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CADTH 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 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, dyslipidemia, or obstructive sleep apnea.

Sponsor: Novo Nordisk Canada Inc.

Final recommendation: Do Not Reimburse

CADTH

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Summary

CADTH

What is the CADTH Reimbursement Recommendation for Wegovy?

CADTH recommends that Wegovy should not be reimbursed by public drug plans for chronic weight management in adult patients.

Why Did CADTH Make This Recommendation?

- Even though results from 4 clinical trials showed that patients treated with Wegovy for 68 weeks lost more body weight compared to those who received placebo, there was no evidence to show this weight loss translates to improvements in weight-related comorbidities (e.g., cardiovascular complications, osteoarthritis [the most common form of arthritis], and sleep apnea) because they were not studied.
- Although results showed improvements in health-related quality of life (HRQoL), the minimally important difference (MID) was not met, and it remains unknown if the differences were clinically meaningful.
- Wegovy is effective for weight loss for up to 2 years with an acceptable side effect profile, but it is unclear whether it meets patient needs for reduced weight-related comorbidities and improved HRQoL.

Additional Information

What Are Overweight and Obesity?

Overweight and obesity are defined as abnormal or excessive fat accumulation that presents a risk to health; obesity corresponds to a higher body mass index (BMI) range than overweight. Obesity is associated with an increased risk of a wide range of illnesses and long-term conditions, including type 2 diabetes, hypertension, gallstones, gastroesophageal reflux disease, and cancer, as well as psychological and psychiatric disorders. It is estimated that 67% of Canadian men and 54% of Canadian women are living with overweight or obesity.

Unmet Needs in Overweight and Obesity

There is a need for treatment options that improve weight-related comorbidities (e.g., diabetes, cardiovascular complications, and sleep apnea), reduce body weight, have an acceptable side effect profile, and provide long-term benefit.

How Much Does Wegovy Cost?

Treatment with Wegovy is expected to cost approximately $4,726 per patient per year.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that semaglutide not be reimbursed 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, type 2 diabetes mellitus, dyslipidemia, or obstructive sleep apnea.

Rationale for the Recommendation

Evidence from 4 placebo-controlled, double-blind (DB) randomized controlled trials (RCTs) demonstrated that treatment with semaglutide injection 2.4 mg resulted in body weight reduction for 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. The STEP 1 (N = 1,961), STEP 2 (N = 1,210), STEP 3 (N = 611), and STEP 4 (N = 803) trials demonstrated that 68 weeks of treatment with semaglutide 2.4 mg once weekly, with a background regimen of 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%. In addition, the STEP 1, STEP 2, and STEP 3 trials demonstrated statistically significant improvements in the percentage of patients with at least 5%, 10%, and 15% reduction in body weight. Comorbidities such as major adverse cardiovascular events, osteoarthritis, and obstructive sleep apnea were not outcomes in the STEP trials. Although there were statistically significant improvements in the 36-Item Short Form Survey (SF-36) Physical Functioning score and the Impact of Weight on Quality of Life Lite for Clinical Trials scale (IWQOL-Lite CT) Physical Function score with semaglutide treatment versus placebo, the MID for the SF-36 Physical Functioning score was not met, and the MID for the IWQOL-Lite CT Physical Function score is unknown. Patients identified a need for treatments that are effective for weight loss and reducing weight-related comorbidities, improve HRQoL, are easy to administer, and have reduced side effects. Semaglutide demonstrated effectiveness in weight loss for up to 2 years with an acceptable side effect profile, but it is unclear whether this translates into a reduction in weight-related comorbidities or improvement in HRQoL.

Discussion Points

- CDEC acknowledged patient and clinician input emphasizing the importance of weight loss as an outcome on its own. However, improvements in weight-related comorbidities and HRQoL were also identified as important outcomes for patients, and the trial evidence does not adequately address these unmet needs.
- CDEC noted that the currently available evidence for an association between reduction in body weight on pharmacotherapy and improvement in weight-related comorbidities is insufficient to make conclusions on how the reductions in body weight with semaglutide treatment observed in the STEP trials might impact weight-related comorbidities.

