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**Medication Policy Manual** **Policy No:** dru787

**Topic: GLP-1 Agonist-Containing Medications for Non-Diabetic Indications** **Date of Origin:** August 1, 2024

- Saxenda (liraglutide)
- Wegovy (semaglutide)
- Zepbound (tirzepatide)

**Committee Approval Date:** April 3, 2025 **Next Review Date:** 2025

**Effective Date:** June 1, 2025

## IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

### Administration of Contract

Coverage for the treatment of weight loss, including GLP-1 Agonist-Containing Medications for Non-Diabetic Indications, is defined by benefit contract language. If treatment of weight loss is a covered benefit, contract language will be applied to determine coverage (see *Appendix 1*).

### Description

The medications in this policy apply to GLP-1 formulations not specifically approved for diabetes. Some medications included in this policy are used in the treatment of obesity and overweight. Note that coverage of these medications for weight loss in obesity or overweight (including obstructive sleep apnea in adults with obesity) is defined by benefit contract language.

*This policy does NOT apply to GLP-1 formulations specifically approved for type 2 diabetes mellitus [e.g., Mounjaro (tirzepatide), Ozempic (semaglutide), and Victoza (liraglutide)], which may be addressed in different policies.*

**Policy/Criteria**

Most contracts require pre-authorization approval of GLP-1 Agonist-Containing Medications for Non-Diabetic Indications (as listed in *Table 1*) prior to coverage.

**I.** Continuation of therapy (COT): GLP-1 Agonist-Containing Medications for Non-Diabetic Indications (as listed in *Table 1*) may be considered medically necessary for COT when criterion A or B below is met.

**A.** For diagnoses NOT listed in the coverage criteria below, full policy criteria must be met for coverage.

**OR**

**B.** For diagnoses listed in the coverage criteria below, criteria 1, 2, and 3 must be met:

**1.** The patient was established on therapy prior to current health plan membership AND documentation that the medication was covered by another health plan.

**AND**

**2.** There is clinical benefit, such as disease stability as detailed in the reauthorization criteria.

**AND**

**3.** Treatment of obesity/overweight (including obstructive sleep apnea with obesity) only: The member benefit contract allows for coverage of medications for weight loss in obesity or overweight. Note that coverage for this indication cannot be approved when a member benefit contract excludes coverage of obesity/overweight treatments, regardless of any clinical criteria met.

***Please note**: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

**II.** New starts (treatment-naïve patients): GLP-1 Agonist-Containing Medications for Non-Diabetic Indications (as listed in *Table 1*) may be considered medically necessary when criterion A and B below are met.

**A.** At least one of the following diagnostic criteria 1, 2, or 3 below is met.

**1.** **Obesity/Overweight**: The member benefit contract allows for coverage of medications for weight loss in obesity/overweight **AND** clinical documentation the patient meets one of the following criteria (a, b, or c):

**a.** Adults, obesity (≥18 years of age): BMI ≥30 kg/m$^2$.

**OR**

**b.** Adults, overweight (≥18 years of age): BMI ≥27 kg/m$^2$ and at least one weight-related comorbid condition (e.g., hypertension, dyslipidemia, type 2 diabetes mellitus [T2DM], pre-diabetes, insulin resistance, obstructive sleep apnea [OSA], cardiovascular

disease [CVD], symptomatic arthritis of lower extremities).

**OR**

**c.** Pediatrics, obesity* (12 through 17 years of age): One of the following criteria is met (i or ii).

**i.** Wegovy (semaglutide): BMI ≥95th percentile standardized for age and sex.

**OR**

**ii.** Saxenda (liraglutide): Baseline BMI corresponding to ≥ 30 kg/m$^2$ for adults based on the Cole Criteria (see *Appendix 2*) **AND** baseline body weight > 60 kg.

***Note**: Only the following products are coverable for obesity in pediatrics: Saxenda (liraglutide) and Wegovy (semaglutide).

**OR**

**2. Wegovy (semaglutide) only: Major adverse cardiovascular event (MACE) secondary prevention** when there is clinical documentation (including but not limited to chart notes) that criteria a, b, and c below are met:

**a.** The patient has cardiovascular disease (CVD) as defined as having at least ONE of the following (criterion i, ii, or iii):

**i.** Myocardial infarction

**OR**

**ii.** Stroke

**OR**

**iii.** Symptomatic peripheral artery disease as evidenced by intermittent claudication with ankle-brachial index less than 0.85 at rest, peripheral arterial revascularization procedure, or amputation due to atherosclerotic disease.

