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Reimbursement Recommendation

Semaglutide (Wegovy)

Indication: As an adjunct to a reduced calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of:

- 30 kg/m^2 or greater (obesity), or
- 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbidity such as hypertension, type 2 diabetes mellitus, dyslipidemia, or obstructive sleep apnea.

Sponsor: Novo Nordisk Canada Inc.

Final recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Wegovy?

Canada's Drug Agency (CDA-AMC) recommends that Wegovy be reimbursed by public drug plans for chronic weight management if certain conditions are met.

Which Patients Are Eligible for Coverage?

Wegovy should only be covered to treat adults who have a body mass index (BMI) of 27 kg/m^2 or greater and pre-existing cardiovascular (CV) disease (CVD), including conditions characterized by narrowed arteries leading to reduced blood flow to the heart, brain, or arms or legs.

What Are the Conditions for Reimbursement?

Wegovy should only be reimbursed if a patient is also on a reduced-calorie diet, has increased physical activity for chronic weight management, and the cost of Wegovy is reduced. For continuation of reimbursement after the first year of treatment, at least a 5% reduction in BMI or total body weight must be documented. Thereafter, patients should be reassessed each year.

Why Did CDA-AMC Make This Recommendation?

- Evidence from a clinical trial showed that Wegovy reduced the incidence of major CV complications in patients with a BMI of 27 kg/m^2 or greater and pre-existing CVD compared with placebo.
- Wegovy meets some of the unmet needs identified by patients, including sustained weight loss for up to 104 weeks and a clinically meaningful improvement in weight-related comorbidities, specifically CV-related.
- Based on the CDA-AMC assessment of the health economic evidence, Wegovy does not represent good value to the health care system at the public list price. A price reduction is therefore required.
- Based on public list prices, Wegovy is estimated to cost the public drug plans approximately $600 million over the next 3 years, although this may be as high as $3.5 billion depending on treatment uptake.

Additional Information

What Are Overweight and Obesity?

Overweight is defined by a BMI of more than 25 kg/m^2 and obesity is defined by a BMI of more than 30 kg/m^2. Obesity is a chronic disease where excess body fat impairs health and increases the risk of long-term health complications. In 2022, the estimated prevalence of obesity was 30% of individuals living in Canada aged 18 years or older.

Summary

Unmet Needs in Overweight and Obesity

Patients identified a need for treatments that are affordable, accessible, and tolerable, which are effective at providing sustained weight loss and reduce the risk of weight-related comorbidities, including CVD and diabetes.

How Much Does Wegovy Cost?

Treatment with Wegovy is expected to cost approximately $5,066 per patient per year.

Recommendation

The Canadian Drug Expert Committee (CDEC) recommends that semaglutide (Wegovy) be reimbursed as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with a BMI of 27 kg/m^2 or greater and established CVD (prior myocardial infarction [MI], prior stroke, or symptomatic peripheral arterial disease [PAD]), only if the conditions listed in Table 1 are met.

This recommendation supersedes the CDEC recommendation for this drug and indication dated October 4, 2022.

Rationale for the Recommendation

Semaglutide (Wegovy) was reviewed by CDEC in October 2022 for the indication "as an adjunct to a reduced calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index of 30 kg/m^2 or greater (obesity), or 27 kg/m^2 or greater (overweight) in the presence of at least 1 weight-related comorbidity such as hypertension, type 2 diabetes mellitus (T2DM), dyslipidemia, or obstructive sleep apnea" and was not recommended for reimbursement. In the current resubmission, evidence from the SELECT study was submitted by the sponsor to address the evidence gap regarding the effects of semaglutide 2.4 mg once weekly on CV outcomes in the indicated population that was noted as a limitation in the recommendation for the weight management indication in 2022. However, the SELECT study only enrolled patients with established CVD. The SELECT study was a phase IIIb, multinational, multicentre, randomized, double-blind, parallel-group, placebo-controlled trial that evaluated the effect of semaglutide (2.4 mg subcutaneous injection once weekly), as adjunct to standard of care for CVD, compared with placebo in patients with an initial BMI of 27 kg/m^2 or greater and established CVD (prior MI, prior stroke, or symptomatic PAD). The SELECT study demonstrated that treatment with semaglutide (2.4 mg once weekly) resulted in added clinical benefit for patients with established CVD compared with placebo in the time to first end point adjudicated-confirmed major CV event (event adjudication committee [EAC]-confirmed major adverse cardiovascular event [MACE]) based on a hazard radio (HR) of 0.80 (95% confidence interval [CI], 0.72 to 0.89). The absolute risk difference at week 156 was −1.1% (95% CI, −1.9% to −0.4%) in favour of semaglutide, which was identified as a clinically meaningful difference for this population. CDEC also noted that there may be a reduction in composite heart failure events and all-cause mortality; however, these end points were not tested for superiority due to a prior failure in the prespecified testing hierarchy.

Patients identified a need for treatments that are affordable, accessible, and tolerable, that are effective at providing sustained weight loss and reducing the risk of weight-related comorbidities (such as CVD and diabetes). As noted in the previous recommendation, CDEC concluded that semaglutide was associated with a significant improvement in change from baseline in body weight over placebo based on the STEP trials (with mean between-group differences ranging from –6.21% to –14.75%). Based on the resubmission evidence, CDEC concluded that treatment with semaglutide 2.4 mg meets some of these needs as it resulted in sustained weight loss for up to 104 weeks and a clinically meaningful improvement in weight-

related comorbidities, specifically CV outcomes. However, there is uncertainty about long-term benefit in terms of sustained weight loss and CV benefit, as well as the impact of potential tolerability concerns.

Using the sponsor submitted price for semaglutide and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for semaglutide was $185,646 per quality-adjusted life-year (QALY) compared with current standard of care. At this ICER, semaglutide is not cost effective at a $50,000 per QALY willingness to pay (WTP) threshold for adult patients with a BMI of 27 kg/m^2 or greater and established CVD. A price reduction is required for semaglutide to be considered cost effective at a $50,000 per QALY threshold. The cost effectiveness of semaglutide for the indicated population who also had T2DM could not be established.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Semaglutide should be reimbursed for adult patients with a BMI ≥ 27 kg/m^2 and established CVD (prior MI, prior stroke, or symptomatic PAD) as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management.	Evidence of a clinical benefit for semaglutide 2.4 mg relative to placebo based on the time to first MACE was demonstrated in the SELECT study, which enrolled patients with a BMI of at least 27 kg/m^2 and established CVD evidenced by prior MI, prior stroke (ischemic or hemorrhagic stroke), or symptomatic PAD (as evidenced by intermittent claudication with ABI < 0.85 at rest, or peripheral arterial revascularization procedure, or amputation due to atherosclerotic disease). The SELECT study excluded patients with diabetes; however, evidence from a post hoc subgroup analysis of the SUSTAIN-6 CVOT included patients with a BMI ≥ 27 kg/m^2, established CVD, and T2DM. Evidence from the SUSTAIN-6 CVOT was considered supportive of reimbursement for patients with T2DM with a BMI ≥ 27 kg/m^2 and established CVD as well.	—
2. The maximum duration of initial authorization is 1 year.	An initial authorization of 1 year was recommended to allow the patient time to reach a therapeutic dose of semaglutide (2.4 mg or maximum tolerated) and then evaluate the benefit of continued treatment at that dose, while also providing flexibility based on patient and clinician availability.	—
Renewal		
3. For renewal after initial authorization, the physician must document a beneficial clinical effect when requesting continuation of reimbursement, defined as at least	A 5% reduction in total body weight or BMI was identified as a clinically meaningful improvement in weight for the management of obesity based on input from clinical experts.	—

Reimbursement condition	Reason	Implementation guidance
a 5% reduction in BMI or total body weight.		
4. For subsequent renewal, the physician must provide proof that the initial response achieved after the first year of treatment with semaglutide has been maintained. Subsequent renewals should be assessed annually.	Annual assessments will help ensure the treatment is used for those benefiting from the therapy and would reduce the risk of unnecessary treatment. The clinical experts indicated to CDEC that weight loss is expected to plateau even with effective treatments, and maintenance of reduced weight is sufficient for subsequent renewals.	—
Pricing		
5. A reduction in price.	The ICER for semaglutide is $185,646 per QALY gained when compared with the current standard of care in patients without T2DM. A price reduction of 67% would be required for semaglutide to achieve an ICER of $50,000 per QALY compared to the current standard of care. In patients with T2DM, the cost effectiveness of using semaglutide (Wegovy) is unknown.	—
Feasibility of adoption		
6. The economic feasibility of adoption of semaglutide must be addressed.	At the submitted price, the incremental budget impact of semaglutide is expected to be greater than $40 million per year from the first year after approval. Over 3 years, the incremental budget impact is expected to be approximately $600 million, although may be as high as $3.5 billion depending on treatment uptake.	—

ABI = ankle-brachial index; BMI = body mass index; CDEC = Canadian Drug Expert Committee; CVD = cardiovascular disease; CVOT = cardiovascular outcomes trial; ICER = incremental cost-effectiveness ratio; MACE = major adverse cardiovascular event; MI = myocardial infarction; PAD = peripheral arterial disease; QALY = quality-adjusted life-years; T2DM = type 2 diabetes mellitus.

