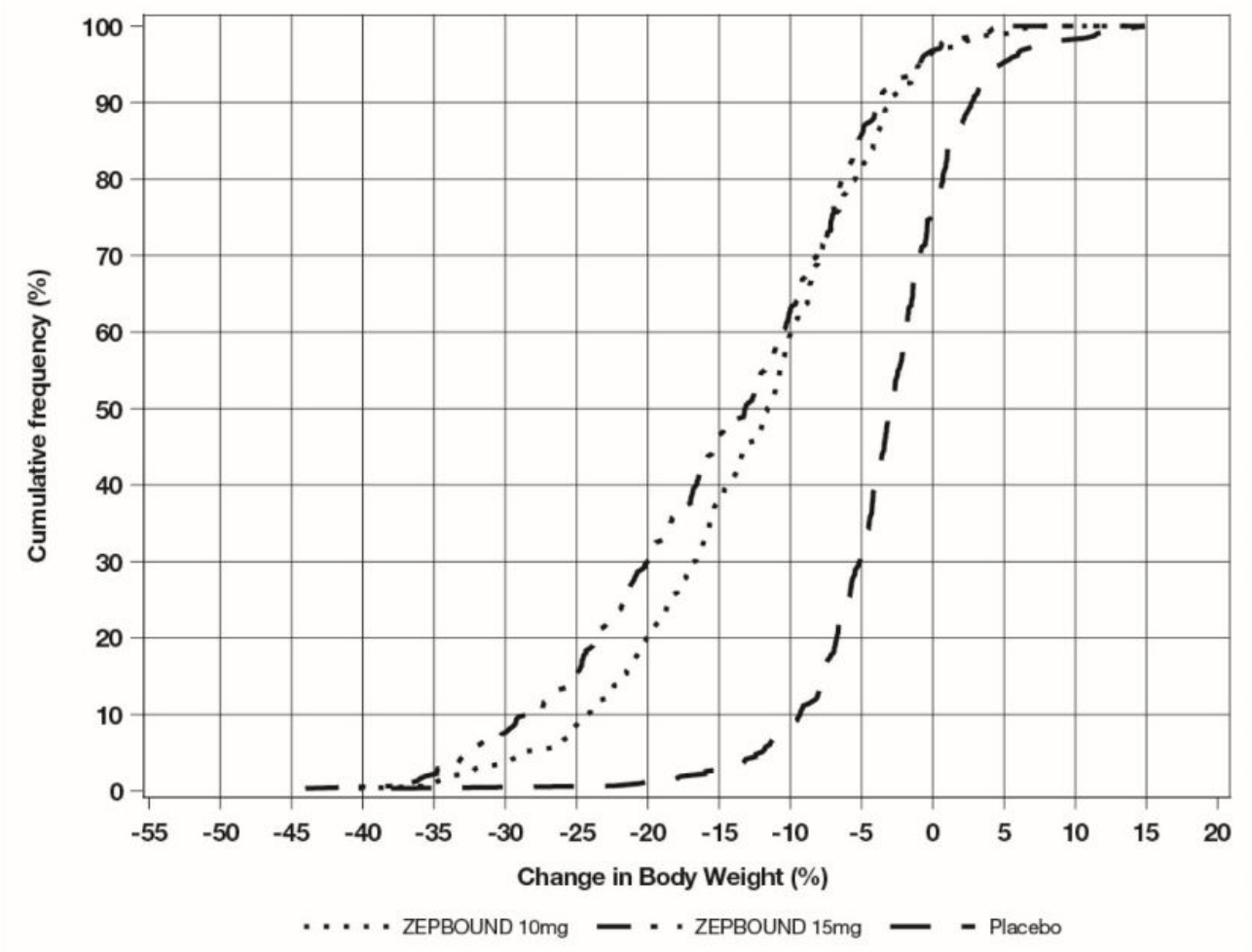
The cumulative frequency distributions of change in body weight are shown in Figure 1 for Study 1 and Figure 2 for Study 2. One way to interpret this figure is to select a change in body weight of interest on the horizontal axis and note the corresponding proportions of patients (vertical axis) in each treatment group who achieved at least that degree of weight reduction. For example, note that the vertical line arising from -10% in Figure 1 intersects the ZEPBOUND 15 mg and placebo curves at approximately 83.5%, and 18.8%, respectively, which correspond to the values shown in Table 3.

Figure 1: Changes in Body Weight (%) from Baseline to Week 72 in Study 1



Note: Based on average percent weight change of each randomized patient within each specific treatment arm from 100 imputed datasets including observed data and imputed data using hybrid approach for missing values.

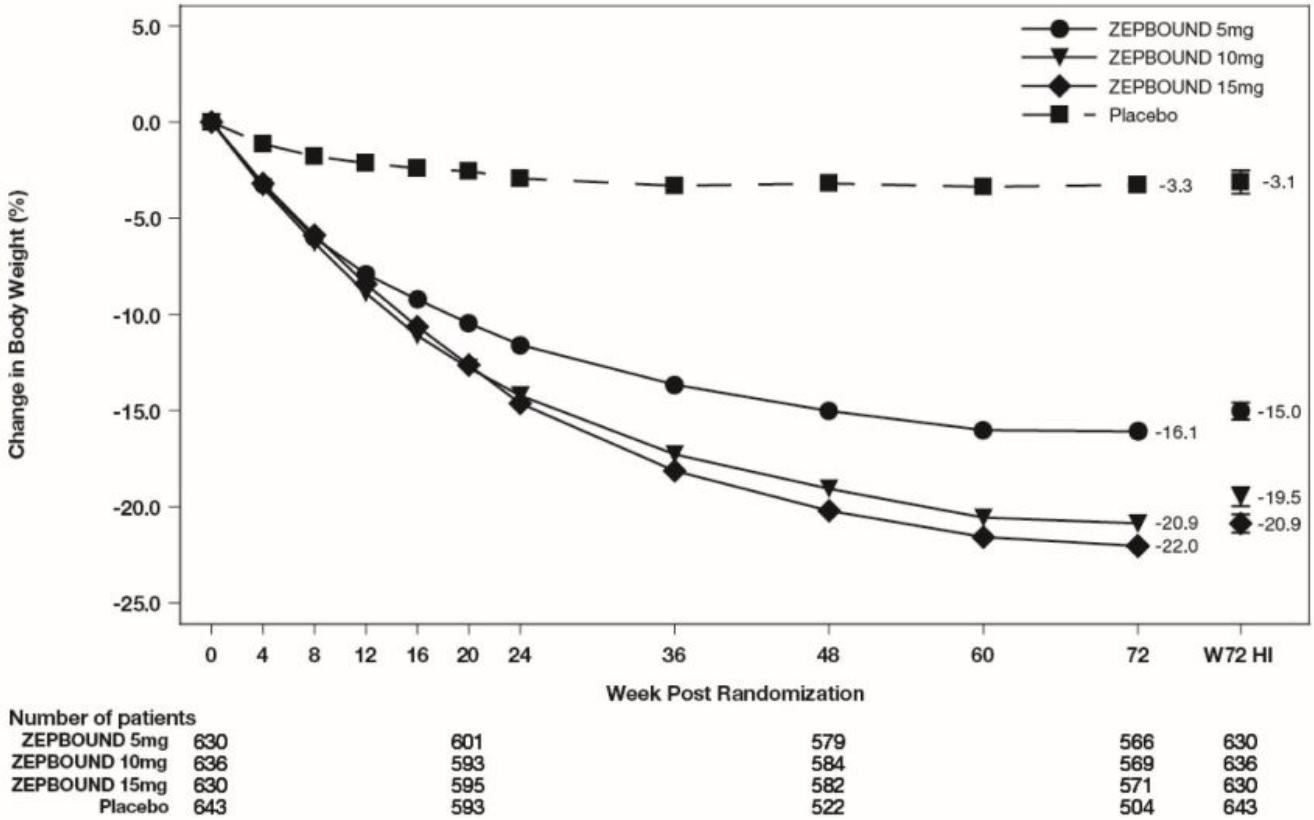
Figure 2: Changes in Body Weight (%) from Baseline to Week 72 in Study 2