**AND**

**b.** The patient has a body mass index (BMI) ≥27 kg/m$^2$.

**AND**

**c.** Attestation that the patient will use optimized pharmacotherapy (such as blood pressure and cholesterol lowering agents) for established cardiovascular disease in combination with the requested agent.

**OR**

**3. Zepbound (tirzepatide) only: Obstructive sleep apnea (OSA)*** when the member benefit contract allows for coverage of medications for weight loss in obesity/overweight **AND** there is clinical documentation (including but not limited to chart notes) that criteria a and b below are met:

**a.** A diagnosis of moderate to severe obstructive sleep apnea (defined as an apnea-hypopnea index [AHI] of ≥ 15 events/hour).

**AND**

**b.** Concurrent diagnosis of obesity (baseline BMI corresponding to ≥ 30 kg/m$^2$). *Note: For coverage criteria regarding overweight (BMI 27-29.9 kg/m$^2$) with certain comorbidities such as OSA, please refer to the above Obesity/Overweight criteria (Section II.A.1).

**AND**

**B.** Attestation the requested medication will be used concomitantly with lifestyle modification (e.g., dietary/caloric restriction, exercise, weight management program, nutritional counseling, behavioral therapy).

**III.** Administration, Quantity Limitations, and Authorization Period

**A.** Regence Pharmacy Services considers GLP-1 Agonist-Containing Medications for Non-Diabetic Indications coverable only under the pharmacy benefit (as self-administered medications).

**B.** When pre-authorization is approved, GLP-1 Agonist-Containing Medications for Non-Diabetic Indications will be authorized in quantities as follows in *Table 1*:

**TABLE 1 GLP-1 Agonist-Containing Medications for Non-Diabetic Indications**

| Product | Quantity Limit |
|---|---|
| Saxenda (liraglutide) | 5 pens/30 days |
| Wegovy (semaglutide) | 4 pens/28 days |
| Zepbound (tirzepatide) | 4 pens/28 days |

**C.** Authorization **shall** be reviewed at least annually to review benefit contract language to confirm ongoing coverage. In addition, attestation must be provided that the requested medication will be used with lifestyle modification and one of the following criteria is met (1, 2, or 3):

**1.** Obesity or overweight: Member benefit contract allows for coverage of medications for weight loss in obesity/overweight AND attestation of one of the following (a or b):

**a.** Adults (≥18 years of age): Patient has a ≥5% body weight reduction from pretreatment baseline OR the dose is currently being titrated upwards.

**OR**

**b.** Pediatrics* (12 through 17 years of age): Patient has a reduction from pretreatment baseline BMI OR the dose is currently being titrated upwards.

***Note**: Only the following products are coverable for obesity in pediatrics: Saxenda (liraglutide) and Wegovy (semaglutide).

**OR**

**2.** Major adverse cardiovascular event prevention: Attestation that the patient will continue to use optimized pharmacotherapy (such as blood

pressure and cholesterol lowering agents) for established cardiovascular disease in combination with the requested agent.

**OR**

**3.** Obstructive sleep apnea: Member benefit contract allows for coverage of medications for weight loss in obesity/overweight **AND** attestation of improvement in signs and symptoms of OSA such as improvement in sleep quality, daytime functioning, or apnea-hypopnea index (AHI) from baseline.

**IV.** GLP-1 Agonist-Containing Medications for Non-Diabetic Indications are considered not medically necessary when used for type 2 diabetes (T2DM) without obesity or overweight. Note: Coverage for obesity or overweight (including obstructive sleep apnea with obesity) is defined by benefit contract language. For patients with T2DM, a lower dose of semaglutide, as Ozempic, has been shown to reduce MACE in patients with T2DM and is a lower cost option.

**V.** GLP-1 Agonist-Containing Medications for Non-Diabetic Indications are considered investigational when used for all other conditions, including but not limited to:

**A.** Coadministration of any two medications for obesity or overweight including medications in this policy, Contrave (naltrexone/bupropion), or Qsymia (phentermine/topiramate).

**B.** Type 1 diabetes (T1D) or diabetic ketoacidosis (DKA).

**C.** Central or mixed sleep apnea.

**D.** Cheyne-Stokes respiration.

**E.** Obstructive sleep apnea (OSA) with major craniofacial abnormalities.

**Position Statement**

***Summary*** [1-4]

- The intent of this policy is to allow coverage of GLP-1 Agonist-Containing Medications for Non-Diabetic Indications when used for overweight with at least one weight-related comorbid condition or obesity; secondary prevention of major adverse cardiovascular events (MACE); or obstructive sleep apnea (OSA) in patients with obesity as outlined in the coverage criteria above.
- Obesity is a primary disease associated with significant morbidity and mortality. Body weight is a physiologically regulated parameter, with obesity being a chronic disease of body weight regulation. Obesity is defined as a body mass index (BMI) of 30 kg/m$^2$ or more. Overweight is defined as a BMI of 27 kg/m$^2$ or more.
- All GLP-1 Agonist-Containing Medications for Non-Diabetic Indications in combination with lifestyle modifications have been shown to result in significantly more weight loss than lifestyle modifications alone for patients with overweight with at least one weight-related comorbid condition or obesity. [5-8]