- CDEC noted that there is an ongoing trial, the SELECT study, comparing semaglutide injection 2.4 mg with placebo for the prevention of major adverse cardiovascular events in patients with overweight or obesity who have established cardiovascular disease but not diabetes mellitus. The results of the study will address the current evidence gap regarding the effects of semaglutide 2.4 mg once weekly on cardiovascular outcomes in the indicated population.
- Normalization of glucose parameters in patients with pre-diabetes at baseline was assessed as an exploratory outcome in the STEP 1, STEP 3, and STEP 4 trials. However, interpretation of these results is limited because it was an exploratory outcome in these trials, and the contribution of weight reduction to this outcome is unclear given the known beneficial effects of semaglutide on glucose metabolism in individuals with diabetes independent of weight reduction.
- CDEC discussed that the effectiveness of semaglutide injection 2.4 mg is likely optimized when combined with lifestyle and behavioural changes, which is how it was administered in the clinical trials. However, structured weight management programs are not widely accessible in Canada, and the generalizability of the trial results to Canadian clinical practice is unclear. Furthermore, the opportunity costs of focusing coverage solely for expensive medications may compromise appropriate development of such programs.
- CDEC also noted that another source of uncertainty in the clinical benefit of semaglutide injection 2.4 mg was the lack of efficacy data beyond 2 years of treatment in the STEP 5 RCT (N = 304) for a therapy that may be used by individuals for indefinite periods due to the chronic nature of obesity and overweight.
- While the STEP 8 trial (N = 338) demonstrated that treatment with semaglutide was associated with statistically significant improvements in weight reduction over liraglutide, there was only blinding for the comparisons of each active treatment versus placebo and not between semaglutide and liraglutide, and this introduces some uncertainty in the efficacy of semaglutide versus liraglutide.
- In 1 sponsor-submitted indirect treatment comparison (ITC) of semaglutide injection 2.4 mg versus other therapies indicated for weight management in individuals with overweight or obesity, [redacted] However, the limitations of the ITC, including heterogeneity in [redacted], study design, and statistical analysis across the included trials and [redacted], meant that conclusions could not be drawn from the ITC.

Background

WHO defines overweight and obesity as abnormal or excessive fat accumulation that poses a risk to health. A BMI of 25 kg/m^2 or greater is considered overweight and a BMI of 30 kg/m^2 or greater is considered obese. The Canadian Health Measures Survey (2019) found that 35.5% of adults between the ages of 18 and 79 were in the overweight category and 24.3% were living with obesity, and the Canadian Task Force on Preventive Health Care (CTFPHC) has reported that 67% of Canadian males and 54% of Canadian females are living with overweight or obesity. There is a wide range of comorbidities associated with obesity, including increased risk of type 2 diabetes, certain cancers, hypertension, cardiovascular disease, and gallstones, as well as psychological and psychiatric issues.

The approach to management of overweight and obesity is multi-pronged, and includes modification of physical activity and behaviour, in addition to medical nutrition therapy. According to the Canadian Adult Obesity Clinical Practice Guidelines, drug therapy for overweight or obesity is indicated only for those with a BMI of 30 kg/m^2 or more, or for those with a BMI of 27 kg/m^2 or more with at least 1 weight-related comorbidity.

Semaglutide injection 2.4 mg 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, type 2 diabetes mellitus, dyslipidemia, or obstructive sleep apnea. The sponsor has requested reimbursement as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial BMI of 35 kg/m^2 or greater and pre-diabetes. Semaglutide is a glucagon-like peptide (GLP)-1 agonist. Semaglutide injection 2.4 mg is available as a solution for subcutaneous injection in a pre-filled pen, and the dosage recommended in the product monograph is 2.4 mg once weekly. Currently, there are 3 other drugs approved for chronic weight management in Canada: orlistat, liraglutide, and the combination of bupropion and naltrexone.

Sources of Information Used by the Committee

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

- a systematic review of 4 placebo-controlled, DB RCTs and 1 RCT comparing semaglutide with liraglutide and with placebo in patients with a BMI of 30 kg/m^2 or greater, or 27 kg/m^2 or greater in the presence of at least 1 weight-related comorbidity (including 1 RCT in patients with type 2 diabetes mellitus)
- a review of 1 indirect treatment comparison (ITC) of semaglutide versus pharmacotherapies for weight management in patients with overweight or obesity
- a review of 1 longer-term, placebo-controlled, DB RCT in patients with a BMI of 30 kg/m^2 or greater, or 27 kg/m^2 or greater in the presence of at least 1 weight-related comorbidity
- patients' perspectives gathered by patient groups: the Gastrointestinal Society, Obesity Canada, Canadian Liver Foundation, Diabetes Canada, and Obesity Matters
- input from public drug plans that participate in the CADTH review process
- one clinical specialist with expertise diagnosing and treating patients with overweight and obesity
- input from 4 clinician groups: Calgary Weight Management Centre, Centre de Médecine Métabolique de Lanaudière, Obesity Canada, and the Canadian Association of Bariatric Physicians and Surgeons
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

