

# Tirzepatide (ZEPBOUND) Subcutaneous Injection for Chronic Weight Management National Drug Monograph December 2023

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

*The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.*

## FDA Approval Information<sup>1</sup>

### Description/Mechanism of Action

- Tirzepatide is a glucose-dependent insulintropic polypeptide (GIP) receptor and glucagon-like peptide-1 (GLP-1) receptor agonist.

### Indication(s) Under Review in This Document

- Tirzepatide (ZEPBOUND) injection 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<sup>2</sup> or greater (obesity) or
  - 27 kg/m<sup>2</sup> or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, type 2 diabetes mellitus (DM), or dyslipidemia)

### Dosage Form(s) Under Review

- Tirzepatide (ZEPBOUND) injection, is available as a pre-filled, single-dose pen for injection that delivers doses of 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.
  - Tirzepatide is administered subcutaneously (SC), once weekly
  - Initial dose is 2.5 mg SC once weekly
  - The weekly dose should be increased by 2.5 mg at 4 week intervals
  - Maintenance doses are 5 mg, 10 mg, and 15 mg SC once weekly.
  - Maximum dose is 15 mg SC once weekly

## Clinical Evidence Summary for Weight Management<sup>2-5</sup>

### Efficacy Considerations

- **SURMOUNT-1** was a randomized, double-blind, Phase 3 multicenter trial evaluating tirzepatide for the management of patients with overweight or obesity. Inclusion criteria were patients with a body mass index (BMI) of  $\geq 30$  kg/m<sup>2</sup>, or  $\geq 27$  kg/m<sup>2</sup> with at least one weight-related coexisting condition (i.e., hypertension, dyslipidemia, obstructive sleep apnea, or cardiovascular [CV] disease), who had one or more unsuccessful dietary efforts to lose weight. Main exclusion criteria were DM or HbA1c  $\geq 6.5\%$ , acute or chronic pancreatitis, and uncontrolled thyroid disease. Additional inclusion and exclusion criteria are noted in the clinical trial publication.
- Patients were randomized to tirzepatide at doses of 5 mg, 10 mg, 15 mg, or placebo. Patients receiving tirzepatide were started on a dose of 2.5 mg SC once weekly and titrated every 4 weeks until the respective study dose was achieved (i.e., at 20 weeks for the 15 mg dose). Trial duration was 72 weeks. All patients received lifestyle intervention that consisted of counseling on a balanced, healthful, reduced-calorie diet and physical activity of at least 150 minutes per week.

- The coprimary endpoints were the percentage change in body weight from baseline to week 72, and the percent of patients who achieved a reduction of  $\geq 5\%$  body weight at week 72. Selected key secondary endpoints including weight reduction of  $\geq 10\%$ ,  $\geq 15\%$ , and  $\geq 20\%$  are also included in Table 1 below.

**Table 1: Results of Coprimary Endpoints and Selected Secondary Endpoints (SURMOUNT-1)<sup>2</sup>**

| Endpoints <sup>a</sup>         | Tirzepatide 5 mg<br>(N=630)                     | Tirzepatide 10 mg<br>(N=636)                    | Tirzepatide 15 mg<br>(N=630)                    | Placebo<br>(N=643)     |
|--------------------------------|---|---|---|------------------------|
| % change in body weight        | -15.0<br>(-15.9 to -14.2)<br>-11.9 <sup>b</sup> | -19.5<br>(-20.4 to -18.5)<br>-16.4 <sup>b</sup> | -20.9<br>(-21.8 to -19.9)<br>-17.8 <sup>b</sup> | -3.1<br>(-4.3 to -1.9) |
| % with $\geq 5\%$ weight loss  | 85.1<br>(81.6 to 88.6)                          | 88.9<br>(85.9 to 91.9)                          | 90.9<br>(88.0 to 93.8)                          | 34.5<br>(29.8 to 39.2) |
| % with $\geq 10\%$ weight loss | 68.5<br>(64.5 to 72.5)                          | 78.1<br>(74.4 to 81.7)                          | 83.5<br>(80.0 to 86.9)                          | 18.8<br>(14.9 to 22.7) |
| % with $\geq 15\%$ weight loss | 48.0<br>(43.9 to 52.1)                          | 66.6<br>(62.6 to 70.6)                          | 70.6<br>(66.7 to 74.5)                          | 8.8<br>(5.9 to 11.7)   |
| % with $\geq 20\%$ weight loss | 30.0<br>(26.4 to 33.6)                          | 50.1<br>(46.0 to 54.2)                          | 56.7<br>(52.6 to 60.8)                          | 3.1<br>(1.1 to 5.1)    |

