BENEFIT EXCLUSION OVERRIDES POLICY

POLICY: Non-Weight Loss Indications – Wegovy and Zepbound Benefit Exclusion Overrides Policy
- Wegovy® (semaglutide subcutaneous injection – Novo Nordisk)
- Zepbound® (tirzepatide subcutaneous injection – Eli Lilly)

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CIGNA NATIONAL FORMULARY COVERAGE:

OVERVIEW

Wegovy and Zepbound are indicated in combination with a reduced-calorie diet and increased physical activity:[1,4]
- To **reduce excess body weight and maintain weight reduction long term** in:
  - **Wegovy and Zepbound:** Adults with overweight in the presence of at least one weight-related comorbid condition.[1,3]
  - **Wegovy and Zepbound:** Adults with obesity.[1,3,4]
  - **Wegovy:** Pediatric patients ≥ 12 years of age with obesity.[1]

Wegovy is also indicated in combination with a reduced-calorie diet and increased physical activity:[1]

- To **reduce the risk of major adverse cardiovascular (CV) events** (CV death, non-fatal myocardial infarction {MI}, or non-fatal stroke) in adults with established CV disease and either **obesity or overweight**.[1,2]
- For the treatment of **non-cirrhotic metabolic dysfunction-associated steatohepatitis (MASH)**, formerly known as non-alcoholic steatohepatitis (NASH), with moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis) in adults.[1,25-26]

Zepbound is indicated in combination with a reduced-calorie diet and increased physical activity:[4]

- To treat **moderate to severe obstructive sleep apnea** (OSA) in adults with **obesity**.

Dosing

In the prescribing information for Wegovy, a recommended dose escalation schedule of 16 weeks is outlined (the 2.4 mg dose would be reached at the start of Week 17).[1] If a patient does not tolerate a dose during dose escalation, consider delaying dose escalation for 4 weeks. For CV risk reduction and weight reduction, the maintenance dose of Wegovy is 2.4 mg (recommended) or 1.7 mg injected subcutaneously (SC) once weekly (QW); consider treatment response and tolerability when selecting the maintenance dose. For MASH, the recommended maintenance dose is 2.4 mg QW. If the patient does not tolerate 2.4 mg QW, the dose can be decreased to 1.7 mg QW. Consider re-escalation to 2.4 mg QW.

In the prescribing information for Zepbound, the recommended starting dose is 2.5 mg SC QW.[9] The 2.5 mg dose is for treatment initiation and is not intended for chronic weight management. After 4 weeks, the dose can be increased to 5 mg QW. The dose can then be increased in 2.5 mg increments, after at least 4 weeks on the current dose. The recommended maintenance doses for weight reduction and long-term maintenance are 5 mg, 10 mg, or 15 mg QW. The recommended maintenance dose in OSA is 10 mg or 15 mg QW. The treatment response and tolerability should be considered when selecting the maintenance dose. If a patient does not tolerate a maintenance dose, consider a lower maintenance dose. The maximum dose is 15 mg QW. The 5 mg, 10 mg, and 15 mg maintenance doses are reached after Week 4, Week 12, and Week 20, respectively.

Clinical Efficacy

Secondary Prevention of MACE

SELECT was a randomized, double-blind, placebo-controlled, event-driven study that assessed Wegovy vs. placebo, when added to standard of care, for the secondary prevention of CV events in adults ≥ 45 years of age with BMI ≥ 27 kg/m^2 and established CV disease without diabetes (n = 17, 604).[2] Established CV disease was defined as one of the following: prior MI, prior stroke (ischemic or hemorrhagic), and/or symptomatic peripheral arterial disease (as evidenced by intermittent claudication with ankle-brachial index < 0.85, peripheral arterial revascularization procedure, or amputation due to atherosclerotic disease). The

trial excluded patients who had received a GLP-1 or GLP-1/GIP agonist within 90 days of enrollment. Patients who developed diabetes during the study remained in the study and received treatment (excluding use of another GLP-1 or GLP-1/GIP agonist). Wegovy was titrated to reach the 2.4 mg QW maintenance dose over 16 weeks. However, if dose escalation led to unacceptable effects, the dose escalation intervals could be extended, treatment could be paused, or maintenance doses < 2.4 mg QW could be used. Very few patients (< 0.1%) were treated with weight-lowering pharmacotherapy at baseline (further detail is not available; however, concomitant GLP-1 agonist use was not allowed).[3] The mean hemoglobin A_{1c} (HbA_{1c}) was just over 5.7%; 67% of patients had a $HbA_{1c} \geq 5.7\%$ (pre-diabetes). The most common prior CV event was MI (68% of patients), followed by stroke (18%), and 4.5% of patients had symptomatic peripheral arterial disease; 8% of patients had two or more of these conditions. At baseline, 91.8% of patients were receiving CV risk-lowering pharmacotherapy, 90% of patients were receiving lipid-lowering agents (87.3% of patients were taking statins, 13.0% of patients were taking ezetimibe, 2.7% of patients were taking fibrates, and 2.0% of patients were taking proprotein convertase subtilisin/kexin type 9 inhibitors), 86.2% of patients were receiving platelet aggregation inhibitors, and 12.6% of patients were receiving antithrombotic medications.[2,3] In addition, 70.2% of patients were taking beta-blockers, 45.0% of patients were taking angiotensin converting enzyme inhibitors, and 29.5% of patients were taking angiotensin receptor blockers.[3] The primary efficacy endpoint was a composite of death from CV causes, non-fatal MI, or non-fatal stroke.[2]

