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CADTH Reimbursement Recommendation

Liraglutide (Saxenda)

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 (obese), or
- 27 kg/m^2 or greater (overweight) in the presence of at least 1 weight-related comorbidity (e.g., hypertension, type 2 diabetes, or dyslipidemia) and who have failed a previous weight management intervention.

Sponsor: Novo Nordisk Canada Inc.

Final recommendation: Do not reimburse

CADTH

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Redactions: Confidential information in this document has been redacted at the request of the sponsor in accordance with the *CADTH Drug Reimbursement Review Confidentiality Guidelines.*

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 Saxenda?

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

Why Did CADTH Make This Recommendation?

- Evidence from 3 studies demonstrated that Saxenda was associated with statistically significant reductions in body weight compared with placebo after 56 weeks of treatment.
- No conclusions could be drawn about long-term benefits, particularly for clinically meaningful improvements in comorbidities identified as priorities by patients, such as diabetes, sleep apnea, osteoarthritis, and cardiovascular complications.
- Patients identified a need for treatments that can improve potential obesity-related comorbidities, such as diabetes, sleep apnea, osteoarthritis, and cardiovascular complications. It is not clear whether Saxenda meets these needs.

Additional Information

What Are Overweight and Obesity?

Persons with a body mass index (BMI) greater than 25 kg/m^2 are considered overweight and those with a BMI greater than 30 kg/m^2 are considered obese. 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, cancer, as well as psychological and psychiatric disorders. It is estimated that 67% of Canadian men and 54% of Canadian women are overweight or living with obesity.

Unmet Needs in Patients Who Are Overweight or Living With Obesity

There is a need for treatment options for patients who are overweight or living with obesity that improve weight-related comorbidities (e.g., diabetes, cardiovascular complications, sleep apnea, and joint pain), reduce body weight, have an acceptable side effect profile, and provide long-term benefit.

How Much Does Saxenda Cost?

Treatment with Saxenda is expected to cost approximately $4,389 per patient in the first year of treatment and $4,564 per patient per year thereafter.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that liraglutide should not be reimbursed as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients.

Rationale for the Recommendation

CDEC reviewed 4 double-blind, placebo-controlled, phase III randomized trials of liraglutide 3 mg once daily in addition to a background regimen of diet and exercise in patients who are overweight with comorbidities or are living with obesity. Three studies demonstrated that liraglutide 3 mg was associated with statistically significant reductions in body weight compared with placebo after 56 weeks of treatment (between groups difference in Study 1839: −5.39%; 95% confidence interval [CI], −5.82 to −4.95; P < 0.0001; Study 1922: −3.97%; 95% CI, −4.84 to −3.11; P < 0.0001; Study 1923: −6.06%; 95% CI, −7.50 to −4.62; P < 0.0001). However, the clinical significance of the observed reductions in body weight is uncertain.

The available data did not demonstrate clinically relevant improvements in other potential obesity-related comorbidities that patients described as important, such as diabetes, sleep apnea, osteoarthritis, and cardiovascular complications. In the extension phase of Study 1839, treatment with liraglutide was associated with a delayed onset of type 2 diabetes mellitus (T2DM) in patients with prediabetes at baseline compared with placebo based on a Weibull analysis, which showed an annualized T2DM incidence rate of 0.8 events and 3.2 events per 100 years of exposure for the liraglutide 3 mg and placebo groups, respectively. However, the analysis of the onset to T2DM did not provide any assessment of goodness of fit of the Weibull model to the data; therefore, the potential bias in the results due to the Weibull model assumptions is unknown. Further, the rate of developing T2DM was low (≤ 1.1%) in both study groups during the 56-week trial; it was 1.8% in the liraglutide arm and 6.2% in the placebo arm at week 160 in the extension phase. Although treatment with liraglutide appeared to decrease the number of apnea events on the Apnea-Hypopnea Index (AHI) in patients with obstructive sleep apnea (OSA) in Study 3970, no difference in the percentage of patients achieving OSA remission was observed after 32 weeks of treatment. Weight-related cardiovascular comorbidity was evaluated as a secondary outcome in all the studies but was not included in the statistical testing hierarchy. Therefore, it is unknown whether the observed reduction in body weight translates into other meaningful outcomes (e.g., reduction in cardiovascular complications or mortality).