A total of 5 patient groups provided 4 submissions (Gastrointestinal Society, a joint input from Obesity Canada and the Canadian Liver Foundation, Diabetes Canada, and Obesity Matters). The Gastrointestinal Society is a national charity that focuses on providing Canadians with trusted, commercial-free, medically sound information on gut and liver diseases and disorders, including obesity. Data for this submission came from a variety of sources, including contact with patients and patient caregivers, the results of published studies, and a survey conducted from October 6, 2020, to January 10, 2021, open to individuals who had experienced obesity. The survey was open internationally, but the majority (96%) of the 2,050 respondents were in Canada. Obesity Canada and the Canadian Liver Foundation provided joint input. Obesity Canada is Canada's leading obesity registered charity association for health professionals, researchers, trainees, students, policy-makers, and people in Canada who are living with obesity. The Canadian Liver Foundation is dedicated to supporting education and research on all forms of liver disease. Data for this submission was based on a survey conducted from February 2022 to March 2022, which was distributed throughout OC and CLF networks, on social media, newsletter mailing lists, and within OC's online patient support community. There were 109 responses from people in Canada living with obesity. More than half of respondents (66%) indicated past or present experience with prescription medications for obesity management, with 57% reporting experience specifically with semaglutide. Diabetes Canada is a national health charity representing millions of people in Canada who are affected by diabetes, and aims to lead the fight against diabetes by helping people live healthy lives, preventing the onset and consequences of diabetes, and discovering a cure. This submission contains patient input from an online survey conducted in March 2022. A total of 29 people in Canada participated in the survey; 3 identified as living with pre-diabetes and 26 identified as living with type 2 diabetes. Among those who answered the question (n = 21), 19 respondents (90%) said they identified as living with overweight or obesity. Two people said they had experience with the drug under review. Obesity Matters is a group of people with common experiences and concerns. The goal of Obesity Matters is to provide an opportunity for communities across Canada to share personal feelings, experiences, and coping strategies, and offer support so they can take action and seek help. The input from Obesity Matters was based on a survey conducted from March 2, 2022, to March 15, 2022, with 104 respondents. A video was also provided in Obesity Matters' input.

The 4 patient group inputs reported that overweight and obesity affect many areas of life, and patients usually present with various comorbid conditions, such as arthritis, hypertension, sleep apnea, gastroesophageal reflux disease, irritable bowel syndrome, high cholesterol, diabetes, fatty liver disease, asthma, osteoarthritis, infertility, cancers, and mental health issues. Overweight and obesity can lead to a multitude of negative impacts including pain and impacts on mobility, regular activities, self image, and patients' families and relationships. A common theme in the submissions was the stigma associated with overweight and obesity, with patients experiencing discrimination from physicians and employers. Regarding current management options, there are very few medication options, and those that are available do not have public or full private coverage. In addition, patients indicated that these drugs have side effects that include nausea, diarrhea, constipation, and headaches. Patients considered it important for them to have a medication for weight management with long-term effectiveness and fewer side effects that are also affordable and easy to administer. Key outcomes identified by the patient advocacy groups as important to individuals

with overweight or obesity are weight loss, reducing weight-related comorbidities, and improving HRQoL.

In the input from the Gastrointestinal Society, those who had tried semaglutide found it easier to adhere to lifestyle modifications while taking that medication. In the input from Diabetes Canada, both people who had tried semaglutide said their ability to maintain or lose weight and meet target blood sugar levels was "much better" on semaglutide injection 2.4 mg than before, although 1 individual indicated improved gastrointestinal side effects on semaglutide injection while the other indicated "much worse" gastrointestinal side effects. One individual from the Obesity Canada and the Canadian Liver Foundation input stated that semaglutide had been very effective and described increased energy and reduction in medication needed to control blood pressure and cholesterol.

Clinician Input

Input From Clinical Experts Consulted by CADTH

According to the clinical expert consulted by CADTH on this review, current therapies do not fully address the multifaceted nature of obesity, as they only target a few of the known pathways involved in managing weight. The clinical expert believed that the majority of individuals who were able to tolerate semaglutide would likely benefit to some extent from treatment; however, individuals who have difficulty reducing portion sizes and have significant hunger are likely the ones to benefit most from the drug. Individuals who do not report issues with significant hunger and overeating may therefore be least likely to benefit.

Individuals most in need of pharmacological intervention are those who are experiencing weight-related comorbidities, according to the clinical expert. To assess response to treatment, markers that are used to monitor improvement in weight-related comorbidities should be measured, such as hemoglobin A1C. With respect to discontinuing treatment, 1 of the key indications for stopping therapy would be the development of gallstones, or treatment failure (gaining weight or failure to lose weight).

The clinical expert also noted that the issue of whether to continue semaglutide immediately after bariatric surgery if a patient happened to be on it before surgery has not been well studied, and there is likely a difference in practice between different surgical centres.

Clinician Group Input

Four clinician groups provided input: Calgary Weight Management Centre, Centre de Médecine Métabolique de Lanaudière, and a joint input from Obesity Canada and the Canadian Association of Bariatric Physicians and Surgeons. The input from the clinician groups was consistent with that provided by the clinical expert consulted by CADTH on this review. The clinician groups believed that semaglutide injection 2.4 mg is likely to replace liraglutide and naltrexone and bupropion in many patients.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a CADTH recommendation for semaglutide:

- considerations for initiation of therapy

- considerations for continuation or renewal of therapy
- considerations for discontinuation of therapy
- generalizability of trial populations to the broader populations in the jurisdictions
- care provision issues
- system and economic issues.