Discussion Points

- **Resubmission:** CDEC discussed the context of the resubmission, which was informed by new clinical and economic information based on the SELECT study, which included a patient population aligned with the weight management indication with established CVD. The sponsor indicated that the issue being addressed by the new evidence included in the resubmission was the impact of semaglutide on weight-related comorbidity, as per the SELECT study. The committee acknowledged the more recent indication that was approved for semaglutide (Wegovy) was “to reduce the risk of non-fatal MI in adults with established CV disease and BMI equal to or greater than 27 kg/m^2,” but noted that the resubmission was submitted under the indication for weight management with

a focus on patients with a history of CVD as per the sponsor's decision. Additional details for this resubmission are described under Submission History.

- **Reimbursement request:** The committee discussed the potential challenges of a recommendation that aligns with the submitted reimbursement request and noted that the request was defined by the sponsor. Acknowledging the challenges, the committee also noted that the evidence that was provided for the resubmission was informed by clinical and economic evidence that is reflective of the reimbursement request. As such, conclusions about potential benefits in weight-related comorbidity, such as CV outcomes, outside of the reimbursement request — that is, on a population without prior history of CVD (prior MI, prior stroke, or symptomatic PAD) — could not be drawn, and hence this recommendation should not be generalized to patients without prior history of CVD (prior MI, prior stroke, or symptomatic PAD).
- **Evidence from the STEP trials:** Due to the nature of the resubmission, the focus of the discussion was on whether the SELECT trial addressed the evidence gap regarding the effects of semaglutide 2.4 mg once weekly on CV outcomes identified in the 2022 recommendation. However, the committee also acknowledged the evidence that was reviewed in 2022 and maintained that evidence from the STEP trials demonstrated 68 weeks of treatment with semaglutide 2.4 mg once weekly, with a background regimen of a reduced-calorie diet and increased physical activity, was associated with statistically significant improvements in percent change from baseline in body weight over placebo, with mean between-group differences ranging from –6.21% to –14.75%. This information supported the definition of a beneficial clinical effect in the renewal criteria, which was based on input from clinical experts and consistent with input received from clinician groups.
- **Health-related quality of life:** Patients identified an improvement in health-related quality of life (HRQoL) as an important outcome for patients with overweight or obesity and established CVD. Evidence from the SELECT study that informed the resubmission was limited with respect to HRQoL outcomes, which were included as supportive secondary or exploratory outcomes. The available evidence suggested that semaglutide 2.4 mg was associated with little to no difference in HRQoL as assessed by the generic EQ-5D index and visual analogue scale (VAS) tools.
- **SUSTAIN-6:** CDEC discussed the SUSTAIN-6 trial post hoc subgroup analysis of patients with T2DM, BMI of 27 kg/m^2 or greater, and established CVD as supportive evidence for the resubmission. The post hoc nature of the analysis introduces bias and the subgroup analysis had fewer patients than needed for adequate power, which complicated the interpretation of the efficacy of semaglutide. Further, the dose studied was 1.0 mg, which is not aligned with the approved 2.4 mg maintenance dose for semaglutide (Wegovy). Time to first occurrence of expanded MACE reached nominal statistical significance and although point estimates for other outcomes were suggestive of a benefit in favour of semaglutide, wide CIs for other end points including nonfatal MI and CV death indicate substantial uncertainty. The committee also noted that the change from baseline in body weight at week 104 was [redacted] versus [redacted] for semaglutide 1.0 mg versus placebo in the exploratory post hoc subgroup analysis.

- **Gap in long-term evidence:** The committee discussed the uncertainty in long-term benefit from treatment with semaglutide due to a gap in the submitted clinical and economic evidence. Tolerability concerns were noted in the SELECT study and patient input described side effects as frustrating or distressing, yet generally manageable. The likelihood of a patient remaining on treatment long-term is uncertain, and relatedly, whether that impacts sustained weight loss and benefit in terms of CV outcomes is also uncertain.
- **Concomitant therapy:** CDEC discussed that the effectiveness of semaglutide 2.4 mg was demonstrated when combined with lifestyle and behavioural changes, which is how it was administered in the SELECT trial (i.e., individualized healthy lifestyle counselling, including diet and physical activity, was offered at every study visit). However, structured weight management programs that are publicly funded are not widely available in Canada. As such, the generalizability of the trial results to patients living in Canda in the absence of lifestyle and behavioural interventions is uncertain. Furthermore, CDEC discussed that allocating funds to this medication could carry significant opportunity costs, potentially hindering the development of publicly funded lifestyle and behavioural programs.
- **Uncertainty in the economic assessment:** The committee discussed uncertainty in the economic evidence. They noted the absence of data to show whether treatment effects, such as reduced CV risk and weight loss, would be sustained long-term. The committee also noted that the recurrence of CV events after the first event is uncertain in terms of volume and intensity. Therefore, if patients remain on treatment, long-term costs will continue to accrue but benefits could decrease over time making semaglutide less cost effective than what was presented. However, the committee acknowledged that there was potential that the economic analysis underestimated health benefits as a robust assessment of long-term use of semaglutide could not be established.
- **Uncertainty in cost effectiveness in T2DM population**: The committee noted that semaglutide is currently indicated for patients with T2DM under the brand name Ozempic. Patients with T2DM, who have a BMI of 27 kg/m^2 or greater and have established CVD would also be eligible to receive Wegovy under the reimbursement recommendation. At the recommended maintenance dose for weight management (2.4 mg weekly), the annual per-patient cost of Wegovy is $5,066 whereas at the recommended dose for T2DM management (1 to 2 mg weekly) the annual per-patient cost of Ozempic is $2,844 to $5,688. Therefore, if eligible patients with T2DM switch from Ozempic to Wegovy this may add costs to the health system. The cost effectiveness of using semaglutide (Wegovy) versus semaglutide (Ozempic) is unknown.
- **Affordability:** The committee discussed the large budget impact associated with reimbursing semaglutide in this population. If there is large treatment uptake the budget impact could exceed $3 billion over 3 years. Price reductions will be important for ensuring semaglutide represents good value and is affordable to implement.

Background

Obesity is a chronic disease where excess body fat impairs health and increases the risk of long-term health complications. The presence of overweight (BMI of more than 25 kg/m^2) and obesity (BMI of more than 30 kg/m^2) are considered major contributors to CVD progression through direct and indirect mechanisms. In 2022, the estimated prevalence of obesity was 30% of individuals living in Canada aged 18 years or older. In a study of patients with atherosclerotic CVD, obesity was among the 30 most common comorbid conditions, with a prevalence of 38%. Worldwide, CVD is among the leading causes of morbidity and mortality and is reported to be one of the leading causes of hospitalization in Canada, alongside stroke.

Standards of Therapy

The Canadian Adult Obesity Clinical Practice Guideline on pharmacotherapy in obesity management specifies that there are 4 medications indicated for long-term obesity management as adjuncts to health-behaviour changes, including liraglutide, naltrexone-bupropion in a combination tablet, orlistat, and semaglutide. The Canadian guideline recognizes all 4 medications as effective in producing clinically significant weight loss and health benefits relative to placebo over a period of at least 1 year. The clinical experts indicated that tirzepatide, at present, is solely approved for adjunct glycemic control in T2DM but is increasingly being prescribed off label for chronic weight management in Canada. Furthermore, patient groups have indicated that semaglutide (Ozempic) has been prescribed off label for weight management as well. The clinical experts indicated that in clinical practice in Canada, semaglutide is being used in patients with diabetes for weight loss.

Drug Under Review

Semaglutide has been approved by Health Canada as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial BMI of 30 kg/m^2 or greater (obesity), or 27 kg/m^2 or greater (overweight) in the presence of at least 1 weight-related comorbidity such as hypertension, T2DM, dyslipidemia, or obstructive sleep apnea. Semaglutide is a selective long-acting glucagon-like peptide-1 (GLP-1) receptor agonist. It is available as a solution in a prefilled pen for subcutaneous injection and the dosage recommended in the semaglutide product monograph is 2.4 mg once weekly.