The Committee considered the absence of effectiveness data beyond 56 weeks, particularly for clinically meaningful improvement in the comorbidities identified as priorities by patients, to be a major limitation because patients who are overweight or living with obesity could remain on treatment for indefinite periods given the chronic nature of the condition. Although a difference in percentage body weight was observed between the liraglutide and placebo groups after 160 weeks in the extension phase of Study 1839, CDEC noted that this difference was smaller than that observed after 56 weeks of treatment; therefore, the clinical benefit for patients was uncertain.

Discussion Points

- The clinical expert and patients noted that reductions in body weight or body mass index (BMI) alone are less clinically meaningful than responses to treatment that include improvement in weight-related comorbidities (e.g., hypertension, dyslipidemia, OSA), improved quality of life, improved survival, prevention of progression of preclinical conditions (e.g., reduced progression from prehypertension to hypertension), reduced cardiovascular and renal events, and reduced osteoarthritis symptoms. These outcomes were also identified as important based on patient group input provided to CADTH. However, CDEC was unable to determine whether treatment with liraglutide would meet these needs given that none of these outcomes were controlled for multiplicity in any of the studies.
- CDEC discussed that the number of patients who developed T2DM in Study 1839 was low. Only 26 of 1,472 patients (1.8%) in the liraglutide group and 46 of 738 patients (6.2%) in the placebo group developed T2DM. Thus, a large proportion (93.8%) of patients with prediabetes would be treated who would not benefit from having diabetes averted. The difference is also modest given that liraglutide's known beneficial effects on glucose metabolism are unrelated to body mass. Therefore, the actual magnitude of clinical benefit remains uncertain. Moreover, there are no direct comparisons with other treatments known to reduce the progression of prediabetes to diabetes.
- No direct comparative evidence of liraglutide compared with other pharmacologic treatments for patients who are overweight or living with obesity was available for this review. Although indirect evidence from 1 network meta-analysis (NMA) may suggest that patients treated with liraglutide 3 mg had greater odds of achieving 5% to 10% weight loss compared with orlistat, confidence in these results is limited by significant heterogeneity and high attrition rates across all the included primary studies and by significant limitations involving the quality of the primary studies and methodological rigour.
- CDEC discussed that the magnitude of the reduction in body weight observed in the studies was of uncertain clinical relevance. The clinical expert stated that the usual amount of weight loss associated with pharmacologic treatment for weight management is typically within the range of 5% to 10%, and that this would be considered adequate to improve weight-related comorbidities such as T2DM and osteoarthritis. However, CDEC noted that the percentage reduction in body weight observed in the studies was on the lower end of this range and that the evidence demonstrating the link between this reduction in body weight and improvement in comorbid conditions was limited.
- Patient input received for this review emphasized the impact of obesity on mental health; however, treatment with liraglutide did not demonstrate clinically meaningful improvements in health-related quality of life (HRQoL) in the trials reviewed. HRQoL was a secondary outcome in each of the trials, but results were inconsistent across measures and studies.
- Based on input from the clinical expert, CDEC discussed that patients who might be prescribed liraglutide are those with pre-existing comorbidities as part of a strategy to ameliorate the effect of comorbidities on long-term health. Further, it is unclear how treatment with liraglutide would compare with alternative approaches that directly address obesity-related comorbidities, such as intensified treatment with antihypertensive, lipid-lowering, or antihyperglycemic drugs.
- Depending on a patients' response to treatment after 28 weeks, the studies permitted recalculation of dietary portions. CDEC noted that this contributed to the uncertainty of the

study results given that there were no details describing how often the diet adjustments happened and if they occurred in a balanced manner across treatment arms. CDEC noted the critical importance of calorie intake to weight management and that an imbalance in this component of the co-intervention may have biased the outcomes in favour of 1 group over the other.

