Tirzepatide (ZEPBOUND®) Monograph

PHARMACY & THERAPEUTICS COMMITTEE
DRUG EVALUATION – SUMMARY PAGE

Drug Name: tirzepatide (ZEPBOUND®)
Manufacturer: Eli Lilly
Therapeutic Class: GLP-1/GIP agonist
Similar Agents: liraglutide (SAXENDA®), semaglutide (WEGOVY®)
REMS: No
Boxed Warning: Yes. Risk of thyroid C-cell tumors. In rats, tirzepatide causes 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. 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.
Date FDA Approved: November 8th, 2023

Executive Summary:

Obesity is a chronic condition that impacts a patient's physical, mental, and financial well-being. Rates of obesity are rising in the United States, making it important to find effective methods of treating and maintaining weight loss. Therapy focuses heavily on diet and exercise to control weight loss, but there is another option for when this is insufficient: pharmacotherapy. There are numerous agents available orally with FDA-approval for weight loss. Many of these have questions surrounding safety and long-term efficacy for weight loss maintenance. Enter GLP-1 agonists: injectable therapies with clinically proven efficacy for weight loss. These medications are now compared with ZEPBOUND®, a combination GLP-1/GIP agonist approved on 11/08/2023 for the same indication.

When compared with WEGOVY®'s trial endpoints, ZEPBOUND®'s trial is associated with higher rates of efficacy for total weight reduction, longer maintenance of weight loss, comparable safety profiles, and lower costs. There are limitations to these trials, such as smaller sample size (670 versus 1971 total participants), that may prevent firm conclusions from being drawn. However, the design of the trials plus cost-data from ICER indicates that ZEPBOUND® may be an excellent new alternative with a unique mechanism of action to maintain weight loss over longer periods of time.

Recommendations:

When all three GLP-1 agonists are available, ZEPBOUND® could be most beneficial for highest rates of initial weight loss and maintenance over time. Patients should be screened for conditions that would be contraindications for this medication, such as MTC. Important counseling points include gastrointestinal side effects, titration schedule, and weekly subcutaneous injection technique. It may be beneficial that the AWP for ZEPBOUND® is cheaper than GLP-1 agonist alternatives, including a copay card for a minimum of $25.

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Table 1: Products in Class

Generic	Brand	Manufacturer	FDA Approval
Tirzepatide	ZEPBOUND®	Eli Lily	11/08/2023
Liraglutide	SAXENDA®	Novo Nordisk	12/23/2014
Semaglutide	WEGOVY®	Novo Nordisk	06/04/2021

INDICATIONS:

Table 2: FDA Labeled Indications:

Drug	Indication(s)			
Tirzepatide/ZEPBOUND®	Chronic weight loss in patients:	30 kg/m2 or greater (obesity) OR	27 kg/m2 or greater (overweight) with a weight-related comorbid condition: Hypertension, dyslipidemia, type 2 diabetes, obstructive sleep apnea, cardiovascular disease	Limits of use: Coadministration with other tirzepatide-containing products or GLP-1 receptor agonist, other weight management products, or patients with a history of pancreatitis.
Liraglutide/SAXENDA®	Chronic weight loss in patients:	30 kg/m2 or greater (obesity) OR	27 kg/m2 or greater (overweight) with a weight-related comorbid condition: Hypertension, type 2 diabetes, or dyslipidemia	Limits of use: Coadministration with other liraglutide-containing products or other GLP-1 receptor agonists, other weight management products, or patients with a history of pancreatitis.
Semaglutide/WEGOVY®	Chronic weight loss in patients:	30 kg/m2 or greater (obesity) OR	27 kg/m2 or greater (overweight) with a weight-related comorbid condition: Hypertension, type 2 diabetes, or dyslipidemia	Limits of use: Coadministration with other semaglutide-containing products or other GLP-1 receptor agonists, other weight management products, or patients with a history of pancreatitis.

BACKGROUND[3]:

Obesity is a chronic disease defined by excess accumulation of body fat. This disease state places those affected at high risk for comorbidities like diabetes, hypertension, dyslipidemia, cancer, heart disease, and death. Beyond physical impact, those with chronic obesity manage a psychological impact too. Social stigma, self image, and much more affect mental health of those affected by obesity.