- Clinical guidelines recommend use of pharmacotherapy as an adjunct to lifestyle modifications based on BMI. No preference is given to any one medication or medication class; however, individual characteristics should be considered. [9 10]
- Wegovy (semaglutide) has been shown to reduce the risk of major adverse cardiovascular events (MACE) when used for secondary prevention in people with overweight or obesity when added to standard of care for cardiovascular disease. Patients with diabetes or NYHA class IV HF were excluded from the trial.
- Zepbound (tirzepatide) has shown a significant and clinically meaningful effect on reducing apnea/hypopnea events in patients with moderate to severe OSA and obesity.
- Individuals with central or mixed sleep apnea, Cheyne-Stokes respiration, or with major craniofacial abnormalities were excluded from the trial.
- While Zepbound (tirzepatide) can help with obstructive sleep apnea symptoms, it does this mainly by helping with weight loss. Therefore, member benefit contract for coverage of medications for weight loss in obesity/overweight applies.
- GLP-1 formulations specifically approved for T2DM, Mounjaro (tirzepatide), Ozempic (semaglutide), and Victoza (liraglutide), have been shown to provide MACE reduction in patients with type 2 diabetes. Coverage criteria for GLP-1 containing products specifically FDA approved for T2DM [e.g., Mounjaro (tirzepatide), Ozempic (semaglutide), and Victoza (liraglutide)] can be found in their respective policies (see *Cross References* table below).
- Clinical guidelines for cardiovascular disease have not yet been updated to include Ozempic (semaglutide). Clinical guidelines for sleep medicine have also not yet been updated to include Zepbound (tirzepatide).
- Standard of care for OSA includes positive airway pressure (PAP), usually in the form of continuous positive airway pressure (CPAP), auto-adjusting positive airway pressure (APAP), or bi-level continuous positive airway pressure (BiPAP). Custom oral appliances may also be beneficial for mild to moderate OSA.
- The safety and effectiveness of GLP-1 Agonist-Containing Medications for Non-Diabetic Indications in conditions other than those included in the coverage criteria (including those found in *Cross References* policies) have not been established.

### *Clinical Efficacy*

Overweight or Obesity [5-8]

- GLP-1 agonist containing medications in conjunction with a reduced-calorie diet and increased physical activity have been shown to decrease weight significantly versus diet and exercise alone in several clinical trials.
- Saxenda (liraglutide)
    - Studied in three 56-week, randomized, double-blind, placebo-controlled trials Study 1 and Study 3 included adults with overweight with at least one weight-related comorbidity or obesity (T2DM excluded), while Study 2 included adults with overweight or obesity and T2DM. Study 3 also required participants to lose at least 5% weight loss with diet prior to study randomization.
        - For Study 1 and Study 2, the primary endpoints were mean percent change in body weight and the percentages of patients achieving at least

a 5% and 10% weight loss from baseline to week 56. For Study 3, the primary endpoints were mean percent change in body weight from randomization to week 56, the percentage of patients not gaining more than 0.5% body weight from randomization to week 56, and the percentage of patients achieving greater than or equal to 5% weight loss from randomization to week 56.

- After 56 weeks, treatment with Saxenda (liraglutide) resulted in a statistically significant reduction in weight compared with placebo in all three studies:
  - Study 1: Saxenda -7.4%, placebo -3.0%
  - Study 2: Saxenda -5.4%, placebo -1.7%
  - Study 3: Saxenda -4.9%, placebo 0.3%
- Statistically significantly greater proportions of patients treated with Saxenda (liraglutide) achieved 5% and 10% weight loss than those treated with placebo at week 56. In Study 3, statistically significantly more patients randomized to Saxenda (liraglutide) than placebo had not gained more than 0.5% of body weight from randomization to week 56.

* Saxenda (liraglutide) was also evaluated in a 56-week, randomized, double-blind, parallel group, placebo-controlled trial in pediatric patients (12 to 17 years of age) with BMI corresponding to ≥30 kg/m2 for adults and BMI ≥95$^{th}$ percentile standardized by age and sex.
  - The primary endpoint was change in BMI standard deviation score (SDS). At week 56, treatment with Saxenda (liraglutide) resulted in statistically significant reduction in BMI SDS from baseline compared to placebo (-0.23 and -0.00, respectively). Of note, mean change from baseline BMI was -4.29 and 0.35, respectively.