Note: Based on average percent weight change of each randomized patient within each specific treatment arm from 100 imputed datasets including observed data and imputed data using hybrid approach for missing values.

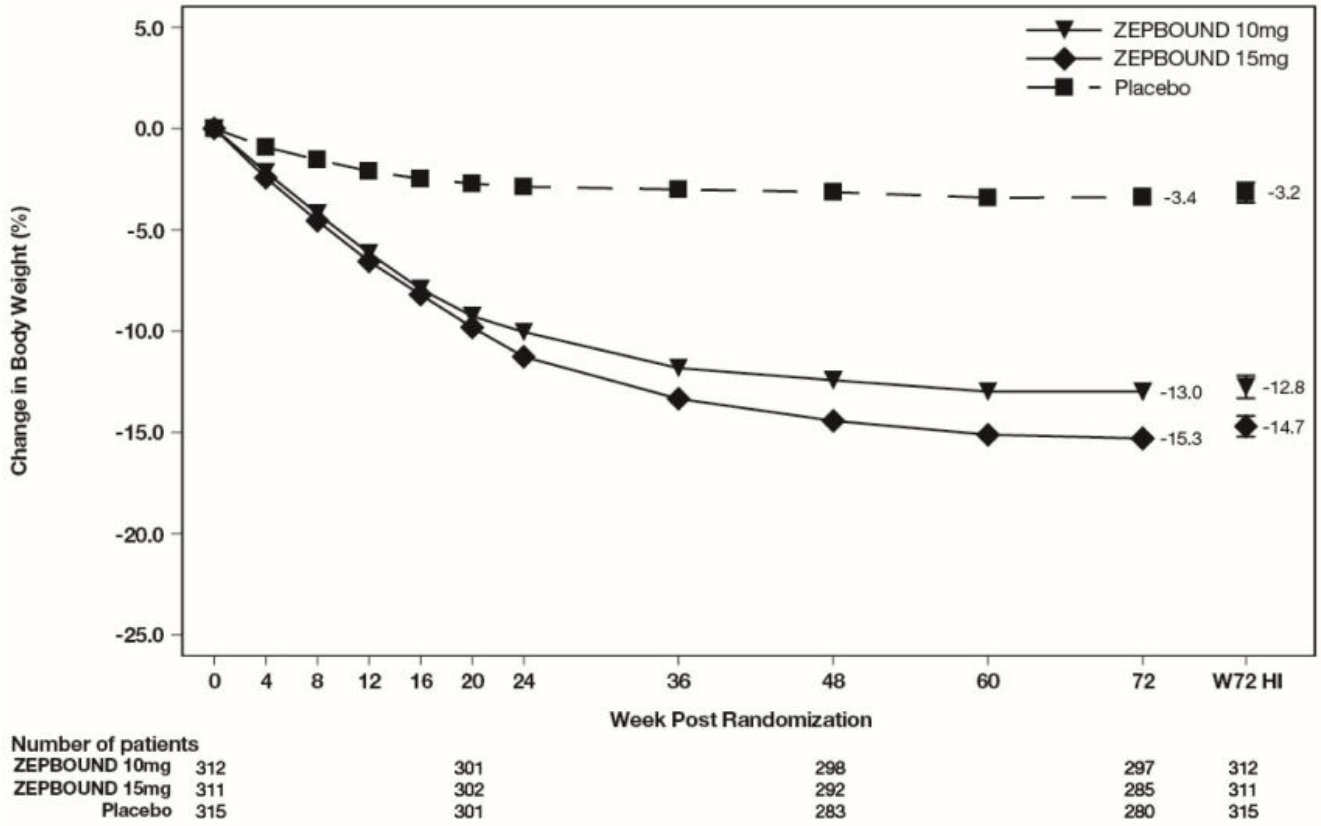
The time courses of weight reduction with ZEPBOUND and placebo from baseline through Week 72 are depicted in Figure 3 for Study 1 and Figure 4 for Study 2.

Figure 3: Change from Baseline (%) in Body Weight in Study 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 4: Change from Baseline (%) in Body Weight in Study 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 Anthropometry and Cardiometabolic Parameters

Changes in waist circumference and cardiometabolic parameters with ZEPBOUND are shown in Table 4 for Study 1 and Study 2.

Table 4: Changes in Anthropometry and Cardiometabolic Parameters at Week 72 in Studies 1 and 2

Intention-to-Treat (ITT) Population[a]	**Study 1**				**Study 2**		
	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**
Waist Circumference (cm)							
Baseline mean	114.0	113.2	114.8	114.4	116.0	114.2	114.6
Change from baseline[b]	-4.0	-14.0	-17.7	-18.5	-3.3	-10.8	-13.1
Difference from placebo[b] (95% CI)		-10.1 (-11.6, -8.6)[e]	-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]
Systolic Blood							