Assessing obesity involves a number of factors. Firstly, body mass index (BMI) is the most common measure due to its easy ability to be measured and its correlation with body fat. Roughly 69 percent of United States adults are either overweight or obese, with 36 percent being classified as "obese". Among children and adolescents, obesity rates are roughly 19.7 percent. It is also important to note that obesity prevalence rates are variable among racial/ethnic groups, with higher rates for Hispanic adults and highest among African American women. These high rates of disease occurrence cost a staggering $173 billion yearly. This financial impact is a reflection of not only direct medical costs but also lower wages, greater work loss, and disability.

Given that obesity is a multifactorial disease state, the first line therapy involves prevention and nonpharmacological intervention. This can include diet, exercise, and assessing barriers to success through behavioral therapy. Studies support associations between weight loss and mortality/morbidity reduction, meaning that it is beneficial to intervene with pharmacological therapy if nonpharmacological options do not achieve goals.

Examples of oral pharmacotherapy include phentermine, orlistat, topiramate, and bupropion/naltrexone. There are also injectable therapies, like semaglutide and liraglutide, that operate as glucagon-like peptide-1 (GLP-1) receptor agonists to reduce appetite and lose weight. These medications are very similar to tirzepatide, a GLP-1 agonist and glucose-dependent insulinotropic polypeptide (GIP) receptor agonist, which is the subject of this monograph. These medications have evidence for greater weight loss than oral medications, generating interest for patients and providers despite being an injectable therapy and expensive price.

CLINICAL PHARMACOLOGY:

Tirzepatide is a GIP and GLP-1 receptor agonist. It binds selectively to and activates both the GIP and GLP-1 receptors, which are the targets for GIP and GLP-1 native in the body. It is an amino acid sequence, including a C20 fatty diacid moiety, that enables albumin binding and prolongs its half-life. GLP-1 typically helps regulate physiological appetite and food intake, with studies noting that GIP may further contribute to food intake regulation.

PHARMACOKINETICS[4]:

Table 3,

Parameters	tirzepatide
Dose (mg/day)	2.5 mg weekly initially, titrating up to 15 mg once weekly
Bioavailability	80%
Absorption	Subcutaneous through the abdomen, thigh, or upper arm
Time to peak concentration	Median 24 hours (8 to 72 hours)
Plasma binding	99%
Volume of distribution	9.7 L
Effect of food	Food does not affect absorption
Active metabolite (s)	Tirzepatide
Protein binding	99%
Half-life	5 days
Excretion	Urine and feces as metabolites
Metabolism	Proteolytic cleavage of the peptide backbone, beta-oxidation of the C20 fatty diacid moiety, and amide hydrolysis.

CLINICAL STUDIES:

COMPARATIVE EFFICACY TRIALS: None currently published, but SURMOUNT-5 is an ongoing clinical trial comparing ZEPBOUND and WEGOVY. It is expected to complete in late 2024.

PIVOTAL RANDOMIZED CONTROLLED TRIALS: ZEPBOUND®

Aronne LJ, Sattar N, Horn DB, et al. Continued Treatment With Tirzepatide for Maintenance of Weight Reduction in Adults With Obesity: The SURMOUNT-4 Randomized Clinical Trial. JAMA. 2024;331(1):38–48. doi:10.1001/jama.2023.24945[1]

