

## CADTH COMMON DRUG REVIEW

# CADTH Canadian Drug Expert Committee Recommendation

(Final)

### **SEMAGLUTIDE (OZEMPIC — NOVO NORDISK CANADA INC.)**

Indication: Diabetes mellitus, type 2 to improve glycemic control.

#### **RECOMMENDATION**

The CADTH Canadian Drug Expert Committee recommends that semaglutide be reimbursed for the treatment of type 2 diabetes mellitus to improve glycemic control, if the following conditions are met:

#### **Conditions for Reimbursement**

##### **Initiation Criteria**

1. Adult patients diagnosed with type 2 diabetes mellitus with inadequate glycemic control.

##### **Administration Criteria**

1. In combination with metformin alone, when diet and exercise plus maximal tolerated dose of metformin do not achieve adequate glycemic control.
2. Semaglutide should not be reimbursed for use as add-on therapy to metformin and another antihyperglycemic drug.

##### **Pricing conditions**

1. Drug plan costs for semaglutide should not exceed the drug plan costs of the least costly currently reimbursed drug used when metformin alone is insufficient to achieve glycemic control in the treatment of patients with type 2 diabetes mellitus.

Service Line: CADTH Drug Reimbursement Recommendation

Version: Final

Publication Date: May 2019

Report Length: 9 Pages

**Disclaimer:** The information in this document is intended to help Canadian health care decision-makers, health care professionals, health systems leaders, and policy-makers make well-informed decisions and thereby improve the quality of health care services. While patients and others may access this document, the document is made available for informational purposes only and no representations or warranties are made with respect to its fitness for any particular purpose. The information in this document should not be used as a substitute for professional medical advice or as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision-making process. The Canadian Agency for Drugs and Technologies in Health (CADTH) does not endorse any information, drugs, therapies, treatments, products, processes, or services.

While care has been taken to ensure that the information prepared by CADTH in this document is accurate, complete, and up-to-date as at the applicable date the material was first published by CADTH, CADTH does not make any guarantees to that effect. CADTH does not guarantee and is not responsible for the quality, currency, propriety, accuracy, or reasonableness of any statements, information, or conclusions contained in any third-party materials used in preparing this document. The views and opinions of third parties published in this document do not necessarily state or reflect those of CADTH.

CADTH is not responsible for any errors, omissions, injury, loss, or damage arising from or relating to the use (or misuse) of any information, statements, or conclusions contained in or implied by the contents of this document or any of the source materials.

This document may contain links to third-party websites. CADTH does not have control over the content of such sites. Use of third-party sites is governed by the third-party website owners' own terms and conditions set out for such sites. CADTH does not make any guarantee with respect to any information contained on such third-party sites and CADTH is not responsible for any injury, loss, or damage suffered as a result of using such third-party sites. CADTH has no responsibility for the collection, use, and disclosure of personal information by third-party sites.

Subject to the aforementioned limitations, the views expressed herein are those of CADTH and do not necessarily represent the views of Canada's federal, provincial, or territorial governments or any third party supplier of information.

This document is prepared and intended for use in the context of the Canadian health care system. The use of this document outside of Canada is done so at the user's own risk.

This disclaimer and any questions or matters of any nature arising from or relating to the content or use (or misuse) of this document will be governed by and interpreted in accordance with the laws of the Province of Ontario and the laws of Canada applicable therein, and all proceedings shall be subject to the exclusive jurisdiction of the courts of the Province of Ontario, Canada.

The copyright and other intellectual property rights in this document are owned by CADTH and its licensors. These rights are protected by the Canadian *Copyright Act* and other national and international laws and agreements. Users are permitted to make copies of this document for non-commercial purposes only, provided it is not modified when reproduced and appropriate credit is given to CADTH and its licensors.

**Redactions:** Confidential information in this document has been redacted at the request of the manufacturer in accordance with the *CADTH Common Drug 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.

## SEMAGLUTIDE (OZEMPIC — NOVO NORDISK CANADA INC.)

Indication: Diabetes mellitus, type 2, to improve glycemic control.

### Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that semaglutide be reimbursed for the treatment of type 2 diabetes mellitus (T2DM) to improve glycemic control, if the following conditions are met:

### Conditions for Reimbursement

#### Initiation Criteria

1. Adult patients diagnosed with T2DM with inadequate glycemic control.

#### Administration Criteria

1. In combination with metformin (MET) alone, when diet and exercise plus maximal tolerated dose of MET do not achieve adequate glycemic control.
2. Semaglutide should not be reimbursed for use as add-on therapy to MET and another antihyperglycemic drug.

#### Pricing Conditions

1. Drug plan costs for semaglutide should not exceed the drug plan costs of the least costly currently reimbursed drug used when MET alone is insufficient to achieve glycemic control in the treatment of patients with T2DM.

### Reasons for the Recommendation

1. One phase III, open-label, randomized controlled trial (RCT) (SUSTAIN-7) demonstrated that semaglutide 0.5 mg and 1 mg administered subcutaneously once weekly was statistically superior compared with dulaglutide for improving glycemic control (change from baseline in glycated hemoglobin [A1C]) and body weight reduction at 40 weeks in patients with T2DM and inadequate glycemic control on treatment with MET. The findings of post hoc subgroup data from three other phase III RCTs (SUSTAIN 2, 3, and 4) were consistent with the findings of SUSTAIN-7 and indicated that semaglutide (0.5 mg and/or 1 mg added on to MET) is likely noninferior to sitagliptin, exenatide, and insulin glargine with respect to reduction in A1C and body weight.
2. In SUSTAIN-2, 3, and 4, exploratory post hoc subgroup analyses based on prior antidiabetic therapy were performed to explore the treatment effect of semaglutide as add-on therapy to one or more antihyperglycemic drugs (i.e., as a third-line drug). However, because of the limitations existing with this approach, such as potential imbalance in baseline characteristics between subgroups, multiplicity and potential inflated type I error, and potential interactions between treatment and background therapy, there was a high degree of uncertainty in the conclusions that could be drawn on the results.
3. The cost-effectiveness of semaglutide could not be assessed because the manufacturer-provided cost-utility analysis was associated with significant limitations and lack of transparency. At the manufacturer-submitted price of \$195.06 per pre-filled pen, semaglutide is more expensive than all other treatment options, with the exception of liraglutide 1.8 mg per day. Based on the clinical evidence provided, a conclusion could be reached that semaglutide has similar effects to some other currently reimbursed second-line antihyperglycemic drugs and there is insufficient information available to justify a price greater than currently reimbursed second-line treatments.

### Discussion Points

- Semaglutide is currently the fifth glucagon-like peptide (GLP)-1 receptor agonist approved for glycemic control in patients with T2DM.
- Semaglutide was compared with other GLP-1 receptor agonists, dipeptidyl-peptidase-4 inhibitors, and insulin glargine in the SUSTAIN trials; however, direct comparisons of semaglutide with other oral antihyperglycemic drugs (OADs) are lacking. The manufacturer provided three separate indirect treatment comparisons (ITCs) in patients inadequately controlled on one OAD that compared semaglutide with other GLP-1 agonists, sodium glucose cotransporter (SGLT)-2 inhibitors, and sulfonylurea (SU). Results of these ITCs suggested a reduction in A1C and body weight with semaglutide versus the comparators; however, the use of separate, sparsely populated networks for each drug class rather than one connected network that included all drugs

relevant to the decision-making comparator set, along with the low methodological quality of the ITCs, lead to the results of the ITCs being uncertain.