- CDEC discussed that the patient population in the clinical trials reviewed may not be representative of patients in Canada who are overweight or living with obesity. The exclusion criteria denied entry to some patients, such as those on medication that causes weight gain and those regaining weight after a previous bariatric surgery, who would be considered clinically relevant patients for chronic weight management with drug therapy.
- The clinical expert noted that drug therapies are most effective when combined with lifestyle and behavioural changes, but that there is no standardized lifestyle modification program used in Canadian clinical practice. Therefore, determining which lifestyle changes are appropriate in conjunction with pharmacotherapy is at the patient and health care provider's discretion.
- CDEC discussed that lifestyle modification programs are not widely accessible in Canadian clinical practice. This was highlighted in the 2019 Obesity Canada Report Card on Access to Obesity Treatments for Adults in Canada, which stated, "there is a profound lack of interdisciplinary teams for obesity management in Canada, despite their recognized benefits in obesity treatment guidelines."

Background

Liraglutide 3 mg (Saxenda) has a Health Canada indication for use 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)
- 27 kg/m^2 or greater (overweight) in the presence of at least 1 weight-related comorbidity (e.g., hypertension, T2DM, or dyslipidemia) and who have failed a previous weight management intervention.

Liraglutide 3 mg is a human glucagon-like peptide-1 (GLP-1) analogue, which acts as a GLP-1 receptor agonist to regulate appetite by increasing feelings of fullness and satiety while lowering feelings of hunger and prospective food consumption. It is available as a 6 mg/mL solution for injection in a pre-filled pen; the Health Canada–approved maintenance dose in adults with an initial BMI of 27 kg/m^2 or greater is 3 mg/day. Treatment with liraglutide 3 mg is initiated at a dose of 0.6 mg daily for 1 week and then titrated at weekly increments of 0.6 mg over a 4-week escalation period to attain the recommended daily maintenance dose of 3 mg/day.

Sources of Information Used by the Committee

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

- a review of 4 phase III, placebo-controlled, randomized clinical studies in a total of 5,358 patients who were overweight or living with obesity
- patients' perspectives gathered by 3 Canadian patient groups: Obesity Canada, Diabetes Canada, and the Gastrointestinal Society
- input from 1 clinical specialist with expertise in chronic weight management
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Patient Input

Three Canadian patient groups (i.e., Obesity Canada, Diabetes Canada, and the Gastrointestinal Society) provided input for this submission. Patient perspectives were obtained through a variety of sources, including surveys, interviews, and published studies. The following is a summary of key input from the perspective of the patient groups:

- Patient groups reported that obesity not only increases the potential for the development of further disease(s), but it leads to inequities in access to employment, health care, and education due to the strong stigma associated with it. Individuals living with obesity also reported frustration with the impact that this chronic and often misunderstood disease has on their overall quality of life.
- Currently, most Canadians living with obesity reported using diet and exercise, medications, or bariatric surgery to combat the disease. Many who diet and exercise have difficulty sustaining their efforts or finding a program that suits their needs, which can lead to depression, hopelessness, and further weight gain. Despite the availability of approved pharmacologic treatments, patients reported adverse effects and/or lack of efficacy from their use and had many concerns about obtaining and paying for the prescriptions of these drugs.
- Patient groups reported that many patients would like a treatment that is effective in the long term, is affordable, and has no or minimal side effects. Patient groups hope that liraglutide 3 mg may help people to better manage their weight, potentially delaying or preventing the development of comorbidities, such as the progression of prediabetes to type 2 diabetes. Furthermore, when asked about outcomes to consider, it was reported that patients focused less on improved weight than improved related comorbidities (e.g., diabetes, hypertension, and sleep apnea) as well as outcomes related to everyday life, such as productivity, energy levels, sleep, activity, and mental health.