Pressure (mmHg)							
Baseline mean	122.9	123.6	123.8	123.0	131.0	130.6	130.0
Change from baseline[b]	-1.0	-6.6	-7.7	-7.4	-1.2	-5.6	-7.1
Difference from placebo[b] (95% CI)		-5.6 (-7.2, -3.9)[e]	-6.7 (-8.4, -5.0)[e]	-6.4 (-8.0, -4.8)[e]		-4.4 (-6.7, -2.1)[e]	-5.9 (-8.3, -3.6)[e]
Diastolic Blood Pressure (mmHg)							
Baseline mean	79.6	79.3	79.9	79.3	79.4	80.2	79.7
Change from baseline[b]	-0.8	-4.9	-5.0	-4.5	-0.3	-2.1	-2.9
Difference from placebo[b] (95% CI)		-4.1 (-5.2, -3.0)[e]	-4.2 (-5.3, -3.0)[e]	-3.7 (-4.8, -2.7)[e]		-1.8 (-3.3, -0.4)[e]	-2.7 (-4.2, -1.2)[e]
Pulse Rate (beats per minute)							
Baseline mean	72.9	72.4	71.8	72.4	74.8	75.9	75.6
Change from baseline[f]	0.1	0.6	2.3	2.6	-0.5	0.6	1.0
Difference from placebo[f] (95% CI)		0.5 (-0.5, 1.5)[e]	2.2 (1.2, 3.2)[e]	2.5 (1.5, 3.4)[e]		1.2 (-0.1, 2.5)[e]	1.5 (0.2, 2.8)[e]
Total Cholesterol (mg/dL)							
Baseline mean[g]	187.5	187.1	190.6	187.5	174.9	173.9	167.0
% change from baseline[b]	-1.8	-3.8	-4.4	-6.3	2.8	-2.8	-1.0
Relative difference from placebo[b] (95% CI)		-2.1 (-4.5, 0.4)[c,e]	-2.7 (-5.1, -0.2)[c,e]	-4.6 (-6.8, -2.2)[c,e]		-5.5 (-8.7, -2.2)[c,e]	-3.8 (-7.1, -0.3)[c,e]
LDL Cholesterol (mg/dL)							
Baseline mean[g]	109.4	108.7	112.3	109.3	92.4	90.5	85.7
% change from	-1.7	-4.6	-5.6	-7.1	7.4	1.8	4.1

baseline[b]							
Relative difference from placebo[b] (95% CI)		-2.9 (-6.6, 0.9)[c,e]	-4.0 (-7.5, -0.5)[c,e]	-5.5 (-8.9, -2.0)[c,e]		-5.2 (-10.1, 0.1)[c,e]	-3.0 (-8.4, 2.6)[c,e]
HDL (mg/dL)							
Baseline mean[g]	46.6	47.6	47.6	47.6	42.7	43.8	42.2
% change from baseline[b]	-0.7	6.9	9.2	8.0	0.2	8.2	9.7
Relative difference from placebo[b] (95% CI)		7.7 (4.6, 10.8)[c,e]	9.9 (6.7, 13.2)[c,e]	8.7 (5.7, 11.8)[c,e]		8.0 (4.2, 11.8)[c,e]	9.5 (5.6, 13.5)[c,e]
Non-HDL (mg/dL)							
Baseline mean[g]	138.3	137.0	140.4	137.5	129.6	127.2	121.9
% change from baseline[b]	-2.3	-8.0	-9.4	-11.7	3.7	-6.6	-5.2
Relative difference from placebo[b] (95% CI)		-5.8 (-8.9, -2.6)[c,e]	-7.2 (-10.3, -4.1)[c,e]	-9.6 (-12.4, -6.6)[c,e]		-9.9 (-14.1, -5.6)[c,e]	-8.5 (-12.9, -4.0)[c,e]
Triglycerides (mg/dL)							
Baseline mean[g]	130.8	128.7	125.7	128.1	165.0	158.8	158.5
% change from baseline[b]	-5.6	-21.2	-23.8	-29.1	-3.3	-27.1	-27.3
Relative difference from placebo[b] (95% CI)		-16.5 (-21.2, -11.4)[c,e]	-19.3 (-23.9, -14.4)[c,e]	-24.9 (-29.1, -20.4)[c,e]		-24.6 (-30.0, -18.7)[c,e]	-24.8 (-30.3, -18.9)[c,e]
HbA1c (%)							
Baseline mean	5.6	5.6	5.5	5.6	8.0	8.0	8.1
Change from baseline[b]	-0.1	-0.4	-0.4	-0.4	-0.5	-2.1	-2.1
Difference from placebo[b] (95% CI)		-0.3 (-0.3, -0.2)[e]	-0.4 (-0.4, -0.3)[e]	-0.4 (-0.4, -0.3)[e]		-1.6 (-1.7, -1.4)[d]	-1.6 (-1.8, -1.4)[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] Not controlled for type I error rate.
[f] Least-squares mean from mixed model for repeated measures adjusted for baseline value and other stratification factors.
[g] Baseline value is the geometric mean.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

ZEPBOUND is a clear, colorless to slightly yellow solution available in pre-filled single-dose pens as follows:

Total Strength per Total Volume	Carton Contents	NDC
2.5 mg/0.5 mL	4 single-dose pens	0002-2506-80
5 mg/0.5 mL	4 single-dose pens	0002-2495-80
7.5 mg/0.5 mL	4 single-dose pens	0002-2484-80
10 mg/0.5 mL	4 single-dose pens	0002-2471-80
12.5 mg/0.5 mL	4 single-dose pens	0002-2460-80
15 mg/0.5 mL	4 single-dose pens	0002-2457-80

16.2 Storage and Handling

- Store ZEPBOUND in a refrigerator at 2°C to 8°C (36°F to 46°F).
- If needed, each single-dose pen can be stored unrefrigerated at temperatures not to exceed 30°C (86°F) for up to 21 days. If ZEPBOUND is stored at room temperature, it should not be returned to the refrigerator.
- Discard if not used within 21 days after removing from the refrigerator.
- Do not freeze ZEPBOUND. Do not use ZEPBOUND if frozen.
- Store ZEPBOUND in the original carton to protect from light.

17 PATIENT COUNSELING INFORMATION

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

Risk of Thyroid C-Cell Tumors

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

Severe Gastrointestinal Adverse Reactions

Inform patients of the potential risk of severe gastrointestinal adverse reactions. Instruct patients to contact their healthcare provider if they have severe or persistent gastrointestinal symptoms *[see Warnings and Precautions (5.2)]*.

Acute Kidney Injury

Advise patients treated with ZEPBOUND of the potential risk of dehydration due to gastrointestinal adverse reactions and take precautions to avoid fluid depletion. Inform patients of the potential risk for worsening renal function and explain the associated signs and symptoms of renal impairment, as well as the possibility of dialysis as a medical intervention if renal failure occurs *[see Warnings and Precautions (5.3)]*.

Acute Gallbladder Disease

Inform patients of the risk of acute gallbladder disease. Instruct patients to contact their healthcare provider for appropriate clinical follow-up if gallbladder disease is suspected *[see Warnings and Precautions (5.4)]*.