Results. Patients were followed for a mean of 39.8 months.[2] At Week 104, approximately 77% of patients receiving Wegovy were taking the target 2.4 mg QW dose (details on the exact proportions of patients on other Wegovy doses are not available; efficacy results are only provided for the 2.4 mg dose). The trial achieved its primary endpoint, demonstrating a statistically significant and superior reduction in MACE for Wegovy vs. placebo. A primary endpoint event occurred in 6.5% vs. 8.0% of patients in the Wegovy vs. placebo groups, respectively (hazard ratio [HR] 0.80; 95% confidence interval [CI]: 0.72, 0.90; P < 0.001). Death from CV events, the first confirmatory secondary endpoint, occurred in 2.5% vs. 3.0% of Wegovy- vs. placebo-treated patients, respectively (HR 0.85; 95% CI: 0.71, 1.01; P = not significant for superiority). Because the difference between groups for death from CV events did not meet the required P-value for superiority, testing was not performed for the remaining confirmatory and secondary endpoints.

MASH

The ESSENCE trial (Part 1 n = 800), a two-part, ongoing. Phase III, multicenter, double-blind, parallel-group trial randomized adults with MASH and stage F2 to F3 fibrosis to Wegovy or placebo, both in addition to standard of care (optimization of treatment for type 2 diabetes, dyslipidemia, and CV risk management).[12,13] Results from Part 1 have been published. Eligible patients were ≥ 18 years of age with histological presence of steatohepatitis with stage F2 to F3 fibrosis according to NASH Clinical Research Network classification and a non-alcoholic fatty liver disease (NAFLD) activity score (NAS) of ≥ 4, with a score of ≥ 1 in each component (steatosis, lobular inflammation, and hepatocyte ballooning), based on central

pathologist evaluation of a baseline liver biopsy. Patients with an average alcohol consumption of ≥ 20 grams/day for women or ≥ 30 grams/day for men or alcohol dependence were excluded.[12,13] Patients taking stable doses of pioglitazone, vitamin E, glucose lowering agent(s), lipid-lowering medication(s), and weight loss medication(s) were allowed to continue these therapies. Rezdiffra™ (resmetirom tablets) was not approved at the time the trial commenced; therefore, no patients were taking Rezdiffra in Part 1 of this trial. Concomitant use of any other GLP-1 or GLP-1/GIP agonist was not allowed. In patients randomized to Wegovy, the dose was escalated over 16 weeks to reach Wegovy 2.4 mg SC QW. Patients could continue to receive a lower dose of Wegovy if they had unacceptable side effects while receiving the designated target dose and would otherwise discontinue the study.[12] The two primary histologic endpoints were: 1) Resolution of steatohepatitis and no worsening of liver fibrosis; and 2) Improvement in liver fibrosis and no worsening of steatohepatitis. In Part 2 of the trial, the primary endpoint will be cirrhosis-free survival at Week 240 (ongoing). Overall, 56% of patients had type 2 diabetes. The mean BMI was 34.6 kg/m^2 and most patients had a BMI ≥ 35 kg/m^2 (41.3%); 31.5% of patients had a BMI ≥ 30 kg/m^2 to < 35 kg/m^2, 20.5% of patients had a BMI of ≥ 25 kg/m^2 to < 30 kg/m^2, and 6.6% of patients had a BMI < 25 kg/m^2. Most patients fulfilled four (27.8%) or five (43.3%) of five metabolic dysfunction-associated metabolic liver disease (MASLD) cardiometabolic criteria (i.e., BMI ≥ 25 kg/m^2 [≥ 23 kg/m^2 Asia] or waist circumference > 94 cm [male] or > 80 cm [female] or ethnicity adjusted equivalent; fasting serum glucose ≥ 100 mg/dL or 2-hour post-prandial glucose ≥ 140 mg/dL or type 2 diabetes or treatment for type 2 diabetes; blood pressure ≥ 130/85 mmHg or specific antihypertensive drug treatment; plasma high-density lipoprotein cholesterol [HDL-C] ≤ 40 mg/dL [male] and ≤ 50 mg/dL [female] or lipid-lowering treatment). Most patients had stage F3 fibrosis (68.8%); 31.3% of patients had stage F2 fibrosis. The mean NAS was 5.05 (5.11 in patients with stage F3 fibrosis and 4.92 in patients with stage F2 fibrosis).

Results. At the time of the primary endpoint assessment 83.5% of patients were taking Wegovy 2.4 mg QW.[13] At the interim analysis (the first 800 patients enrolled in the trial), the between-group differences for both primary endpoints were significant for Wegovy vs. placebo. Wegovy demonstrated a significant improvement in liver fibrosis with no worsening of steatohepatitis, as well as resolution of steatohepatitis with no worsening of liver fibrosis. At Week 72, 62.9% vs. 34.1% of patients treated with Wegovy vs. placebo, respectively, achieved resolution of steatohepatitis with no worsening of liver fibrosis (estimated difference 28.7%; 95% CI: 21.1%, 36.2%; P < 0.001). In addition, at Week 72, 36.8% vs. 22.4% of patients treated with Wegovy vs. placebo, respectively, had a reduction in liver fibrosis with no worsening of steatohepatitis (estimated difference 14.4%; 95% CI: 7.5%, 21.3%; P < 0.001). Confirmatory secondary endpoints also generally favored Wegovy (e.g., resolution of steatohepatitis with improvement in liver fibrosis, weight change). At Week 72, the proportion of patients with both resolution of steatohepatitis and improvement in fibrosis was 32.7% vs. 16.1% of patients receiving Wegovy vs. placebo, respectively (difference 16.5%; 95% CI: 10.2% to 22.8%, respectively; P < 0.001). The mean change in body weight was -10.5% vs. -2.0% for Wegovy vs. placebo, respectively (difference -8.5%; 95% CI:

-9.6%, -7.4%; P < 0.001). Improvements in liver enzymes, non-invasive liver tests, and other metabolic parameters also favored Wegovy. Among patients with F2 fibrosis (Wegovy vs. placebo), 45.0% vs. 22.7% of patients, respectively, had improvement of fibrosis, 37.1% vs. 42.4% of patients, respectively, had no change in fibrosis, and 17.9% vs. 34.8% of patients, respectively, had worsening of fibrosis. Part 2 of the trial is ongoing and expected to read out in 2029.

OSA

The SURMOUNT-OSA (n = 469) trials were two 52-week, Phase III, multicenter, double-blind, randomized trials that evaluated the efficacy and safety of maximally tolerated Zepbound (10 mg or 15 mg QW) in adults with obesity (without diabetes) and moderate to severe OSA.[5] Two patient populations were included. In Trial 1, patients were unable or unwilling to use positive airway pressure (PAP) therapy, and in Trial 2, patients had been using PAP therapy for ≥ 3 months at the time of screening and planned to continue PAP therapy during the trial. All patients had a diagnosis of moderate to severe OSA with an apnea-hypopnea index (AHI) ≥ 15 events/hour as diagnosed with polysomnography, home sleep apnea test, or other methods that met local guidelines prior to Visit 1. Patients had a BMI of ≥ 30 kg/m^2 (≥ 27 kg/m^2 in Japan) despite the history of at least one self-reported unsuccessful dietary effort to lose weight. Key exclusion criteria were the presence of type 1 or type 2 diabetes (HbA_{1c} ≥ 6.5% at Visit 1), change in weight of > 5 kg in the past 3 months, planned surgery for sleep apnea or obesity, diagnosis of central or mixed sleep apnea with the percentage of mixed or central apneas/hypopneas ≥ 50%, or diagnosis of Cheyne Stokes respiration, diagnosis of obesity hypoventilation syndrome or daytime hypocapnia, active device treatment of OSA other than PAP therapy (e.g., dental appliance), and major craniofacial abnormalities that may affect breathing. In addition, use of medications (prescribed or over-the-counter) or alternative remedies to promote weight loss in the past 3 months was not allowed, this included other GLP-1 or GLP-1/GIP agonists. Of note, although patients with diabetes at baseline were excluded, if a patient developed diabetes while in the study, the patient was referred to their usual care provider. The decision to further evaluate, to initiate antihyperglycemic therapy, and the choice of antihyperglycemic medication was at the discretion of the provider. Following a 4-week screening period, patients were assigned to Trial 1 or Trial 2 and randomly assigned to receive Zepbound or placebo SC QW. All patients received regular lifestyle counseling sessions focused on the maintenance of healthy nutrition, adherence to a 500 calorie/day deficit, and ≥ 150 minutes per week of physical activity. The dose of Zepbound was escalated over a period of up to 20 weeks starting at 2.5 mg SC QW and increased by 2.5 mg every 4 weeks during the dose-escalation period until the patient reached the maximum tolerated dose of 10 mg or 15 mg SC QW at Week 20. Dose modification was permitted for the management of intolerable gastrointestinal (GI) symptoms. Patients who did not tolerate ≥ 10 mg even after one de-escalation and re-escalation attempt were discontinued from the study intervention but remained in the study for continued follow-up. During the first 24 weeks of the treatment period (20-week dose escalation plus 4 weeks), patients unable to tolerate 2.5 mg or 5 mg were discontinued from the study intervention but remained in the study. For patients unable to tolerate any dose escalation between 7.5 mg and 15 mg (inclusive), a

dose de-escalation step with subsequent re-escalation by 2.5 mg every 4 weeks up to the maximum tolerated dose was allowed in a blinded fashion, to reach either the 10 mg or 15 mg dose. Only one cycle of dose de-escalation and re-escalation was permitted during the first 24 weeks of the treatment period. The 10 mg maintenance dose was used in patients who tolerated 10 mg, but not 12.5 mg or 15 mg even following one de-escalation and re-escalation attempt. In addition, patients who tolerated 12.5 mg, but not 15 mg even after one de-escalation and re-escalation attempt, continued 10 mg as their maximum tolerated dose. Patients who tolerated 15 mg continued 15 mg as their maximum tolerated dose.