The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Clinical Evidence

Pivotal Studies and Protocol-Selected Studies

Description of Studies

Four placebo-controlled DB RCTs — STEP 1 (N = 1,961), STEP 2 (N = 1210), STEP 3 (N = 611), and STEP 4 (N = 803) — compared semaglutide 2.4 mg once weekly to placebo, and 1 open-label RCT compared semaglutide 2.4 mg once weekly to liraglutide and placebo (STEP 8, N = 338), all over 68 weeks of treatment. All patients in the included studies had overweight (BMI of 27 kg/m^2 or greater with at least 1 weight-related comorbidity) or obesity (BMI of 30 kg/m^2 or greater), and patients enrolled in STEP 2 also had type 2 diabetes. All studies were funded by the sponsor and all were multi-centre, and 2 studies (STEP 1 and STEP 2) had Canadian sites. STEP 4 included a 20-week run-in period where all patients were titrated to the target dose of semaglutide 2.4 mg once weekly before randomization at week 20. All patients in the STEP trials received counselling regarding diet and physical activity. In STEP 3, the first 8 weeks of the study consisted of a 1,000 to 1,200 kcal/day low-calorie diet, after which patients were gradually transitioned to a less strict hypo-caloric diet consisting of conventional foods. In STEP 8, there was no blinding between semaglutide and liraglutide, but blinding was maintained between active treatment and placebo. The primary outcome of all studies was the percent reduction in body weight from baseline to week 68, and the co-primary outcome of STEP 1, STEP 2, and STEP 3 was patients achieving at least a 5% reduction in body weight by week 68. Other confirmatory secondary outcomes controlled for multiplicity included patients achieving at least a 10% (3 studies), 15% (3 studies), or 20% (1 study) reduction in body weight by week 68, and change from baseline to week 68 in the physical function component of the SF-36 v2 acute (SF-36, 4 studies).

Across studies, the mean age of patients was 46 to 49 years, with the exception of STEP 2, where the mean age was 55 years. The majority of patients were female, with the exception of STEP 2, where there was a roughly equal percentage of females and males in the study. The vast majority of patients were White (75% to 93%) across the studies, with the exception of STEP 2, where about 60% of patients were White and 27% were Asian. Baseline body weight in STEP 1, STEP 3, and STEP 8 was approximately 105 kg, slightly lower (approximately 100 kg) in STEP 2, which focused on patients with type 2 diabetes, and lowest in STEP 4 at the end of the run-in period (approximately 96 kg). Baseline hemoglobin A1C was approximately 5.7% in STEP 1 and STEP 3; 5.5% in STEP 8; 5.4% in STEP 4, which featured the run-in; and much higher in STEP 2 (8.1%), which enrolled patients with type 2 diabetes.

Efficacy Results

Body Weight

Percent change from baseline to week 68 in body weight was a primary outcome in all studies. There was a statistically significant difference in percent change in body weight for semaglutide versus placebo in STEP 1 (difference between groups = −12.44%; 95% confidence interval [CI], −13.37% to −11.51%; P < 0.0001), STEP 2 (difference between groups = −6.21%; 95% CI, −7.28% to −5.15%; P < 0.0001), STEP 3 (difference between groups = −10.27%; 95% CI, −11.97% to −8.57%; P < 0.0001), and STEP 4 (difference between groups = −14.75%; 95% CI, −16.00% to −13.50%; P < 0.0001), and there was a statistically significant difference in percent change in body weight for semaglutide versus liraglutide in STEP 8 (difference between groups = −9.4%; 95% CI, −12.0% to −6.8%; P < 0.001).

Patients achieving a 5% reduction from baseline in body weight was a co-primary outcome in STEP 1, STEP 2, and STEP 3, and there were greater percentages of patients in the semaglutide group than in the placebo group who achieved a 5% weight loss by week 68 in STEP 1 (odds ratio [OR] = 11.22; 95% CI, 8.88 to 14.19; P < 0.0001), STEP 2 (OR = 4.88; 95% CI, 3.58 to 6.64; P < 0.0001), and STEP 3 (OR = 6.11; 95% CI, 4.04 to 9.26; P < 0.0001). In STEP 4, where it was a supportive secondary outcome, the OR was 8.52 (95% CI, 5.93 to 12.24) for semaglutide versus placebo.

Patients achieving a weight reduction from baseline of at least 10%, 15%, and 20% were confirmatory secondary outcomes in STEP 8, and greater percentages of patients in the semaglutide group than the liraglutide group achieved at least 10% reduction (OR = 6.3; 95% CI, 3.5 to 11.2; P < 0.001), at least 15% reduction (OR = 7.9; 95% CI, 4.1 to 15.4; P < 0.0001), and at least 20% reduction (OR = 8.2; 95% CI, 3.5 to 19.1; P < 0.0001). Similarly, there were statistically significant differences in favour of semaglutide for percentages of patients with at least a 10%, 15%, and 20% reduction in STEP 1, STEP 2, and STEP 3.