Drug Plan Input

The drug plans requested clarification regarding the potential target patient population and the anticipated treatment duration of liraglutide. The clinical expert considered that it would be reasonable to consider pharmacotherapy in patients with a BMI between 27 kg/m^2 and 30 kg/m^2 without a comorbidity as second-line therapy after lifestyle changes, although this would be beyond the Health Canada–approved indication. The expert felt that patients would regain the weight they had lost if pharmacologic treatment for weight management was discontinued; therefore, such treatments would need to be continued in the long term, even in patients whose BMI dropped below 30 kg/m^2 (or 27 kg/m^2 in patients with weight-related

comorbidities). The public drug plans also requested clarification regarding re-treatment in patients who regain weight or if liraglutide 3 mg becomes ineffective over time after an initial desired response. The clinical expert noted that if there is no benefit after a patient tries weight loss medication for the first time, it is unlikely they will respond better to it in the future. Therefore, it is unlikely that the drug will be prescribed for the same indication again in that patient.

Clinical Evidence

Clinical Trials

The systematic review included 4 phase III, randomized controlled trials (Study 1839, Study 1922, Study 1923, and Study 3970) evaluating the efficacy of liraglutide 3 mg to reduce and maintain weight in adult patients who are overweight or living with obesity. The Study 1839, and Study 1923 were conducted in patients without diabetes (N = 3,731 and 422, respectively), whereas Study 1922 and Study 3970 were conducted in patients with T2DM (N = 846) and OSA (N= 359), respectively. All studies were parallel-group, multi-centre, double-blind, placebo-controlled trials conducted in multiple sites and multiple countries (at least 2), including Canada.

In all studies, patients were randomly assigned to receive once-daily subcutaneous injections of liraglutide at a dose of 3 mg or matching placebo with background counselling on lifestyle modification involving reduced-calorie intake and increased physical activity for all participating patients. The study duration was 32 weeks for Study 3970 and 56 weeks for Study 1839, Study 1922, and Study 1923. In addition to its 56-week main phase, Study 1839 had a 104-week extension phase involving patients diagnosed with prediabetes at screening. Thus, in Study 1839, the total treatment duration in patients with prediabetes at screening was 160 weeks. Overall, the treatment groups in all included studies were well-balanced with respect to baseline demographics and other characteristics.

The overall rates of treatment discontinuation in Study 1839 (main phase), Study 1922, and Study 1923 ranged from 23.4% to 28.1% with liraglutide 3 mg and 20.7% to 34.0% with placebo. In Study 3970, treatment discontinuation rates for the liraglutide and placebo groups were 25.6% and 20.7%, respectively. The corresponding rates for the Study 1839 extension were 47.4% and 55.0% for liraglutide and placebo, respectively. Overall, adverse events (AEs) were the leading cause for discontinuing treatment with liraglutide 3 mg, although withdrawal of consent occurred at a higher rate than AEs in 1 study. For the placebo group, the main reasons for treatment discontinuation included the withdrawal of consent, ineffective therapy, and AEs.

The main limitations of the reviewed evidence were that patients with comorbidities were underrepresented, and none of the included studies had an active comparator group.

Outcomes

Outcomes were defined a priori in the CADTH systematic review protocol. Of these, the Committee discussed the following primary outcomes:

- the percentage change from baseline in fasting body weight at week 56

- the proportion of patients losing 5% or more of baseline fasting body weight (5% responders) at week 56
- the proportion of patients losing more than 10% of baseline fasting body weight (10% responders) at week 56
- the percentage of patients maintaining run-in fasting weight loss at week 56
- the time to new onset of T2DM in patients with prediabetes at week 160
- change from baseline in severity of OSA at week 32
- change in patients' HRQoL.