Submission History

Initial Submission

In 2022, semaglutide 2.4 mg was first reviewed by CDEC for weight management. CDEC issued a recommendation that semaglutide 2.4 mg not be listed as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial BMI of 30 kg/m^2 or greater (obesity) or 27 kg/m^2 or greater (overweight) in the presence of at least 1 weight-related comorbidity such as hypertension, T2DM, dyslipidemia, or obstructive sleep apnea.

The clinical review report on semaglutide (Wegovy) used to inform the reimbursement recommendation for semaglutide (Wegovy) are both available on the project website.

Basis of Resubmission

Rationale for the 2022 recommendation included evidence from 4 placebo-controlled, double-blind, randomized controlled trials (RCTs) that demonstrated that treatment with semaglutide 2.4 mg injection reduced body weight in individuals with an initial BMI of 30 kg/m^2 or greater (obesity) or 27 kg/m^2 or greater (overweight) in the presence of at least 1 weight-related comorbidity but did not demonstrate improvement in or prevention of weight-related comorbidities. Comorbidities such as MACE, osteoarthritis, and obstructive sleep apnea were not outcomes in the STEP trials.

CDEC noted there was an ongoing trial, the SELECT study, comparing semaglutide 2.4 mg injection with placebo for the prevention of MACE in patients with overweight or obesity who have established CVD but not diabetes mellitus. CDEC concluded that the results of this study will address the evidence gap regarding the effects of semaglutide 2.4 mg once weekly on CV outcomes in the indicated population.

Therefore, the objective of this report is to review and critically appraise the clinical evidence submitted by the sponsor on the beneficial and harmful effects of semaglutide 2.4 mg solution for subcutaneous injection in chronic weight management in patients with a BMI of 27 kg/m^2 or greater and established CVD (MI, stroke, or PAD).

Sponsor Clarifying Note on Resubmission

In 2024, Health Canada issued an indication for semaglutide injection (Wegovy) to reduce the risk of nonfatal MI in adults with established CVD and BMI of 27 kg/m^2 or greater. This indication was based on the evidence from the SELECT trial.

The sponsor indicated that the revised reimbursement request, namely adults with established CVD and BMI of 27 kg/m^2 or greater, is fully encompassed in the weight management indication and is the same population for which the CV indication was granted for.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 1 RCT in patients with established CVD and overweight or obesity and without diabetes, and 1 RCT in patients with T2DM at high risk of CV events
- patients' perspectives gathered by 6 patient groups: Gastrointestinal Society (GI Society), Obesity Canada, Obesity Matters, Fatty Liver Alliance, HeartLife Foundation, and Diabetes Canada
- input from public drug plans that participate in the reimbursement review process
- two clinical specialists with expertise diagnosing and treating patients with overweight and obesity and CVD

- input from 4 clinician groups: TotalCardiology Rehabilitation, Cardiac Rehabilitation and Secondary Prevention Program, Obesity Canada, and the Canadian Association for Bariatric Physicians and Surgeons
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Perspectives of Patients, Clinicians, and Drug Programs

The full patient and clinician group submissions received are available in the consolidated patient and clinician group input document for this review on the project website.

The information in this section is a summary of input provided by the patient and clinician groups who responded to the call for input and from the clinical experts consulted for this review.

Patient Group Input

Input for this review was submitted by 6 patient groups: GI Society, Obesity Canada, Obesity Matters, Fatty Liver Alliance, HeartLife Foundation, and Diabetes Canada. Input from the GI Society, Obesity Canada, and Diabetes Canada was based on surveys of individuals with obesity or diabetes conducted between 2021 and 2024. The GI Society also included input from an in-person focus group in 2023 for individuals with obesity. Input from the HeartLife Foundation was gathered through interviews and discussions with individuals with CVDs and their health care providers. The Fatty Liver Alliance gathered physician insights on metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH), supplemented by a 2022 to 2023 US survey of patients with nonalcoholic fatty liver disease or nonalcoholic steatohepatitis. Obesity Matters also provided feedback on the CDEC reimbursement recommendation issued for the initial 2022 review of semaglutide for weight management.

Patient groups highlighted the significant physical and mental health impact of obesity and related conditions, including CVDs, diabetes, and MASLD-MASH. Common symptoms included mobility limitations, chronic pain, fatigue, swelling, shortness of breath, dizziness, and nausea, affecting daily life. Comorbidities were prevalent; in the 2021 survey from GI Society, 91% of respondents reported comorbidities such as arthritis (51%), hypertension (33%), sleep apnea (30%), gastroesophageal reflux disease (29%), irritable bowel syndrome (29%), high cholesterol (25%), and diabetes (24%). Input from Diabetes Canada also noted high comorbidity rates for patients with diabetes, including high blood pressure, foot or eye problems, nerve damage, heart disease, and kidney-related comorbidities. Obesity not only contributes to these conditions but also complicates disease management and reduces quality of life. Mental health challenges, including anxiety, mood disorders, and social isolation due to stigma, especially in health care, were widely reported.

The patient groups highlighted weight loss as a key treatment outcome, along with reducing risk of comorbidities (e.g., CVD), improvements in quality of life, and increased ability to perform everyday tasks. When choosing a new therapy, most patients primarily value efficacy (i.e., significant and sustained weight loss) and affordability.

Patient groups emphasized that traditional lifestyle modifications, such as diet and exercise, are often ineffective for long-term weight management. Few medication options exist, with semaglutide, liraglutide, and naltrexone-bupropion being commonly prescribed, but none have public or full private coverage, making cost the biggest barrier. Survey respondents who reported benefits of these treatments in managing obesity described them as 'life-changing,' with most (94%) considering side effects to be manageable. However, it was also noted that these medications lack long-term effectiveness, with many individuals gaining the weight back within 5 years. Bariatric surgery, while currently considered the gold standard for obesity treatment, carries risks of severe side effects, weight gain after surgery, and long wait times, making it a last-resort option.

Patients with experience receiving semaglutide described several benefits, including substantial weight loss. It was highlighted that semaglutide also improved management of comorbidities, such as CVD, and improved quality of life. Thus, it was identified that semaglutide could address multiple health conditions simultaneously. Patients with experience with semaglutide also highlighted the side effects — most commonly common nausea, vomiting, and constipation — were typically temporary and manageable, and the once-weekly administration reduced treatment burden.

Obesity Matters provided additional feedback on the 2022 draft CDEC reimbursement recommendation for semaglutide (Wegovy). The feedback indicated that while the initial draft recommendation acknowledged the effect of semaglutide on body weight reduction and the increased risk of comorbidities observed with obesity, it did not conclude that weight reduction can directly reduce comorbidities. The feedback also critiqued the rationale for a negative reimbursement recommendation, noting this overlooks the agency of individuals actively working with specialists to make lifestyle changes. The feedback also indicated that the previous recommendation did not adequately consider cost as a barrier to treatment, patient perspectives, or the direct impact of treatment costs on quality of life, or how public reimbursement would reduce long-term costs associated with obesity-related comorbidities and conditions or offer actionable solutions for integrating semaglutide into existing health care systems.

Input From Clinical Experts Consulted for This Review

The clinical experts identified the following as limitations with weight management medications: barriers to public access, not all patients experience weight loss with treatment, and some patients experience adverse effects that necessitate stopping the drug. Specific to bariatric surgery, the clinical experts noted that in addition to barriers to access, not all patients are interested in pursuing this option because of the potential risks associated with surgery.

Based on input from the clinical experts consulted for this review, semaglutide 2.4 mg has been used for weight management in Canada since it was approved by Health Canada in 2021. The clinical experts indicated that the anticipated place of semaglutide with regards to pharmacotherapy for chronic weight management is as a first-line treatment. The clinical experts advised that semaglutide would be combined with therapies that reduce cardiorenal risk, including combination with renin-angiotensin-aldosterone system (RAAS) inhibitors (angiotensin-converting enzyme [ACE] or angiotensin receptor blockers [ARB]) and SGLT2 inhibitor therapies as well as other standard of care to improve CV outcomes. The clinical experts indicated

that there is currently no high-level evidence to support combination with other pharmacotherapy for weight management; however, they noted there is relevant evidence from small studies (e.g., a retrospective cohort study on the effect of combined GLP-1 receptor agonists and bupropion-naltrexone in weight loss). The clinical experts indicated that specialists in obesity use combination therapy in practice where needed and appropriate and where cost and insurance coverage are not limiting factors. The clinical experts indicated that the most common combination is GLP-1 receptor agonists combined with bupropion-naltrexone.

