

Wegovy (semaglutide) for Cardiovascular Risk Reduction

Disclaimer

Clinical guidelines are developed and adopted to establish evidence-based clinical criteria for utilization management decisions. Clinical guidelines are applicable according to policy and plan type. The Plan may delegate utilization management decisions of certain services to third parties who may develop and adopt their own clinical criteria.

Coverage of services is subject to the terms, conditions, and limitations of a member's policy, as well as applicable state and federal law. Clinical guidelines are also subject to in-force criteria such as the Centers for Medicare & Medicaid Services (CMS) national coverage determination (NCD) or local coverage determination (LCD) for Medicare Advantage plans. Please refer to the member's policy documents (e.g., Certificate/Evidence of Coverage, Schedule of Benefits, Plan Formulary) or contact the Plan to confirm coverage.

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 18 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/m²; **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. 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**
2. Member continues to adhere to lifestyle modifications, including a reduced calorie diet and increased physical activity; **AND**
3. Wegovy continues to be prescribed at a dose of 2.4 mg subcutaneously once weekly; **AND**
4. 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 to⁷, the following:

- 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)

⁷The 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.

NOTE: While the clinical evidence supports the medical necessity of Wegovy (semaglutide) for weight management in obese and some overweight individuals with or without ASCVD, as outlined in Pharmacy Guideline - Weight Loss Agents (PG070), coverage depends on the specific terms of the member's benefit plan. Members should refer to their specific plan documents or contact the Plan to confirm coverage details for weight loss medications.

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 <ul style="list-style-type: none"> Inclusion criteria 	17,604 patients <ul style="list-style-type: none"> Age ≥45 years BMI ≥27 kg/m² Established CVD (prior MI, prior stroke, or symptomatic PAD) Without diabetes
Exclusion criteria	<ul style="list-style-type: none"> 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

	<ul style="list-style-type: none"> Active malignancy within past 5 years
Rationale for population criteria	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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

References

1. AHA Newsroom. Major CVD event risk cut by 20% in adults without diabetes, with overweight or obesity. American Heart Association. Available online at: <https://newsroom.heart.org/news/major-cvd-event-risk-cut-by-20-in-adults-without-diabetes-with-overweight-or-obesity>.
2. American Diabetes Association Professional Practice Committee. 10. Cardiovascular disease and risk management: standards of care in diabetes-2024. *Diabetes Care*. 2024;47(Suppl 1):S179-S218.
3. American Diabetes Association Professional Practice Committee. 15. Management of diabetes in pregnancy: standards of care in diabetes-2024. *Diabetes Care*. 2024;47(Suppl 1):S282-S294.
4. American Diabetes Association Professional Practice Committee. 6. Glycemic goals and hypoglycemia: standards of care in diabetes-2024. *Diabetes Care*. 2024;47(Suppl 1):S111-S125.
5. American Diabetes Association Professional Practice Committee. 8. Obesity and weight management for the prevention and treatment of type 2 diabetes: standards of care in diabetes-2024. *Diabetes Care*. 2024;47(Suppl 1):S145-S157.
6. American Diabetes Association Professional Practice Committee. 9. Pharmacologic approaches to glycemic treatment: standards of care in diabetes-2024. *Diabetes Care*. 2024;47(Suppl 1):S158-S178.
7. Arnett DK et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;140(11):e563-e595.
8. Blood Pressure Lowering Treatment Trialists' Collaboration. Pharmacological blood pressure lowering for primary and secondary prevention of cardiovascular disease across different levels of blood pressure: an individual participant-level data meta-analysis. *Lancet*. 2021; 397:1625–1636. doi: 10.1016/S0140-6736(21)00590-0
9. de Ferranti SD et al. Type 1 diabetes mellitus and cardiovascular disease: a scientific statement from the American Heart Association and American Diabetes Association. *Diabetes Care*. 2014;37(10):2843-2863.
10. Eisenberg D et al. 2022 American Society for Metabolic and Bariatric Surgery (ASMBS) and International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO): Indications for metabolic and bariatric surgery. *Surg Obes Relat Dis*. 2022;18(12):1345-1356.
11. Ettehad D, Connor A, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, Chalmers J, Rodgers A, Rahimi K. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet*. 2016; 387:957–967. doi: 10.1016/S0140-6736(15)01225-8
12. FDA approves first treatment to reduce risk of serious heart problems specifically in adults with obesity or overweight. News release. FDA. March 8, 2024. Accessed March 8, 2024. <https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-reduce-risk-serious-heart-problems-specifically-adults-obesity-or>