Change in severity of OSA from baseline was reported as a standalone primary end point in Study 3790. The remaining outcomes were reported as co-primary end points in the other studies' (Study 1839 main phase, Study 1922, and Study 1923) first 3 outcomes. The percentage change in fasting body weight and the proportion of patients losing at least 5% of baseline fasting body weight (5% responders) were common co-primary outcomes in all 3 studies. The third co-primary end point was the proportion of patients losing more than 10% of baseline fasting body (10% responders) in 2 of the studies (Study 1839 main phase and Study 1922), and the percentage of patients maintaining run-in fasting weight loss in Study 1923. Time to new onset of T2DM was a co-primary end point in Study 1839, reported only in the extension phase conducted in patients with prediabetes at screening.

Baseline body weight was used to assess weight-based outcomes such as the percentage change in fasting body weight, the proportion of patients losing at least 5% of their body weight, and the proportion of patients losing 10% or more of their baseline body weight after a pre-specified treatment duration.

All body weight measurements were made while the patients were fasting.

The presence of T2DM was determined by assessing glycemic control parameters. Time to onset of T2DM was considered as the annualized incidence rate, defined as the number of new cases of T2DM per 100 patient-years of exposure.

The severity of OSA was evaluated using AHI scores, defined as the number of apneas or hypopneas per hour of sleep recorded by polysomnography. OSA severity is classified based on the AHI as follows:

- None or minimal: AHI less than 5 per hour
- Mild: AHI of 5 or more per hour but less than 15 per hour
- Moderate: AHI of 15 or more per hour but less than 30 per hour
- Severe: AHI of 30 or more per hour

Efficacy

Percentage Change in Body Weight From Baseline

Primary analysis results from the main phase of Study 1839 showed that liraglutide 3 mg was superior to placebo for percentage weight loss from baseline after 56 weeks of treatment, with a treatment difference of −5.39% (95% CI, −5.82 to −4.95; P < 0.0001). The other studies reported consistent findings with the main phase of Study 1839 as shown by the following treatment estimate differences:

- Study 1839 extension: difference = −4.32% (95% CI, −4.94 to −3.70, not controlled for multiplicity)
- Study 1922: difference = −3.97% (95% CI, −4.84 to −3.11; P < 0.0001)
- Study 1923: difference = −6.06% (95% CI, −7.50 to −4.62; P < 0.0001)
- Study 3970: difference = −4.15% (95% CI, −5.21 to −3.09, not controlled for multiplicity)

5% Responders

Primary analysis results from the main phase of Study 1839 showed that liraglutide 3 mg was superior to placebo for the odds of achieving at least 5% reduction from baseline body weight after 56 weeks of treatment (odds ratio [OR] = 4.80; 95% CI, 4.12 to 5.60, P < 0.0001). The other studies reported consistent findings:

- Study 1839 extension: OR = 3.22 (95% CI, 2.63 to 3.94, not controlled for multiplicity)
- Study 1922: OR = 6.81 (95% CI, 4.34 to 10.68; P < 0.0001)
- Study 1923: OR = 3.86 (95% CI, 2.44 to 6.09; P < 0.0001)
- Study 3970: OR = 3.92 (95% CI, 2.41 to 6.38, not controlled for multiplicity)

10% Responders

Primary analysis results from the main phase of Study 1839 showed that liraglutide 3 mg was superior to placebo for the odds of achieving at least 10% reduction from baseline body weight after 56 weeks of treatment (OR = 4.34; 95% CI, 3.54 to 5.32; P < 0.0001). The other studies reported consistent findings with the pivotal study:

- Study 1839 extension: OR = 3.09 (95% CI, 2.35 to 4.05, not controlled for multiplicity)
- Study 1922: OR = 7.10 (95% CI, 3.48 to 14.48; P < 0.0001)
- Study 1923: OR = 5.30 (95% CI, 2.79 to 10.08, not controlled for multiplicity)
- Study 3970: OR = 18.96 (95% CI, 5.69 to 63.14, not controlled for multiplicity)

Maintaining Fasting Run-In Weight Loss

Primary analysis results from Study 1923 showed that liraglutide 3 mg was superior to placebo for the odds of maintaining fasting run-in weight loss after 56 weeks of treatment (OR = 4.82; 95% CI, 3.01 to 7.71; P < 0.0001). No other study measured this outcome.