Acute Pancreatitis

Inform patients of the potential risk for pancreatitis. Instruct patients to discontinue ZEPBOUND promptly and contact their healthcare provider if pancreatitis is suspected (severe abdominal pain that may radiate to the back, and which may or may not be accompanied by vomiting) *[see Warnings and Precautions (5.5)]*.

Hypersensitivity Reactions

Inform patients that serious hypersensitivity reactions have been reported with use of tirzepatide. Advise patients on the symptoms of hypersensitivity reactions and instruct them to stop taking ZEPBOUND and seek medical advice promptly if such symptoms occur *[see Warnings and Precautions (5.6)]*.

Hypoglycemia

Inform patients of the risk of hypoglycemia and educate patients on the signs and symptoms of hypoglycemia. Advise patients on insulin or insulin secretagogue therapy that they may have an increased risk of hypoglycemia when using ZEPBOUND and to report signs and/or symptoms of hypoglycemia to their healthcare provider *[see Warnings and Precautions (5.7)]*.

Diabetic Retinopathy Complications

Inform patients with type 2 diabetes mellitus to contact their healthcare provider if changes in vision are experienced during treatment with ZEPBOUND *[see Warnings and Precautions (5.8)]*.

Suicidal Behavior and Ideation

Advise patients to report emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior. Inform patients that if they experience suicidal thoughts or behaviors, they should stop taking ZEPBOUND *[see Warnings and Precautions (5.9)]*.

Pregnancy

Advise a pregnant patient of the potential risk to a fetus. Advise patients to inform their healthcare provider if they are pregnant or intend to become pregnant during treatment with ZEPBOUND. Advise patients that there will be a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ZEPBOUND during pregnancy *[see Use in Specific Populations (8.1)]*.

Contraception

Use of ZEPBOUND may reduce the efficacy of oral hormonal contraceptives. 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 with ZEPBOUND and for 4 weeks after each dose escalation *[see Drug Interactions (7.2), Use in Specific Populations (8.3), and Clinical Pharmacology (12.3)]*.

Missed Doses

Inform patients if a dose is missed, it should be administered as soon as possible within 4 days after the missed dose. If more than 4 days have passed, the missed dose should be skipped and the next dose should be administered on the regularly scheduled day. In each case, inform patients to resume their regular once weekly dosing schedule *[see Dosage and Administration (2.3)]*.

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ZEP-0001-USPI-20231108

Medication Guide
ZEPBOUND™ (ZEHP-bownd)
(tirzepatide)
injection, for subcutaneous use

What is the most important information I should know about ZEPBOUND?
ZEPBOUND may cause serious side effects, including:

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

What is ZEPBOUND?

- ZEPBOUND is an injectable prescription medicine that may help adults with obesity, or with excess weight (overweight) who also have weight-related medical problems, lose weight and keep it off.
- ZEPBOUND should be used with a reduced-calorie diet and increased physical activity.
- ZEPBOUND contains tirzepatide and should not be used with other tirzepatide-containing products or any GLP-1 receptor agonist medicines.
- It is not known if ZEPBOUND is safe and effective when taken with other prescription, over-the-counter, or herbal weight loss products.
- It is not known if ZEPBOUND can be used in people who have had pancreatitis.
- It is not known if ZEPBOUND is safe and effective for use in children under 18 years of age.

Do not use ZEPBOUND if:

- you or any of your family have ever had a type of thyroid cancer called MTC or if you have an endocrine system condition called MEN 2.
- you have had a serious allergic reaction to tirzepatide or any of the ingredients in ZEPBOUND. See the end of this Medication Guide for a complete list of ingredients in ZEPBOUND.

Before using ZEPBOUND, tell your healthcare provider about all of your medical conditions, including if you:

- have or have had problems with your pancreas or kidneys.
- have severe problems with your stomach, such as slowed emptying of your stomach (gastroparesis) or problems with digesting food.
- have a history of diabetic retinopathy.
- are pregnant or plan to become pregnant. ZEPBOUND may harm your unborn baby. Tell your healthcare provider if you become pregnant while using ZEPBOUND.
  - **Pregnancy Exposure Registry:** There will be a pregnancy exposure registry for women who have taken ZEPBOUND during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. Talk to your healthcare provider about how you can take part in this registry or you may contact Eli Lilly and Company at 1-800-LillyRx (1-800-545-5979).
  - **Birth control pills by mouth may not work as well while using ZEPBOUND.** If you take birth control pills by mouth, your healthcare provider may recommend another type of birth control for 4 weeks after you start ZEPBOUND and for 4 weeks after each increase in your dose of ZEPBOUND. Talk to your healthcare provider about birth control methods that may be right for you while using ZEPBOUND.
- are breastfeeding or plan to breastfeed. It is not known if ZEPBOUND passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby while using ZEPBOUND.

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

Before using ZEPBOUND, tell your healthcare provider if you are taking medicines to treat diabetes including insulin or sulfonylureas which could increase your risk of low blood sugar. Talk to your healthcare provider about low blood sugar levels and how to manage them.

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

How should I use ZEPBOUND?

- Read the **Instructions for Use** that comes with ZEPBOUND.
- Use ZEPBOUND exactly as your healthcare provider tells you to. A healthcare provider should show you how to prepare to inject your dose of ZEPBOUND before injecting the first time.
- ZEPBOUND is injected under the skin (subcutaneously) of your stomach (abdomen), thigh, or upper arm.
- **Use ZEPBOUND 1 time each week, at any time of the day.**
- You may change the day of the week you use ZEPBOUND as long as the time between the 2 doses is at least **3** days (72 hours).
- If you miss a dose of ZEPBOUND, take the missed dose 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 take your next dose on the regularly scheduled day. **Do not** take **2** doses of ZEPBOUND within **3** days (72 hours) of each other.
- ZEPBOUND may be taken with or without food.
- Change (rotate) your injection site with each weekly injection. You may use the same area of your body but be sure to choose a different injection site in that area. **Do not** use the same site for each injection.
- In case of overdose, get medical help or contact a Poison Center expert right away at 1-800-222-1222. Advice is also available online at poisonhelp.org.