- SUSTAIN-6 was a cardiovascular (CV) harms outcome trial designed to demonstrate CV safety of semaglutide as mandated by the US FDA and other regulators for antidiabetic drugs. SUSTAIN-6 was designed to demonstrate noninferiority of semaglutide compared with placebo on the risk of major adverse cardiac events (MACE). Superiority testing was outside of the statistical hierarchy. The two-year trial results showed that the proportion of patients with first MACE (CV death, non-fatal myocardial infarction, and non-fatal stroke) was lower with semaglutide (6.6%) compared with placebo (8.9%). Treatment with either dose of semaglutide was also associated with numerically lower events of non-fatal myocardial infarction and non-fatal stroke, while the number of deaths from CV causes was similar across treatment groups. The estimated hazard ratio for first MACE was 0.74 (95% confidence interval [CI], 0.58 to 0.95, below the predefined noninferiority margin of 1.8), indicating that semaglutide statistically significantly reduced the risk of experiencing first MACE by 26% when compared with placebo in patients with existing CV disease.
- Currently, one other GLP-1 receptor agonist (liraglutide) and two SGLT-2 inhibitors (canagliflozin and empagliflozin) have Health Canada indications for add-on use in the population with T2DM at high risk of CV events. Although results of SUSTAIN-6 suggest that semaglutide does not increase the risk of certain CV events (e.g., MACE) and may reduce the risk of CV events as compared with placebo, it is important to note that semaglutide does not have a Health Canada indication for CV risk reduction or for specific use in patients with diabetes at higher CV risk.
- Semaglutide was associated with fewer patients developing new or worsening nephropathy as compared with those who received placebo in SUSTAIN-6. However, the proportions of patients who developed diabetic retinopathy complications were higher in the semaglutide groups compared with the placebo groups (████ with semaglutide 0.5 mg, █████ with semaglutide 1 mg, and approximately █████ with placebo).
- As the price reduction required for semaglutide is dependent on the negotiated price of comparators, a greater reduction in price may be required for semaglutide than indicated by the manufacturer.

## Background

Semaglutide is a selective long-acting GLP-1 receptor agonist and has a Health Canada-approved indication for the improvement of glycemic control in adult patients with T2DM, in combination with diet and exercise when MET is inappropriate due to contraindications or intolerance, or when adequate glycemic control has not been achieved with diet and exercise plus the maximum tolerated dose of MET, dual therapy with MET and an SU, or dual therapy with basal insulin and MET. The manufacturer requested reimbursement for semaglutide in combination with MET for patients who have not achieved adequate glycemic control with MET alone (second-line treatment), and in combination with MET plus SU for patients who have not achieved adequate glycemic control with MET in combination with SU (third-line treatment).

The recommended route of administration for semaglutide is subcutaneously in the abdomen, thigh, or upper arm. It is recommended that a patient begins with a once-weekly sub-therapeutic dose of 0.25 mg, followed by an increase to 0.5 mg per week after four weeks. For patients that require additional glycemic control after four weeks, the dose may be increased to 1 mg once weekly, which is the maximum recommended dose. Semaglutide is available as a pre-filled multi-dose pen delivering doses of 0.25 mg or 0.5 mg, as well as a pre-filled pen that delivers a dose of 1 mg.

## Summary of Evidence Considered by CDEC

The committee considered the following information prepared by the CADTH Common Drug Review (CDR): a systematic review of eight RCTs of semaglutide, a critique of the manufacturer-submitted ITCs, and a critique of the manufacturer's pharmacoeconomic evaluation. The committee also considered input from a clinical expert with experience in treating patients with diabetes, and patient group-submitted information about outcomes and issues important to patients.

## Summary of Patient Input

Two patient groups, Diabetes Canada and Patient Commando, provided patient input for this submission. Information for the patient input submissions was obtained from online surveys, personal interviews and group discussions, social media platforms, a website

story collection, and community responses to a program (carried out by one of the patient groups). The following is a summary of key input from the perspective of the patient groups:

- T2DM is a chronic progressive disease without a cure that brings a common set of symptoms and risk of complications. Beyond the physical impact, T2DM has a burden on patients' emotional, social, and financial well-being.
- Poor glucose control is serious and problematic, and can lead to a range of serious comorbidities, such as heart disease, blindness, kidney disease, and lower limb amputations. Both patient groups indicated the complexity of treatment modalities for diabetes and the need for constant monitoring and self-management.
- While one patient group indicated that the majority of its respondents reported improvements in meeting glycemic control targets after initiation on their current treatment and were "satisfied" or "very satisfied" with these treatments for diabetes, the other group reported that an increasing number of patients escalated to insulin therapy. In addition, this group noted geographical access inequalities, institutional protocols, and access to specialized diabetes teams as components of treatment that further complicate the access to treatment.
- Both groups expressed a strong desire for medications that can normalize and stabilize blood glucose levels and improve hemoglobin A1C without causing weight gain or hypoglycemia, be safe and affordable, be easily administered with minimal disruption to lifestyle, minimize the risk of diabetes-related complications, avoid polypharmacy, and reduce or eliminate the need for insulin. The need to attend to the broader needs of patients, taking a holistic approach, was also noted.