Time to Onset of T2DM

The primary analysis of 1 study (Study 1839 extension) showed that the time to progression to new onset of T2DM in patients with prediabetes at baseline was nearly 3 times as long for patients treated with liraglutide 3 mg compared with those treated with placebo. The treatment estimate (based on a Weibull analysis) was 2.681 (95% CI, 1.856 to 3.872; P < 0.0001) in favour of liraglutide 3 mg.

Change in OSA Severity

The primary analyses in 1 study (Study 3970) showed that after 32 weeks of treatment, patients treated with liraglutide 3 mg achieved a statistically significantly greater reduction in the severity of OSA than those treated with a placebo. The estimated treatment difference in AHI score was −6.10 events/hour (95% CI, −11.0 to −1.19; P = 0.0150) in favour of liraglutide 3 mg.

Delaying the onset of T2DM and reducing the severity of OSA were among the improvements in weight-related comorbidities that patients expect from treatments for overweight and obesity.

Change in HRQoL

The included studies also reported patients' HRQoL outcomes evaluated using various validated tools, including Impact of Weight on Quality of Life-Lite questionnaire, the Short Form (36) Health Survey, the Treatment Related Impact Measure-Weight, and the Diabetes Treatment Satisfaction Questionnaire. However, HRQoL was a secondary end point in all the studies and was analyzed without controlling for multiplicity. Thus, a firm conclusion could not be drawn about the effectiveness of liraglutide 3 mg to improve HRQoL in patients who are overweight or living with obesity.

Harms (Safety)

The overall AE rates associated with liraglutide 3 mg were between 80.1% and 94.7%, and between 69.3% and 89.4% with placebo. The most common AEs (i.e., occurring in ≥ 5% of patients) across the included studies were nausea (26.7% to 47.6% for liraglutide versus 6.7% to 17.1% for placebo), diarrhea (16.5% to 25.6% for liraglutide versus 7.7% to 14.3% for placebo), and constipation (11.9% to 26.9% for liraglutide versus 6.7% to 12.4% for placebo).

Serious adverse event (SAE) rates were between 3.4% to 15.1% for liraglutide 3 mg compared with 2.4% to 12.9% with placebo. The most frequent SAE with liraglutide 3 mg (i.e., occurring in ≥ 1% of patients) was hepatobiliary disorders (up to 2.5%, only in Study 1839) and infections and infestations (2.3%, only in Study 1839). Neoplasm (i.e., benign, malignant, and unspecified) rates were 1.7%, 1.9%, and 2.1% in Study 1922, Study 1923, and Study 1839 extension, respectively.

The percentage of patients who discontinued treatment prematurely due to an AE was higher with liraglutide 3 mg than placebo in all the studies. The discontinuation rate due to AEs ranged from 8.6% to 13.3% in the liraglutide 3 mg group compared with 3.3% to 11.1% in the placebo group.

In the 56-week main phase of Study 1839, 1 death occurred in the liraglutide 3 mg group, and 2 deaths occurred in the placebo group. At the end of the extension phase of Study 1839 (160 weeks), each group had a total of 2 deaths, corresponding to mortality rates of 0.1% and 0.3% for the liraglutide 3 mg and placebo groups, respectively. Both deaths in the liraglutide 3 mg group and 1 death in the placebo group were due to cardiovascular-related causes, and 1 death in the placebo group was due to pulmonary fibrosis. In Study 1923, 1 patient in the placebo group died from cardiac failure. No deaths were reported during Study 1922 or Study 3970.