- Wegovy (semaglutide)
  * Studied in three randomized, double-blind, placebo-controlled trials in which weight reduction was assessed after 68-weeks of treatment (52 weeks at maintenance dose). Study 1 and Study 3 included adults with overweight with at least one weight-related comorbidity or obesity (T2DM excluded), while Study 2 included adults with overweight or obesity and T2DM.
    - For all three studies, the primary endpoints were mean percent change in body weight and the percentages of patients achieving at least 5% weight loss from baseline to week 68. Treatment with Wegovy (semaglutide) resulted in a statistically significant reduction in weight compared to placebo. Greater proportions of patients treated with Wegovy (semaglutide) achieved 5%, 10%, and 15% weight loss than those treated with placebo. Percent change from baseline for BMI were as follows:
      - Study 1: Wegovy -14.9%, placebo -2.4%
      - Study 2: Wegovy -9.6%, placebo -3.4%
      - Study 3: Wegovy -16.0%, placebo -5.7%

* Study 4 was a 68-week randomized, double-blind, placebo withdrawal trial in adults with overweight with at least one weight-related comorbidity or obesity (T2DM excluded). All patients received the active drug for 20 weeks, followed by switch to placebo by 11% of the study participants.
    - The primary endpoint was mean percent change in body weight from week 20 to week 68. From randomization (week 20) to week 68, treatment with Wegovy (semaglutide) resulted in a statistically significant reduction in body weight compared with placebo (-7.9% vs. 6.9%, respectively).
* SELECT was a large (N= 17,604), randomized, double-blind, placebo-controlled, event-driven superiority trial in adults with pre-existing cardiovascular disease and overweight or obesity but without T2DM. A total of 17,604 patients were enrolled; 8803 were assigned to receive semaglutide and 8801 to receive placebo. The mean (±standard deviation) duration of exposure to semaglutide or placebo was 34.2±13.7 months, and the mean duration of follow-up was 39.8±9.4 months.
    - The primary cardiovascular end point was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke in a time-to-first-event analysis. A primary cardiovascular end-point event occurred in 569 of the 8803 patients (6.5%) in the semaglutide group and in 701 of the 8801 patients (8.0%) in the placebo group (hazard ratio, 0.80; 95% confidence interval, 0.72 to 0.90; P<0.001).
* Wegovy (semaglutide) was also evaluated in a 68-week, randomized, double-blind, parallel group, placebo-controlled trial in pediatric patients (12 to 17 years of age) with BMI ≥95$^{th}$ percentile standardized by age and sex.
    - The primary endpoint was percent change in BMI from baseline to week 68. At week 68, Wegovy (semaglutide) resulted in a statistically significant reduction in percent BMI compared with placebo (-16.1% vs. 0.6%, respectively), and greater proportions of patients receiving Wegovy (semaglutide) achieved at least a 5% reduction in baseline BMI than those treated with placebo (77.1% vs. 19.7%, respectively).

- Zepbound (tirzepatide)
    * Studied in two randomized, double-blind, placebo-controlled trials (SURMOUNT-1 and SURMOUNT-2) in which weight reduction was assessed after 72 weeks of treatment (at least 52 weeks at maintenance dose). Study 1 included adults with overweight with at least one weight-related comorbidity or obesity (T2DM excluded), while Study 2 included adults with overweight or obesity and T2DM.
    * The primary endpoints were mean percent change in body weight and the percentage of patients achieving at least a 5% weight reduction from baseline at 72 weeks. After 72 weeks of treatment, both studies saw a statistically significant reduction in body weight compared with placebo, and greater proportions of patients treated with Zepbound (tirzepatide) 5 mg, 10 mg, and 15 mg achieved at least 5% weight reduction compared to placebo. The mean percent change in body weight from baseline to week 72 for 5 mg, 10 mg, 15 mg, and placebo were as follows:
        - SURMOUNT-1: -15.0%, -19.5%, -20.9%, -3.1%, respectively.

- SURMOUNT-2: Not applicable (5 mg dose not evaluated), -12.8%, -14.7%, -3.2%, respectively.

* Among patients treated with 10 mg and 15 mg, greater proportions of patients achieved at least 10%, 15%, and 20% weight reduction compared to placebo.

