Oscar Clinical Guideline: Wegovy (semaglutide) for Cardiovascular Risk Reduction (PG194, Ver. 1)

Wegovy (semaglutide) for Cardiovascular Risk Reduction

Summary

Cardiovascular disease (CVD) is a leading cause of morbidity and mortality worldwide. Atherosclerotic cardiovascular disease (ASCVD), which includes conditions such as coronary heart disease, cerebrovascular disease, and peripheral arterial disease, is responsible for the majority of CV events. Established ASCVD is defined as a history of myocardial infarction, stroke, or symptomatic peripheral arterial disease. Patients with established ASCVD are at high risk for recurrent CV events and mortality.

Obesity and overweight are major modifiable risk factors for the development and progression of ASCVD. Excess adipose tissue, particularly visceral fat, contributes to the pathogenesis of ASCVD through multiple mechanisms, including insulin resistance, dyslipidemia, inflammation, and endothelial dysfunction. Weight loss achieved through lifestyle modifications and pharmacotherapy has been shown to improve CV risk factors, but until recently, there was limited evidence that weight loss medications could reduce CV events in patients with established ASCVD.

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are a class of medications initially developed for the treatment of type 2 diabetes mellitus (T2DM). In addition to their glucose-lowering effects, GLP-1

RAs have been shown to promote weight loss, reduce blood pressure, and improve lipid profiles. Several GLP-1 RAs, including liraglutide and semaglutide, have demonstrated CV benefits in patients with T2DM and high CV risk.

Wegovy (semaglutide) is a glucagon-like peptide-1 receptor agonist (GLP-1 RA) administered subcutaneously once weekly. Initially approved for chronic weight management in adults with obesity or overweight and at least one weight-related comorbidity, Wegovy has recently received an additional indication from the U.S. Food and Drug Administration (FDA) to reduce the risk of major adverse cardiovascular events (MACE) in adults with established atherosclerotic cardiovascular disease (ASCVD) who also have either obesity or overweight.

- This new indication provides an additional treatment option for cardiovascular (CV) risk reduction in this high-risk population, complementing lifestyle modifications and guideline-directed medical therapy. It is important to note that Wegovy is not indicated for CV risk reduction in patients without established ASCVD.
- While Wegovy has shown promise in other potential indications, such as non-alcoholic fatty liver disease/non-alcoholic steatohepatitis (NAFLD/NASH) and endothelial dysfunction, its use for these conditions remains investigational at this time, and further research is needed to establish its efficacy and safety in these contexts.

NOTE: This clinical policy specifically addresses the use of Wegovy (semaglutide) to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with established cardiovascular disease and either obesity or overweight. It does not apply to the use of Wegovy for other indications, such as chronic weight management in members without established cardiovascular disease. All other indications for Wegovy will be evaluated based on the relevant clinical policy or on an individual basis in accordance with the member's benefit plan.

- Coverage of prescription drugs prescribed for the treatment of obesity or for use in any weight reduction, weight loss, or dietary control varies depending on a member’s benefit policy.
    - Please refer to the applicable benefit plan document to determine benefit availability and the terms and conditions of coverage.
    - Please refer to the Plan's Weight Loss Agents (PG070) Clinical Guideline for specific coverage criteria related to the use of Wegovy and other GLP-1 receptor agonists for weight management in members without established ASCVD. The Plan's Weight Loss Agents (PG070) Clinical Guideline only applies to members whose Plan covers prescription drugs prescribed for the treatment of obesity or for use in any weight reduction, weight loss, or dietary control.

Definitions

"**Atherosclerotic cardiovascular disease (ASCVD)**" refers to conditions such as coronary heart disease, cerebrovascular disease, and peripheral arterial disease, which are responsible for the majority of CV events.

"**Cardiovascular disease (CVD)**" refers to a group of disorders of the heart and blood vessels, including coronary heart disease, cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease, and venous thromboembolism.

"**Established ASCVD**" is defined as a history of myocardial infarction, stroke, or symptomatic peripheral arterial disease.

"**Guideline-directed medical therapy (GDMT)**" refers to the use of evidence-based therapies for cardiovascular risk reduction, which may include high-intensity statin therapy, antiplatelet therapy and/or anticoagulation, antihypertensive medications, and ACE inhibitor or ARB therapy, unless contraindicated or not tolerated.

"**Major adverse cardiovascular events (MACE)**" is a commonly used composite endpoint in cardiovascular outcomes trials that typically includes cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke.