Indirect Evidence

A targeted literature search was conducted for indirect evidence on the comparative efficacy and safety of liraglutide 3 mg, in the absence of head-to-head studies directly comparing liraglutide 3 mg with relevant active comparators meeting the protocol criteria for the CADTH Reimbursement Review on Saxenda. One systematic review with an NMA comparing 5 weight loss drugs was identified and included in the Reimbursement Review. The systematic review was published in 2016 and included randomized controlled trials (RCTs) that evaluated liraglutide 3 mg and orlistat (both of interest to the Reimbursement Review). Other drugs

investigated were an extended-release tablet of naltrexone hydrochloride 8 mg combined with bupropion hydrochloride 90 mg, lorcaserin, and phentermine-topiramate. The NMA had a total of 29 relevant RCTs, including one 3-armed RCT comparing orlistat and liraglutide with placebo, 3 RCTs of liraglutide versus placebo, and 16 RCTs of orlistat versus placebo. The remaining RCTs were placebo-controlled trials involving naltrexone-bupropion (4 trials), lorcaserin (3 trials), and phentermine (2 trials). Only the comparisons between liraglutide and orlistat were of interest to this review.

The NMA was conducted using a random-effects Bayesian model with Markov chain Monte Carlo methods. The primary efficacy outcome was the proportion of patients with 5% or greater weight loss from baseline at 1 year. Other efficacy outcomes assessed were the proportion of patients with at least 10% weight loss and the incremental change in weight from baseline over placebo after 1 year of follow-up. The only safety outcome assessed was the proportion of patients discontinuing treatment due to AEs.

Overall, the NMA results suggest that patients treated with liraglutide 3 mg had greater odds of achieving 5% and 10% weight loss than those treated with orlistat. Treatment discontinuation due to AEs occurred more frequently with liraglutide 3 mg than with orlistat. However, confidence in these results is limited by significant heterogeneity, high attrition rates across all the included primary studies, and significant limitations involving the quality of the primary studies and methodological rigour.

Economic Evidence

Cost and Cost-Effectiveness

Liraglutide is available as a daily 3 mg subcutaneous injection. Liraglutide is initiated at a dose of 0.6 mg which is increased weekly up to the 3 mg dose. Liraglutide is supplied in a pack of 5 pre-filled pens for a total of 90 mg. Based on the unit cost for the pack ($375.10), the annual cost per patient is $4,389 in the first year and $4,564 thereafter.

A cohort multi-state Markov model was developed to simulate the progression of adult patients either receiving liraglutide as an adjunct therapy to diet and exercise or not receiving liraglutide (diet and exercise alone). The model estimates the impact of treatments on long-term costs and quality-adjusted life-years (QALYs) by assessing temporal changes on a range of risk factors (BMI, glycemic status, and cardiometabolic risk factors) associated with weight-related complications and events (acute coronary syndrome, stroke, cancer, sleep apnea, and knee replacement). The probability of patients developing these complications and events were derived from risk prediction models except the probability of temporary reversal of prediabetes, which was derived from Study 1839. The risk of death throughout the model is related to the risk of fatal events, the increased risk post non-fatal events, and the underlying age- and gender-specific population mortality. Treatment effectiveness is modelled indirectly through changes in BMI and cardiometabolic risk factors and directly through the effect on progression to diabetes and the temporary reversal of prediabetes. Treatment is assumed to be discontinued for all patients at 1 year for the Health Canada indication and at 3 years for the reimbursement request population. Those discontinuing treatment were assumed to return to their baseline values over a period of 3 years. For non-responders to liraglutide, the patient pathway was assumed to be consistent with that of patients receiving diet and

exercise alone. The time horizon in the base case was 40 years to capture the maximum lifetime of patients who start therapy, with a 1.5% annual discount rate for costs and effects.