Major Adverse Cardiovascular Event (MACE) Prevention[7 11]

- The cardiovascular evidence for Wegovy (semaglutide) was based on the phase III, randomized, double-blind, SELECT trial, which enrolled 17,604 patients (aged ≥45 years, BMI ≥27 kg/m$^2$) who have overweight or obesity with established cardiovascular disease (CVD) and no history of diabetes.
- Patients received once-weekly subcutaneous semaglutide at a dose of 2.4 mg or placebo in addition to standard of care. Note: the maximum semaglutide dose in diabetes is 2 mg weekly.
- The study's primary endpoint was the composite outcome of the first occurrence of major cardiovascular event (MACE) defined as cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. This is the classical definition of MACE and has been used as the primary endpoint in multiple cardiovascular outcomes trials (CVOTs).
- Wegovy (semaglutide) was associated with a 20% relative risk reduction in MACE during a mean exposure period of 33 months. However, there was no statistically significant difference in cardiovascular death. Death from cardiovascular causes, the first confirmatory secondary endpoint, showed a non-significant 15% reduction (HR, 0.85; P = 0.07).
- Patients in the trial had established CVD, defined as having either a previous myocardial infarction, stroke, or symptomatic peripheral arterial disease (PAD).
- Symptomatic PAD was defined as having intermittent claudication, peripheral arterial revascularization, or amputation due to atherosclerotic disease.
- Intermittent claudication may manifest as leg pain during exercise due to insufficient blood supply and may be a sign of plaque build-up in the arteries. It may also be associated with cramping, numbness, tingling, pain, or weakness with exercise and improved with rest. And ankle-brachial test is often done to help identify intermittent claudication. This test compares the blood pressure in your ankle with the blood pressure in your arm; a significantly lower blood pressure in the leg (ankle–brachial index <0.85) may be indicative of PAD. A MRA (magnetic resonance angiography), CTA (computed tomography angiography), vascular ultrasound, or arteriogram may also help verify a blockage as well as magnitude of the blockage.
- Peripheral arterial revascularization procedures such as percutaneous transluminal angioplasty, bypass surgery or atherectomy may be done to restore blood flow and help reduce pain from intermittent claudication. In severe cases, amputation may be performed.
- The efficacy/safety for use in people who have overweight or obesity without prior heart attacks or at high risk for cardiovascular events (primary prevention) is unknown.
- In the SELECT trial, Wegovy (semaglutide) was added to standard of care for cardiovascular disease. Standard of care typically includes blood-thinning medications

(such as aspirin), statins (such as atorvastatin), blood pressure medications (such as metoprolol).

- Patients with diabetes type 2 (T2DM) and/or NYHA class IV heart failure were excluded; there are no data to support the efficacy of Wegovy (semaglutide 2.4 mg weekly) in reducing the incidence of MACEs in these population. However, for patients with T2DM, there is evidence from randomized controlled trials that a lower dose of semaglutide indicated for T2DM (Ozempic), may be effective in lowering MACE risk and is a lower cost option for these patients.

Obstructive Sleep Apnea (OSA)[8 12]

- The approval of Zepbound (tirzepatide) for obstructive sleep apnea (OSA) was primarily based on the results of the SURMOUNT-OSA trials, which consisted of two phase 3, double-blind, placebo-controlled studies. These trials evaluated Zepbound (tirzepatide) 10 mg or 15 mg weekly in adults with moderate-to-severe OSA and obesity with or without positive airway pressure (PAP) therapy compared to placebo for 12 months.
- Patients in the trials were adults aged 18 years or older with moderate-to-severe OSA, defined as an apnea-hypopnea index (AHI) of 15 or more events per hour. Additionally, patients needed to have obesity, with a body-mass index (BMI) of 30 kg/m² or higher.
- In both trials, patients on Zepbound (tirzepatide) had clinically significant reductions in the primary endpoint of apnea-hypopnea index (AHI) at 52 weeks compared to placebo.
    * Patients who received Zepbound (tirzepatide) without PAP therapy had 25 fewer breathing disruptions per hour compared to 5 fewer in patients who received placebo.
    * In patients who also received PAP therapy, those who received Zepbound (tirzepatide) had 29 fewer breathing disruptions per hour compared to 6 fewer in patients who received placebo. However, the effectiveness of Zepbound (tirzepatide) in comparison to PAP therapy remains uncertain because patients were instructed to stop using their PAP machines for 7 days before their sleep tests.
- After one year, 40-50% of patients who received Zepbound (tirzepatide) achieved remission or had mild, non-symptomatic OSA, compared to ~15% of patients who received placebo.