<sup>a</sup> compared to baseline

<sup>b</sup> difference vs. placebo

- Treatment with tirzepatide 5 mg, 10 mg, or 15 mg resulted in a significant weight reduction compared to placebo, with significantly more patients experiencing weight loss of  $\geq 5\%$ ,  $\geq 10\%$ , and  $\geq 20\%$  ( $P < 0.001$  for all primary endpoint treatment dose comparisons vs. placebo). Improvements were also seen in additional secondary endpoints of waist circumference, lipids, blood pressure, and fasting insulin. It was also noted that 95.3% of patients with pre-diabetes at baseline and in the tirzepatide treatment groups had reverted to normoglycemia compared to 61.9% of patients in the placebo group. The mean change in weight with tirzepatide was -16.1 kg (5 mg), -22.2 kg (10 mg), and -23.6 kg (15 mg) compared to -2.4 kg with placebo.
- Patients had a mean BMI of 38 kg/m<sup>2</sup> at baseline. Patient comorbidities at screening included: 32.3% hypertension, 29.8% dyslipidemia, 16.6% with anxiety or depression, 12.8% osteoarthritis, 10.5% asthma or chronic obstructive pulmonary disease, 7.8% obstructive sleep apnea, 7.1% nonalcoholic fatty liver disease, 5.4% gout, 3.1% atherosclerotic cardiovascular disease, and 2.2% polycystic ovary syndrome.
- SURMOUNT-2** was a randomized, double-blind, Phase 3 multicenter trial evaluating tirzepatide for the management of patients with overweight or obesity and type 2 DM. Inclusion criteria were patients with a BMI of  $\geq 27$  kg/m<sup>2</sup> and diagnosis of type 2 DM, with a HbA1c of 7 to 10% on stable therapy. Selected exclusion criteria were type 1 DM, acute or chronic pancreatitis, any lifetime history of suicide attempt. Additional inclusion and exclusion criteria are noted in the clinical trial publication.
- Patients were randomized to tirzepatide at doses of 10 mg, 15 mg, or placebo. Patients receiving tirzepatide were started on a dose of 2.5 mg SC once weekly and titrated every 4 weeks until the respective study dose was achieved (i.e., at 12 weeks for the 10 mg dose, 20 weeks for the 15 mg dose). Trial duration was 72 weeks. All patients received lifestyle intervention that consisted of counseling on a balanced, healthful, reduced-calorie diet and physical activity of at least 150 minutes per week.
- The coprimary endpoints were the percentage change in body weight from baseline to week 72, and the percent of patients who achieved a reduction of  $\geq 5\%$  body weight at week 72. Selected key secondary endpoints including weight reduction of  $\geq 10\%$ ,  $\geq 15\%$ , and  $\geq 20\%$ , as well as change from baseline HbA1c are also included in Table 2 below.