The primary endpoint was the superiority of Zepbound vs. placebo for the change in the AHI from baseline.[5] Several key secondary endpoints were assessed, including the proportion of patients with an AHI reduction of ≥ 50%, the proportion of patients with an AHI of < 5 events/hour or with an AHI of 5 to 14 events/hour and a score of ≤ 10 on the Epworth Sleepiness Scale (ESS; scores range from 0 to 24 with higher scores indicating greater daytime sleepiness), percent change in body weight, change in high-sensitivity C-reactive protein (hsCRP), change in sleep apnea specific hypoxic burden, changes in patient-reported outcome measures, and the change in systolic blood pressure. In Trial 1, the mean BMI was 39.1 kg/m^2 and the mean AHI was 51.5 events/hour. Most patients had severe OSA (63%). In Trial 2, the mean BMI was 38.7 kg/m^2 and the mean AHI was 49.5 events/hour. Most patients had severe OSA (68%).

Results. In both trials, Zepbound was superior to placebo for the primary endpoint. In Trial 1, the change in AHI at Week 52 with Zepbound was superior to placebo (-25.3 events/hour [95% CI: -29.3, -21.2] vs. -5.3 events/hour [95% CI: -9.4, -1.1], respectively; estimated treatment difference of -20.0 events/hour; 95% CI: -25.8, -14.2; P < 0.001).[5] In Trial 2, the change in AHI at Week 52 with Zepbound was superior to placebo (-29.3 events/hour [95% CI: -33.2, -25.4] vs. -5.5 events/hour [95% CI: -9.9, -1.2], respectively; estimated treatment difference of -23.8 events/hour; 95% CI: -26.9, -17.9; P < 0.001). Additionally, patients in both trials who received Zepbound had significant reductions in sleep apnea-specific hypoxic burden. The proportion of patients with a reduction in the AHI of ≥ 50% at Week 52 and the proportion of patients with an AHI of < 5 events/hour or an AHI of 5 to 14 events/hour and an ESS of ≤ 10 at Week 52 also favored Zepbound. Patients receiving Zepbound in both trials had significant reductions in body weight, systolic blood pressure, and hsCRP concentrations as well.

Guidelines

MASH

Available recommendations for MASH predate the availability of the published ESSENCE trial data and the approval of Wegovy for MASH. Note: The titles and verbiage within individual publications may not reflect the current MASH or MASLD nomenclature due to the timing of the respective publication. The nomenclature used in this section is reflective of that used within each publication.

The American Association for the Study of Liver Diseases (AASLD) Practice Guidance on the Clinical Management of NAFLD (2023) was updated in October

2024 to address the approval of Rezdiffra for MASLD.[14] Some recommendations regarding other therapies (e.g., GLP-1 agonists) are also made. Regardless of treatment, the management of MASLD should include comprehensive lifestyle modification (e.g., nutrition, exercise, and behavior modification) and optimal control of comorbid metabolic conditions. Further, given the comorbidity profile of individuals with MASLD, CV risk management is an important aspect of medical management. MASH can only be definitively diagnosed by histologic exam (biopsy), in practice, patient selection is based on evidence of steatosis and fibrosis as determined by non-invasive liver disease assessments (NILDAs) in patients with cardiometabolic risk factors without other causes of steatosis, notably, alcohol consumption of > 20 g/day for women and > 30 g/day for men. There are no FDA-approved NILDAs to diagnose MASH with stage F2 to F3 fibrosis or to monitor the response to pharmacotherapy. In general, imaging-based NILDAs such as liver stiffness measurement by vibration-controlled transient elastography (VCTE) or magnetic resonance elastography have better accuracy in assessing fibrosis vs. blood-based tests. In general, magnetic resonance spectroscopy and magnetic resonance imaging proton density fat fraction are considered the most accurate quantitative measures of hepatic steatosis, followed by VCTE-controlled attenuation parameter score and gray scale ultrasound. However, for the purpose of selecting patients for treatment with non-quantitative imaging evidence of hepatic steatosis (e.g., ultrasonographic evidence) in individuals with at least one cardiometabolic risk factor and F2 or F3 fibrosis may be sufficient. Liver biopsy is not typically recommended for fibrosis staging in current clinical practice; however, histologic exam remains the gold standard to quantify fibrosis if performed previously (historical biopsy obtained reasonably recently, e.g., within 3 years). Since NILDAs are more readily available than liver biopsy, it is recommended that more current data (e.g., within 6 to 12 months) be utilized to determine patients who are appropriate candidates for treatment. Regardless of treatment, the management of MASLD should include comprehensive lifestyle modification (e.g., nutrition, exercise, and behavior modification) and optimal control of comorbid metabolic conditions.

The American Diabetes Association (ADA) Standards of Care (2025) provide recommendations for the management of patients with type 2 diabetes and MASLD or MASH.[18] In adults with type 2 diabetes, MASLD, and overweight or obesity, a GLP-1 agonist (i.e., liraglutide, semaglutide) or GLP-1/GIP agonist (i.e., tirzepatide) with potential benefits in MASH, in addition to healthy interventions for weight loss, is recommended for glycemic management. In adults with type 2 diabetes and MASH or those at high-risk for liver fibrosis (based on non-invasive tests), pioglitazone, GLP-1 agonists, or a GLP-1/GIP agonist is preferred for glycemic management due to potential beneficial effects on MASH.