## Clinical Trials

The CDR systematic review included eight RCTs (SUSTAIN-1 to -7 and the Seino study) of patients with T2DM (N = 308 to 3,297).

These trials evaluated the efficacy and safety of semaglutide 0.5 mg or 1 mg once weekly, alone or in combination with an OAD such as MET or MET plus a SU, or basal insulin, compared with placebo or active comparators in adults with T2DM with inadequate glycemic control with background therapy. All three placebo-controlled trials (SUSTAIN-1, 5 and 6) and one active-controlled trial (SUSTAIN-2) included a randomized, double-blind treatment period, and all other active-controlled trials had an open-label design (SUSTAIN-3, -4, -7, and the Seino study). The primary objective of the included trials was to compare the effect of semaglutide once weekly with its respective comparators on change in hemoglobin A1C from baseline, except for SUSTAIN-6 and the Seino study. "Time from randomization to first occurrence of MACE" was the primary outcome in SUSTAIN-6. The occurrence of treatment-emergent adverse event (AE) was the primary outcome in the Seino study. The occurrence of diabetes-related comorbidities (macrovascular and microvascular) was also measured in the only CV outcomes trial (SUSTAIN-6). Change in body weight, body mass index, blood pressure, and blood lipid profile were evaluated in all trials. Health-related quality of life (HRQoL) was evaluated in all trials but SUSTAIN-1 and the Seino study. Noninferiority of treatment with semaglutide versus active comparators on glycemic control was assessed in four SUSTAIN trials (SUSTAIN-2, -3, -4, and -7). Noninferiority of treatment with semaglutide compared with placebo on increase in CV events was assessed in patients who had prior or concomitant CV conditions in SUSTAIN-6. In SUSTAIN-2, -3, -4, -6, and -7, superiority of semaglutide compared with placebo or active treatment for either change in hemoglobin A1C or change in body weight was tested if the noninferiority test criterion for the primary end point was met. Treatment duration of the included trials ranged from 30 weeks to 104 weeks.

Key limitations of the trials include uncertainty in data interpretation related to the outcome measures outside of the hierarchical testing procedure, which was used for controlling for possible inflated type I error; lack of subgroup-specific noninferiority margins; lack of adjustment for multiplicity with subgroup analyses; missing data in most of the trials; and the appropriateness of mixing patients who were controlled on two prior OADs with those controlled on one OAD in one analysis. In SUSTAIN-2, -3, and -4, which comprised patients treated with semaglutide as second- or third-line therapy, subgroup analyses based on prior antidiabetic therapy were performed. However, these were post hoc analyses and were exploratory in nature; therefore, interpreting the results of the subgroup analyses is difficult because of the potential imbalance of patients' baseline characteristics across the subgroups, complexity of testing interaction effect, and the inconsistency between statistical significance and clinical importance. None of the reviewed studies were designed specifically to assess the effects of semaglutide added onto two antihyperglycemic drugs. Sustain-7 was the only study that enrolled a patient population receiving one OAD as background therapy (i.e., semaglutide as second-line treatment).

## Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, the committee discussed the following:

- glycemic control (e.g., change in A1C)
- body weight (e.g., change in body weight)
- risk of CV events in patients with existing CV disease
- HRQoL was assessed by generic and diabetes-specific questionnaires
- AEs, serious adverse events (SAEs), AEs leading to premature treatment discontinuation, and notable harms.