The clinical experts deferred to the baseline characteristics of the SELECT trial population to identify patients who would most likely respond to treatment with semaglutide, where response is defined as reduced risk of future CV outcomes and weight loss. Of note, the clinical experts highlighted that the trial population included patients with pre-existing history of CVD of which 64.5% of patients had prediabetes (hemoglobin A1C > 5.7% per American criteria). Overall, the clinical experts advised that most patients with a BMI of 27 kg/m^2 or greater would be appropriate to treat for the chronic weight management indication, and that patients with established CVD (including heart failure [HF]), T2DM, multiple risk factors, severe disease, or a high BMI are most in need of an intervention for secondary prevention of future events and to improve symptom burden.

When considering which patients would be least suitable for treatment with semaglutide, the clinical experts deferred to the product monograph for absolute contraindications and patients with potential increased risk of adverse effects (e.g., history of pancreatitis, gallbladder disease, diabetic retinopathy, severe renal impairment, gastrointestinal conditions).

Although weight loss is an outcome that can be easily monitored in practice, the clinical experts advised that recurrence of CV events and symptoms are equally as important. The clinical experts further advised that patient-reported outcome tools are used to measure response to treatment.

The clinical experts indicated that treatment with semaglutide would be long-term unless the following occurred: excessive weight loss or poor nutritional status (may also be considered for dose reduction), renal failure (may be continued depending on overall nutritional status and if tolerating otherwise), side effects (e.g., persistent severe nausea, vomiting, and diarrhea), development of a contraindication, pregnant or planning to become pregnant, and cost and/or loss of coverage. The experts indicated that the occurrence of a repeat CV event while on treatment with semaglutide would not be considered treatment failure, noting that it would be too uncertain to determine if treatment was associated with delayed onset of a second CV event in an individual. Additionally, the clinical experts advised that pausing treatment for an elective surgery may be considered given reports of slow gastrointestinal transit which can increase the risk of aspiration with endotracheal intubation.

The clinical experts advised that a specialist is not required to prescribe semaglutide because family physicians and primary care providers have been prescribing semaglutide (Ozempic) for diabetes and obesity and are familiar with its side effect profile and monitoring.

Clinician Group Input

A total of 4 clinician groups provided input for this resubmission: TotalCardiology Rehabilitation (5 clinicians), the Cardiac Rehabilitation and Secondary Prevention Program (Western University, Division of Cardiology;

5 clinicians), with a joint input from Obesity Canada and the Canadian Association for Bariatric Physicians and Surgeons (CABPS) (18 total clinicians). TotalCardiology Rehabilitation is a multidisciplinary group of family physicians, internists, and cardiologists that are the sole providers of cardiac rehabilitation for the city of Calgary and surrounding area. The Western University Cardiac Rehabilitation and Secondary Prevention Program delivers comprehensive, multidisciplinary rehabilitation care, including secondary prevention through lifestyle and pharmacotherapeutic interventions. The CABPS is a group of specialists in Canada with experience treating obesity. Obesity Canada is a national registered charity association that assisted with coordination of the group clinician response from CABPS.

The clinician group input was largely consistent with that of the clinical experts. Both the clinician group and experts highlighted the limitations of currently available weight management treatment options and barriers to patients accessing them. CABPS noted that obesity management currently follows the 2020 Canadian Adult Obesity Clinical Practice Guidelines, which recommends lifestyle modification, supported by psychological or behavioural therapy, pharmacotherapy, and bariatric surgery. Clinician groups further highlighted that lifestyle modifications alone are often insufficient to achieve the weight loss needed to improve obesity-related complications like T2DM and MASLD. Clinician groups noted that liraglutide, semaglutide, and bupropion-naltrexone are the most effective long-term pharmacologic treatments due to their impact on neuroendocrine pathways associated with obesity. Clinician groups also outlined the role of medical bariatric centres in providing multidisciplinary care and differentiated them from nonmedical weight loss clinics. CABPS expressed that obesity treatment should extend beyond weight loss to address dysfunctional adipose tissue driving adverse health outcomes. The clinician group overview of therapies reducing cardiorenal risk in patients with comorbid CVD was consistent with expert input. Clinician groups also added that patients with atherosclerotic CVD become eligible for cardiac rehabilitation, which combines lifestyle and pharmacotherapeutic interventions.

Both clinicians and experts agreed that a primary treatment goal of CVD is to reduce the incidence of CV events, but clinician groups also suggested additional goals of weight management and improved glycemic control, when applicable. Both clinicians and experts highlighted the access challenges and potential risks associated with bariatric surgery. Both noted a need for additional treatment options that address both CV risk and weight reduction, noting that existing treatments for weight loss and CVD can lack long-term effectiveness and fail to directly target weight management. Clinician groups noted this as particularly true for patients with obesity who do not have diabetes, for which there are currently no targeted treatment options. Clinician groups noted that these significant treatment gaps contribute to a persisting high risk of morbidity and mortality in these populations.

In contrast to clinical expert input, which noted that semaglutide would be combined with other therapies that reduce CV risk (i.e., RAAS inhibitors, SGLT2), clinician groups indicated that semaglutide would be used as first-line treatment alongside lifestyle modifications. The clinician groups noted it is unnecessary to first try other treatments before semaglutide, given its effectiveness in achieving substantial weight loss and improving obesity-related health outcomes. Clinician groups anticipate that semaglutide could shift current treatment paradigms, noting its efficacy approaches that of bariatric surgery and could reduce the number of patients requiring surgery. The patient type indicated by clinician groups who they felt would benefit most

from semaglutide aligned exactly with that of the experts. The clinician groups added that semaglutide might also benefit patients with diabetes who require additional cardiovascular protection, or those without diabetes who are at a high cardiovascular risk and have difficulty achieving weight loss through lifestyle modifications alone. The Cardiac Rehabilitation and Secondary Prevention Program estimated that 78% of their patients participating in cardiac rehabilitation do not have diabetes and that 45% of patients who complete the rehabilitation program could potentially benefit from additional therapy such as semaglutide. Patients least suitable for treatment, identified by clinician groups and experts, also aligned. According to clinician groups, patients with obesity are identified through self-identification or by health care providers using diagnostic tools such as BMI, waist circumference, and staging systems such as the Edmonton Obesity Staging System, which also classifies degree of associated conditions (e.g., T2DM or impaired mobility). However, CABPS noted that there are currently no methods of identifying which patients are likely to respond to semaglutide.

Physician group input was consistent with expert insights on the use of weight loss to assess treatment response but emphasized additional markers of treatment benefit. Clinician groups highlighted improvements in prediabetes, lipids, blood pressure, mobility, and quality of life as equally important. Conversely, TotalCardiology Rehabilitation indicated that there is no definitive evidence that the absence of weight loss precludes other treatment benefits. CABPS provided specific criteria for a meaningful treatment response, including a 5% reduction in total body weight in 3 months of treatment (aligning with expert input) and improved lab markers, reduced osteoarthritis pain, and the ability to proceed with procedures like hip replacement. Clinician groups also suggested initial evaluations every 4 to 6 weeks, then every 3 months, recognizing variability based on clinician and patient preference.

Both clinician groups and experts agreed that semaglutide treatment should be continued indefinitely, with clinician groups likening the regimen to statin therapy or acetylsalicylic acid after an MI. The clinician groups suggested that semaglutide discontinuation be considered in the following scenarios: presence of treatment intolerance or intolerable side effects that do not improve over time with appropriate countermeasures, pancreatitis, pregnancy or planning pregnancy, lack of meaningful treatment response, lack of affordability, or a more effective treatment becomes available in the future that requires semaglutide discontinuation. Clinician groups noted that semaglutide treatment could be delivered in family medicine and primary care clinics, community-based obesity management or metabolic medicine clinics, or hospital-based medical and surgical centres. Like the experts, clinician groups indicated that any health care provider with experience managing obesity could prescribe semaglutide, noting this role should not be restricted to specialists alone.

Drug Program Input

Input was obtained from the drug programs that participate in the reimbursement review process. The following items were identified as key factors that could potentially impact the implementation of a recommendation of semaglutide: relevant comparators, considerations for continuation or renewal of therapy, considerations for prescribing of therapy, as well as systemic and economic issues. The clinical experts consulted for this review provided advice on the potential implementation issues raised by the drug programs and are presented in Table 2.

In 2022, semaglutide 2.4 mg was first reviewed by CDEC for the weight management indication. The implementation questions and corresponding responses from the clinical experts consulted for the past review were summarized in the clinical review report on semaglutide (Wegovy) used to inform the reimbursement recommendation for semaglutide (Wegovy). These documents are available on the project website.