"**Obesity**" is a chronic, relapsing, multifactorial disease defined by excess adiposity that presents a risk to health.

"**Overweight**" is defined as a body mass index (BMI) ≥27 kg/m².

Medical Necessity Criteria for Initial Authorization

The Plan considers **Wegovy (semaglutide)** medically necessary when **ALL** of the following criteria are met:

1. The medication is prescribed by or in consultation with a cardiologist or endocrinologist; ***AND***
2. The member is 45 years of age or older; ***AND***
3. The member has established atherosclerotic cardiovascular disease, defined as having a history of one or more of the following:
    a. Prior myocardial infarction; ***and/or***
    b. Prior stroke (ischemic or hemorrhagic); ***and/or***

c. Symptomatic peripheral arterial disease, defined as:
    i. Intermittent claudication with ankle-brachial index <0.85 at rest; ***or***
    ii. Prior peripheral arterial revascularization procedure; ***or***
    iii. Amputation due to atherosclerotic disease; ***AND***
4. The member has either obesity or is overweight, defined as a body mass index (BMI) ≥27 kg/m^2; ***AND***
5. The member does not have a history of type 1 or type 2 diabetes; ***AND***
6. The member has a hemoglobin A1c <6.5% (48 mmol/mol) measured within the last 3 months; ***AND***
7. Wegovy will be used as an adjunct to guideline-directed medical therapy (GDMT) for cardiovascular risk reduction, which will include, unless contraindicated or not tolerated:
    a. High-intensity statin therapy; ***and***
    b. Antiplatelet therapy and/or anticoagulation as indicated; ***and***
    c. Antihypertensive medications to achieve a goal blood pressure of <130/80 mmHg; ***and***
    d. ACE inhibitor or ARB therapy; ***AND***
8. Wegovy will be used in combination with a reduced calorie diet and increased physical activity; ***AND***
9. Wegovy will not be used concurrently with other semaglutide-containing products or any other GLP-1 receptor agonists; ***AND***
10. The member has not undergone prior bariatric/weight loss surgery (e.g., gastric bypass, sleeve gastrectomy, biliopancreatic diversion with duodenal switch); ***AND***
11. If member is female of reproductive potential, member is not pregnant and using effective contraception; ***AND***
12. The prescribed maintenance dose of Wegovy is 2.4 mg injected subcutaneously once weekly.
    a. Initiation and Escalation: The starting dose is 0.25 mg injected subcutaneously once weekly. The dose should be increased by 0.25 mg every 4 weeks until the maintenance dose of 2.4 mg once weekly is reached.
    b. Maintenance: The prescribed maintenance dose is 2.4 mg injected subcutaneously once weekly.

If the above prior authorization criteria are met, the requested product will be authorized for 6-months.

Medical Necessity Criteria for Reauthorization

Wegovy (semaglutide) will be reauthorized for an additional 6-months if the member meets **ALL** of the following:

1. Documentation of a positive clinical response to Wegovy, as evidenced by improvement in one or more of the following cardiovascular risk factors from baseline:
    a. Reduction in systolic blood pressure of at least 5 mmHg; ***and/or***
    b. Achievement and maintenance of an LDL-C level of less than 70 mg/dL (1.8 mmol/L); ***and/or***
    c. Achievement and maintenance of a high-sensitivity C-reactive protein level of less than 2 mg/L; ***and/or***
    d. Maintenance of hemoglobin A1c <6.5% (for members with prediabetes at baseline); ***AND***
2. Member continues to use Wegovy as an adjunct to guideline-directed medical therapy for cardiovascular risk reduction, including:
    a. High-intensity statin therapy, unless contraindicated or not tolerated; ***and***
    b. Antiplatelet therapy and/or anticoagulation as indicated; ***and***
    c. Antihypertensive medications to maintain a blood pressure of <130/80 mmHg; ***and***
    d. ACE inhibitor or ARB therapy, unless contraindicated or not tolerated; ***AND***
3. Member continues to adhere to lifestyle modifications, including a reduced calorie diet and increased physical activity; ***AND***
4. Wegovy continues to be prescribed at a dose of 2.4 mg subcutaneously once weekly; ***AND***
5. Member has not developed any conditions that preclude the continued use of Wegovy, such as:
    a. Pregnancy; ***and/or***
    b. Personal history of type 1 or type 2 diabetes; ***and/or***
    c. Personal history of pancreatitis; ***and/or***
    d. Personal history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2.