The sponsor's reimbursement request is for patients with a BMI of 35 kg/m^2 or greater who are pre-diabetic. There were no pre-planned subgroup analyses from any of the included studies that focused on this subgroup, although the sponsor provided a post hoc subgroup analysis from [redacted] in patients with a BMI of 35 kg/m^2 or greater and who are pre-diabetic according to the America Diabetes Association (ADA) definition. The mean percent change from baseline body weight in this subgroup versus placebo was [redacted]. There were [redacted] of patients treated with semaglutide ([redacted] with placebo) in this subgroup who achieved a 5% or greater reduction in weight. Thus, the results in this subgroup appeared consistent with those reported for the entire population in [redacted].

Change from baseline to week 68 in waist circumference was also a confirmatory secondary outcome in STEP 1, STEP 2, STEP 3, and STEP 4. The mean waist circumference was reduced for semaglutide versus placebo in STEP 1 (treatment difference = −9.42 cm; 95% CI, −10.30 to −8.53; P < 0.0001), STEP 2 (−4.88 cm; 95% CI, −5.97 to −3.79; P < 0.0001), STEP 3 (−8.34 cm; 95% CI, −10.08 to-6.59; P < 0.0001), and STEP 4 (−9.74 cm; 95% CI, −10.94 to −8.54; P < 0.0001). The change from baseline to week 68 was a supportive secondary outcome in STEP 8, and the difference between semaglutide and liraglutide was −6.6 cm (95% CI, −9.1 to −4.2).

Health-Related Quality of Life

Health-related quality of life (HRQoL) was studied using the SF36 in STEP 1, STEP 2, STEP 3, and STEP 4, and the mean change from baseline in Physical Functioning on the SF36

was a confirmatory secondary outcome in each of these studies. There was a statistically significant improvement in change in Physical Functioning score for semaglutide versus placebo in STEP 1 (1.80; 95% CI, 1.18 to 2.42; P < 0.0001), STEP 2 (1.52; 95% CI, 0.44 to 2.61; P = 0.0061), and STEP 4 (2.45; 95% CI, 1.59 to 3.32; P < 0.0001); in STEP 3 the difference between groups was not statistically significant (0.84; 95% CI, −0.23 to 1.92; P = 0.1249). The MID for the SF36 Physical Functioning score is 3.

Responses on the Impact of Weight on Quality of Life Lite for Clinical Trials scale (IWQOL-Lite CT) Physical Function score were reported as confirmatory secondary outcomes in STEP 1 and STEP 2. The difference between semaglutide and placebo in the mean change from baseline to week 68 in scores in STEP 1 was 9.43 (95% CI, 7.50 to 11.35; P < 0.0001) and in STEP 2 was 4.83 (95% CI, 1.79 to 7.86; P = 0.0018). The MID for this instrument is not known.

Normalization of Glucose Parameters

Glycemic status (normoglycemic, pre-diabetes, diabetes) was assessed in all studies except STEP 2, which enrolled patients who already had type 2 diabetes. In STEP 8, in patients who were normoglycemic at baseline, the percentage of patients transitioning to pre-diabetes was [redacted] for semaglutide, liraglutide, and placebo, respectively. No patients progressed to diabetes. In STEP 1, STEP 3, and STEP 4, 3% of patients taking semaglutide in each study progressed to pre-diabetes, while 6% to 13% of patients progressed to pre-diabetes in the placebo group.

In patients who were considered to have pre-diabetes at baseline, in STEP 8, 90% of those taking semaglutide became normoglycemic by end of study, compared to 65% with liraglutide and 13% with placebo, while 3%, 3%, and 10% in the semaglutide, liraglutide, and placebo groups, respectively, progressed to diabetes. In the STEP 1, STEP 3, and STEP 4 trials, 83% to 90% of patients taking semaglutide became normoglycemic, compared to 48% to 68% with placebo. In the semaglutide group, no patients in STEP 3 or STEP 4, and 1% of patients in STEP 1, progressed to diabetes while in the placebo group [redacted] in STEP 4, 1% of patients in STEP 3, and 3% of patients in STEP 1 progressed to diabetes.

Harms Results

In STEP 8, 95% of patients in the semaglutide and placebo groups and 96% of those in the liraglutide group reported at least 1 adverse event (AE) while on treatment during the study. The most common AEs were gastrointestinal (GI)-related, such as nausea (61% with semaglutide versus 59% with liraglutide versus 22% with placebo) and constipation (39% versus 32% versus 24%, respectively). In the placebo-controlled studies (STEP 1, STEP 2, STEP 3, and STEP 4, AEs occurred in 88% to 96% of patients taking semaglutide, and between 75% and 96% of those in the placebo groups. GI disorders were the most common AE in the semaglutide groups in these studies, including nausea (semaglutide versus placebo: 14% to 58% versus 5% to 22%) and diarrhea (14% to 36% versus 7% to 22%).