Change in A1C from baseline was the primary efficacy outcome in all included trials, except for SUSTAIN-6 and the Seino study. Time from randomization to first occurrence of MACE was the primary outcome in SUSTAIN-6, and the occurrence of AEs was the primary outcome in the Seino study.

## Efficacy

### *Glycemic Control*

Semaglutide used as first-line, second-line, or third-line therapy was associated with statistically significant reductions in hemoglobin A1C after 30 to 56 weeks compared with placebo or active treatment. Semaglutide 1 mg was more likely to be related to a greater reduction in A1C compared with semaglutide 0.5 mg, though none of the trials statistically compared the doses of semaglutide. SUSTAIN-2, -3, -4, and -7 were noninferiority trials, and the results suggested that semaglutide was noninferior and superior to the active controls for the change from baseline in hemoglobin A1C based on predefined noninferiority margins of 0.3% or 0.4%. The change in A1C versus placebo or an active control was considered clinically relevant by the clinical expert consulted by CDR.

First-line therapy (add-on to diet/exercise):

- When compared with placebo, the between-group difference in hemoglobin A1C reduction was  $-1.43\%$  to  $-1.53\%$  (SUSTAIN-1).

Second-line therapy (add-on to MET):

- When compared with sitagliptin, the between-group difference in hemoglobin A1C reduction was [REDACTED] (subgroup data from SUSTAIN-2).
- When compared with exenatide, the between-group difference in hemoglobin A1C reduction was [REDACTED] (subgroup data from SUSTAIN-3).
- When compared with insulin glargine, the between-group difference in hemoglobin A1C reduction was [REDACTED] (subgroup data from SUSTAIN-4).
- When compared with dulaglutide, the between-group difference in hemoglobin A1C reduction was  $-0.40\%$  to  $-0.41\%$  (SUSTAIN-7).

Third-line therapy (add-on to MET plus SU or MET plus thiazolidinedione):

- When compared with sitagliptin, the between-group difference in hemoglobin A1C reduction was [REDACTED] (subgroup data from SUSTAIN-2).
- When compared with exenatide, the between-group difference in hemoglobin A1C reduction was [REDACTED] (subgroup data from SUSTAIN-3).
- When compared with insulin glargine, the between-group difference in hemoglobin A1C reduction was [REDACTED] (subgroup data from SUSTAIN-4).

### *Body Weight*

Semaglutide used as first-line, second-line, or third-line therapy was also associated with statistically significant reductions in weight after 30 to 56 weeks compared with placebo or active treatment. Semaglutide 1 mg was more likely to be related to a greater reduction in weight compared with semaglutide 0.5 mg. The change in weight versus placebo or an active control was considered clinically relevant by the clinical expert consulted by CDR.

## First-line therapy (add-on to diet/exercise):

- When compared with placebo, the between-group difference in weight reduction was  $-2.75$  kg to  $-3.56$  kg (SUSTAIN-1).

## Second-line therapy (add-on to MET):

- When compared with sitagliptin, the between-group difference in weight reduction was [REDACTED] (subgroup data from SUSTAIN-2).
- When compared with exenatide, the between-group difference in weight reduction was [REDACTED] (subgroup data from SUSTAIN-3).
- When compared with insulin glargine, the between-group difference in weight reduction was [REDACTED] (subgroup data from SUSTAIN-4).
- When compared with dulaglutide, the between-group difference in weight reduction was  $-2.26$  kg to  $-3.55$  kg (SUSTAIN-7).

## Third-line therapy (add-on to MET plus SU or MET plus thiazolidinedione):

- When compared with sitagliptin, the between-group difference in weight reduction was [REDACTED] (subgroup data from SUSTAIN-2).
- When compared with exenatide, the between-group difference in weight reduction was [REDACTED] (subgroup data from SUSTAIN-3).
- When compared with insulin glargine, the between-group difference in weight reduction was [REDACTED] (subgroup data from SUSTAIN-4).