Experimental or Investigational / Not Medically Necessary

Wegovy (semaglutide) for any other indication or use is considered not medically necessary by the Plan, as it is deemed to be experimental, investigational, or unproven. Non-covered indications include, but are not limited to[11], the following:

- Weight management or weight loss in members without established atherosclerotic cardiovascular disease (ASCVD), including:
    - Obesity

    - Overweight
    - Metabolic syndrome
    - Polycystic ovary syndrome (PCOS)
- Type 1 diabetes mellitus
- Alzheimer's disease
- Disordered eating behaviors
- Endothelial dysfunction
- Idiopathic intracranial hypertension
- Impaired glucose tolerance or prediabetes without established ASCVD
- Major Depressive Disorder (MDD)
- Non-alcoholic fatty liver disease (NAFLD) or non-alcoholic steatohepatitis (NASH)
- Parkinson's Disease (PD)
- Polycystic Ovarian Syndrome (PCOS)

  [1]*The above list of experimental and investigational uses is not exhaustive. The fact that an indication is not listed above does not imply that Wegovy is medically necessary for that use. All requests for Wegovy (semaglutide) for non-FDA approved indications will be reviewed on an individual basis in accordance with the member's benefit policy and applicable Clinical Guidelines.*

Appendix

In the SELECT trial (NCT03574597), Wegovy (semaglutide)2.4 mg once weekly was compared to placebo in 17,604 adults with established ASCVD and either overweight or obesity, but without diabetes. After a median follow-up of 3.3 years, Wegovy significantly reduced the risk of the composite primary outcome of CV death, non-fatal myocardial infarction, or non-fatal stroke by 20% compared to placebo (hazard ratio 0.80, 95% CI 0.72-0.90). Wegovy also led to significant weight loss, with a mean reduction of 9.4% from baseline compared to 0.9% with placebo.

Table 1: SELECT Trial - Key Details, Results, and Insights

Aspect	Details
Trial name	SELECT (Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity) [ClinicalTrials.gov Identifier: NCT03574597]
Intervention	Semaglutide 2.4 mg subcutaneously once weekly vs placebo

Study population • **Inclusion criteria**	17,604 patients • Age ≥45 years • BMI ≥27 kg/m^2 • Established CVD (prior MI, prior stroke, or symptomatic PAD) • Without diabetes
Exclusion criteria	• Type 1 or 2 diabetes • HbA1c ≥6.5% at screening • Recent MI, stroke, unstable angina, or TIA within 60 days • NYHA Class IV heart failure • Chronic kidney disease/dialysis • History of pancreatitis • Personal/family history of MEN2 or MTC • Active malignancy within past 5 years
Rationale for population criteria	• High-risk population for CVD events • PAD included as it has similar/higher event rates vs prior MI/stroke alone • Diabetes excluded to evaluate CV benefit independent of glycemic control
Study design	Randomized, double-blind, placebo-controlled, event-driven trial
Number of sites	>750 sites across 6 continents
Mean follow-up	39.8 months
Primary endpoint	Time to first MACE (CV death, non-fatal MI, or non-fatal stroke)
Key secondary endpoints	Time to CV death, heart failure composite, all-cause death
Primary endpoint results	• Composite MACE: 6.5% with semaglutide vs 8.0% with placebo • HR 0.80 (95% CI 0.72-0.90), p<0.001
Key secondary endpoint results	• CV death: 2.5% with semaglutide vs 3.0% with placebo, HR 0.85 (0.71-1.01) • Heart failure composite: 3.4% vs 4.1%, HR 0.82 (0.71-0.96)† • All-cause death: 4.3% vs 5.2%, HR 0.81 (0.71-0.93)†
Weight loss	9.4% with semaglutide vs 0.9% with placebo at week 104

Adverse events	• Serious AEs: 33.4% with semaglutide vs 36.4% with placebo • AEs leading to discontinuation: 16.6% vs 8.2% (mostly GI)
Conclusions	In patients with overweight/obesity and CVD but no diabetes, semaglutide reduced risk of MACE by 20% compared to placebo, with greater weight loss but more AEs leading to discontinuation

HR = hazard ratio, CI = confidence interval, MACE = major adverse cardiovascular events, CV = cardiovascular, MI = myocardial infarction, PAD = peripheral artery disease, TIA = transient ischemic attack, NYHA = New York Heart Association, MEN2 = multiple endocrine neoplasia type 2, MTC = medullary thyroid carcinoma, GI = gastrointestinal, AEs = adverse events

[†] Nominal p-values not reported for hierarchical testing due to non-significant CV death

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