***Guidelines*** [9 10 13-15]

- Recently updated American Academy of Pediatrics (AAP) 2023 obesity guidelines recommend use the of pharmacotherapy as an adjunct to lifestyle modifications based on age and BMI. These guidelines do not give preference for any one medication over another. Specific recommendations include the following:
    * Pediatricians and other primary health care providers should offer adolescents 12 years and older with obesity (BMI ≥95$^{th}$ percentile) weight loss pharmacotherapy, according to medication indications, risks, and benefits, as an adjunct to health behavior and lifestyle treatment.
    * Pediatricians and other primary health care providers should offer referral for adolescents 13 years of age and older with severe obesity (BMI ≥120% of the 95$^{th}$ percentile for sex and age) for evaluation for metabolic and bariatric surgery.

    * Deliver the best available intensive treatment to all children with overweight and obesity. There is no evidence to support either watchful waiting or unnecessary delay of appropriate treatment of children with obesity.
    * May offer children ages 8 through 11 years of age with obesity weight loss pharmacotherapy, according to medication indications, risks, and benefits, as an adjunct to health behavior and lifestyle treatment.
    * The medical costs of untreated childhood obesity are well-documented and add urgency to provide payment for treatment.

- The 2015 Endocrine Society obesity guidelines recommend use of pharmacotherapy as an adjunct to lifestyle modifications based on BMI. Note that these guidelines were published nearly a decade ago prior to more widespread use of GLP-1 agonist-containing medications for overweight and obesity. They include the following recommendations:
    * Tools such as pharmacotherapy (BMI ≥27 kg/m$^2$ with comorbidity or BMI ≥30 kg/m$^2$) and bariatric surgery (BMI ≥35 kg/m$^2$ with comorbidity or BMI ≥40 kg/m$^2$) should be used as adjuncts to behavioral modification to reduce food intake and increase physical activity when possible.
    * Drugs may amplify adherence to behavior change and may improve physical functioning such that increased physical activity is easier for those who cannot exercise initially.
    * Patients who have a history of being unable to successfully lose and maintain weight and who meet label indications are candidates for weight loss medications.
    * No specific medications are recommended over others for initial pharmacotherapy unless the individual has certain comorbid conditions (e.g., patients with T2DM should use antidiabetic medications that also promote weight loss such as GLP-1 agonists or SGLT-2 inhibitors).
- The 2023 American Heart Association/American College of Cardiology guidelines recommend antiplatelets and/or oral anticoagulants, beta blockers, and/or ACE inhibitors/ARB for secondary prevention.
    * The management of comorbidities is important for cardiovascular health, including optimal lipid management and blood pressure management.
    * Statins remain first line therapy for lipid lowering in patients with cardiovascular disease. High-intensity statin therapy is recommended with the aim of achieving a ≥50% reduction in LDL-C levels to reduce the risk of MACE. Several adjunctive therapies (e.g., ezetimibe, proprotein convertase subtilisin kexin type 9 [PCSK9] inhibitors, bempedoic acid) may be used in select populations if statins are inadequate/ not tolerated. The use of nonprescription or dietary supplements, including fish oil and omega-3 fatty acids or vitamins, is not recommended given the lack of benefit in reducing cardiovascular events.
    * In adults with chronic cardiovascular disease who have hypertension, a blood pressure target of <130/<80 mm Hg is recommended to reduce CVD events and all-cause death. Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), or beta blockers are recommended as first-line therapy for compelling indications (e.g., recent MI or angina), with additional

antihypertensive medications (e.g., dihydropyridine calcium channel blockers [CCB], long-acting thiazide diuretics, and/or mineral corticoid receptor antagonists) added as needed to optimize BP control.

  * In patients with CCD who have type 2 diabetes, the use of either an SGLT2 inhibitor or a GLP-1 receptor agonist with proven cardiovascular benefit is recommended to reduce the risk of MACE.
  * For patients with CCD and overweight or obesity in whom pharmacologic therapy is warranted for further weight reduction, a GLP-1 receptor agonist can be beneficial in addition to counseling for diet and physical activity and it is reasonable to choose semaglutide over liraglutide.
  * Use of glucagon-like peptide-1 (GLP-1) receptor agonists are recommended for select groups of patients with cardiovascular disease including groups without diabetes.