What are the possible side effects of ZEPBOUND?
ZEPBOUND may cause serious side effects, including:

- See **"What is the most important information I should know about ZEPBOUND?"**
- **severe stomach problems.** Stomach problems, sometimes severe, have been reported in people who use ZEPBOUND. Tell your healthcare provider if you have stomach problems that are severe or will not go away.
- **kidney problems (kidney failure).** Diarrhea, nausea, and vomiting may cause a loss of fluids (dehydration) which may cause kidney problems. It is important for you to drink fluids to help reduce your chance of dehydration.
- **gallbladder problems.** Gallbladder problems have happened in some people who use ZEPBOUND. Tell your healthcare provider right away if you get symptoms of gallbladder problems which may include:
  - pain in your upper stomach (abdomen)
  - fever
  - yellowing of skin or eyes (jaundice)
  - clay-colored stools
- **inflammation of your pancreas (pancreatitis).** Stop using ZEPBOUND and call your healthcare provider right away if you have severe pain in your stomach area (abdomen) that will not go away, with or without vomiting. You may feel the pain from your abdomen to your back.
- **serious allergic reactions.** Stop using ZEPBOUND and get medical help right away if you have any symptoms of a serious allergic reaction including:
  - swelling of your face, lips, tongue or throat
  - problems breathing or swallowing
  - severe rash or itching
  - fainting or feeling dizzy
  - very rapid heartbeat
- **low blood sugar (hypoglycemia).** Your risk for getting low blood sugar may be higher if you use ZEPBOUND with medicines that can cause low blood sugar, such as a sulfonylurea or insulin. **Signs and symptoms of low blood sugar may include:**
  - dizziness or light-headedness
  - sweating
  - confusion or drowsiness
  - headache
  - blurred vision
  - slurred speech
  - shakiness
  - fast heartbeat
  - anxiety, irritability, or mood changes
  - hunger
  - weakness
  - feeling jittery
- **changes in vision in patients with type 2 diabetes.** Tell your healthcare provider if you have changes in vision during treatment with ZEPBOUND.
- **depression or thoughts of suicide.** You should pay attention to any changes in your mood, behaviors, feelings, or thoughts. Call your healthcare provider right away if you have any changes to your mental health that are new, worse, or worry you.

The most common side effects of ZEPBOUND include:

- nausea
- diarrhea
- vomiting
- constipation
- stomach (abdominal) pain
- indigestion
- injection site reactions
- feeling tired
- allergic reactions
- belching
- hair loss
- heartburn

Talk to your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of ZEPBOUND. Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ZEPBOUND?

- Store ZEPBOUND in the refrigerator between 36°F to 46°F (2°C to 8°C). Store ZEPBOUND in the original carton until use to protect it from light.
- If needed, each single-dose pen can be stored at room temperature up to 86°F (30°C) for up to 21 days. If ZEPBOUND is stored at room temperature, it should not be returned to the refrigerator.
- Discard if not used within 21 days after removing from the refrigerator.
- Do not freeze ZEPBOUND. Do not use ZEPBOUND if frozen.

Keep ZEPBOUND and all medicines out of the reach of children.

General information about the safe and effective use of ZEPBOUND.
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use ZEPBOUND for a condition for which it was not prescribed. Do not give ZEPBOUND to other people, even if they have the same condition you have. It may harm them. You can ask your pharmacist or healthcare provider for information about ZEPBOUND that is written for health professionals.

What are the ingredients in ZEPBOUND?
Active ingredient: tirzepatide
Inactive ingredients: sodium chloride, sodium phosphate dibasic heptahydrate, and water for injection. Hydrochloric acid solution and/or sodium hydroxide solution may have been added to adjust the pH.
ZEPBOUND™ is a trademark of Eli Lilly and Company.
Marketed by: Lilly USA, LLC, Indianapolis, IN 46285, USA
Copyright © 2023, Eli Lilly and Company. All rights reserved.
For more information, go to www.zepbound.com or call 1-800-545-5979.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Issued: 11/2023

ZEP-0001-MG-20231108

INSTRUCTIONS FOR USE

INSTRUCTIONS FOR USE
ZEPBOUND™ (ZEHP-bownd)
(tirzepatide)
injection, for subcutaneous use

2.5 mg/0.5 mL single-dose pen
5 mg/0.5 mL single-dose pen
7.5 mg/0.5 mL single-dose pen
10 mg/0.5 mL single-dose pen
12.5 mg/0.5 mL single-dose pen
15 mg/0.5 mL single-dose pen
use 1 time each week

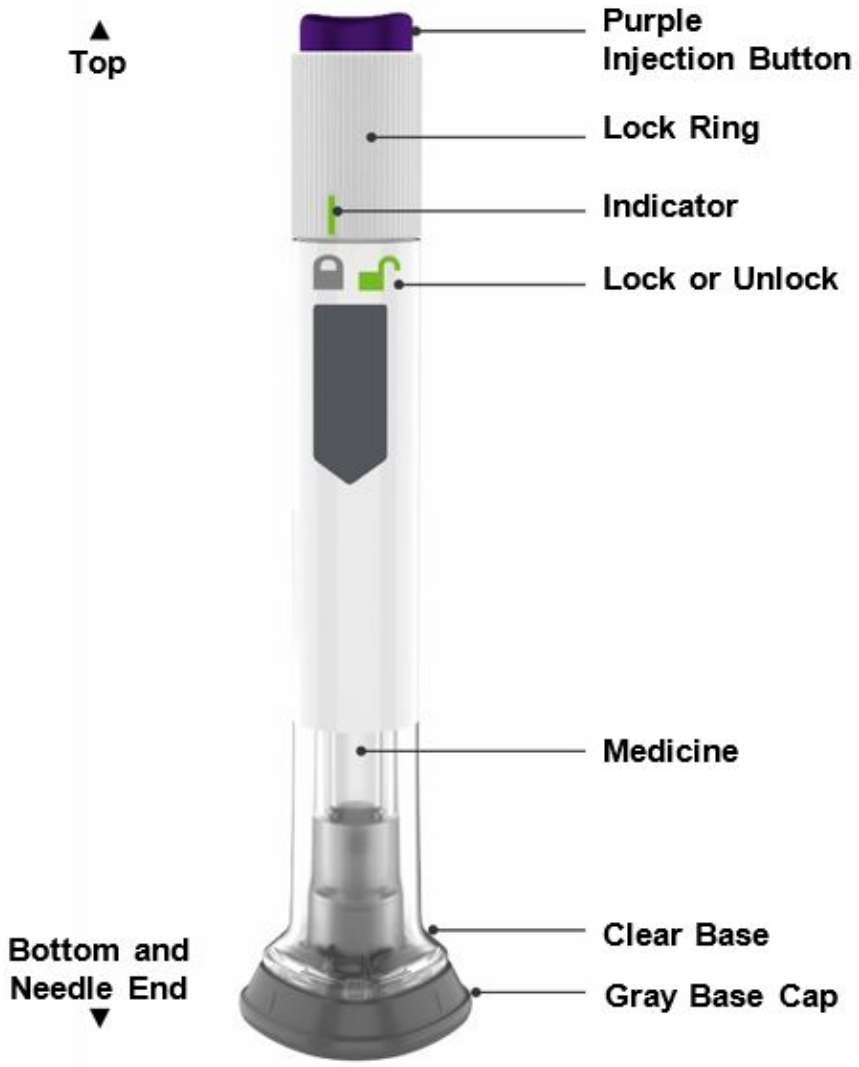
Important information you need to know before injecting ZEPBOUND

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

Talk to your healthcare provider about how to inject ZEPBOUND the right way.