Table 2: Responses to Questions From the Drug Programs

Drug program implementation questions	Response
Relevant comparators	
Treatments for chronic weight management (naltrexone and bupropion, liraglutide, and orlistat) are not a benefit with the participating public drug programs. As such, the drug plans did not identify any issue with the comparator (placebo) in the SELECT trial.	This is a comment from the drug plans to inform CDEC deliberations.
Considerations for continuation or renewal of therapy	
If a patient is unable to tolerate the target maintenance dose at week 16 after initiation of therapy (in reference to the dose escalation regimen of 16 weeks per recommended dose in the product monograph), should they be considered for renewal?	The clinical experts advised that treatment with semaglutide should be continued for the potential benefits in CV outcomes despite not tolerating the target maintenance dose. The clinical experts noted that many patients are unable to tolerate the semaglutide 2.4 mg dose but can still derive benefit from the medication at a lower dose. CDEC notes that only 77% of patients were receiving the semaglutide 2.4 mg dose at any point in the SELECT study and for patients who did not reach the semaglutide 2.4 mg target dose at any time in the study, the maximum semaglutide dose was 1.7 mg for 8%, 1.0 mg for 7%, 0.5 mg for 5%, and 0.24 mg for 3% of patients. CDEC further notes that there was no subgroup analysis based on the dose received. As such, there is some uncertainty in the evidence for a clinical benefit at a lower dose.
Considerations for prescribing of therapy	
If a patient is unable to tolerate the target maintenance dose, should treatment with semaglutide be discontinued? In other words, would patients receiving a lower maintenance dose equally benefit from semaglutide and be considered for reimbursement?	As previously mentioned, the clinical experts advised that treatment with semaglutide should be continued for the potential benefits in CV outcomes despite not tolerating the target maintenance dose of 2.4 mg. Based on experience in clinical practice, the clinical experts indicated that patients receiving semaglutide 0.25 mg, 0.5 mg, or 1.0 mg weekly have experienced weight loss. Therefore, the clinical experts advised to continue treatment at the maximum tolerated dose and in particular, where the patient is deriving benefit in terms of weight loss, appetite reduction, and improved quality of life. The CDA-AMC review team notes that the recommended dose and dosage adjustment outlined in the product monograph for semaglutide (Wegovy) advised that “If patients do not tolerate the therapeutic/maintenance 2.4 mg dose, the dose can be temporarily decreased to 1.7 mg weekly, for a maximum

Drug program implementation questions	Response
	of 4 weeks. Patients should re-escalate to the therapeutic/ maintenance 2.4 mg dose." Refer to CDEC notes in the previous item.
System and economic issues	
Cost of therapy per year: $5,069.67 Pan-Canadian net budget impact based on sponsor submitted estimates: • year 1: $61,256,584 • year 2: $125,470,998 • year 3: $194,033,613. Three-year total: $380,761,195	This is a comment from the drug plans to inform CDEC deliberations.

CDA-AMC = Canada's Drug Agency; CDEC = Canadian Drug Expert Committee; CV = cardiovascular.

Clinical Evidence

Systematic Review

Description of Study

The SELECT trial (N = 17,609) was a phase IIIb, multinational, multicentre, randomized, double-blind, parallel-group, placebo-controlled trial that evaluated the effect of semaglutide 2.4 mg subcutaneous injection compared with placebo in reducing the risk of MACE (CV death, nonfatal MI, or nonfatal stroke) in patients with established CVD and overweight or obesity and without diabetes. The key secondary objective of the trial was to evaluate the effect of semaglutide in mortality compared with placebo. Patients were randomized in a 1:1 ratio to receive once-weekly treatment with either semaglutide 2.4 mg or placebo, both as an adjunct to standard of care for CVD.

A total of 8,805 patients were randomized to receive semaglutide 2.4 mg and 8,804 patients were randomized to receive placebo. The mean age of patients in the semaglutide 2.4 mg group was 61.6 years (SD = 8.9 years) and 61.6 years (SD = 8.8 years) in the placebo group. The mean BMI of patients in the semaglutide 2.4 mg group was 33.30 kg/m^2 (SD = 5.03 kg/m^2) and 33.37 kg/m^2 (SD = 5.04 kg/m^2) in the placebo group. Most patients in the full analysis set (FAS) had a history of MI — 5,962 patients (67.7%) in the semaglutide 2.4 mg group and 5,944 patients (67.5%) in the placebo group. The mean duration of follow-up was 39.9 months (SD = 9.3 months) in the semaglutide 2.4 mg group and 39.7 months (SD = 9.5 months) in the placebo group. The mean duration of exposure to semaglutide 2.4 mg was 33.3 months (SD = 14.4 months) and to placebo was 35.1 months (SD = 13.0 months).

Efficacy Results

Key efficacy results are based on the in-trial observation period with a data cut-off date of July 18, 2023.

Major Adverse CV Event (CV Death, Nonfatal MI, or Nonfatal Stroke)

At the data cut-off date, the percentages of patients (in the FAS) with their first EAC-confirmed MACE (consisting of CV death, nonfatal MI, or nonfatal stroke) were 6.5% of 8,803 patients in the semaglutide 2.4 mg group and 8.0% of 8,801 patients in the placebo group. Semaglutide 2.4 mg was favoured over placebo (adjusted HR = 0.80; 95% CI, 0.72 to 0.90). The absolute risk difference in time to first EAC-confirmed MACE between semaglutide 2.4 mg and placebo at week 156 was −1.1% (95% CI, −1.9% to −0.4%).

Consultation with the clinical experts did not identify relevant potential treatment effect modifiers to examine for this review. However, BMI was identified as the most relevant for the purpose of this review to inform expert committee deliberations.

CV Death

At the data cut-off date, the percentages of patients (in the FAS) with an EAC-confirmed CV death (including undetermined cause of death) were 2.5% in the semaglutide 2.4 mg group and 3.0% in the placebo group (HR = 0.85; 95% CI, 0.71 to 1.01). The absolute risk difference in time to EAC-confirmed CV death between semaglutide 2.4 mg and placebo at week 156 was 0% (95% CI, −0.5% to 0.4%).

HF Composite (CV Death, or Hospitalization for HF or Urgent HF Visit)

At the data cut-off date, the percentages of patients (in the FAS) with their first EAC-confirmed composite HF outcome (comprising of CV death, HF requiring hospitalization, or urgent HF visit) were 3.4% in the semaglutide 2.4 mg group and 4.1% in the placebo group (HR = 0.82; 95% CI, 0.71 to 0.96). The absolute risk difference in time to EAC-confirmed composite HF outcome between semaglutide 2.4 mg and placebo at week 156 was −0.2% (95% CI, −0.8% to 0.3%).

All-Cause Death

At the data cut-off date, the percentages of patients (in the FAS) with an EAC-confirmed all-cause death were 4.3% in the semaglutide 2.4 mg group and 5.2% in the placebo group (HR = 0.81; 95% CI, 0.71 to 0.93). The absolute risk difference in time to EAC-confirmed all-cause death between semaglutide 2.4 mg and placebo at week 156 was −0.5% (95% CI, −1.1% to 0.1%).

Nonfatal MI

At the data cut-off date, the percentages of patients (in the FAS) with their first EAC-confirmed nonfatal MI were 2.7% in the semaglutide 2.4 mg group and 3.7% in the placebo group (HR = 0.72; 95% CI, 0.61 to 0.85).

Nonfatal Stroke

At the data cut-off date, the percentages of patients (in the FAS) with their first EAC-confirmed nonfatal stroke were 1.7% in the semaglutide 2.4 mg group and 1.9% in the placebo group (HR = 0.93; 95% CI, 0.74 to 1.15).

Hemoglobin A1C of 6.5% or Greater

Classification of glycaemic status was according to the American Diabetes Association Standards of Medical Care in Diabetes published in 2018. Accordingly, a patient with hemoglobin A1C greater than or equal to 6.5% has diabetes.

At the data cut-off date, 306 patients (3.5% of the FAS) in the semaglutide 2.4 mg group and 1,059 patients (12.0% of the FAS) in the placebo group experienced a first occurrence of hemoglobin A1C of 6.5% or greater (HR = 0.27; 95% CI, 0.24 to 0.31).

Composite Nephropathy Event

The 5-component composite nephropathy end point consisted of onset of persistent macroalbuminuria (urinary albumin-to-creatinine ratio > 300 mg/g), persistent 50% reduction in estimated glomerular filtration rate (eGFR) compared with baseline, onset of persistent eGFR of less than 15 mL/min/1.73 m^2, initiation of chronic renal replacement therapy (i.e., dialysis or transplant), or renal death.

At the data cut-off date, 155 patients (1.8% of the FAS) in the semaglutide 2.4 mg group and 198 patients (2.2% of the FAS) in the placebo group experienced a first composite nephropathy event (HR = 0.78; 95% CI, 0.63 to 0.96).

Body Weight

The mean treatment difference in the percent change from baseline in body weight at week 104 between semaglutide 2.4 mg and placebo was −8.51% (95% CI, −8.75% to −8.27%).