CADTH identified the following key limitations with the sponsor's pharmacoeconomic analysis:

- Duration of treatment could not be modified in the model. The sponsor's analysis for the full Health Canada indication did not permit treatment with liraglutide to be used beyond 1 year. The CADTH clinical expert felt that patients who responded would continue to remain on treatment after 1 year if there was continued weight loss. Although the maximum time a patient could spend on liraglutide was set to 3 years for those who met the reimbursement request, the CADTH clinical expert felt that patients who had a positive response could remain on liraglutide beyond 3 years.
- The CADTH clinical expert anticipates that after 2 years of treatment curtailment, risk factors (e.g., weight) and outcomes would be the same for patients on standard care and liraglutide. However, the sponsor assumed lifetime benefits associated with short-term weight loss.
- The sponsor reported benefits of liraglutide on outcomes that lacked sufficient evidence from Study 1839, such as knee replacements and stroke.
- The sponsor assumed that patients with prediabetes at baseline who temporarily revert to normal glucose levels would incur zero costs to the health system. The CADTH clinical expert felt that these patients would unlikely have a drastic change in their treatment management.
- Non-responders to liraglutide, defined as those failing to meet a 5% reduction in weight, were assumed to have the same long-term outcomes as patients who only received standard care. However, more than 20% of patients in the trial who received standard care alone achieved a response. Therefore, the sponsor assumed that patients who experience no weight loss on liraglutide have better outcomes than patients who experience no weight loss from diet and exercise alone.
- The model is highly complex, and the user guide provided did not provide sufficient details to outline how the model operated. This restricted the flexibility of changes CADTH could make to the model.

CADTH undertook reanalyses to address limitations in the sponsor's submission including assuming no benefit beyond 2 years of treatment discontinuation, removing complications other than diabetes from the analysis, applying costs to patients with "temporary T2DM reversal," and focusing only on the reimbursement request population. CADTH was unable to address the limitation associated with maximum duration of treatment and could only explore reduced outcomes for liraglutide non-responders as a scenario analysis. The cost-effectiveness for the full Health Canada indication could not be determined due to significant uncertainty regarding long-term use of liraglutide and the inability to explore this within the sponsor's submitted model. Based on the reimbursement request population, in the CADTH base case, the incremental cost-effectiveness ratio (ICER) for liraglutide compared with standard care is $196,876 per QALY compared with diet and exercise. However, this assumes that patients who experience no weight loss on liraglutide have better outcomes than patients who experience no weight loss from diet and exercise alone. In a scenario analysis, CADTH assumed that patients who fail to achieve 5% weight loss have similar outcomes regardless of whether they received liraglutide or diet and exercise alone, resulting in an ICER of $346,556 per QALY. To achieve cost-effectiveness at a $50,000 per QALY threshold, the price of liraglutide would need to be reduced by at least 62% or at least 74% when outcomes

for non-responders are accounted for. The results assume that treatment is stopped at 3 years. If liraglutide is taken for longer, the ICER will likely increase, and further price reductions will be needed.

Budget Impact

The sponsor estimated the incremental budget impact of reimbursing liraglutide to be $488,093,354 over 3 years for the full Health Canada indication and $222,587,425 for the reimbursement request population. CADTH identified limitations with the submitted analysis and undertook reanalyses that estimated the incremental budget impact of reimbursing liraglutide to be $590,820,493 over 3 years for the full Health Canada indication and $315,238,245 for the reimbursement request population.

Members of the Canadian Drug Expert Committee (CDEC)

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Sally Bean, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Allen Lefebvre, Dr. Kerry Mansell, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

Initial meeting date: May 19, 2021

Regrets: None

Conflicts of interest: None

Reconsideration meeting date: August 18, 2021

Regrets: One CDEC member did not attend.

Conflicts of interest: None