In STEP 8, serious adverse events (SAEs) occurred in 8% of participants treated with semaglutide, 11% with liraglutide, and 7% with placebo. The most common SAEs were "neoplasms benign, malignant and unspecified," occurring in 2% of patients in the semaglutide and liraglutide groups, and 1% with placebo. In the placebo-controlled studies, SAEs occurred in 8% to 10% of patients in the semaglutide group and 3% to 9% of patients in the placebo group.

In STEP 8, permanent discontinuation of trial treatment due to AEs occurred in 3% of patients taking semaglutide, 13% of those taking liraglutide, and 4% of those in the placebo group. The most common reason for discontinuation of trial treatment was GI disorder, occurring in 1% of patients in the semaglutide and placebo groups, and 6% of those in the liraglutide group. Permanent discontinuation of trial treatment due to AEs occurred in 6% to 7% of those in the semaglutide groups and 3% to 4% of those in the placebo groups in STEP 1, STEP 2, and STEP 3, and in 2% of patients in the semaglutide group and 3% of patients in the placebo group in STEP 4, where patients had a 20-week run-in period.

There was no more than 1 death in any group in any of the included trials.

GI disorders were the most common of all the notable harms, as noted previously. In STEP 8, other notable harms included gallbladder-related disorders in 1% of patients in the semaglutide and placebo groups, and 3% of those in the liraglutide group. There were no cases of acute pancreatitis or hypoglycemia in the semaglutide or placebo groups, and 1 case of acute pancreatitis and 1 case of hypoglycemia in the liraglutide group. Other notable harms (for semaglutide, liraglutide, and placebo, respectively), included cardiovascular disorders (13%, 14%, and 11%), injection site reactions (0, 11%, and 6%), and psychiatric disorders (6%, 15%, and 11%).

In the placebo-controlled trials, for semaglutide versus placebo, gallbladder-related disorders occurred in between 0.2% and 5% versus between 1% and 3%, with the most common event being cholelithiasis (0.2% to 3% versus 1% to 3%). Very few patients had acute pancreatitis, between 0 and 0.2% in each group. Cardiovascular (CV) disorders for semaglutide versus placebo occurred in 5% to 12% versus 10% to 12% of patients and adjudicated CV events in 0.2% to 2% versus 0 to 1%, and hypoglycemia in 0.5% to 0.6% versus 0 to 1% in STEP 1, STEP 3, and STEP 4. In STEP 2, where patients also had type 2 diabetes, CV events occurred in 6% of those taking semaglutide and 3% of those in the placebo group. Injection site reactions for semaglutide versus placebo occurred in 3% to 5% versus 2% to 7%, and psychiatric disorders in 6% to 15% versus 4% to 13%.

Critical Appraisal

The included trials were reasonably well conducted with respect to randomization, blinding, and control for multiplicity in statistical testing. Blinding in the STEP 1, STEP 2, STEP 3, and STEP 4 trials may have been somewhat compromised, however, by the fact that the primary outcome is based on a readily measurable, objective measure (weight loss) that individuals can self-monitor, and by the large imbalance in GI AEs, a well-known complication of GLP-1 agonists. The only active-controlled trial, STEP 8, lacked blinding between active groups (semaglutide and liraglutide). The relatively long run-in (20 weeks) in STEP 4 may have resulted in a selected population that were already responding to the drug and tolerating semaglutide before being randomized, in addition to biasing results in favour of semaglutide, as placebo patients experienced rebound weight gain from discontinuing semaglutide. The fact that the analyses were post hoc in the subgroup of patients with a BMI of 35 kg/m^2 or greater and who were pre-diabetic is a significant limitation, and it is not clear why only data from [redacted] was presented for this subgroup.

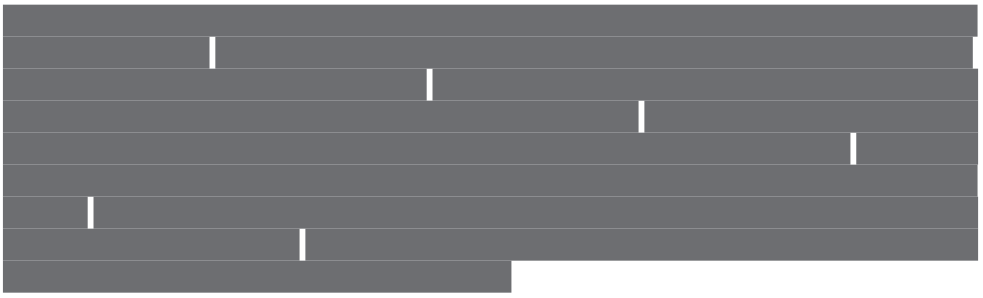
The structured diet and lifestyle measures that were background therapy in each of the STEP trials may present a generalizability issue, as these measures are unlikely to be available for the majority of individuals living in Canada who start semaglutide. The included studies were all 68 weeks in duration, and this is unlikely to be of sufficient duration to assess long-term

efficacy and safety of semaglutide. Most notably, none of the included trials were able to formally assess the impact of semaglutide treatment on development of comorbidities or prevention of cardiovascular events.