The analyses at weeks 156 and 208 were not performed as planned because more than 10% of patients in FAS missed the relevant annual study visit due to trial termination. However, an analysis of the percent change from baseline in body weight was performed at week 208 and the estimated treatment difference (based on the in-trial period) between semaglutide 2.4 mg and placebo was −8.7% (95% CI, −9.42% to −7.88%). The on-treatment analysis, which defined treatment exposure as the observation period until first time off treatment for greater than 35 days, estimated the treatment difference (−10.2%; 95% CI, −11.0% to −9.42%), which was similar with the result from the main analysis for change in body weight at week 208.

EQ-5D Index Score and EQ VAS Score

The EQ-5D-5L questionnaire is a patient-reported outcome tool used to estimate HRQoL. The tool includes a descriptive system that provides a description of problems experienced by the respondent according to dimensions, a VAS that provides a score indicating overall self-rated health (score ranges from 0 to 100), and an index score that ranges from 0 to 1. A higher score indicates better self-reported health status.

The treatment difference in the change from baseline in the EQ-5D index score at week 104 between semaglutide 2.4 mg and placebo was 0.01 (95% CI, 0.01 to 0.02).

The treatment difference in the change from baseline in the EQ VAS score at week 104 between semaglutide 2.4 mg and placebo was 1.60 (95% CI, 1.16 to 2.04).

Weight-Related Sign and Symptom Measure

The weight-related sign and symptom measure (WRSSM) is a patient-reported outcome tool (a self-rated VAS) used to assess the presence and bother associated with weight-related symptoms. Specifically, it is used to assess the impact of multifaceted aspects of obesity on symptom experience in individuals with overweight or obesity. The total score ranges from 0 to 4, with higher scores indicating worse symptomatology.

The mean change from baseline in WRSSM total score at week 104 was −0.26 (SD = 0.71) in the semaglutide 2.4 mg group and −0.12 (SD = 0.68) in the placebo group. The between-group difference was not estimated.

Cardiometabolic Risk Factors

Efficacy results on cardiometabolic risk factors (change from baseline in systolic blood pressure, change from baseline in total cholesterol, and change from baseline in high-density lipoprotein cholesterol at week 104) were used to inform the accompanying pharmacoeconomic analysis.

Harms Results

Harms results are based on the in-trial observation period with a data cut-off date of July 18, 2023.

Adverse Events

As described in the clinical study report, nonserious adverse events (AEs) not fulfilling any of the prespecified criteria were not systematically collected. The focus of the safety evaluation per the clinical study report for the SELECT trial was based on reporting of serious AEs (SAEs) and other systematically collected events (i.e., AEs of special interest).

Serious Adverse Events

The proportion of patients with an SAE was 33.41% (2,941 of 8,803 patients) in the semaglutide 2.4 mg group and 36.40% (3,204 of 8,801 patients) in the placebo group. The most frequently reported SAEs (by preferred term) (frequency ≥ 2.0%) were coronary arterial stent insertion, acute MI, and unstable angina.

Withdrawals Due to AEs

The proportion of patients who permanently stopped treatment due to AEs was 16.60% (1,461 patients) in the semaglutide 2.4 mg group and 8.16% (718 patients) in the placebo group. The most frequently reported AEs (by preferred term) that led to permanent treatment discontinuation (frequency ≥ 2.0%) were nausea and diarrhea.

The proportion of patients who had their treatment interrupted or withdrawn due to AEs was 30.32% (2,669 patients) in the semaglutide 2.4 mg group and 16.00% (1,408 patients) in the placebo group. The most frequently reported AEs (by preferred term) that led to treatment interruption or dose withdrawn (frequency ≥ 2.0%) were: nausea, diarrhea, vomiting, constipation, and decreased appetite.

Mortality

There were 375 all-cause deaths (4.26%) in the semaglutide 2.4 mg group and 458 all-cause deaths (5.20%) in the placebo group. There were 371 investigator-reported SAEs with fatal outcome (4.21%) in the semaglutide 2.4 mg group and 460 investigator-reported SAEs with fatal outcome (5.23%) in the placebo group.

Notable Harms

The AEs of special interest identified for this review included CV AEs, cholelithiasis, nausea, vomiting, constipation, gastroesophageal reflux disease, and pancreatitis. SAEs of cardiac disorders were reported in 11.45% (1,008 patients) in the semaglutide 2.4 mg group and 13.45% (1,184 patients) in the placebo group. All other AEs of special interest were reported in less than 2% of patients in each group.

Critical Appraisal

Internal Validity

The SELECT trial had a group sequential design — a type of adaptive clinical trial design that plans for interim analyses at predetermined points during follow-up and as data are collected in the trial. This design offers structured opportunities to make earlier decisions when the intervention shows a significant benefit and improves efficiency in research by allowing adjustments in the trial design to be made compared with traditional, fixed-period RCTs. However, this design requires strong and appropriately conservative statistical plans due to the potential for unblinding, investigator influence, overestimation of treatment effect, and increase chance of inflated type I error. As will be described, the SELECT trial design, conduct, and analysis mitigate some of these potential limitations.

Overall, baseline characteristics were similar between groups, suggesting randomization successfully distributed potential confounders. In consultation with the clinical experts, the baseline characteristics did not reflect any notable imbalances in known prognostic factors for CV events and treatment effect modifiers. As such, the review team concluded that the methods to achieve allocation and allocation concealment for randomization were appropriate and that the risk of bias arising from the randomization process was low.

The percentage of patients who discontinued the study was relatively small and similar between the groups (approximately 3%). The reasons for discontinuing the study (patient withdrawal and loss to follow-up) were also similar between the groups and therefore the risk of attrition bias was likely low. The overall treatment discontinuation rates were similar between groups (approximately 30%). An imbalance in discontinuation of treatment due to AEs was observed (16.3% in the semaglutide 2.4 mg group and 7.9% in the placebo group). This imbalance could have contributed to differential unblinding, as these participants with treatment emergent adverse events — many of which were gastrointestinal in nature — might have inferred their assignment to semaglutide. Similarly, investigators might have formed expectations based on these observations, thereby introducing the potential for performance and reporting bias. While the observed difference between groups in treatment discontinuation due to lack of effect was relatively smaller, it was still differential (0.7% in the semaglutide 2.4 mg group and 2.8% in the placebo group) and therefore does not completely negate the potential impact on reporting and performance biases (i.e., relatively less concerning for biases). However, appropriate methods for adjudicating events in a robust and standardized

way were employed and safeguards to prevent operational bias (in the context of a group sequential design) were reportedly in place; therefore, the review team concluded the probability for introducing bias into the results was low.

Supplementary analyses of absolute risk difference were conducted at week 156 of the trial to assess the robustness of various end points. A total of 27.3% of randomized patients in the trial did not have a visit at week 156 due to trial closure. The trial was event driven and would not be completed until the target number of primary end point events was reached. While the general assumption for censored observations was that the risk of experiencing an event was not changed by censoring, the potential for bias in the estimated cumulative incidence at week 156 would arise only if patients who were censored due to what was termed as trial closure in the clinical study report had a different risk of MACE compared with those who remained in the study. However, the definition of trial closure in the clinical study report is not entirely clear. Administrative censoring included trial completion, lost to follow-up, and patient withdrawal. The implications of administrative censoring for the robustness of absolute risk difference in MACE is difficult to determine based on the available information. The review team noted that the between-group distribution in administrative censoring, including trial closure, was similar and therefore if bias exists, it is unlikely an important factor in the cumulative incidence estimates. Furthermore, a total of 79.4% of randomized patients in the trial did not have a visit at week 208 due to trial closure. The review team considered this large percentage of missing data to seriously undermine the validity and reliability of the percent change from baseline in body weight at week 208 reported by Ryan et al. (2024). There is a high chance that missing information was due to informative censoring and in the absence of additional analyses evaluating the missing data patterns, it is not possible to draw firm conclusions on the results from the analyses on body weight at week 208.

The use of a single interim analysis in the SELECT trial reduces the risk of bias compared to multiple interim tests in a trial that uses the group sequential design. For the primary end point, the final analysis was adjusted for the group sequential design by using the likelihood ratio ordering. The similarity between the unadjusted and adjusted estimates suggested that the single interim analysis had little influence on the final effect size and the reported treatment effect was unlikely influenced by type I error associated with the group sequential design. Further, given the trial continued to its final analysis without stopping for efficacy, the concern for treatment effect inflation due to early termination does not apply.