**Table 2: Results of Coprimary Endpoints and Selected Secondary Endpoints (SURMOUNT-2)<sup>3</sup>**

| Endpoints <sup>a</sup>    | Tirzepatide 10 mg<br>(N=312)                               | Tirzepatide 15 mg<br>(N=311)                                 | Placebo<br>(N=315) |
|---------------------------|--|--|--------------------|
| % change in body weight   | -12.8 (SE 0.6)<br>-9.6 (95% CI -11.1 to -8.1) <sup>b</sup> | -14.7 (SE 0.5)<br>-11.6 (95% CI -13.0 to -10.1) <sup>b</sup> | -3.2 (SE 0.5)      |
| % with >= 5% weight loss  | 79%<br>OR 8.3 (5.6 to 12.3) <sup>b</sup>                   | 83%<br>OR 10.5 (6.8 to 16.1) <sup>b</sup>                    | 32%                |
| % with >= 10% weight loss | 61%<br>OR 16.1 (9.9 to 26.1) <sup>b</sup>                  | 65%<br>OR 19.4 (11.9 to 31.7) <sup>b</sup>                   | 9%                 |
| % with >= 15% weight loss | 40%<br>OR 25.2 (12.2 to 52.1) <sup>b</sup>                 | 48%<br>OR 36.1 (17.5 to 74.5) <sup>b</sup>                   | 3%                 |
| % with >= 20% weight loss | 22%<br>OR 25.6 (8.7 to 75.4) <sup>b</sup>                  | 31%<br>OR 42.2 (14.4 to 123.5) <sup>b</sup>                  | 1%                 |
| Change in % HbA1c         | -2.07 (SE 0.06)<br>ETD -1.55 (-1.74 to -1.37) <sup>b</sup> | -2.08 (SE 0.07)<br>ETD -1.57 (-1.76 to -1.37) <sup>b</sup>   | -0.51 (SE 0.07)    |

CI=confidence interval; ETD=estimated treatment difference; OR=odds ratio; SE=standard error

<sup>a</sup> compared to baseline

<sup>b</sup> difference vs. placebo; p<0.0001

- Treatment with tirzepatide 10 mg or 15 mg resulted in a significant difference in the coprimary endpoints of weight reduction compared to placebo and patients experiencing weight loss of >= 5%, as well as the secondary endpoints of >= 10% and >= 20% weight reduction. Improvements with tirzepatide treatment at the two doses compared to placebo were also seen in the secondary endpoints of change from baseline in HbA1c, fasting glucose, and fasting insulin. Pooled tirzepatide treatment results demonstrated a reduction in blood pressure and lipids compared to placebo. The mean change in weight with tirzepatide was -12.9 kg (10 mg) and -14.8 kg (15 mg) compared to -3.2 kg with placebo.
- Patients had a mean BMI of 36 kg/m<sup>2</sup> at baseline. Patient comorbidities at randomization included: 66% hypertension, 61% dyslipidemia, 17% nonalcoholic fatty liver disease, 15% osteoarthritis, 12% with anxiety or depression, 10% atherosclerotic cardiovascular disease, 8% asthma or chronic obstructive pulmonary disease, 8% obstructive sleep apnea, 6% gout, and 1% polycystic ovary syndrome.
- **SURMOUNT-3** evaluated tirzepatide for the management of overweight or obesity (BMI >= 30 kg/m<sup>2</sup>, or >= 27 kg/m<sup>2</sup>) with at least one weight-related comorbidity, excluding diabetes. After achievement of >= 5% reduction in body weight from baseline from an intensive lifestyle intervention period of 12 weeks, patients were randomized to treatment with tirzepatide, titration to maximum tolerated dose (MTD) (10 mg or 15 mg; 86.4% received tirzepatide MTD 15 mg), or placebo. Lifestyle counseling visits were provided quarterly thereafter. At randomization, patients were reported to have lost a mean weight of 6.9%. Complete trial duration was 72 weeks and excluded patients with DM. The coprimary endpoint of treatment with tirzepatide resulted in additional weight reduction of 18.4% from randomization compared to placebo in which there was a weight regain of 2.5%. For the other coprimary endpoint, 87.5% of patients treated with tirzepatide were reported to have a weight loss of >= 5% after randomization, compared to 16.5% of patient in the placebo group. These coprimary endpoints and selected secondary endpoints including weight reduction of >= 10%, >= 15%, and >= 20% are included in Table 3 below.