### *Risk of Cardiovascular Events in Patients With Existing Cardiovascular Disease*

Risk of CV events was examined in patients with existing CV disease in SUSTAIN-6. The results showed that the proportion of patients with first MACE (consisting of CV death, non-fatal myocardial infarction, and non-fatal stroke) was lower with semaglutide (6.6%) therapy than with placebo (8.9%). Treatment with either dose of semaglutide was also associated with numerically lower events of non-fatal myocardial infarction and non-fatal stroke, while the number of deaths from CV causes was similar across treatment groups. The estimated hazard ratio was 0.74 (95% CI, 0.58 to 0.95, below the noninferiority margin of 1.8), indicating that semaglutide statistically significantly reduced the risk of experiencing a MACE by 26% when compared with placebo in patients with existing CV disease. Treatment with semaglutide was also associated with numerically lower events of revascularization, unstable angina pectoris requiring hospitalization, or hospitalization for heart failure.

### *Health-Related Quality of Life*

HRQoL was improved for all treatment groups within trials, but statistically significant differences between treatment groups were not always observed.

## Harms (Safety)

The AE profile of semaglutide appears to be similar to other drugs in the GLP-1 class and no new safety signals were identified based on the included trials. The overall frequency of AEs was similar between treatment groups within trials. In the placebo-controlled trials (except for SUSTAIN-6), AEs were reported by 56% to 69% of patients treated with semaglutide, and by 54% to 58% of patients treated with placebo. In the active-controlled trials, AEs were reported by 68% to 75% of patients with semaglutide, and 62% to 76% of patients with other active treatments.

SAEs were reported by 4% to 7% of patients who received placebo, 5% to 9% of patients who received semaglutide (2% to 3% of these SAEs were gastrointestinal disorders), and 2% to 8% of patients who received other active treatments. The frequency of AEs leading to treatment discontinuation were 4% to 7% in the placebo group, 3% to 10% in the semaglutide group, and 1% to 7% in other active treatment groups. The frequency of gastrointestinal disorders was higher in the semaglutide group compared with placebo or active comparator that was not a GLP-1 receptor agonist, such as sitagliptin or insulin. The frequency of hypoglycemia was highest in the insulin glargine group in SUSTAIN-4 (39.4%). The risk of hypoglycemia for semaglutide was similar to the other GLP-1 receptor agonists (such as exenatide and dulaglutide), and was lower than sitagliptin and insulin glargine. Severe hypoglycemia was reported infrequently in the included trials.

Patients in SUSTAIN-6 reported higher AE rates compared with the other SUSTAIN trials. The incidence of AEs was 88% to 89%. The rates of SAEs were 32.1%, 29.3%, and 34.9% in patients who received semaglutide 0.5 mg, semaglutide 1 mg, and placebo, respectively. The rates of AEs leading to premature treatment discontinuation were 11.5% to 14.5% in the semaglutide groups and 6.7% in the placebo groups. Furthermore, proportions of new or worsening nephropathy were numerically lower in the semaglutide groups than in the placebo groups, while proportions of patients experiencing diabetic retinopathy complications were numerically higher in the semaglutide groups than in the placebo groups: ■■■ with semaglutide 0.5 mg, ■■■ with semaglutide 1 mg, ■■■ with placebo 0.5 mg, and ■■■ with placebo 1 mg.

### Indirect Treatment Comparisons

The manufacturer submitted three separate ITCs for patients inadequately control on one OAD that compared semaglutide with other GLP-1 agonists, SGLT-2 inhibitors, and SU. Results of these ITCs suggested a reduction in A1C and body weight with semaglutide versus the comparators; however, the data should be interpreted with caution due to the use of separate networks for each drug class rather than one connected network that included all drugs relevant to the decision-making comparator set, and the relatively poor quality of these ITCs.

The ITC that examined all-cause mortality among patients with T2DM treated with GLP-1 agonists, dipeptidyl-peptidase-4 inhibitors, or SGLT-2 inhibitors suggested that the risk of death among those who received semaglutide was similar to other therapies, with the exception of empagliflozin. These data should be interpreted with caution due to potential heterogeneity in trial and patient characteristics of the included studies that was not adequately explored in the ITC.