The ADA Consensus Report on MASLD in People with Diabetes (2025) largely provides recommendations similar to those outlined in the ADA standards of care for patients with type 2 diabetes and MASLD or MASH.[15] In patients with at-risk MASH (stage F2 to F3 fibrosis) Rezdiffra may be considered after treatment optimization for obesity and/or diabetes therapies for at least 6 to 12 months. The addition of Rezdiffra should be initiated by a hepatologist or gastroenterologist with

expertise in MASH. For the treatment of diabetes, preference should be given to treatments with evidence of safety and effectiveness for steatohepatitis from high-quality trials (e.g., GLP-1 agonists and/or pioglitazone, or GLP-1/GIP agonist), with the dual purpose of treating hyperglycemia and steatohepatitis. Once cirrhosis is established there are no effective treatments. Similar to the AASLD update, the report acknowledges the data are limited for combination use of Rezdiffra with medications often used for comorbidities in MASLD (e.g., pioglitazone, GLP-1 agonist, or GLP-1/GIP agonist). People with obesity and type 2 diabetes should make it a priority to optimize lifestyle and medical management with a GLP-1 agonist, pioglitazone, or their combination, or a GLP-1/GIP agonist with potential benefits for steatohepatitis.

The American Academy of Clinical Endocrinology Clinical Practice Guideline (co-sponsored by AASLD) [2022] for the Diagnosis and Management of NAFLD in Primary Care and Endocrinology Settings discusses medications that have been proven to be effective for the treatment of liver disease and cardiometabolic conditions associated with NAFLD or NASH.[16] The use of obesity pharmacotherapy in adjunct to lifestyle modification for individuals with obesity and NAFLD or NASH with a goal of ≥ 5%, and preferably ≥ 10%, weight loss is recommended, when this is not effectively achieved by lifestyle modification alone. For chronic weight management in individuals with a BMI ≥ 27 kg/m^2 and NAFLD or NASH obesity pharmacotherapy should be considered (preference is given to Wegovy [2.4 mg/week, best evidence] or Saxenda [3 mg/day]). These therapies must be considered as adjuncts to lifestyle modification for individuals with obesity and NAFLD or NASH to promote cardiometabolic health and treat or prevent type 2 diabetes, CV disease, and other end-stage manifestations of obesity.

The American Heart Association Scientific Statement on NAFLD and CV risk (2022) provides several key take-away messages for healthcare providers.[17] NASH is recognized as a contributor to, and marker for, increased atherosclerotic CV disease risk. Many risk factors for NAFLD are also risk factors for atherosclerotic CV disease; NAFLD can be considered a risk enhancer when atherosclerotic CV disease risk is assessed. Similar to the other publications, lifestyle intervention is the key therapeutic intervention for patients with NAFLD. Dietary modification, increased physical activity, weight loss, and alcohol avoidance are strongly encouraged. Weight loss pharmacotherapy such as phentermine, Qsymia® (phentermine/topiramate extended-release capsules), Contrave® (naltrexone/bupropion extended-release tablets), high-dose liraglutide, high-dose semaglutide, and orlistat may be appropriate and effective to achieve sustained weight loss in some patients with BMI > 30 or ≥ 27 kg/m^2 with comorbidities; however, the role of these agents in the management of NAFLD and NASH is currently undefined. Bariatric surgery should be considered in patients with NAFLD or NASH with BMI > 35 kg/m^2 as it is the most effective intervention for achieving sustained weight loss in such individuals with a median body weight loss of 21% to 30%.

Sleep Apnea

The American Academy of Sleep Medicine (2017) recommends that diagnostic testing for OSA be performed in combination with a comprehensive sleep evaluation.[6] Polysomnography is the standard diagnostic test for the diagnosis of OSA in adults in whom there is concern for OSA based on the sleep evaluation. Polysomnography is accepted as the gold standard test for the diagnosis of OSA. In some cases, and within the appropriate context, the use of home sleep apnea test as the initial sleep study may be acceptable, however, polysomnography should be used when home sleep apnea test results do not provide satisfactory posttest probability of confirming or ruling out OSA.

Available treatment guidelines for OSA do not specifically mention the GLP-1 agonists. The American Thoracic Society clinical practice guideline on the role of weight management in the treatment with adults with OSA (2018) recommends that patients with OSA who are overweight or obese (BMI ≥ 25 kg/m^2) participate in comprehensive lifestyle intervention that includes a reduced calorie diet, exercise/increased physical activity, and behavioral counseling.[7] For patients with OSA and a BMI ≥ 27 kg/m^2 who have not had an improvement in weight despite a comprehensive weight-loss lifestyle program, and have no contraindications (no active CV disease), evaluation for anti-obesity medication is suggested. The guideline also cites agreement with the American Association of Clinical Endocrinologists and the American College of Endocrinology guidelines (2016)[19], which state the weight-loss goal in patients with overweight or obesity with OSA should be ≥ 7% to 11% of total body weight.[7] In patients with a BMI ≥ 35 kg/m^2, referral for bariatric surgery evaluation is suggested.

The American College of Physicians clinical practice guideline for the management of OSA (2013) recommends that all overweight and obese patients diagnosed with OSA be encouraged to lose weight.[8] Continuous PAP is recommended as initial therapy for patients with OSA. Mandibular advancement devices are recommended for patients with OSA who prefer such devices or for those with adverse events associated with continuous PAP treatment.