**Table 3: Results of Coprimary Endpoints and Selected Secondary Endpoints (SURMOUNT-3)<sup>4</sup>**

| Endpoints <sup>a</sup>              | Tirzepatide MTD<br>(N=287)                              | Placebo<br>(N=292) |
|-------------------------------------|---|--------------------|
| % change in body weight, LSM (SE)   | -18.4 (0.7)<br>-20.8 (95% CI -23.2, -18.5) <sup>b</sup> | 2.5 (1.0)          |
| % with >= 5% weight loss, LSM (SE)  | 87.5 (2.2)<br>OR 34.6 (95% CI 19.2, 62.6) <sup>b</sup>  | 16.5 (3.0)         |
| % with >= 10% weight loss, LSM (SE) | 76.7 (2.7)<br>OR 34.7 (95% CI 17.6, 68.3) <sup>b</sup>  | 8.9 (2.4)          |
| % with >= 15% weight loss, LSM (SE) | 65.4 (3.0)<br>OR 48.2 (95% CI 19.2, 121.0) <sup>b</sup> | 4.2 (1.8)          |
| % with >= 20% weight loss, LSM (SE) | 44.7 (3.0)<br>OR 40.4 (95% CI 12.2, 133.8) <sup>b</sup> | 2.2 (1.3)          |

LSM=least squares mean; MTD=maximum tolerated dose; OR=odds ratio; SE=standard error

<sup>a</sup> compared to randomization (after 12-week intensive lifestyle intervention lead-in)

<sup>b</sup> difference vs. placebo (P<0.001)

- **SURMOUNT-4** included a 36-week open-label treatment period with tirzepatide, followed by randomization to placebo or continued treatment with tirzepatide for an additional 52 weeks. Inclusion criteria were patients with a body mass index (BMI) of >= 30 kg/m<sup>2</sup>, or >= 27 kg/m<sup>2</sup> with at least one weight-related coexisting condition (i.e., hypertension, dyslipidemia, obstructive sleep apnea, or cardiovascular [CV] disease). Select exclusion criteria were diabetes, prior or planned surgery for obesity, and treatment with another medication that promotes weight loss.
- During the 36-week open-label lead-in period, patients were started on tirzepatide 2.5 mg once weekly and weekly dose was titrated up by 2.5 mg every 4 weeks until they achieved a maximum tolerated dose of either 10 mg or 15 mg once weekly. At the end of the lead-in period, patients were randomized 1:1 to continue tirzepatide or switch to placebo. Throughout the entire study, patients had lifestyle counseling including diet and exercise recommendations.

The primary endpoint was percent change in body weight from the start of randomization (week 36) to week 88. Selected key secondary endpoints were number of participants maintaining 80% or more of the body weight lost during the lead-in period, and participants reaching weight reduction of >= 5%, >= 10%, >= 15%, and >= 20% from week 0 to week 88. See Table 4. Continued treatment with tirzepatide resulted in a significantly higher number of patients maintaining weight loss compared to placebo.

**Table 4: Results of Primary Endpoint and Selected Secondary Endpoints (SURMOUNT-4)<sup>5</sup>**

| Endpoints <sup>a</sup>   | Tirzepatide MTD<br>(n=335)     | Placebo<br>(N=335) |
|--|--------------------------------|--------------------|
| % change in body weight week 36 to 88, LSM (95% CI)                    | -5.5 (-6.8, -4.2) <sup>a</sup> | 14 (12.8, 15.2)    |
| Number of patients maintaining at least 80% weight lost in lead-in (%) | 300 (89.5) <sup>a</sup>        | 55 (16.6)          |
| Number with >= 5% weight loss <sup>b</sup> (%)                         | 326 (97.3) <sup>a</sup>        | 235 (70.3)         |
| Number with >= 10% weight loss <sup>b</sup> (%)                        | 309 (92.1) <sup>a</sup>        | 155 (46.2)         |
| Number with >= 15% weight loss <sup>b</sup> (%)                        | 282 (84.1) <sup>a</sup>        | 87 (25.9)          |
| Number with >= 20% weight loss <sup>b</sup> (%)                        | 233 (69.5) <sup>a</sup>        | 42 (12.6)          |