Indirect Comparisons

Description of Studies

One ITC, submitted by the sponsor, was reviewed and its objectives were to determine the efficacy and safety of weekly semaglutide 2.4 mg when compared to relevant pharmacological comparators for weight management in patients with overweight or obesity. The study authors conducted a systematic literature review (SLR) and Bayesian network meta-analysis (NMA).



Efficacy Results

The models with the best fit (base case models) are reported below:

Harms Results

Critical Appraisal

The reported ITC was based on a broad SLR, with study inclusion criteria reported transparently. A study protocol was finalized before conducting the review. The analyses were appropriately conducted and reported. The patients in the included studies match the people who would use this intervention in the real world. Key efficacy and safety outcomes were reported. There was some unaddressed clinical heterogeneity with regard to . Further, it is unclear how the different approaches to across trials might have impacted the results. Credible intervals were likely due to the use of Reporting of

methods was not comprehensive as [redacted] was not reported, making it challenging to assess the impact of risk of bias. Sensitivity analyses to explore the impact of [redacted].

Other Relevant Evidence

Description of Studies

STEP 5 was the only 2-year (104-week) RCT in the STEP series of studies. Like STEP 1, STEP 2, STEP 3, and STEP 4, STEP 5 was a DB placebo-controlled trial, although it was not pivotal and thus did not meet the inclusion criteria for the systematic review.

STEP 5 was conducted at 41 sites in Canada, the US, and Europe, and randomized 304 participants with overweight or obesity, 1:1, to either semaglutide or placebo. Outcomes were similar to the other STEP trials, with the co-primary outcome being percent change from baseline in body weight and the percentage of patients achieving a 5% or greater weight reduction. Confirmatory secondary outcomes included the percent of patients who achieved a 10% or greater reduction in weight by week 104, 15% or greater reduction in weight by week 104, and change from baseline to week 104 in waist circumference, systolic blood pressure, and SF-36 (Physical Functioning).

Inclusion and exclusion criteria were similar to the STEP 1, STEP 3, STEP 4, and STEP 8 studies. Adults with a BMI of 30.0 kg/m^2 or greater, or 27.0 kg/m^2 or greater with at least 1 weight-related comorbidity and a history of at least 1 unsuccessful attempt at losing weight, were included. To be randomized, patients also had to have kept a food diary, have a PHQ-9 score below 15 at randomization, and no suicidal behaviour or ideation before randomization.

Patients received semaglutide 2.4 mg once weekly as an adjunct to reduced-calorie diet and increased physical activity, versus matching placebo.

Efficacy Results

Semaglutide evoked a statistically significantly greater percent reduction in weight from baseline to week 104 versus placebo, with a treatment difference in change in body weight between groups of −12.6% (95% CI, −15.3 to −9.8; P < 0.0001). The other co-primary outcome was patients achieving a 5% or greater reduction in weight from baseline to week 104, and this occurred in 77% of those taking semaglutide compared to 34% of those in the placebo group, a statistically significant difference between groups [redacted]

Harms Results

AEs were experienced by [redacted] of patients taking semaglutide and [redacted] of patients in the placebo group, while [redacted] of patients taking semaglutide and [redacted] in the placebo group had an SAE. The most common AEs for semaglutide versus placebo were [redacted]. Among other notable harms for semaglutide versus placebo, [redacted]

Critical Appraisal

The limitations of this study are similar to those seen with the other STEP trials, such as the potential for unblinding to occur due to an obvious treatment effect or due to notable harms like GI AEs that occur much more frequently with semaglutide than placebo. The

generalizability issues with STEP 5 mirror those of the other STEP trials, notably the structured weight management regime that patients followed in the trial, which is unlikely to be available to individuals in most areas of Canada. Despite the longer follow up in STEP 5 (104 weeks versus 68 weeks in the other STEP trials), STEP 5 was again not designed or powered to assess the impact of semaglutide on the development of weight-related comorbidities such as cardiovascular disease.