Design	Methods	Results
December 11th, 2023 **Duration of Study:** 88 weeks **Study Size:** 670 **Purpose:** To assess the effect of tirzepatide, with diet and physical activity, on the maintenance of weight reduction.	**Inclusion Criteria:** • Body mass index (BMI) ≥ 30 • Body mass index (BMI) ≥ 27 and at least 1 weight related complication (hypertension, dyslipidemia, obstructive sleep apnea, or cardiovascular disease) • 18 years of age or older **Exclusion Criteria:** • Diabetes • Prior or planned surgical treatment for obesity • Treatment with a medication that promotes weight loss within 3 months prior to enrollment **Primary Endpoint:** • Percent change in body weight from randomization (week 36) to week 88 **Secondary Endpoints:** • Participants at week 88 maintaining at least 80% of body weight loss during 36-week open label period • Time during 52-week double-blind treatment period to first occurrence of participants returning to greater than 95% baseline body weight for those who lost at least 5% during double blind period • Change in absolute body weight and waist circumference • Proportion of participants achieving weight reduction thresholds of at least 5%, 10%, 15%, 20%, and 25% • Change in relevant lab values (see definitions) • Safety assessments related to treatment-emergent adverse events, serious adverse events, and early discontinuation of study drug **Definitions:** • **Relevant lab values:** glycemic parameters, fasting insulin, lipids, blood pressure, and patient-reported outcomes measured by the SF-36 v2 and IWQOL-Lite-CT **Treatment Groups:** **1.** Tirzepatide treated group **2.** Placebo treated group	**Primary Endpoints:** • Mean percent change in weight was -5.5% with tirzepatide versus +14% with placebo (difference -19.4%) **Secondary Endpoints:** • **% at week 88 maintaining 80% body weight loss:** 89.5% versus 16.6% of placebo • **Time to event:** tirzepatide redued risk of returning to 95% baseline body weight (hazard ratio 0.02) • **Change in absolute body weight and waist circumference:** -4.7 and -4.3% respectively for tirzepatide compared with 11.1 and 7.8% respectively for placebo • **Participants achieving body weight reduction:** ○ ≥5%: 326 (97.3%, tirzepatide), 235 (70.3%, placebo) ○ ≥10%: 309 (92.1%, tirzepatide), 155 (46.2%, placebo) ○ ≥15%: 282 (84. 1%, tirzepatide), 87 (25.9%, placebo) ○ ≥20%: 233 (69.5%, tirzepatide), 42 (12.6%, placebo) ○ ≥25%: 183 (54.5%, tirzepatide), 17 (5%, placebo) • **Changes in body weight from week 36-64:** -5.4% (tirzepatide) and +10% (placebo) **Adverse Effects:** • **Participants with ≥ adverse event:** 202 (60.3%, tirzepatide) and 187 (55.8%, placebo) ○ ≥5%: COVID-19 (47, 14%), diarrhea (36, 10.7%), nausea (27, 8.1%), vomiting (19, 5.7%), upper respiratory tract infection (8, 2.4%) • **Serious adverse events:** 10 for both • **Events leading to discontinuation:** 6 total for tirzepatide, including diarrhea (2), cardiac failure congestive (1), abdominal pain (1), vomiting (1), increased pancreatic enzymes (1) • **Special Events:** ○ Malignancies (3), adjudicated major adverse cardiovascular events (3), severe/serious gastrointestinal events (6), hypoglycemia <54 mg/dL (2) **Limitations:** No dose adjustments were allowed after randomization, no evaluation of effects of intensive behavioral therapy for maintenance of body weight reduction. Toleration of initial treatment with 10 or 15 mg tirzepatide may represent a subgroup of the general population. **Conclusion:** Adults with obesity or overweight who achieve meaningful weight reduction during a 36-week tirzepatide lead-in treatment period, those who continued treatment with a maximum tolerated dose tirzepatide for 52 further weeks demonstrated superior weight maintenance and reduction compared to placebo.

Placebo Controlled Trial: WEGOVY®

Wilding JPH, Batterham RL, Calanna S, et al. Once-weekly semaglutide in adults with overweight or obesity. New England Journal of Medicine. 2021;384(11):989-1002. doi:10.1056/nejmoa2032183[2]