- The 2019 American Academy of Sleep Medicine (AASM) guideline recommends positive airway pressure therapy for patients with a high number of apnea or hypopnea events per hour (usually 15 or more) or other high-risk characteristics.
  * The primary goal of obstructive sleep apnea (OSA) therapy is to resolve symptoms, improve sleep quality, and normalize the apnea-hypopnea index (AHI).
  * Patients diagnosed with OSA are advised to address modifiable risk factors, such as weight loss and avoiding sedating substances.
  * A 2019 meta-analysis from the American Academy of Sleep Medicine (AASM) found that continuous PAP (CPAP) therapy significantly reduces OSA severity and improves daytime sleepiness. Additionally, a retrospective cohort study of Medicare beneficiaries showed that older adults with OSA who initiated CPAP therapy had significantly lower all-cause mortality and major adverse cardiovascular events compared to those without therapy. However, no randomized trial has demonstrated a mortality benefit from PAP therapy.
- Educational interventions including proper use of PAP should be given with initiation of PAP therapy. The AASM guidelines recommend oral appliances as a first-line treatment for patients with mild-to-moderate OSA and as an alternative for those with severe OSA who are unable to tolerate CPAP. Oral appliances improve sleep parameters such as the apnea-hypopnea index (AHI), arousal index, and oxygen desaturation index, though CPAP remains more effective.[16]

***Safety*** [5-8 17 18]

- The most common adverse reactions (incidence ≥5%) with GLP-1 agonist-containing medications include nausea, diarrhea, constipation, vomiting, injection site reactions, headache, hypoglycemia, dyspepsia, fatigue, dizziness, abdominal pain, increased lipase, hair loss, upper abdominal pain, pyrexia, gastroesophageal reflux disease, eructation, and gastroenteritis.
- GLP-1 agonist-containing medications have Boxed Warnings regarding the potential risk for medullary thyroid carcinoma. An increased incidence of thyroid C-cell tumors was observed in pre-clinical studies with GLP-1 agonists in animals. The relevance of

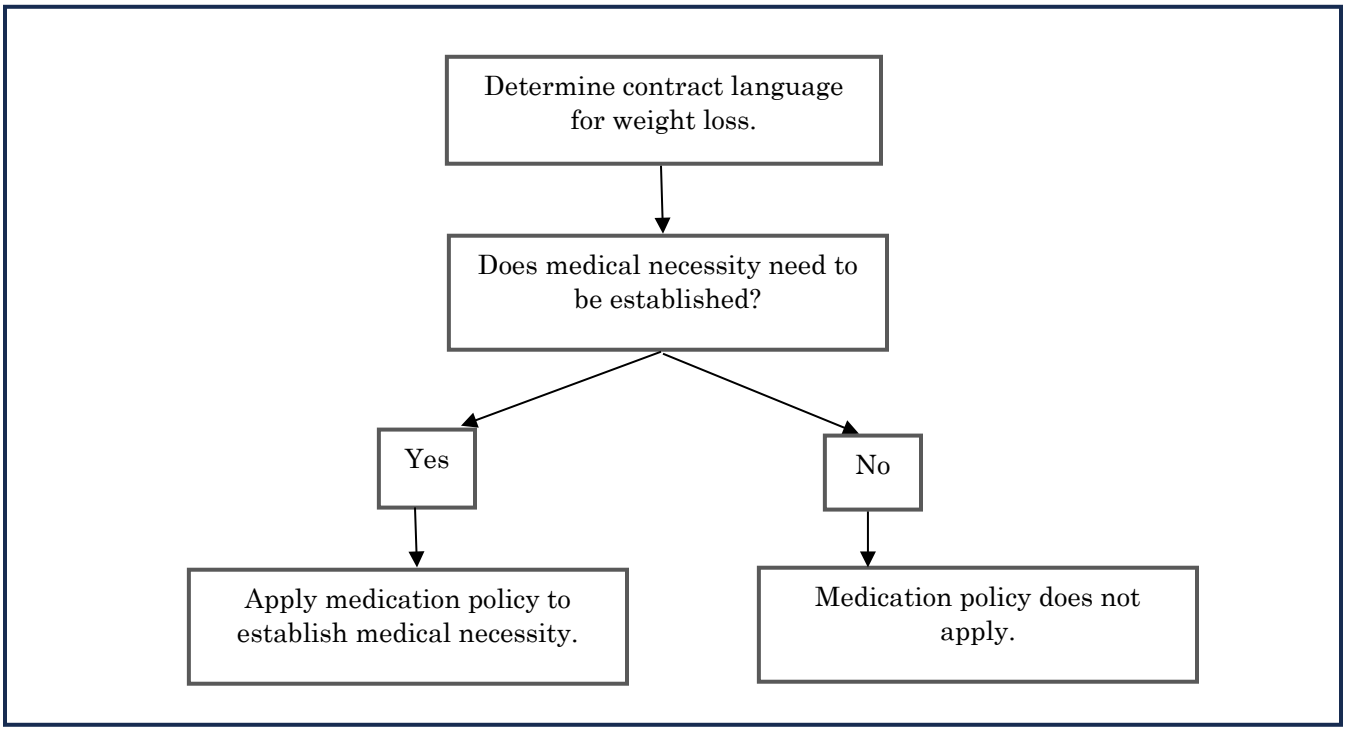
this effect for humans is unknown.