- ZEPBOUND is a single-dose prefilled pen.
- ZEPBOUND is used 1 time each week.
- Inject under the skin (subcutaneously) only.
- You or another person can inject into your stomach (abdomen) or thigh.
- Another person can inject into the back of your upper arm.

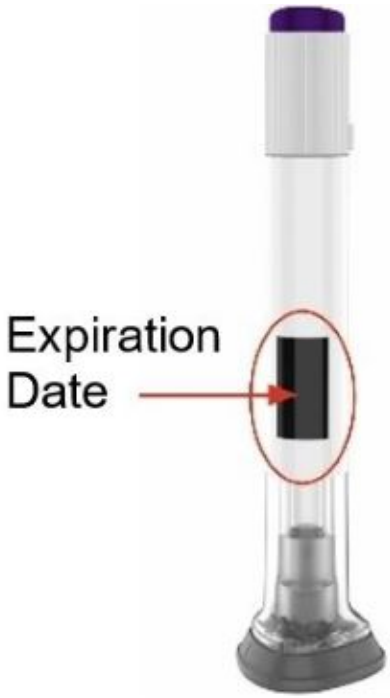
Guide to parts



Preparing to inject ZEPBOUND

Remove the pen from the refrigerator.
Leave the gray base cap on until you are ready to inject.

Check the pen label to make sure you have the right medicine and dose, and that it has not expired.
Inspect the pen to make sure that it is not damaged.



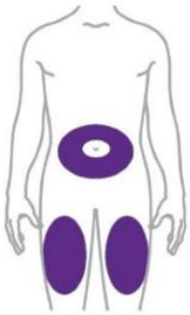
Make sure the medicine:

- is not frozen
- is not cloudy
- is colorless to slightly yellow
- does not have particles

Wash your hands.

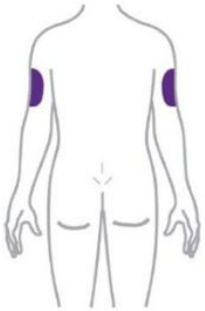
Step 1

Choose your injection site



Your healthcare provider can help you choose the injection site that is best for you.

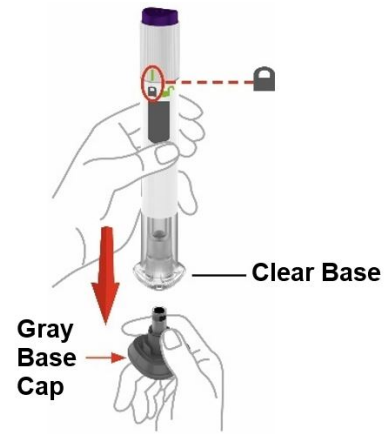
You or another person can inject the medicine in your stomach (abdomen) or thigh.



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.

Step 2

Pull off the gray base cap

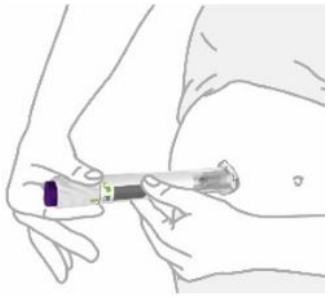


Make sure the pen is **locked**.
Do not unlock the pen until you place the clear base on your skin and are ready to inject.

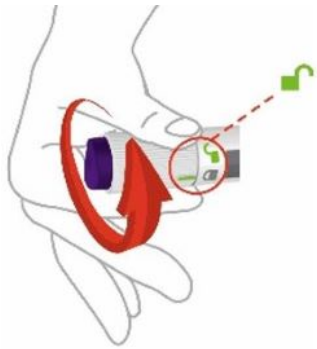
Pull the gray base cap straight off and throw it away in your household trash.
Do not put the gray base cap back on – this could damage the needle.
Do not touch the needle.

Step 3 **Place clear base on skin, then unlock**

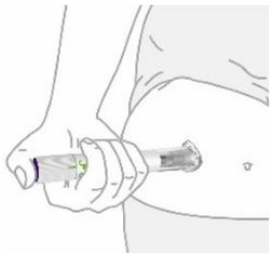
Place the clear base flat against your skin at the injection site.



Unlock by turning the lock ring.



Step 4 **Press and hold up to 10 seconds**



Press and hold the purple injection button for up to 10 seconds.
Listen for:

- First click = injection started
- Second click = injection completed

You will know your injection is complete when the gray plunger is

visible.

After your injection, place the used pen in a sharps container.
See **Disposing of your used pen.**

Disposing of your used pen

- Put your used pen in an FDA-cleared sharps disposal container right away after use. **Do not** throw away (dispose of) pens in your household trash.
- If you do not have an FDA-cleared sharps disposal container, you may use a household container that is:
  - made of a heavy-duty plastic,
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
  - upright and stable during use,
  - leak-resistant, and
  - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.
- **Do not** recycle your used sharps disposal container.

Storage and handling

- Store your pen in the refrigerator between 36°F to 46°F (2°C to 8°C).
- You may store your pen at room temperature up to 86°F (30°C) for up to 21 days. If you store the pen at room temperature, do not return the pen to the refrigerator.
- Discard the pen if not used within 21 days after removing from the refrigerator.
- **Do not** freeze your pen. If the pen has been frozen, throw the pen away and use a new pen.
- Store your pen in the original carton to protect your pen from light.
- The pen has glass parts. Handle it carefully. If you drop the pen on a hard surface, **do not** use it. Use a new pen for your injection.
- Keep your ZEPBOUND pen and all medicines out of the reach of children.

Commonly asked questions

What if I see air bubbles in my pen?

Air bubbles are normal.

What if my pen is not at room temperature?

It is not necessary to warm the pen to room temperature.

What if I unlock the pen and press the purple injection button before pulling

off the gray base cap?

Do not remove the gray base cap. Throw away the pen and get a new pen.

What if there is a drop of liquid on the tip of the needle when I remove the gray base cap?

A drop of liquid on the tip of the needle is normal. **Do not** touch the needle.

Do I need to hold the injection button down until the injection is complete?

This is not necessary, but it may help you keep the pen steady against your skin.

I heard more than 2 clicks during my injection—2 loud clicks and 1 soft one. Did I get my complete injection?

Some people may hear a soft click right before the second loud click. That is the normal operation of the pen. **Do not** remove the pen from your skin until you hear the second loud click.

