CADTH

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

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.

Recommendation: Do Not Reimburse

Version:	1.0
Publication Date:	August 2022
Report Length:	14 Pages

Single Technology

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

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 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.

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 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 co-morbidity but did not demonstrate improvement in or prevention of weight-related comorbidities. The STEP 1 (N = 1961), STEP 2 (N = 1210), 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 minimally important difference (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 health-related quality of life (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 prediabetes 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 patients 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 patients 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 patients 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

The World Health Organization (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 to be 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 Preventative Health Care (CTFPHC) has reported that 67% of Canadian males and 54% of Canadian females are living with overweight or obesity. There are a wide range of co-morbidities associated with obesity, ranging from increased risk of type 2 diabetes, certain cancers, hypertension, cardiovascular disease, 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 co-morbidity.

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 co-morbidity 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 prediabetes. 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, double-blind (DB) randomized controlled trials (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 co-morbidity (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 co-morbidity
- 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 - Obésité 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 of Obesity Canada and the Canadian Liver Foundation, Diabetes Canada, and Obesity Matters). The Gastrointestinal Society (The GI 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 from Canada. Obesity Canada and the Canadian Liver Foundation provided a joint input. Obesity Canada (OC) is Canada's leading obesity registered charity association for health professionals, researchers, trainees, students, policy makers and Canadians living with obesity. The Canadian Liver Foundation (CLF) is dedicated to supporting education and research into all forms of liver disease. Data for this submission was based on a survey conducted from February to March 2022, which was distributed throughout OC and CLF networks, on social media, newsletter mailing lists as well as within OC's online patient support community. There were a total of 109 responses from Canadians living with obesity. Over 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 the millions of Canadians who are affected by diabetes and leads 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 prediabetes and 26 identified as living with type 2 diabetes. Among those who answered the question (n=21), 19 respondents (90%) said they identify as living with overweight or obesity. Two people said they have 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, coping strategies, and offer support so they can take action and seek the help they deserve. The input from Obesity Matters was based on a survey conducted from March 2 to 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 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 the disease, 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 less side effects that are also affordable and easy to administer. Key outcomes identified by the patient advocacy groups as important to patients with overweight or obesity are weight loss, reducing weight-related comorbidity and improving HRQoL.

In the input by The GI Society, those who had tried semaglutide found it easier to adhere to lifestyle modifications while taking that medication. In the input by Diabetes Canada, both people 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, though 1 patient indicated improved gastrointestinal side effects semaglutide injection while the other patient indicated "much worse" gastrointestinal side effects. One patient 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 patients who were able to tolerate semaglutide would likely benefit to some extent from treatment, however patients who have difficulty reducing portion sizes and have significant hunger are likely the ones to benefit most from the drug. Patients who do not report issues with significant hunger and overeating may therefore be least likely to benefit.

Patients most in need of pharmacological intervention are those who are experiencing weight-related co-morbidities, according to the clinical expert. In order to assess response to treatment, markers that are used to monitor improvement in weight-related

co-morbidities should be measured, such as HbA1c. 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 prior to 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 of Obesity Canada - Obésité 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/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=1961), STEP 2 (N=1210), STEP 3 (N=611), and STEP 4 (N=803), compared semaglutide 2.4 mg once weekly to placebo, and one 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/m2 or greater with at least 1 weight-related comorbidity) or obesity (BMI of 30 kg/m2 or greater), and patients enrolled in STEP 2 also had type 2 diabetes. All studies were funded by the sponsor and all were multicentre, and 2 studies (STEP 1 and 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 prior to 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 1000 to 1200 kcal/day low calorie diet after which patients were gradually transitioned to a less strict hypo-caloric diet comprised 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 to 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) and 20% (1 study) reduction in body weight by week 68, and change from baseline to week 68 in the physical function component of the Short Form 36 v2 acute (SF36, 4 studies).

Across studies, the mean age of patients was 46 to 49 years of age 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, and slightly lower (approximately 100 kg) in STEP 2, which focused on patients with type 2 diabetes and even lower in STEP 4 at the end of the run-in period (approximately 96 kg). Baseline HbA1c was approximately 5.7% in STEP 1 and 3, 5.5% in STEP 8, and 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 each of STEP 1 (difference between groups of –12.44%; 95% confidence interval [CI], –13.37 to –11.51; P < 0.0001), STEP 2 (difference between groups of -6.21%; 95% CI, -7.28% to -5.15%; P < 0.0001), STEP 3 (difference between groups of -10.27%; 95% CI, -11.97% to -8.57%; P < 0.0001, and STEP 4 (difference between groups of -14.75%; 95% CI, -16.00% to -13.50%; P < 0.0001), and a statistically significant difference in percent change in body weight for semaglutide versus liraglutide in STEP 8 (difference between groups of -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 to 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 each of STEP 1 (odds ratio [OR] of 11.22; 95% CI, 8.88 to 14.19]; P < 0.0001), STEP 2 (OR of 4.88; 95% CI, 3.58 to 6.64; P < 0.0001) and STEP 3 (OR of 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 of 6.3; 95% CI, 3.5 to 11.2; P < 0.001), at least 15% reduction (OR of 7.9; 95% CI, 4.1 to 15.4; P < 0.0001), and at least 20% reduction (OR of 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 to 3.