<sup>a</sup> p<0.001

<sup>b</sup> from week 0 to week 88

### Safety Results from the SURMOUNT-1 Clinical Trial<sup>2</sup>

- Adverse events in at least 5% of patients in any treatment group are included in Table 2 below. The most common adverse events leading to discontinuation with tirzepatide injection were nausea, diarrhea, abdominal pain, and vomiting. Serious adverse events were reported in 6.3% of patients overall. Adverse events of special interest included pancreatitis (one case in each of the 3 treatment groups and placebo), cholelithiasis (reported to be similar among the tirzepatide and placebo groups), cholecystitis and acute cholecystitis (reported more frequently in the tirzepatide group compared to placebo, although incidence was noted to be  $\leq 0.6\%$ ). Major depressive disorder or suicidal ideation was reported in one patient receiving tirzepatide 5 mg, 2 patients each on tirzepatide 10 mg and 15, and no patients in the placebo group.

**Table 5: Adverse Events with Tirzepatide Compared to Placebo for Weight Management<sup>2</sup>**

| Adverse Events (AE)              | Tirzepatide 5 mg<br>N=630 (%) | Tirzepatide 10 mg<br>N=636 (%) | Tirzepatide 15 mg<br>N=636 (%) | Placebo<br>N=643 (%) |
|----------------------------------|-------------------------------|--------------------------------|--------------------------------|----------------------|
| Nausea                           | 24.6                          | 33.3                           | 31.0                           | 9.5                  |
| Diarrhea                         | 18.7                          | 21.2                           | 23.0                           | 7.3                  |
| Constipation                     | 16.8                          | 17.1                           | 11.7                           | 5.8                  |
| Dyspepsia                        | 8.9                           | 9.7                            | 11.3                           | 4.2                  |
| Vomiting                         | 8.3                           | 10.7                           | 12.2                           | 1.7                  |
| Decreased appetite               | 9.4                           | 11.5                           | 8.6                            | 3.3                  |
| Headache                         | 6.5                           | 6.8                            | 6.5                            | 6.5                  |
| Abdominal Pain                   | 4.9                           | 5.3                            | 4.9                            | 3.3                  |
| Alopecia                         | 5.1                           | 4.9                            | 5.7                            | 0.9                  |
| Dizziness                        | 4.1                           | 5.5                            | 4.1                            | 2.3                  |
| Eructation                       | 3.8                           | 5.2                            | 5.6                            | 0.6                  |
| Injection site reaction          | 2.9                           | 5.7                            | 4.6                            | 0.3                  |
| Discontinued treatment due to AE | 4.3                           | 7.1                            | 6.2                            | 2.6                  |
| Serious adverse events           | 6.3                           | 6.9                            | 5.1                            | 6.8                  |

### Safety Considerations<sup>1</sup>

- Boxed Warning:**
  - Tirzepatide causes thyroid C-cell tumors in rats. It is unknown whether tirzepatide 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.
  - Tirzepatide 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.
- Contraindications:**
  - Personal or family history of MTC or in patients with MEN 2.
  - Known serious hypersensitivity to tirzepatide or any of the excipients in ZEPBOUND.
- Other Warnings / Precautions:**
  - Pancreatitis: Has been reported in clinical trials. Discontinue promptly if pancreatitis is suspected.
  - Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin: 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.
  - Hypersensitivity Reactions: Hypersensitivity reactions have been reported. Discontinue tirzepatide if