I am not sure if my pen worked the right way.

Check to see if you have received your dose. Your dose was delivered the right way if the gray plunger is visible. Also, see **Step 4** of the instructions.
If you do not see the gray plunger, contact Lilly at 1-800-Lilly-Rx (1-800-545-5979) for further instructions. Until then, store your pen safely to avoid an accidental needle stick.

What if there is a drop of liquid or blood on my skin after my injection?

This is normal. Press a cotton ball or gauze over the injection site. **Do not** rub the injection site.

Other information

- If you have vision problems, **do not** use your pen without help from a person trained to use the ZEPBOUND pen.

Where to learn more

- If you have questions or problems with your ZEPBOUND pen, contact Lilly at 1-800-Lilly-Rx (1-800-545-5979) or call your healthcare provider.
- For more information about the ZEPBOUND pen, visit our website at www.zepbound.com.

Scan this code to launch www.zepbound.com

Marketed by:
Lilly USA, LLC
Indianapolis, IN 46285, USA

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This Instructions for Use has been approved by the U.S. Food and Drug Administration.
Revised: November 2023

ZEP-0002-PEN-IFU-20231109

PACKAGE LABEL - Zepbound™, 2.5 mg/0.5 mL, Carton, 4 Single-Dose Pens

NDC 0002-2506-80

Zepbound™

(tirzepatide) injection

2.5 mg/0.5 mL

4 x 2.5 mg/0.5 mL prefilled pens

Rx Only

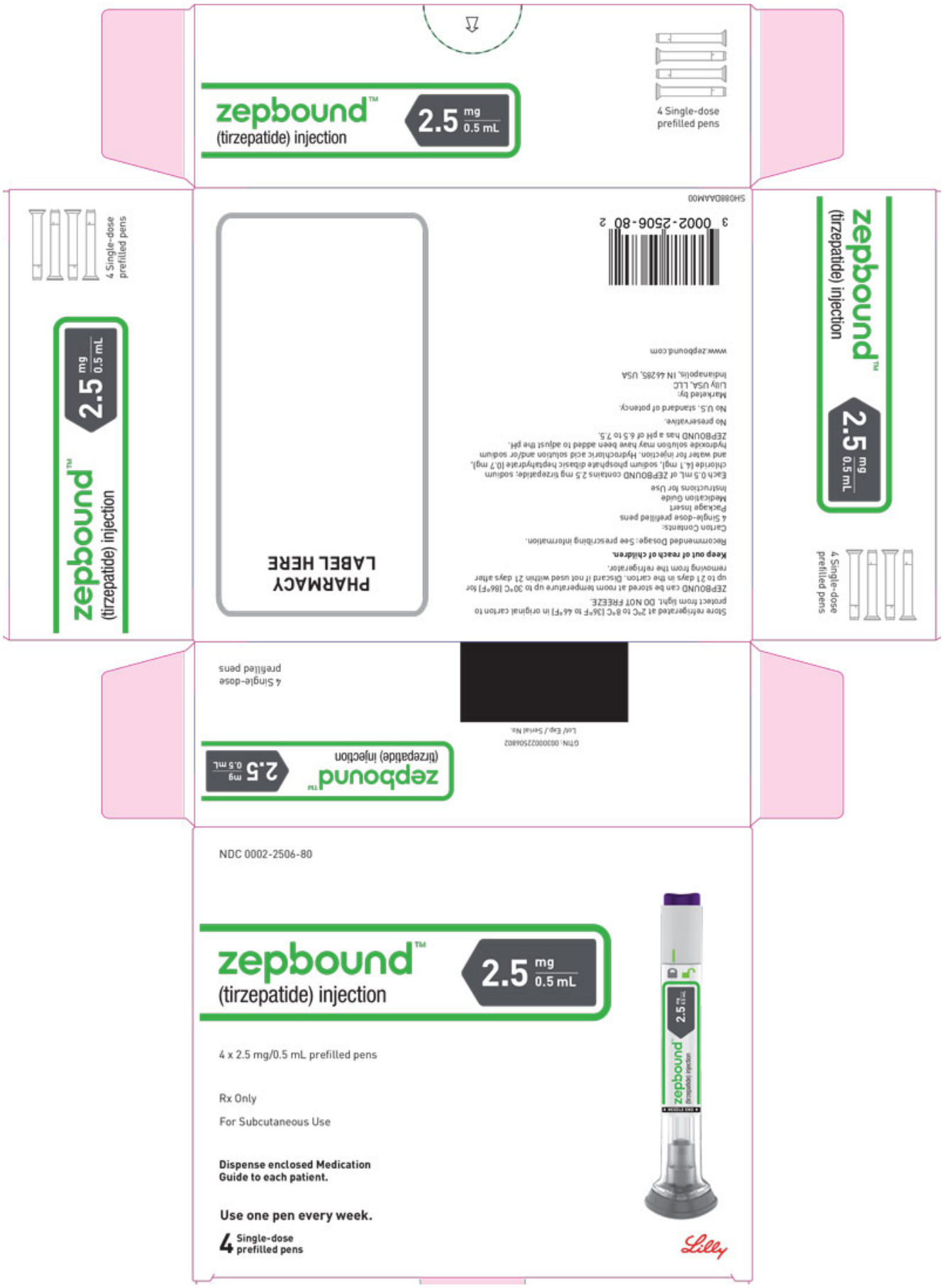
For Subcutaneous Use

Dispense enclosed Medication Guide to each patient.

Use one pen every week.

4 Single-dose prefilled pens

Lilly



PACKAGE LABEL - Zepbound™, 5 mg/0.5 mL, Carton, 4 Single-Dose Pens

NDC 0002-2495-80

Zepbound™

(tirzepatide) injection

5 mg/0.5 mL

4 x 5 mg/0.5 mL prefilled pens

Rx Only

For Subcutaneous Use

Dispense enclosed Medication Guide to each patient.

Use one pen every week.

4 Single-dose prefilled pens

Lilly

PACKAGE LABEL - Zepbound™, 7.5 mg/0.5 mL, Carton, 4 Single-Dose Pens

NDC 0002-2484-80

Zepbound™

(tirzepatide) injection

7.5 mg/0.5 mL

4 x 7.5 mg/0.5 mL prefilled pens

Rx Only

For Subcutaneous Use

Dispense enclosed Medication Guide to each patient.

Use one pen every week.

4 Single-dose prefilled pens

Lilly

PACKAGE LABEL - Zepbound™, 10 mg/0.5 mL, Carton, 4 Single-Dose Pens

NDC 0002-2471-80

Zepbound™

(tirzepatide) injection

10 mg/0.5 mL

4 x 10 mg/0.5 mL prefilled pens

Rx Only

For Subcutaneous Use

Dispense enclosed Medication Guide to each patient.