Design	Methods	Results

March 18th, 2021
 	
Duration of Study:
68 weeks
 	
Study Size: 1961
 	
Purpose:
To assess the effect of semaglutide 2.4mg, with diet and physical activity, on the maintenance of weight reduction.
	Inclusion Criteria:
	• Body Mass Index (BMI) ≥ 30
	• Body Mass Index (BMI) ≥ 27 and at least 1 weight-related comorbidity (hypertension, dyslipidemia, obstructive sleep apnea, or cardiovascular disease)
	• 18 years of age or older
	Exclusion Criteria:
	• Diabetes
	• Glycated hemoglobin level of 48 mmol per mol (6.5%) or greater
	• History of chronic pancreatitis
	• Acute pancreatitis within 180 days before enrollment
	• Previous surgical obesity treatment
	• Use of antiobesity medication within 90 days before enrollment
	Primary Endpoint:
	• Percentage change in body weight from baseline to week 68
	• Achievement of 5% body weight reduction or more from baseline to week 68
	Secondary Endpoints:
	• Achievement of body weight reduction 10% and 15% or more by week 68
	• Waist circumference change from baseline
	• Systolic blood pressure
	• Physical functioning score on the SF-36 and IWQOL-Lite-CT
	• Body composition (total fat, lean body mass, and visceral fat)
	Safety Assessments:
	• Number of adverse events during the on-treatment period
	• Serious adverse events occurring between baseline and week 75
	• Independent external event adjudication committee reviewed selected adverse events and deaths (cardiovascular and acute pancreatitis)
	Treatment Groups:
	1. Semaglutide group
	2. Placebo group
		Primary Endpoints:
		• Percentage change in body weight from baseline to week 68
		  ○ -14.9% (semaglutide) versus -2.4% (placebo)
		• Achievement of 5% body weight reduction or more from baseline to week 68
		  ○ 1047 participants (86.4%, semaglutide) versus 182 (31.5%, placebo)
		Secondary Endpoints:
		• Achievement of body weight reduction 10% and 15% or more by week 68
		  ○ 10%: 838 (69.1%, semaglutide) versus 69 (12%, placebo)
		  ○ 15%: 612 (50.5%, semaglutide) versus 28 (4.9%, placebo)
		• Waist circumference change from baseline
		  ○ -13.54cm (semaglutide) versus -4.13 (placebo)
		• Systolic blood pressure
		  ○ -6.16mmHg (semaglutide) versus -1.06 (placebo)
		• Questionnare Scores:
		  ○ SF-36: 2.21 (semaglutide) versus 0.41 (placebo)
		  ○ IWQOL-Lite-CT: 14.67 (semaglutide) versus 5.25 (placebo)
		Safety Assessments:
		• Number of adverse events during the on-treatment period: 1171 (89.7%, semaglutide)
		  ○ Types of Events (≥10%): Nausea (577, 44.2%), diarrhea (412, 31.5%), vomiting (324, 24.8%), constipation (306, 23.4%), nasopharyngitis (281, 21.5%), headache (198, 15.2%), dyspepsia (135, 10.3%), abdominal pain (130, 10%), upper respiratory tract infection (114, 8.7%)
		• Serious adverse events occurring between baseline and week 75: 128 (9.8%, semaglutide)
		  ○ Adverse events leading to discontinuation of drug or placebo: 92 (7%. Semaglutide)
		  ○ Fatal events: 1 (0.1%)
		Limitations:
		• Short duration of the trial with no long-term follow-up
		• Exclusion of persons with type 2 diabetes, limited demographics
		• Ability to extrapolate motivated subjects' results to general populace
		Conclusion: In participants classified as overweight or obese, 2.4 mg of semaglutide once weekly (plus lifestyle intervention) was associated with clinically relevant reduction in body weight over a 68 week timeframe.

LEGEND: RCT=Randomized controlled trial, DB=double-blind

GUIDELINES (IF ANY)[5]: Information is not detailed in any current guidelines. Last guideline revisions were in 2013 for AHA/ACC/TOS Management of Overweight and Obesity in Adults.

CONTRAINDICATIONS/WARNINGS[4]: Serious hypersensitivity to tirzepatide or any component of the formulation; serious hypersensitivity reactions including anaphylaxis and angioedema have been reported; a personal or family history of medullary thyroid carcinoma or in patients with multiple endocrine neoplasia syndrome type 2 (MEN 2).

BOXED WARNING(S)[4]: Yes. Risk of thyroid C-cell tumors. In rats, tirzepatide causes 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. 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.

REMS[4]: No REMS program

ISMP ALERTS[4]: No ISMP alerts

PRECAUTIONS[4]:

Precaution/Warning	Description
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.
Acute Kidney Injury	Monitor renal function in patients reporting adverse reactions (like vomiting) than can lead to volume depletion.
Acute Gallbladder Disease	Has been reported in clinical trials. If cholecystitis is suspected, gallbladder studies and clinical follow up are indicated.
Acute Pancreatitis	Has been reported in clinical trials. Discontinue promptly if pancreatitis is suspected. Do not restart if pancreatitis is confirmed.
Hypersensitivity Reactions	Serious hypersensitivity reactions have been reported postmarketing with tirzepatide. If suspected, advise patients to promptly seek medical attention and discontinue ZEPBOUND®.
Hypoglycemia	Concomitant use with an insulin secretagogue or insulin may increase risk of hypoglycemia. Reducing dose of these medications may be necessary. Inform patients of risk and signs/symptoms.
Diabetic Retinopathy	Has not been studied in patients with non-proliferative diabetic retinopathy requiring acute therapy, proliferative diabetic retinopathy, or diabetic macular edema. Monitor for progression.
Suicidal Behavior and Ideation	Monitor for depression or suicidal thoughts. Discontinue ZEPBOUND® if symptoms develop.