Clinical success in OSA has been described by several publications. The American Academy of Sleep Medicine (2019) cites a clinically significant threshold of ≥ 15 events/hour (on AHI)[9] and a clinical practice guideline for the treatment of OSA and snoring with oral appliance therapy (2015) from the American Academy of Sleep Medicine and American Academy of Dental Sleep Medicine[10] notes that treatment success is usually defined as a reduction in the AHI to a specific level (e.g., post-treatment AHI < 5 events/hour, or a > 50% reduction in AHI). Of note, a meta-analysis on the impact of weight reduction on AHI reported that weight reduction in patients with obesity and OSA was associated with improvements in the severity of OSA. A BMI reduction of 20% was associated with an AHI reduction of 57%; further weight reduction beyond 20% in BMI was associated with a smaller effect on AHI.[11]

POLICY STATEMENT

This Benefit Exclusion Overrides policy has been developed to authorize coverage of the targeted drug(s) for approved medical conditions, except weight loss. This Benefit Exclusion Overrides policy is not applicable if clients have weight loss as a covered benefit. In the clinical criteria, as appropriate, an asterisk (*) is noted next to the specified gender. In this context, the specified gender is defined as follows: males are defined as individuals with the biological traits of a male, regardless of the individual's gender identity or gender expression; females are defined as individuals with the biological traits of a female, regardless of the individual's gender identity or gender expression. Because of the specialized skills required for evaluation and diagnosis of patients treated with Wegovy for metabolic dysfunction-associated steatohepatitis (MASH)/non-alcoholic steatohepatitis (NASH) as well as the monitoring required for adverse events and long-term efficacy, approval requires Wegovy for MASH/NASH to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below.

Documentation: Documentation is required for use of Wegovy for MASH/NASH as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory results, medical test results, claims records, prescription receipts, and/or other information. All documentation must include patient-specific identifying information.

I. Wegovy is(are) covered as medically necessary when the following criteria is(are) met for FDA-approved indication(s) or other uses with supportive evidence (if applicable):

1. **Major Adverse Cardiovascular Event(s) Risk Reduction in a Patient with Established Cardiovascular Disease with Overweight or Obesity.** Approve for 1 year if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve if the patient meets ALL of the following (i, ii, iii, iv, and v):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Patient has a current BMI ≥ 27 kg/m^2; AND
     - **iii.** Patient meets ONE of the following (a, b, or c):
       - **a)** Patient has had a prior myocardial infarction; OR
       - **b)** Patient has had a prior stroke; OR
         Note: This does not include a transient ischemic attack (TIA).
       - **c)** Patient has a history of symptomatic peripheral arterial disease as evidenced by ONE of the following [(1), (2), or (3)]:
         - **(1)** Intermittent claudication with ankle-brachial index < 0.85; OR
         - **(2)** Peripheral arterial revascularization procedure; OR
         - **(3)** Amputation due to atherosclerotic disease; AND
     - **iv.** According to the prescriber, the medication will be used in combination with optimized pharmacotherapy for established cardiovascular disease; AND
     - **v.** The medication will be used concomitantly with behavioral modification and a reduced-calorie diet; OR

B) Patient is Continuing Therapy with Wegovy. Approve if the patient meets ALL of the following (i, ii, iii, iv, and v):
Note: For a patient who has not completed 1 year of initial therapy, refer to Initial Therapy criteria above.
i. Patient is ≥ 18 years of age; AND
ii. At baseline, patient had a BMI ≥ 27 kg/m^2; AND
Note: This refers to baseline prior to Wegovy.
iii. Patient meets ONE of the following (a, b, or c):
a) Patient has had a prior myocardial infarction; OR
b) Patient has had a prior stroke; OR
c) Patient has a history of symptomatic peripheral arterial disease as evidenced by ONE of the following [(1), (2), or (3)]:
(1) Intermittent claudication with ankle-brachial index < 0.85; OR
(2) Peripheral arterial revascularization procedure; OR
(3) Amputation due to atherosclerotic disease; AND
iv. According to the prescriber, the medication will be used in combination with optimized pharmacotherapy for established cardiovascular disease; AND
v. The medication will be used concomitantly with behavioral modification and a reduced-calorie diet.

2. Metabolic Dysfunction-Associated Steatohepatitis (MASH)/Non-Alcoholic Steatohepatitis (NASH). Approve for 1 year if the patient meets the ONE of the following (A or B):
A) Initial Therapy: Approve if the patient meets ALL of the following (i, ii, iii, iv, v, vi, vi, and viii):
i. Patient is ≥ 18 years of age; AND
ii. Patient does not have cirrhosis; AND
iii. The diagnosis of MASH/NASH is confirmed by ONE of the following (a or b):
a) Patient has had a liver biopsy AND meets BOTH of the following [(1) and (2)]:
(1) Liver biopsy has been performed within the 3 years preceding treatment with Wegovy **[documentation required]**; AND
(2) Liver biopsy shows non-alcoholic fatty liver disease activity score of ≥ 4 with a score of ≥ 1 in ALL of the following ([i], [ii], and [iii]) **[documentation required]**:
(i) Steatosis; AND
(ii) Ballooning; AND
(iii) Lobular inflammation; OR
b) Patient has had ONE of the following imaging exams performed within the 6 months preceding treatment with Wegovy [(1), (2), or (3)] **[documentation required]**:
(1) Elastography; OR
Note: Examples of elastography include, but are not limited to vibration-controlled transient elastography (e.g., FibroScan), transient elastography, magnetic resonance elastography, acoustic radiation force impulse imaging, shear wave elastography.