Economic Evidence

Table 1: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target populations	**Health Canada 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 1 weight-related comorbidity such as hypertension, type 2 diabetes mellitus, dyslipidemia, or obstructive sleep apnea. **Reimbursement request**: As an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial BMI of 35 kg/m^2 or greater and pre-diabetes.
Treatment	Semaglutide 2.4 mg weekly for no more than 2 years as an adjunct to a reduced-calorie diet and increased physical activity.
Submitted Price	Semaglutide (Wegovy): $363.51 per carton of 4 pre-filled, single-dose pens, regardless of strength (0.25 mg, 0.5 mg, 1 mg, 1.7 mg, or 2.4 mg)
Treatment cost	The 28-day cost of semaglutide is $363.51, regardless of dose.
Comparator	Standard care: Reduced-calorie diet and increased physical activity (defined as 500 kilocalorie per day deficit plus 150 minutes per week of physical activity).
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	40 years
Key data source	STEP clinical trials
Key limitations	• The sponsor assumes that weight loss that is not sustained will have a large positive impact on many obesity-related comorbidities such as cancer and stroke. No evidence from the trial was shown to impact comorbidities outside of glycemic control (i.e., pre-diabetes and T2DM). The risk equations in the model assume that weight loss has an instantaneous impact on comorbidities. They are also based on the assumption that prior weight has no influence on the risk of developing comorbidities. The clinical expert consulted by CADTH felt there was insufficient evidence to support a link between short-term weight loss and improvement in many weight-related comorbidities identified by the sponsor. Likewise, evidence from the literature does not support these conclusions. • The sponsor assumes that weight reduction leads to instantaneously lower mortality risk unrelated to the prevention of comorbidities. The clinical expert felt there was insufficient evidence to support this assertion. Likewise, evidence from the literature shows that mortality risk after sustained weight loss from bariatric surgery was only seen after 5 to 6 years, although this may be linked to the prevention of

Component	Description
	comorbidities, as opposed to the direct impact of weight loss itself. • The sponsor assumes semaglutide will only be given for a maximum of 2 years and that treatment discontinuation after 1 year will not influence weight regain. The clinical expert felt that there would be limited desire to discontinue treatment at an arbitrary time point unless there was weight regain or intolerable side effects. Evidence from the STEP 1 extension trial showed rapid weight regain after treatment discontinuation; therefore, the average weight of a cohort receiving semaglutide is likely to increase when more patients discontinue treatment. • A mapping algorithm was used to determine the utility for a given BMI score using SF-36 data from the STEP 1 trial. CADTH noted the same mapping algorithm produced different results when mapping SF-36 data to EQ-5D from the SCALE trial. CADTH notes a large cohort study measured EQ-5D directly across multiple BMI scores without the need for mapping. • The sponsor assumed individuals would regain all the weight lost in the 3 years following treatment discontinuation at a rate of 33% a year. Evidence from the STEP extension trial shows weight regain of 64% after one year following treatment discontinuation. • The full Health Canada population covers a very broad heterogenous population. There is a high degree of uncertainty regarding the magnitude of benefit associated with semaglutide in specific subgroups of the indication, such as those who are overweight with a weight-related comorbidity. • The potential negative health consequences associated with weight cycling was not explored in the model.
CADTH reanalysis results	• CADTH undertook reanalyses to address limitations in the sponsor's economic evaluation, including: assuming no additional benefit once weight had been regained; removing comorbidities other than diabetes from the analysis; removing BMI as an independent risk factor for mortality; using a different value set for BMI related utility; using data from the STEP 1 extension trial to determine weight regain following treatment discontinuation; assuming 3 years of treatment use; and explicitly linking treatment discontinuation to average weight of the cohort. • In the CADTH base case, the ICER for semaglutide was $204,928 per QALY compared with standard of care (incremental costs: $9,385; incremental QALYs: 0.046) in the reimbursement request population. A price reduction of 71% would be required for semaglutide to be considered cost-effective at a $50,000 per QALY threshold. ◦ A scenario analysis was conducted on the full Health Canada indication, but CADTH notes there is a high degree of uncertainty regarding the accuracy, and it should only be viewed as exploratory. In this analysis, the ICER was $223,572 per QALY. ◦ Scenario analysis results showed fairly similar results when including sleep apnea as an additional preventable comorbidity, removing pre-diabetes cost savings and delay in T2DM onset, removing the stopping rule, and, assuming all weight is regained 2 years following treatment discontinuation. In these scenario analyses the ICER varied from $178,937 to $247,859 per QALY.

BMI = body mass index; ICER = incremental cost-effectiveness ratio; LY = life-year; QALY = quality-adjusted life-year; T2DM = type 2 diabetes mellitus.

Budget Impact

CADTH did not conduct a base-case analysis, as there is a high degree of uncertainty. Instead, CADTH presented a series of scenario analyses to test the impact of alternative assumptions related to potential market share of semaglutide and public reimbursement rates. In these scenario analyses, the budget impact could increase up to $4,138,911,478 and $676,362,279 over 3 years in the full Health Canada indication and reimbursement request, respectively.

CADTH

CDEC Information

Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed.

Meeting date: July 28, 2022

Regrets: 3 expert committee members did not attend.

Conflicts of interest: None