ADVERSE EFFECTS[4]:

Table:

Adverse Effect	Description
Gastrointestinal	Constipation (6-17%), decreased appetite (5-11%), diarrhea (12-23%), nausea (12-29%), vomiting (5-13%)
Immunologic	Antibody development (51-65%, neutralizing 2-3%)
Cardiovascular	Hypotension (1-2%), sinus tachycardia (5-10%)
Dermatologic	Alopecia (4-5%)
Hypersensitivity	Reaction (2-5%)
Local	Injection-site reaction (3-8%)
Nervous System	Dizziness (4-5%), fatigue (5-7%)

DRUG INTERACTIONS[4]:

Drug Class	Description
GLP-1 Agonists (X)	Tirzeptide may enhance the adverse/toxic effect of GLP-1 agonists
Sulfonylureas (D)	Tirzepatide may enhance the hypoglycemic effect of solfonylureas
Insulin (D)	Tirzepatide may enhance the hypoglycemic effect of insulins
Oral Hormonal Contraceptives (D)	Tirzepatide may decrease the serum concentration of hormonal contraceptives

PRODUCT AVAILABILITY[4]: Available in a subcutaneous solution injection form only. Subject to backorder.

DOSING:

Trade Name	Strength (s)	Usual Starting Dose	Maximum dosage	Special Instructions
ZEPBOUND® **(tirzepatide)**	2.5, 5, 7.5, 10, 12.5, 15 mg/0.5mL	2.5mg	15mg	2.5 mg weekly for 4 weeks, then increase in 2.5mg/week increments every 4 weeks
WEGOVY® **(semaglutide)**	0.25, 0.5, 1, 1.7, 2.4 mg/0.5mL	0.25mg	2.4mg	0.25 mg weekly for 4 weeks, then increase in designated increments every 4 weeks

COST:

Trade Name	AWP (Redbook Cost)	Cost/month supply
ZEPBOUND®	$1271.84	$1271.84
WEGOVY®	$1618.82	$1618.82
SAXENDA®	$1618.82	$1618.82

CONCLUSION(S):

Based on current studies and cost available, ZEPBOUND® could be associated with higher rates of weight loss and lower costs compared with GLP-1 agonists with the same FDA-label approvals. Though the Institute for Clinical and Economic Review indicates that GLP-1 agonists like semaglutide exceed cost-effectiveness thresholds, there is evidence to suggest that ZEPBOUND® may benefit costs over the long term. The attached clinical trial indicated sustained weight loss over a period of 88 weeks, surpassing data from both oral and alternative GLP-1 agonist therapies. Sustained weight loss is important, as chronic obesity is associated with $92,235 greater per person alongside worse quality of life. Additionally, ZEPBOUND® reached 15% weight loss at higher rates than WEGOVY®, showing the potential for higher efficacy rates. It is also important to note safety. ZEPBOUND® shared several adverse events with WEGOVY®, like diarrhea, but clinical trials showed lower rates when comparing the two drugs (10.7% versus 31.5% respectively). They also share important contraindications/precautions, such as pancreatitis and thyroid C-carcinoma. When higher associated rates of efficacy and safety are combined with lower AWP pricing, ZEPBOUND® becomes an appealing new product in comparison to other GLP-1 agonists available for use in the same population for chronic weight management.

RECOMMENDATION:

When ZEPBOUND®, WEGOVY®, and SAXENDA® are all available, ZEPBOUND® may be the cheapest and associated with the highest safety and efficacy rates in a short period. Additionally, it may be the best product for long-term continuation, as its clinical trials measured the longest duration of the available weight loss products. This product's clinical trials excluded patients planning for bariatric surgery and those diagnosed with diabetes. Therefore, ZEPBOUND® should not be started in these populations or patients with contraindications/precautions like pancreatitis or thyroid C-cell carcinoma. Insurance preference should be considered as well when identifying the best injectable weight-loss therapy.

REFERENCES

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6. ZEPBOUND, SAXENDA, WEGOVY [Micromedex Redbook]. Micromedex