The proportional hazards assumption for the primary end point was evaluated graphically using Schoenfeld residuals and the standardized score process, which the investigators reported as being met. However, an early deviation in the slope suggested a violation of the proportional hazards assumption in the first 12 months, although the stabilization afterward indicated the issue was not persistent over the full duration of the study. The statistical analysis plan for the SELECT trial did not describe methods to assess the potential impact of this violation on the results. While visual inspection of the score process suggested a time-dependent effect on the proportional hazards, there was no clear evidence that this influenced the confirmatory results in a meaningful way.

The superiority hypothesis was tested for each confirmatory secondary end point under multiplicity control using a stagewise hierarchical testing scheme according to the prespecified order. The statistical testing

strategy for the confirmatory secondary end points used a separate alpha spending function to control type I error rate at a 1-sided level of 2.5%, which aligned with the P value adjustment for the group sequential design. Importantly, the end points — the composite heart failure outcome and all-cause death — could not formally be interpreted for superiority because the prespecified hierarchical testing procedure failed to reach statistical significance with the analysis of CV deaths, meaning they should be interpreted as exploratory rather than confirmatory. The SELECT trial performed statistical comparisons for the nonconfirmatory secondary end points and some exploratory end points. However, the statistical comparisons were not included in the approach to adjust for multiple comparisons and therefore increase the risk of type I error. The absence of a prespecified multiplicity control strategy for these end points limits the strength of conclusions that can be drawn from the observed differences between groups.

The number of events contributing to the subgroup analyses according to a BMI of 40 kg/m^2 or greater were considered few (< 50 events in each treatment group), and the sample sizes for these 2 subgroups were considered small (< 10% of patients randomized in each group), thereby lowering the certainty in the consistency of the treatment effect for the primary end point in these subgroups.

The main analysis of the time-to-event end points assumed independent censoring of patients who withdrew from the trial or were lost to follow-up, while deaths from causes not included in the end point were handled as censored observations but not part of the independent censoring assumption. Sensitivity analyses (addressing the independent censoring assumption and assessing the potential impact of missing data for patients who had withdrawn from the trial or were lost to follow-up) and a supplementary analysis (assessing the influence of the competing risk of death from causes not included in the end point) were performed for the confirmatory end points. The results of the sensitivity analyses were consistent with the main analyses, the review team judged that the risk of bias due to handling of these intercurrent events and missing outcomes data for the confirmatory end points was low. Of note, the tipping point sensitivity analysis was conducted only for the primary analysis and not for the key secondary confirmatory analyses. The review team had concerns about the 2 additional sensitivity analyses that were described as applying to patients who withdrew consent or were lost to follow-up; however, because these sensitivity analyses yielded similar results to the primary analysis (which was further supported by the tipping point sensitivity analysis) and other confirmatory analyses, this suggests that the assumption of independent censoring was reasonable and that the trial's conclusions are likely robust.

For all objectives, the primary estimand (intention to treat) was used to evaluate the treatment effect irrespective of adherence to treatment or changes to background medication. Although this approach to handling of intercurrent events may be reflective of clinical practice, it can be a limitation for the interpretation of efficacy results given that these intercurrent events also have an effect on CV risk. Further, the proportion of patients who discontinued treatment was relatively high (approximately 30%). A supplementary analysis based on the first on-treatment period was performed for the confirmatory end points to evaluate the effect in all patients who had remained on their randomized treatment. As the results were consistent with the main analysis, the review team judged that the risk of bias due to treatment discontinuation was low for the confirmatory end points. The proportion of patients initiating a CV-related medication, SGLT2 inhibitors, and metformin after randomization was overall slightly higher with placebo compared with semaglutide 2.4 mg. In

consultation with the clinical experts, it was concluded that there is a potential for bias against semaglutide 2.4 mg in the assessment of CV outcomes due to this slight imbalance in prescribing of these medications.

Continuous supportive secondary end points at week 104 were analyzed with multiple imputation used for missing values under a missing-at-random assumption, which was likely not plausible as there were notable imbalances in the reasons for treatment discontinuation between groups. A sensitivity analysis that was planned to address this assumption for missing data were performed for the change from baseline in body weight at week 104. As the results were consistent with the main analysis, the review team judged that the risk of bias due to missing outcomes data for this end point was low. No sensitivity analysis was planned for change from baseline in EQ-5D, where missing outcome data were relatively high (approximately 16%) at week 104. As such, the review team concluded there is a potential for risk of bias due to missing outcomes data for these end points.

WRSSM was an exploratory end point because the measure was not sensitive to weight loss in a psychometric evaluation per the clinical study report of the SELECT trial. The sponsor indicated that the WRSSM tool was under development at the time of the trial and as such, no further evidence of its measurement properties in the population of interest was submitted by the sponsor.

External Validity

Evidence from the SELECT trial addressed the evidence gap on the effects of semaglutide 2.4 mg on CV outcomes, which was raised in the previous submission for the weight management indication, but only for a subset of patients in the indicated population.

There was overlap of the trial population with the reimbursement criteria requested by the sponsor for the resubmission — patients with a BMI of 27 kg/m^2 or greater and established CVD (MI, stroke, and/or PAD). The clinical experts consulted for this review agreed that the inclusion criteria captured the target population with established CVD (including HF) seen in practice and in need of an intervention for secondary prevention of future CV events. Notably, most patients in the trial had prediabetes according to the American Diabetes Association Standards of Medical Care in Diabetes published in 2018 (hemoglobin A1C ≥ 5.7% to < 6.5%). However, it is important to note that there is a small distinction in the diagnosis of prediabetes according to the Diabetes Canada Clinical Practice Guidelines (hemoglobin A1C ≥ 6.0% to < 6.5%). In consultation with the clinical experts, no major concern with the generalizability of results due to this difference was identified.

As treatment with semaglutide 2.4 mg is not expected to be limited to patients who do not have diabetes in practice, the review team identified the exclusion criterion for a hemoglobin A1C level of 6.5% or higher to be a concern for the generalizability of results to the target population. The investigator indicated that the trial population did not include patients with type 1 and T2DM to remove any confounding that a diagnosis of diabetes could have on future CV risk. For more information on this evidence gap and how evidence from the SUSTAIN-6 trial addressed the gap, refer to the study addressing the gap in the Systematic Review section.

In consultation with the clinical experts, it was concluded that comparison with placebo added to standard of care for CVD (i.e., antihypertensives, lipid-lowering drugs, anticoagulants, acetylsalicylic acid, and other antiplatelet drugs) was appropriate given that none of the current and accessible standard of care therapies

to treat or prevent CVD directly target weight loss. Regarding the standard of care for CVD used in the trial, the clinical experts advised that semaglutide would be combined with therapies that reduce cardiorenal risk in practice, including in combination with ACE inhibitors, ARBs, statins, and SGLT2 inhibitors.

Long-Term Extension Study

The sponsor did not submit a long-term extension study for this review.

Indirect Evidence

The sponsor did not submit indirect evidence for this review.

Study Addressing a Gap in the Evidence From the Systematic Review

Study Description

Data from the SUSTAIN-6 trial (N = 3,297) was submitted to address the effects of semaglutide on CV outcomes in the target reimbursement population (patients with a BMI of 27 kg/m^2 or greater and established CVD) who also have T2DM. SUSTAIN-6 (N = 3,297) was a long-term, multicentre, multinational, randomized, double-blind, parallel-group, controlled trial that evaluated the CV safety and long-term outcomes of semaglutide compared to placebo, when added to standard of care, in patients with T2DM at high risk of CV events. Patients were randomized 1:1:1:1 to receive a once-weekly subcutaneous injection of either semaglutide 0.5 mg, semaglutide 1.0 mg, or volume-matched placebo. Treatment duration spanned 104 weeks and consisted of a 4-week to 8-week dose escalation period, followed by a 96-week to 100-week treatment maintenance period, and then a 5-week follow-up period.

From the SUSTAIN-6 trial data, a post hoc subgroup analysis was conducted, which included patients with a BMI of 27 kg/m^2 or greater, and established CVD and T2DM. Post hoc subgroup analyses were conducted to determine if the efficacy observed in this patient population was consistent with the SELECT trial, and therefore the enrolment criteria for this subgroup replicated that of the SELECT trial (i.e., limiting the subpopulation to patients with prior MI, stroke [excluding TIA], and/or PAD) with a BMI criterion of 27 kg/m^2 or higher. Consistent with exclusion criteria for all SUSTAIN-6 trial participants, patients in the post hoc subgroup analyses did not have type 1 diabetes and had not used GLP-1 receptor agonists or pramlintide within 90 days before screening. Although there were 2 maintenance doses used in the overall SUSTAIN-6 study (0.5 mg and 1.0 mg), only patients who had received 1.0 mg were included in the post hoc subgroup analyses, as this dose was considered most comparable to that of the SELECT trial. However, the SUSTAIN-6 trial post hoc subgroup participants had still received a lower dose of semaglutide (1.0 mg) compared to participants in the SELECT trial (2.4 mg). As the post hoc subgroup analyses were the most relevant for the purposes of this review, the results summarized in this section only include those pertaining to this subgroup.