- suspected.
- Acute Kidney Injury: Monitor renal function in patients with renal impairment reporting severe adverse gastrointestinal reactions that could lead to volume depletion.
  - Severe Gastrointestinal Disease: Use may be associated with gastrointestinal adverse reactions, sometimes severe. Has not been studied in patients with severe gastrointestinal disease and is not recommended in these patients.
  - Diabetic Retinopathy Complications in Patients with a History of Diabetic Retinopathy: 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.
  - Acute Gallbladder Disease: Has occurred in clinical trials. If cholelithiasis is suspected, gallbladder studies and clinical follow-up are indicated.
  - Suicide Behavior and Ideation: Suicidal behavior and ideation have been reported in clinical trials for other chronic weight loss medications. Avoid use in patients with a history of suicidal attempts or active suicidal ideation. Monitor patients for the emergence or worsening of depression, suicidal thoughts or behaviors, and/or unusual changes in mood or behavior. Tirzepatide should be discontinued in patients who experience suicidal thoughts or behaviors.
  - Weight loss offers no benefit to a pregnant patient and may cause fetal harm. Tirzepatide may cause fetal harm and should be discontinued when pregnancy is recognized.
  - People of reproductive potential using oral contraceptives should be advised to switch to a non-oral contraceptive method or add a barrier method of contraception for 4 weeks after initiating tirzepatide and for 4 weeks after each tirzepatide dose escalation. This is due to tirzepatide delaying gastric emptying, which may
- **Adverse Reactions:**
    - The most common adverse reactions, reported in  $\geq 5\%$  of patients treated with tirzepatide are nausea, diarrhea, decreased appetite, vomiting, constipation, dyspepsia, abdominal pain, injection site reactions, fatigue, hypersensitivity reactions, eructation, hair loss, gastroesophageal reflux disease, dizziness.

### Other Considerations<sup>6,7</sup>

- FDA approval of tirzepatide as an adjunct to diet and exercise to improve glycemic control in adults with type 2 DM was based on results from the following five clinical trials: monotherapy (SURPASS-1); as an add-on to metformin, sulfonylureas, and/or sodium-glucose co-transporter 2 inhibitors (SGLT2 inhibitors) (SURPASS-2, -3, and -4); and in combination with basal insulin with or without metformin (SURPASS-5). The dose of tirzepatide used in these clinical trials was 5 mg, 10 mg, and 15 mg subcutaneously (SC) once weekly, and was compared with placebo, semaglutide 1 mg, insulin degludec, and/or insulin glargine. (Refer to PBM Drug Monograph for tirzepatide in type 2 DM, August 2022).
- In the clinical trial evaluating glycemic control of tirzepatide compared to semaglutide in patients with type 2 DM (SURPASS-2), the secondary outcome of change in body weight from baseline to week 40 was significantly greater with tirzepatide 5 mg (-7.6 kg), tirzepatide 10 mg (-9.3 kg), and tirzepatide 15 mg (-11.2 kg), compared with semaglutide 1.0 mg (-5.7 kg) SC injection once weekly. In addition, 65% to 80% of patients receiving tirzepatide achieved  $\geq 5\%$  weight reduction compared to 54% of patients treated with semaglutide 1 mg; 34% to 57% on tirzepatide had a  $\geq 10\%$  weight reduction vs. 24% on semaglutide; and 15% to 36% on tirzepatide experienced a reduction in weight of  $\geq 15\%$  compared to 8% on semaglutide.<sup>6</sup>
- Direct comparison trials of tirzepatide with other medications at doses approved for chronic weight management are not available at this time. In addition, data are needed to determine benefit of weight loss with tirzepatide on cardiovascular and other long-term outcomes. According to a systematic review and meta-analysis, results of percentage body weight change vs. baseline with other medications currently FDA approved for chronic weight management were reported as follows: naltrexone/bupropion -4.11%; orlistat -3.16%; phentermine/topiramate -7.97%; liraglutide -4.68%; semaglutide -11.41%.<sup>7</sup>

**Other Therapeutic Options<sup>1,2,7-10</sup>**

Tirzepatide and medications FDA approved for chronic weight management are provided in Table 5 below.