The sponsor's reimbursement request is for patients with a BMI of 35 kg/m^2 or greater and who are pre-diabetic. There were no pre-planned subgroup analyses from any of the included studies that focussed on this subgroup, though 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 semaglutide-treated patients ([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 to 4. The mean waist circumference was reduced for semaglutide versus placebo in each of STEP 1 (treatment difference of -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 to 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), and 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 function 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 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, 3, and 4, 3% of semaglutide patients 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 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, 3 and 4 trials, 83% to 90% of semaglutide patients 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 patients in the liraglutide group reported at least 1 adverse event (AE) while on treatment during the study. The most common AE were gastrointestinal (GI)-related, such as nausea (61% semaglutide vs 59% liraglutide vs 22% placebo) and constipation (39% vs. 32% vs. 24%). In the placebo-controlled studies, STEP 1 to 4, AEs occurred in 88% to 96% of semaglutide patients and between 75% and 96% of placebo patients. GI disorders were the most common AE in the semaglutide groups in these studies, including nausea (semaglutide vs placebo: 14% to 58% vs 5% to 22%) and diarrhea (14% to 36% vs 7% to 22%).

In STEP 8, serious adverse events (SAEs) occurred in 8% of semaglutide-treated patients, 11% in liraglutide, and 7% of placebo patients. The most common SAE were in the 'neoplasms benign, malignant and unspecified', occurring in 2% of patients in each of the semaglutide and liraglutide groups, and 1% with placebo. In the placebo-controlled studies, STEP 1 to 4, SAE 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 AE occurred in 3% of semaglutide patients, 13% of liraglutide patients, and 4% of placebo patients. The most common reason for discontinuation of trial treatment was GI disorder, occurring in 1% of semaglutide and placebo patients, and 6% of liraglutide patients. Permanent discontinuation of trial treatment due to AE occurred in 6% to 7% of semaglutide patients and 3% to 4% with placebo in STEP 1 to 3, and in 2% of semaglutide patients and 3% of placebo patients 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 was the most common of all the notable harms, and as noted above. In STEP 8, other notable harms included gallbladder-related disorders in 1% of semaglutide and placebo patients, and 3% of liraglutide patients. 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), included cardiovascular disorders (13%, 14%, 11%), injection site reactions (0, 11%, and 6%), and psychiatric disorders (6%, 15%, and 11%).

In the placebo-controlled trials, 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% vs 1% to 3%). Very few patients had acute pancreatitis, between 0 and 0.2% of patients 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% of patients, hypoglycemia in 0.5% to 0.6% versus 0 to 1% in STEPS 1, 3, and 4, respectively. In STEP 2, where patients also had Type 2 diabetes, CV events

occurred in 6% of semaglutide patients and 3% placebo patients. Injection site reactions for semaglutide versus placebo occurred in 3% to 5% versus 2% to 7% of patients 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 to 4 trials may have been compromised somewhat, however, by the fact that the primary outcome is based on a readily measurable, objective measure (weight loss) that patients can self-monitor, and by the large imbalance in GI AE, 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 drug and tolerating semaglutide before being randomized, as well as biasing results in favour of semaglutide, as placebo patients experienced rebound weight gain from discontinuing semaglutide. The fact that the analyses in the subgroup of patients with a BMI of 35 kg/m^2 or greater and who are pre-diabetic were post hoc 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 going to be available for the majority of Canadian patients 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 co-morbidities or prevention of cardiovascular events.

Indirect Comparisons

Description of studies

One indirect treatment comparison (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).

[redacted]

Efficacy Results

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

- [redacted]
- [redacted]
- [redacted]
- [redacted]

Harms Results

[redacted]

Critical Appraisal

The reported ITC was based on a broad systematic literature review, with study inclusion criteria reported transparently. A study protocol was finalised [redacted] prior to conducting the review. [redacted]
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. [redacted] There was some unaddressed clinical heterogeneity with regards to [redacted]. Further it is unclear how the different approaches to [redacted] across trials might have impacted the results. [redacted] Credible intervals were [redacted] likely due to the use of [redacted] 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 to 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, USA and Europe, and randomized 304 patients 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 1,3,4 and 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 co-morbidity 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 of <15 at randomization, and no suicidal behaviour or ideation prior to randomization.

Patients received semaglutide SC 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 was achieved by 77% of semaglutide patients and 34% of placebo patients, a statistically significant difference between groups. [redacted]

Harms Results

AEs were experienced by [redacted] of semaglutide patients and [redacted] of patients in the placebo group, while [redacted] of semaglutide patients and [redacted] in the placebo group had an SAE. The most common AE, semaglutide vs 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 AE 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 patients in most areas of Canada. Despite the longer follow up in STEP 5 (104 weeks vs 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 co-morbidities such as cardiovascular disease.

Economic Evidence

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 one 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 body mass index (BMI) of 35 kg/m^2 or greater and prediabetes.
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 x 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 + 150 minutes per week of physical activity).
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LY
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., prediabetes 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 though this may be linked to the prevention of comorbidities as opposed to the direct impact of weight loss itself. • The sponsor assumes semaglutide will only be given for a maximum of two years and that treatment discontinuation after one 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 who receive 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.

Component	Description
	• The sponsor assumed patients would regain all the weight lost in the three years post treatment discontinuation at a rate of 33% a year. Evidence from the STEP extension trial shows weight regain of 64% after one year post 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 post treatment discontinuation; assuming three 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 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 two years post 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 three years in the full Health Canada indication and reimbursement request respectively.

Canadian Drug Expert Committee (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