Use one pen every week.

4 Single-dose prefilled pens

Lilly

PACKAGE LABEL - Zepbound™, 12.5 mg/0.5 mL, Carton, 4 Single-Dose Pens

NDC 0002-2460-80

Zepbound™

(tirzepatide) injection

12.5 mg/0.5 mL

4 x 12.5 mg/0.5 mL prefilled pens

Rx Only

For Subcutaneous Use

Dispense enclosed Medication Guide to each patient.

Use one pen every week.

4 Single-dose prefilled pens

Lilly

PACKAGE LABEL - Zepbound™, 15 mg/0.5 mL, Carton, 4 Single-Dose Pens

NDC 0002-2457-80

Zepbound™

(tirzepatide) injection

15 mg/0.5 mL

4 x 15 mg/0.5 mL prefilled pens

Rx Only

For Subcutaneous Use

Dispense enclosed Medication Guide to each patient.

Use one pen every week.

4 Single-dose prefilled pens

Lilly

ZEPBOUND

tirzepatide injection, solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0002-2506
Route of Administration	SUBCUTANEOUS		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
tirzepatide (UNII: OYN3CCI6QE) (tirzepatide - UNII:OYN3CCI6QE)	tirzepatide	2.5 mg in 0.5 mL

Inactive Ingredients	
Ingredient Name	**Strength**
Sodium Phosphate, Dibasic, Heptahydrate (UNII: 70WT22SF4B)	0.7 mg in 0.5 mL
Sodium Chloride (UNII: 451W47IQ8X)	4.1 mg in 0.5 mL
Hydrochloric Acid (UNII: QTT17582CB)	
Sodium Hydroxide (UNII: 55X04QC32I)	
Water (UNII: 059QF0KO0R)	

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:0002-2506-80	4 in 1 CARTON	11/08/2023	
1	NDC:0002-2506-01	0.5 mL in 1 SYRINGE; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		
2	NDC:0002-2506-61	4 in 1 CARTON	11/08/2023	
2		0.5 mL in 1 SYRINGE; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA217806	11/08/2023	

ZEPBOUND

tirzepatide injection, solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0002-2495
Route of Administration	SUBCUTANEOUS		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
tirzepatide (UNII: OYN3CCI6QE) (tirzepatide - UNII:OYN3CCI6QE)	tirzepatide	5 mg in 0.5 mL

Inactive Ingredients

Ingredient Name	Strength
Sodium Phosphate, Dibasic, Heptahydrate (UNII: 70WT22SF4B)	0.7 mg in 0.5 mL
Sodium Chloride (UNII: 451W47IQ8X)	4.1 mg in 0.5 mL
Hydrochloric Acid (UNII: QTT17582CB)	
Sodium Hydroxide (UNII: 55X04QC32I)	
Water (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0002-2495-80	4 in 1 CARTON	11/08/2023	
1	NDC:0002-2495-01	0.5 mL in 1 SYRINGE; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA217806	11/08/2023	

ZEPBOUND

tirzepatide injection, solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0002-2484
Route of Administration	SUBCUTANEOUS		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
tirzepatide (UNII: OYN3CCI6QE) (tirzepatide - UNII:OYN3CCI6QE)	tirzepatide	7.5 mg in 0.5 mL

Inactive Ingredients

Ingredient Name	Strength
Sodium Phosphate, Dibasic, Heptahydrate (UNII: 70WT22SF4B)	0.7 mg in 0.5 mL
Sodium Chloride (UNII: 451W47IQ8X)	4.1 mg in 0.5 mL
Hydrochloric Acid (UNII: QTT17582CB)	
Sodium Hydroxide (UNII: 55X04QC32I)	
Water (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date

1	NDC:0002-2484-80	4 in 1 CARTON	11/08/2023	
1	NDC:0002-2484-01	0.5 mL in 1 SYRINGE; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA217806	11/08/2023	

ZEPBOUND

tirzepatide injection, solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0002-2471
Route of Administration	SUBCUTANEOUS		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
tirzepatide (UNII: OYN3CCI6QE) (tirzepatide - UNII:OYN3CCI6QE)	tirzepatide	10 mg in 0.5 mL

Inactive Ingredients

Ingredient Name	Strength
Sodium Phosphate, Dibasic, Heptahydrate (UNII: 70WT22SF4B)	0.7 mg in 0.5 mL
Sodium Chloride (UNII: 451W47IQ8X)	4.1 mg in 0.5 mL
Hydrochloric Acid (UNII: QTT17582CB)	
Sodium Hydroxide (UNII: 55X04QC32I)	
Water (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0002-2471-80	4 in 1 CARTON	11/08/2023	
1	NDC:0002-2471-01	0.5 mL in 1 SYRINGE; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA217806	11/08/2023	

ZEPBOUND

tirzepatide injection, solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0002-2460
Route of Administration	SUBCUTANEOUS		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
tirzepatide (UNII: OYN3CCI6QE) (tirzepatide - UNII:OYN3CCI6QE)	tirzepatide	12.5 mg in 0.5 mL

Inactive Ingredients

Ingredient Name	Strength
Sodium Phosphate, Dibasic, Heptahydrate (UNII: 70WT22SF4B)	0.7 mg in 0.5 mL
Sodium Chloride (UNII: 451W47IQ8X)	4.1 mg in 0.5 mL
Hydrochloric Acid (UNII: QTT17582CB)	
Sodium Hydroxide (UNII: 55X04QC32I)	
Water (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0002-2460-80	4 in 1 CARTON	11/08/2023	
1	NDC:0002-2460-01	0.5 mL in 1 SYRINGE; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA217806	11/08/2023	

ZEPBOUND

tirzepatide injection, solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0002-2457
Route of Administration	SUBCUTANEOUS		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
tirzepatide (UNII: OYN3CCI6QE) (tirzepatide - UNII:OYN3CCI6QE)	tirzepatide	15 mg in 0.5 mL

Inactive Ingredients

Ingredient Name	Strength
Sodium Phosphate, Dibasic, Heptahydrate (UNII: 70WT22SF4B)	0.7 mg in 0.5 mL
Sodium Chloride (UNII: 451W47IQ8X)	4.1 mg in 0.5 mL
Hydrochloric Acid (UNII: QTT17582CB)	
Sodium Hydroxide (UNII: 55X04QC32I)	
Water (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0002-2457-80	4 in 1 CARTON	11/08/2023	
1	NDC:0002-2457-01	0.5 mL in 1 SYRINGE; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA217806	11/08/2023	

Labeler - Eli Lilly and Company (006421325)

Revised: 11/2023 Eli Lilly and Company