**Table 6: Medications Used in Chronic Weight Management<sup>1,2,7-10</sup>**

| Drug                       | Formulary status   | REMS | CS  | Route        | Dose Titration | Frequency         | % wt loss <sup>a</sup> | >=5% wt loss         | >=10% wt loss        | DC due to AE      |
|----------------------------|--------------------|------|-----|--------------|----------------|-------------------|------------------------|----------------------|----------------------|-------------------|
| naltrexone/<br>bupropion   | No-Buy             | No   | No  | Oral tablet  | Yes            | Twice daily       | 4.1% <sup>b</sup>      | 55% <sup>c</sup>     | 30% <sup>c</sup>     | 12% <sup>c</sup>  |
| orlistat                   | VANF<br>PA-F (CFU) | No   | No  | Oral capsule | No             | Three times daily | 3.2% <sup>b</sup>      | 45% <sup>c</sup>     | 20% <sup>c</sup>     | 10% <sup>c</sup>  |
| phentermine/<br>topiramate | VANF<br>PA-F (CFU) | Yes  | Yes | Oral capsule | Yes            | Once daily        | 8.0% <sup>b</sup>      | 74% <sup>c</sup>     | 54% <sup>c</sup>     | 10% <sup>c</sup>  |
| liraglutide<br>(SAXENDA)   | NF<br>(CFU)        | No   | No  | SC injection | Yes            | Once daily        | 4.7% <sup>b</sup>      | 63% <sup>c</sup>     | 34% <sup>c</sup>     | 13% <sup>c</sup>  |
| semaglutide<br>(WEGOVY)    | NF<br>(CFU)        | No   | No  | SC injection | Yes            | Once weekly       | 11.4% <sup>b</sup>     | 86% <sup>d</sup>     | 69% <sup>d</sup>     | 7% <sup>d</sup>   |
| Tirzepatide<br>(ZEPBOUND)  | TBD                | No   | No  | SC injection | Yes            | Once weekly       | 12%-19% <sup>e</sup>   | 85%-91% <sup>e</sup> | 69%-84% <sup>e</sup> | 4-7% <sup>e</sup> |

AE=adverse events; CFU=criteria for use; CS=controlled substance; DC=discontinuation; NF=non-formulary; PA-F=prior authorization, facility level; REMS=Risk Evaluation and Mitigation Strategy; SC=subcutaneous; TBD=to be determined; VANF=VA National Formulary; wt=weight