(2) Computed tomography; OR
(3) Magnetic resonance imaging; AND

iv. Patient meets ONE of the following prior to treatment with Wegovy (a or b) **[documentation required]**:
a) Patient has stage F2 fibrosis; OR
b) Patient has stage F3 fibrosis; AND

v. According to the prescriber, the patient has ONE or more of the following metabolic risk factors that are managed according to standard of care (a, b, c, d, e):
a) Central obesity;
b) Hypertriglyceridemia;
c) Reduced high-density lipoprotein cholesterol;
d) Hypertension;
e) Elevated fasting plasma glucose indicative of diabetes or pre-diabetes; AND

vi. According to the prescriber, patient meets ONE of the following (a or b):
a) Female* patient: Alcohol consumption is < 20 grams/day; OR
Note: One standard drink (or one alcoholic drink equivalent) contains roughly 14 grams of pure alcohol, which is found in 12 ounces of regular beer, 5 ounces of wine, or 1.5 ounces of distilled spirits.
b) Male* patient: Alcohol consumption < 30 grams/day; AND
Note: One standard drink (or one alcoholic drink equivalent) contains roughly 14 grams of pure alcohol, which is found in 12 ounces of regular beer, 5 ounces of wine, or 1.5 ounces of distilled spirits.

vii. The medication will be used in combination with appropriate diet and exercise therapy; AND

viii. The medication is prescribed by or in consultation with an endocrinologist, gastroenterologist, or hepatologist; OR

B) Patient is Currently Receiving Wegovy: Approve if the patient meets ALL of the following (i, ii, iii, iv, v, and vi):
Note: A patient who has received < 1 year of therapy or who is restarting therapy should be considered under criterion A (Initial Therapy).

i. Patient has completed ≥ 1 year of therapy with Wegovy AND according to the prescriber, the patient has not had worsening of fibrosis or MASH/NASH; AND
Note: This applies to a patient starting their second (or more) year of therapy with Wegovy (i.e., the patient has already completed 1 year or more of therapy with Wegovy).

ii. According to the prescriber, patient has not progressed to stage F4 (cirrhosis); AND

iii. According to the prescriber, metabolic risk factors are managed according to standard of care; AND

iv. According to the prescriber, patient meets ONE of the following (a or b):
a) Female* patient: Alcohol consumption is < 20 grams/day; OR
Note: One standard drink (or one alcoholic drink equivalent) contains roughly 14 grams of pure alcohol, which is found in 12 ounces of regular beer, 5 ounces of wine, or 1.5 ounces of distilled spirits.
b) Male* patient: Alcohol consumption < 30 grams/day; AND

Note: One standard drink (or one alcoholic drink equivalent) contains roughly 14 grams of pure alcohol, which is found in 12 ounces of regular beer, 5 ounces of wine, or 1.5 ounces of distilled spirits.

v. The medication will be used in combination with appropriate diet and exercise therapy; AND

vi. The medication is prescribed by or in consultation with an endocrinologist, gastroenterologist, or hepatologist.

*Refer to the Policy Statement

II. Zepbound is(are) covered as medically necessary when the following criteria is(are) met for FDA-approved indication(s) or other uses with supportive evidence (if applicable):

1. Obstructive Sleep Apnea, Moderate to Severe, in a Patient with Obesity.
Approve for 1 year if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve if the patient meets ALL of the following (i, ii, iii, iv, and v):

i. Patient is ≥ 18 years of age; AND

ii. Patient has a current BMI ≥ 30 kg/m^2; AND

iii. Patient has had a sleep study that shows BOTH of the following (a and b):

a) Patient has been diagnosed with moderate to severe obstructive sleep apnea; AND

b) Patient has an apnea-hypopnea index ≥ 15 events per hour; AND

Note: A diagnosis of moderate obstructive sleep apnea is an apnea-hypopnea index of ≥ 15 events per hour and a diagnosis of severe sleep apnea is an apnea-hypopnea index ≥ 30 events per hour. The apnea-hypopnea index is the number of apneas and hypopneas during 1 hour of sleep.

iv. The patient does NOT meet either of the following (a or b):

Note: A patient who has one or more of the following conditions/diagnoses below is not approved.

a) Central sleep apnea with percent of central apneas/hypopneas ≥ 50%; OR

b) Cheyne Stokes respiration; AND

v. The medication will be used concomitantly with behavioral modification and a reduced-calorie diet; OR

B) Patient is Continuing Therapy with Zepbound. Approve if the patient meets ALL of the following (i, ii, iii, and iv):

Note: For a patient who has not completed 1 year of initial therapy, refer to Initial Therapy criteria above.

i. Patient is ≥ 18 years of age; AND

ii. At baseline, patient had a BMI ≥ 30 kg/m^2; AND

Note: This refers to baseline prior to Zepbound.

iii. Patient has completed ≥ 1 year of therapy with Zepbound AND the patient meets BOTH of the following (a and b):

a) Patient has lost ≥ 10% of baseline body weight; AND

b) According to the prescriber, patient has stability in obstructive sleep apnea signs or symptoms; AND
Note: Examples of signs or symptoms of obstructive sleep apnea include but are not limited to snoring, excessive daytime sleepiness, fatigue.

iv. The medication will be used concomitantly with behavioral modification and a reduced-calorie diet.

CONDITIONS NOT COVERED

- **Wegovy® (semaglutide subcutaneous injection – Novo Nordisk)**
- **Zepbound® (tirzepatide subcutaneous injection – Eli Lilly)**

is(are) considered not medically necessary for ANY other use(s) including the following (this list may not be all inclusive; criteria will be updated as new published data are available):

1. **Weight Loss**. Coverage is determined by the member's prescription benefit coverage of weight loss drugs.