### Cost and Cost-Effectiveness

Semaglutide is available as a solution in a pre-filled multi-dose disposable pen in 1.5 mL or 3 mL cartridges, equivalent to 2 mg or 4 mg semaglutide. The starting dose of semaglutide is 0.25 mg weekly; after four weeks the dose should be increased to 0.5 mg weekly. After an additional four weeks, the dose can be increased to 1 mg once weekly. At the manufacturer's submitted price of \$195.06 per pre-filled pen, the annual treatment cost per patient is \$2,544.

The manufacturer submitted a cost-utility analysis over a 40-year time horizon from the perspective of a Canadian public health care payer. Analysis was conducted for two populations: those who do not achieve adequate glycemic control with metformin (second-line treatment) and those who do not achieve adequate glycemic control with metformin and sulfonyleurea (third-line treatment). The second-line treatment analysis compared both semaglutide 0.5 mg and 1 mg weekly with weekly regimens (dulaglutide 1.5 mg weekly and exenatide extended-release 2 mg weekly) and daily regimens (liraglutide 1.2 mg , liraglutide 1.8 mg , lixisenatide 20 mcg, sitagliptin 100 mg, insulin glargine 0.53 IU/kg, canagliflozin 300 mg, dapagliflozin 10 mg, empagliflozin 25 mg, and glyburide 15 mg). For third-line treatment, the same comparators were considered, with the exception of glyburide. The model incorporated a variety of health states relating to the important micro and macrovascular complications associated with diabetes, the incidence of hypoglycemic events, and the associated impact of complications and events on mortality.

In the manufacturer's analysis for second-line treatment, glyburide had the lowest costs and fewest quality-adjusted life-years (QALYs). Relative to glyburide, canagliflozin was the next most cost-effective treatment, followed by semaglutide 1 mg. The manufacturer reported the incremental cost per QALY gained (incremental cost-utility ratio [ICUR]) for canagliflozin versus glyburide was \$10,827, and the ICUR for semaglutide 1 mg versus canagliflozin was \$714,488. For third-line treatment, canagliflozin had the lowest costs. Relative to canagliflozin, semaglutide 1mg was the next most cost-effective treatment. The manufacturer reported that the ICUR for semaglutide 1 mg versus canagliflozin was \$136,653.

CADTH identified the following key limitations:

- A major concern is the clinical data used to inform the economic model. A comprehensive network meta-analysis (NMA) incorporating all treatment options and all clinical outcomes is required to fully assess the relative effectiveness of each treatment option considered. This has led to the evidence for treatments being inconsistent. For example, instead of providing a single NMA comparing all second-line treatments, three separate NMAs are provided covering different groups of second-line treatment. However, for certain treatments, data from single clinical trials are used, whereas for other treatments, data from the NMA were used. Thus, a consistent base comparator is not available across these analyses and comparisons are de facto based on naive indirect comparisons, which are inappropriate.



- The CADTH clinical review team noted that the NMAs used to inform the economic analysis for third-line treatment were not representative of the patient population as the study population was not specific to patients who were not adequately controlled on metformin and SU, and were therefore inappropriate for this analysis.
- The submitted model was not transparent and there were conceptual problems in how diabetes progression was modelled. Verification of the model code was not possible and there were concerns given the inconsistency of results provided by the manufacturer.
- The manufacturer included a disutility associated with body mass index. CADTH noted that it is unclear whether utility decrements for weight gain derived from larger weight differences (13 kg to 30 kg) can be applied in a proportional manner to the smaller weight differences observed in the NMA of second-line therapies.

CADTH noted significant limitations with the submitted economic analysis that could not be corrected. As such, CADTH concluded that the manufacturer's economic submission did not provide an appropriate basis to assess the cost-effectiveness of semaglutide. The manufacturer suggested that if semaglutide was lowered in price by 28%, its incremental cost-effectiveness ratio versus canagliflozin would be less than \$50,000.

## CDEC Members

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Peter Jamieson, Mr. Allen Lefebvre, Ms. Heather Neville, Dr. Rakesh Patel, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

## April 10, 2019 Meeting

### Regrets

Two CDEC members did not attend.

### Conflicts of Interest

None