<sup>a</sup> vs. baseline, compared to CLI or placebo

<sup>b</sup> Shi Q, et al. Lancet 2022<sup>5</sup>

<sup>c</sup> Khera R, et al. JAMA 2016<sup>6</sup>

<sup>d</sup> STEP 1, NEJM 2021<sup>8</sup>

<sup>e</sup> SURMOUNT-1, NEJM 2022<sup>2</sup>

**Projected Place in Therapy<sup>1-14</sup>**

- As noted in the VA/DoD Clinical Practice Guideline for the Management of Adult Overweight and Obesity (2020), overweight (BMI 25 to 29.9 kg/m<sup>2</sup>) and obesity (BMI >= 30 kg/m<sup>2</sup>) is of significant concern for the U.S. healthcare system; with the high prevalence in the population, along with the association with an increased risk of related health conditions including type 2 DM, hypertension, dyslipidemia, metabolic syndrome, osteoarthritis, obstructive sleep apnea, as well as all-cause mortality. In addition, it is noted that obesity is a common risk factor for developing non-alcoholic fatty liver disease (NAFLD) (aka metabolic dysfunction-associated steatotic liver disease or MASLD), a primary cause of chronic liver disease. In VA, based on BMI, the prevalence of obesity has been reported to be 45% of the population, with 36% overweight. This is noted to be higher compared with the general U.S. population.
- Comprehensive lifestyle intervention is the foundation of weight management and is considered a clinically supported weight management program that targets all three aspects of weight management: behavioral, dietary, physical activity; in VA, this is the MOVE! Weight Management Program. In patients with overweight or obesity, comprehensive lifestyle intervention is associated with greater weight loss compared with minimal intervention or usual care controls.
- Pharmacotherapy provides additional weight reduction in patients receiving comprehensive lifestyle intervention. In addition to a significant reduction in weight, results from medication trials have noted an improvement in surrogate endpoints of select chronic conditions; although, results have been variable depending on the medication. The VA/DoD Clinical Practice Guideline for the Management of Adult Overweight and Obesity suggests that weight management medications for long-term weight loss be offered to patients with a BMI >= 30 kg/m<sup>2</sup> and to those with a BMI >= 27 kg/m<sup>2</sup> who also have obesity associated conditions, as an adjunct to comprehensive lifestyle intervention.
- Tirzepatide has recently been FDA approved for chronic weight management based on data from placebo-

controlled trials. Without data from direct comparison trials at doses used for weight management, the place in therapy of tirzepatide among the available medications for chronic weight management is unclear at this time. There are currently five other medications FDA approved for chronic weight management. Of these, orlistat and phentermine/topiramate are available on the VA National Formulary, with Prior Authorization at the Facility level according to criteria for use; liraglutide (SAXENDA) and semaglutide (WEGOVY) are available non-formulary with criteria for use. Naltrexone-bupropion is not available in VA.

- Based on results from a meta-analysis, the percent of patients that achieved  $\geq 5\%$  reduction in weight per the respective medications are as follows: 74% on phentermine/topiramate; 63% on liraglutide; 55% on naltrexone/bupropion; and 45% on orlistat. In the STEP 1 placebo-controlled trial, approximately 86% of patients treated with semaglutide (WEGOVY) 2.4 mg weekly achieved  $\geq 5\%$  reduction in weight. In the SURMOUNT-1 weight management trial with tirzepatide, 85%, 89% and 91% of patients achieved  $\geq 5\%$  reduction in weight on the 5 mg, 10 mg, and 15 mg weekly doses, respectively. Compared to placebo, treatment with tirzepatide SC injection once weekly also resulted in a significant reduction in the coprimary endpoint of percentage weight reduction from baseline of 15.0%, 19.5%, and 20.9% with doses of 5 mg, 10 mg and 15 mg, respectively (vs. 3.1% reduction with placebo). As one of the key secondary endpoints, approximately 57% of patients receiving tirzepatide 15 mg weekly achieved  $\geq 20\%$  reduction in body weight. SURMOUNT-2 evaluated tirzepatide for weight management in patients with type 2 DM and 79% (10 mg weekly) to 83% (15 mg weekly) of patients achieved weight reduction of  $\geq 5\%$ . Although not a direct comparison, approximately 69% of patients with type 2 DM being treated with semaglutide 2.4 mg weekly for overweight or obesity achieved  $\geq 5\%$  reduction in weight.
- Use of tirzepatide for chronic weight management contains a Boxed Warning for risk of thyroid C-cell tumors, as well as several additional warnings and precautions (i.e., pancreatitis; acute gallbladder disease; hypoglycemia; acute kidney injury; hypersensitivity; diabetic retinopathy complication in patients with a history of diabetic retinopathy; severe gastrointestinal disease; suicide behavior and ideation). The most common adverse events reported with tirzepatide in the clinical trial for weight management were primarily gastrointestinal.
- When selecting a weight management medication, a number of factors should be considered including each drug's efficacy, side effects, warnings and precautions, the patient's comorbidities, as well as the cost of the medication. As noted previously, treatment with a weight management medication should be in conjunction with comprehensive lifestyle intervention.

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