The CV-related efficacy outcomes investigated in the SUSTAIN-6 trial were consistent with that of the SELECT trial. The primary end point was time from randomization to first occurrence of a MACE, defined as CV death, nonfatal MI, or nonfatal stroke. Secondary end points identified by clinical experts as most

relevant to this review were time from randomization to first occurrence of all-cause death, nonfatal MI, or nonfatal stroke.

Demographics and Baseline Characteristics

Patients in the SUSTAIN-6 trial post hoc subgroup analyses had a mean age of [redacted], a mean T2DM disease duration of [redacted], and a mean BMI of [redacted] Most patients across both groups had triglyceride levels greater than or equal to [redacted] with a mean triglyceride level of [redacted]. The eGFR of patients across both groups were primarily between [redacted] with a mean eGFR of [redacted] Most patients were taking antihypertensive medication [redacted] and/or lipid-lowering drugs [redacted] For CV history, only data for prior heart failure was provided, and [redacted] of patients in the semaglutide group had prior heart failure compared to [redacted] of the placebo group. Data for other CV inclusion criteria (MI, stroke, and PAD) were not provided.

Results

The outcomes reported for the post hoc subgroup efficacy analyses align with the key outcomes identified for this review. Of all efficacy outcomes included in the post hoc subgroup analysis, only the key secondary outcome of time from randomization to first occurrence of expanded MACE demonstrated nominal statistical significance; however, this outcome was not among those of interest for the purposes of this review. The remaining CV-related outcomes demonstrated numerical improvement in the semaglutide group compared to the placebo group; however, they did not achieve statistical significance. The overall safety profile of semaglutide observed in the post hoc subgroup of the SUSTAIN-6 trial was consistent with that of the SELECT trial, with fewer CV SAEs with semaglutide 1.0 mg versus placebo.

Critical Appraisal

The post hoc nature of the subgroup analysis in the SUSTAIN-6 trial introduces important internal validity concerns and risk of bias. Because the subgroup was not prespecified, the analysis is exploratory rather than confirmatory, increasing the risk of spurious findings due to multiple comparisons. Additionally, patients in the SUSTAIN-6 trial were not randomized within the subgroup of interest, meaning that unmeasured confounders could bias the treatment effect estimate. Among all CV-related end points, only expanded MACE reached nominal significance, which may have been due to inadequate power. As a result, it is challenging to interpret the efficacy of semaglutide 1.0 mg in this patient subgroup.

The small sample size of the post hoc subgroup limits the generalizability of findings, given that 80% to 90% of people living in Canada with T2DM with overweight or obesity and 32% worldwide have CVD. The high prevalence of potentially eligible individuals in Canada, combined with significant heterogeneity in CVD presentation, driven by factors like age, diabetes duration, glycemic control, and comorbidities, limits the generalizability of findings. A major limitation of the SUSTAIN-6 trial in the context of the current resubmission is that the dosages evaluated in the trial do not align with the proposed Health Canada recommended therapeutic and maintenance dose of semaglutide (Wegovy), which is 2.4 mg once weekly. More specifically, the study evaluated semaglutide 0.5 mg and 1.0 mg. The focus of the post hoc subgroup of the SUSTAIN-6

trial was on the 1.0 mg as, according to the sponsor, it is most comparable to the dosage in the SELECT trial; however, this remains a significant limitation to the generalizability of the evidence.

Economic Evidence

Table 3: Cost and Cost Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Markov Model
Target population	Adult patients with a body mass index ≥ 27 kg/m^2 and established CVD.
Treatment	Semaglutide (Wegovy)
Dose regimen	2.4 mg once weekly for no more than 3 years as an adjunct to a reduced-calorie diet and increased physical activity
Submitted price	Semaglutide (Wegovy): $388.64 per multiuse, prefilled, single dose pens, regardless of strength (0.25 mg, 0.5 mg, 1 mg, 1.7 mg, or 2.4 mg). Each pen contains 4 doses.
Treatment cost	Annual cost of semaglutide is $5,066 per patient ($4,182 assuming 82.5% compliance)
Comparator	Standard of care (reduced-calorie diet and increased physical activity)
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	40 years
Key data sources	SELECT and SUSTAIN-6 clinical trials
Key limitations	• The sponsor's submitted economic model uses risk equations, based on a function of risk factors such as BMI and SBP, to estimate CV events associated with semaglutide. However, CV events were directly captured in the SELECT trial. The analysis does not accurately replicate results from the SELECT trial which question the validity of the modelling approach. • The sponsor's analysis included patients with T2DM, who may be receiving treatment for T2DM which could include lower dose semaglutide (Ozempic). Therefore, when considering patients with T2DM, no treatment (i.e., reduced-calorie diet and increased physical activity) is not the most relevant comparator. The cost effectiveness of using semaglutide in patients with T2DM at the recommended dose for weight management versus the recommended dose for T2DM management is unknown. • The sponsor assumed all patients discontinue treatment with semaglutide at 3 years. This does not align with the product monograph or anticipated use in clinical practice according to clinical experts consulted by CDA-AMC. In practice, it is expected that patients will remain on treatment unless there are intolerable side effects as evidence shows treatment benefit is linked to time on therapy. It was not possible to conduct an appropriate analysis assessing the impact long-term use of semaglutide (beyond 3 years) in terms of cost effectiveness. • The sponsor extrapolates 3 years of treatment on semaglutide over a 40-year time horizon assuming long-term sustained impact on T2DM onset and cancer development. No evidence was presented to support the continued benefit of semaglutide after treatment discontinuation (at 3 years). The analysis therefore likely overestimates the post-discontinuation benefit associated with semaglutide.

Component	Description
	• The sponsor assumes that weight reduction leads to instantaneously lower mortality risk unrelated to the prevention of comorbidities, such as CV events. This is counter to evidence presented in the SELECT trial which shows that CV events are the main driver for reduction in mortality. The sponsor's analysis incorrectly attributes the reason for mortality reduction associated with semaglutide use making any mortality predictions from the submitted model unsuitable.
CDA-AMC reanalysis results	• CDA-AMC undertook revisions to the sponsor's analysis to address the following limitations: focusing on patients without T2DM (to address the appropriate comparison); removing comorbidities other than diabetes and CV events from the analysis; assuming treatment effects persist for 1 year after treatment discontinuation; replicating mortality outcomes from the trial; and, assuming equivalence in outcomes 4 years posttreatment discontinuation. • In the CDA-AMC base case, the ICER for semaglutide is $185,646 per QALY gained compared with standard of care (incremental costs: $9,595; incremental QALYs: 0.05) in the revised population (excluding patients with T2DM). A price reduction of 67% would be required for semaglutide to be considered cost effective at a $50,000 per QALY threshold.

BMI = body mass index; CDA-AMC = Canada's Drug Agency; CV = cardiovascular; CVD = cardiovascular disease; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life-year; SBP = systolic blood pressure; T2DM = type 2 diabetes mellitus.

Budget Impact

CDA-AMC did not conduct a base-case analysis as there is a high degree of uncertainty in several analysis parameters. Instead, CDA-AMC increased the proportion of the eligible population enrolled in public plans to better reflect the increased age of patients who have had a CVD event relative to the overall adult population enrolled in public plans. This underlying analysis resulted in an estimated 3-year budgetary impact of $597,965,020 (year 1: $96,284,813, year 2: $197,094,448, year 3: $304,585,759). Due to high amounts of remaining uncertainty, CDA-AMC conducted a series of scenarios varying the proportion of patients with overweight or obesity who have had a prior CVD event, as well as the predicted uptake of semaglutide in that population. Cumulative 3-year budget impact estimates for these varied assumptions ranged from $149 million to $3.6 billion. The expected budgetary impact of reimbursing semaglutide for patients with a BMI of 27 kg/m^2 or greater who have prior CVD is therefore substantial and highly uncertain.

CDEC Information

Members of the Committee

Dr. Peter Jamieson (Chair), Dr. Sally Bean, Daryl Bell, Dan Dunsky, Dr. Trudy Huyghebaert, Morris Joseph, Dr. Dennis Ko, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Nicholas Myers, Dr. Krishnan Ramanathan, Dr. Marco Solmi, Dr. Edward Xie, and Dr. Peter Zed.

Meeting date: April 24, 2025

Regrets: One expert committee member did not attend.

Conflicts of interest: One expert committee member did not participate due to considerations of conflict of interest.

Canada's Drug Agency
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Questions or requests for information about this report can be directed to Requests@cda-amc.ca.