13. Halcox, J.P., Roy, C., Tubach, F. et al. C-reactive protein levels in patients at cardiovascular risk: EURIKA study. *BMC Cardiovasc Disord* 14, 25 (2014). <https://doi.org/10.1186/1471-2261-14-25>
14. Joseph JJ et al. Comprehensive management of cardiovascular risk factors for adults with type 2 diabetes: a scientific statement from the American Heart Association. *Circulation*. 2022;145(9):e722-e759.
15. Kehra AM, Powell-Wiley TM. SELECTing Treatments for Cardiovascular Disease — Obesity in the Spotlight. *New England Journal of Medicine*. 2023; DOI: 10.1056/NEJMe2312646
16. Leite AR, Angélico-Gonçalves A, Vasques-Nóvoa F, Borges-Canha M, Leite-Moreira A, Neves JS, Ferreira JP. Effect of glucagon-like peptide-1 receptor agonists on cardiovascular events in overweight or obese adults without diabetes: A meta-analysis of placebo-controlled randomized trials. *Diabetes Obes Metab*. 2022 Aug;24(8):1676-1680. doi: 10.1111/dom.14707. Epub 2022 May 3. PMID: 35373878.
17. Lincoff AM, Brown-Frandsen K, Calhoun HM, et al. Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes. *New England Journal of Medicine*. 2023; DOI: 10.1056/NEJMoa2307563
18. Lincoff AM, Brown-Frandsen K, Colhoun HM, Deanfield J, Emerson SS, Esbjerg S, Hardt-Lindberg S, Hovingh GK, Kahn SE, Kushner RF, Lingvay I, Oral TK, Michelsen MM, Plutzky J, Tornøe CW, Ryan DH; SELECT Trial Investigators. Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes. *N Engl J Med*. 2023 Dec 14;389(24):2221-2232. doi: 10.1056/NEJMoa2307563. Epub 2023 Nov 11. PMID: 37952131.
19. Mares AC, Chatterjee S, Mukherjee D. Semaglutide for weight loss and cardiometabolic risk reduction in overweight/obesity. *Curr Opin Cardiol*. 2022 Jul 1;37(4):350-355. doi: 10.1097/HCO.0000000000000955. Epub 2022 Feb 16. PMID: 35175229.
20. Marso SP et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2016;375(19):1834-1844.
21. Powell-Wiley TM, Poirier P, Burke LE, Després J-P, Gordon-Larsen P, Lavie CJ, Lear SA, Ndumele CE, Neeland IJ, Sanders P, St-Onge M-P; on behalf of the American Heart Association Council on Lifestyle and Cardiometabolic Health; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Epidemiology and Prevention; and Stroke Council. Obesity and cardiovascular disease: a scientific statement from the American Heart Association. *Circulation*. 2021;143:e984–e1010. doi: 10.1161/CIR.0000000000000973
22. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, Macfadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ; JUPITER Trial Study Group. Reduction in C-reactive protein and LDL cholesterol and cardiovascular event rates after initiation of rosuvastatin: a prospective study of the JUPITER trial. *Lancet*. 2009 Apr 4;373(9670):1175-82. doi: 10.1016/S0140-6736(09)60447-5. Epub 2009 Mar 28. PMID: 19329177.
23. Ryan DH, Lingvay I, Colhoun HM, Deanfield J, Emerson SS, Kahn SE, Kushner RF, Marso S, Plutzky J, Brown-Frandsen K, Gronning MOL, Hovingh GK, Holst AG, Ravn H, Lincoff AM. Semaglutide Effects on Cardiovascular Outcomes in People With Overweight or Obesity (SELECT) rationale and design. *Am Heart J*. 2020 Nov;229:61-69. doi: 10.1016/j.ahj.2020.07.008. Epub 2020 Jul 17. PMID: 32916609.
24. Samson SL et al. American Association of Clinical Endocrinology Consensus Statement: Comprehensive Type 2 Diabetes Management Algorithm - 2023 Update. *Endocr Pract*. May 2023;29(5):305-340.
25. Virani SS, et al. 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA guideline for the management of patients with chronic coronary disease: a report of the American Heart Association/American

College of Cardiology Joint Committee on Clinical Practice Guidelines. Circulation. 2023;148:e9–e119. doi: 10.1161/CIR.0000000000001168

26. Wegovy® approved in the US for cardiovascular risk reduction in people with overweight or obesity and established cardiovascular disease. News release. Novo Nordisk. March 8, 2024. Accessed March 8, 2024. <https://www.novonordisk.com/news-and-media/news-and-ir-materials/news-details.html?id=167030>

27. Wegovy (semaglutide) [prescribing information]. Plainsboro, NJ: Novo Nordisk Inc; March 2024

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