2. **Concomitant Use with Glucagon-Like Peptide-1 (GLP-1) Agonists or GLP-1/ Glucose-Dependent Insulinotropic Polypeptide (GIP) Agonists.** In the SELECT trial, patients could not receive concomitant GLP-1 agonists or GLP-1/GIP1 agonists.[2,3] Patients who developed diabetes during the study remained in the study and received other forms of treatment (not GLP-1 agonists or GLP-1/GIP agonists). Further, the SELECT and ESSENCE trials excluded patients who had received a GLP-1 or GLP-1/GIP agonist within 90 days of enrollment.[2,3,12,13] The SURMOUNT OSA trial did not include patients taking other GLP-1 agonists.[5] The GLP-1 agonists and the GLP-1/GIP agonist should not be combined with each other or with any other GLP-1 agonists or GLP-1/GIP agonist. There are other GLP-1 and GLP-1/GIP products not included in this policy that are FDA-approved for type 2 diabetes or chronic weight management. Note: Examples of other GLP-1 agonists include but are not limited to exenatide subcutaneous (SC) injection, Ozempic (semaglutide SC injection), Rybelsus (semaglutide tablets), Saxenda (liraglutide subcutaneous injection), Trulicity (dulaglutide SC injection), and liraglutide SC injection (Victoza, generic). An example of a GLP-1/GIP agonist is Mounjaro (tirzepatide SC injection).

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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	10/23/2024

Selected revision	Zepbound was added to the Policy. The Policy title was changed to Non-Weight Loss Indications – Wegovy and Zepbound. Previously titled Non-Weight Loss Indications – Wegovy. Wegovy **Major Adverse Cardiovascular Event(s) Risk Reduction in a Patient with Established Cardiovascular Disease who is Either Obese or Overweight.** Initial Therapy. The criterion requiring that the patient has a BMI ≥ 27 kg/m^2 was clarified to state that the patient has a "current" BMI ≥ 27 kg/m^2. Patient is Continuing Therapy with Wegovy: The criterion that required the patient was able to tolerate the Wegovy maintenance dose of 1.7 mg once weekly or 2.4 mg once weekly was removed. Zepbound **Obstructive Sleep Apnea, Moderate to Severe, in a Patient with Obesity.** A new FDA-approved indication was added to the Policy.	01/08/2025
Selected Revision	Wegovy **Major Adverse Cardiovascular Event(s) Risk Reduction in a Patient with Established Cardiovascular Disease who is Either Obese or Overweight.** Initial Therapy. For the requirement that a patient has had a prior stroke, a note was added to clarify that this does not include a transient ischemic attack (TIA). Zepbound **Obstructive Sleep Apnea, Moderate to Severe, in a Patient with Obesity.** Initial Therapy. The requirement that a patient had a sleep study was modified to remove the timeframe that the sleep study was within the past 1 year. A patient is still required to have a sleep study. Conditions Not Covered: **Concomitant Use with Other Medications FDA-Approved for Weight Loss**. This condition not recommended for approval was clarified to state that concomitant use with other medications FDA-approved for weight loss is not recommended. Previously, the requirement did not specify medications were "FDA-approved" for weight loss. The note with examples of weight loss medications was updated to reflect product availability for medications FDA-approved for weight loss. **Concomitant Use with Glucagon-Like Peptide-1 (GLP-1) Agonists or GLP-1/ Glucose-Dependent Insulinotropic Polypeptide (GIP) Agonists.** The note was updated to reflect availability for other GLP-1 or GLP-1/GIP agonists.	05/28/2025
Selected Revision	Wegovy: **Major Adverse Cardiovascular Event(s) Risk Reduction in a Patient with Established Cardiovascular Disease in a Patient with Overweight or Obesity.** This condition of approval was re-worded from "in an overweight or obese patient" to "in a patient with overweight or obesity".	07/09/2025
Selected Revision	**Policy Statement**: The following was added to the Policy Statement: In clinical criteria, as appropriate, an asterisk (*) is noted next to the specified gender. In this context, the specified gender is defined as follows: males are defined as individuals with the biological traits of a male, regardless of the individual's gender	08/27/2025

	identity or gender expression; females are defined as individuals with the biological traits of a female, regardless of the individual's gender identity or gender expression. Because of the specialized skills required for evaluation and diagnosis of patients treated with Wegovy for (MASH)/non-alcoholic steatohepatitis (NASH) as well as the monitoring required for adverse events and long-term efficacy, approval requires Wegovy for MASH/NASH to be prescribed by or in consultation with a physician who specializes in the condition being treated. **Documentation:** A requirement for documentation was added for the use of Wegovy for metabolic dysfunction-associated steatohepatitis MASH/NASH. Documentation may include, but is not limited to, chart notes, laboratory results, medical test results, claims records, prescription receipts, and/or other information. All documentation must include patient-specific identifying information. <u>Wegovy</u>: **Metabolic Dysfunction-Associated Steatohepatitis (MASH)/Non-Alcoholic Steatohepatitis (NASH).** A new condition of approval was added to FDA-Approved Indications. Conditions Not Covered: **Concomitant Use with Other Medications FDA-Approved for Weight Loss.** This condition not recommended for approval was removed.	

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