- Serious gastrointestinal events such as ileus, obstruction, and pancreatitis have been reported post market. Risk of acute pancreatitis is small and likely a class effect, which has been appreciated with more extensive post-marketing clinical experience. A 2014 FDA and European Medicines Agency (EMA) assessment of pancreatic safety of incretin-based drugs stated a causal association between incretin-based drugs and pancreatitis or pancreatic cancer could not be established. Both agencies continue to investigate this safety signal.
- There have also been reports of suicidal thoughts or actions in patients taking GLP-1 agonist-containing medications. In January 2024, the FDA stated that their preliminary evaluation did not suggest a causal link. However, because of the small number of suicidal thoughts and actions observed in this population, they cannot definitively rule out a small risk may exist; therefore, the FDA is continuing to evaluate the issue.
- Evidence from the weight-loss STEP trials have suggested reductions of muscle mass and bone density. The long-term implications of this, as well as any impacts of weight rebound on cardiovascular outcomes are unknown.

***Investigational Uses*** [5-8]

- Co-administration of medications for obesity or overweight
    * Co-administration of medications for obesity or overweight including medications in this policy, Contrave (naltrexone/bupropion), or Qsymia (phentermine/ topiramate) has not been studied.
    * The FDA prescribing information for the medications included in this policy states that the safety and effectiveness of these medications in combination with other products intended for weight loss have not been established.
    * Because the impact to safety and effectiveness is unknown, co-administration is considered investigational and therefore not covered.
- Type 1 diabetes (T1D) / diabetic ketoacidosis (DKA)
    * There are no well-designed, randomized controlled trials that demonstrate a benefit to using medications for obesity or overweight in this policy in T1D.
    * The FDA approved prescribing information for the GLP1-agonists approved for T2DM states that these medications should not be used in patients with T1D or for the treatment of DKA, as it would not be effective in these settings.
- Patients with central or mixed sleep apnea, Cheyne-Stokes respiration, or significant craniofacial abnormalities were excluded from the Zepbound (tirzepatide) trials for obstructive sleep apnea (SURMOUNT-OSA). Consequently, there is a lack of evidence regarding the safety and efficacy of Zepbound (tirzepatide) in these patient populations.

**Appendix 1: GLP-1 Agonist-Containing Medications for Non-Diabetic Indications – Administration of Contract Language and Medication Policy** [a]




[a] Coverage of GLP-1 Agonist-Containing Medications for Non-Diabetic Indications in obesity or overweight (including obstructive sleep apnea in adults with obesity) is defined by benefit contract language.

**Appendix 2: International Obesity Task Force BMI Cut-offs for Obesity by Sex and Age for Pediatric Patients Aged 12 Years and Older (Cole Criteria)** [15]

| Age (years) | BMI corresponding to adult BMI of 30 kg/m² | |
|---|---|---|
| | Males | Females |
| 12 | 26.02 | 26.67 |
| 12.5 | 26.43 | 27.24 |
| 13 | 26.84 | 27.76 |
| 13.5 | 27.25 | 28.20 |
| 14 | 27.63 | 28.57 |
| 14.5 | 27.98 | 28.87 |
| 15 | 28.30 | 29.11 |
| 15.5 | 28.60 | 29.29 |
| 16 | 28.88 | 29.43 |
| 16.5 | 29.14 | 29.56 |
| 17 | 29.41 | 29.69 |
| 17.5 | 29.70 | 29.84 |

| Cross References |
| --- |
| Non-Incretin Medications for Obesity and Overweight, Medication Policy Manual, Policy No. dru778 |
| GLP-1 Agonist-Containing Medications for Diabetes, Medication Policy Manual, Policy No. dru750 |
| Non-preferred Drugs, Medication Policy Manual, Policy No. dru760 |

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*Revision History*

| Revision Date | Revision Summary |
|---|---|
| 4/3/2025 | Added criteria for use in obstructive sleep apnea (OSA) for Zepbound (tirzepatide). |
| 12/12/2024 | • Removed acute use language in continuation of therapy criteria.<br>• Clarified MACE indication is for secondary prevention. No change to intent.<br>• Updated policy to further highlight requirement of obesity benefit for coverage when used for obesity/overweight. No change to intent.<br>• Updated new start and continuation of therapy criteria to require clinical documentation. |
| 6/20/2024 | New policy effective 8/1/2024. |

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