Canadian Journal of Health Technologies

CADTH

June 2021 Volume 1 Issue 6

CADTH Reimbursement Recommendation

Semaglutide (Rybelsus)

Indication: Semaglutide is indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM:

- as monotherapy when metformin is considered inappropriate due to intolerance or contraindications
- in combination with other medicinal products for the treatment of diabetes.

Sponsor: Novo Nordisk Canada Inc.

Final Recommendation: Reimburse with conditions

CADTH

ISSN: 2563-6596

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

What is the CADTH reimbursement recommendation for Rybelsus?

CADTH recommends that Rybelsus should be reimbursed by public drug plans for the treatment of type 2 diabetes if certain conditions are met.

What are the conditions for reimbursement?

Rybelsus should only be reimbursed if it is used in addition to metformin or other antihyperglycemic agents and it does not cost more than glucagon-like peptide-1 receptor agonists, dipeptidyl peptidase-4 inhibitors, and sodium-glucose cotransporter-2 inhibitors.

Which patients are eligible for coverage?

Rybelsus should only be covered to treat adult patients with type 2 diabetes when it is used as an add-on treatment to metformin or other antihyperglycemic agents.

Why did CADTH make this recommendation?

Evidence from 6 clinical trials demonstrated that Rybelsus was equal to or better in terms of lowering blood glucose than some of the other treatments for type 2 diabetes. At the submitted price, Rybelsus is more costly than some glucagon-like peptide-1 receptor agonists, and all dipeptidyl peptidase-4 inhibitors, sodium-glucose cotransporter-2 inhibitors, and other oral diabetes treatments.

Key Messages

- Clinical evidence suggests that Rybelsus should be reimbursed to treat type 2 diabetes in adults if it is used in addition to metformin or other antihyperglycemic agents and does not cost more than glucagon-like peptide-1 receptor agonists, dipeptidyl peptidase-4 inhibitors, and sodium-glucose cotransporter-2 inhibitors.
- Rybelsus is more costly than most similar diabetes treatments.
- Rybelsus is expected to increase budgets by more than $38 million over 3 years.
- To account for the high treatment cost, the price of Rybelsus should be reduced.
- If Rybelsus is not reimbursed as an add-on treatment for patients with type 2 diabetes, there are several other alternative treatments available for these patients.

What is type 2 diabetes?

Type 2 diabetes occurs when the body does not properly use or make enough insulin, which leads to high blood sugar levels. Common symptoms include extreme fatigue, unusual thirst, frequent urination, and weight change. Approximately 3.8 million people in Canada were living with diabetes in 2020, and about 90% of patients have type 2 diabetes.

What is Rybelsus?

Rybelsus is approved by Health Canada for use in addition to diet and exercise to improve blood glucose control in adults with type 2 diabetes. It is a pill that can be taken alone or with other treatments for diabetes.

Rybelsus is a selective glucagon-like peptide-1 receptor agonist and acts on the same as the glucagon-like peptide-1 that naturally occurs in the body. When glucose levels are high, Rybelsus increases insulin secretion and decreases glucagon secretion, which lowers blood glucose and slows the time it takes for food to empty from the stomach.

How much does Rybelsus cost?

Treatment with Rybelsus is expected to cost $2,543 per patient per year.

What other treatments are available for type 2 diabetes?

Other treatments available for type 2 diabetes, include other glucagon-like peptide-1 receptor agonists, as well as dipeptidyl peptidase-4 inhibitors, and sodium-glucose cotransporter-2 inhibitors, sulfonylureas, meglitinides, thiazolidinediones, alpha-glucosidase inhibitors, and insulin.

Unmet needs in type 2 diabetes

Even though there are other treatments for type 2 diabetes, some patients still have uncontrolled disease and need other treatment options. The other GLP-1 treatments available in Canada must be injected. Rybelsus may be used in patients who need treatment with a GLP-1, but who do not want to take an injection.

How much do other treatments cost?

The per patient per year costs range from $1,295 to $3,413 for GLP-1 receptor agonists, $804 to $1,168 for dipeptidyl peptidase-4 inhibitors, and $996 to $1,055 for sodium-glucose cotransporter-2 inhibitors.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that oral semaglutide should be reimbursed as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM), only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

The efficacy and safety of oral semaglutide was reviewed in 6 randomized clinical trials in patients with T2DM as an add-on to metformin (PIONEER 2 and 5), as an add-on to 1 or 2 oral antihyperglycemic agents (OADs) (PIONEER 3, 4, 5, and 10), or as an add on to insulin with or without metformin (PIONEER 5 and 8). In the active comparator trials (PIONEER 2, 3, and 4), oral semaglutide was evaluated as a second- or third-line therapy. In the placebo-controlled trials (PIONEER 5 and 8), all 3 doses of oral semaglutide (3 mg, 7 mg, and 14 mg) were superior to placebo in reducing A1C levels after 26 weeks of treatment. Based on the outcome of A1C reduction after 26 weeks of treatment, oral semaglutide (14 mg) was superior when compared to empagliflozin (PIONEER 2; between-group difference: −0.4% (95% CI, −0.6 to −0.3, P < 0.0001) and was noninferior when compared to liraglutide (PIONEER 4; between-group difference: −0.1% (95% CI, −0.3 to 0.0, P < 0.0001). Both oral semaglutide 7 mg and 14 mg were superior to sitagliptin (PIONEER 3; between-group difference: −0.3% (95% CI, −0.4 to −0.1, P < 0.0001) and −0.5% (95% CI, −0.6 to −0.4, P < 0.0001), respectively. This clinical evidence suggests that oral semaglutide, the first oral glucagon-like peptide-1 receptor agonist (GLP-1 RA) approved by Health Canada, meets the needs of patients with T2DM as a treatment that improves glycemic control. Oral semaglutide provides patients with an alternative formulation to subcutaneous options used to treat hyperglycemia in T2DM, including subcutaneous semaglutide.

CADTH identified limitations with the submitted economic evaluation relating to the patient population being assessed, the lack of comparative cardiovascular outcomes data, quality of life data, and lack of transparency with the model resulting in uncertainty in the cost-effectiveness of oral semaglutide. At a submitted price of $6.97 per tablet (regardless of the dose) the daily cost of oral semaglutide ($6.97) is more costly than all SGLT-2 based products ($2.45 to $3.24), DPP-4 based products ($2.20 to $3.47), and some GLP-1 RAs, depending on dose ($3.55 to $9.34).

Implementation Guidance

1. Oral semaglutide should not be reimbursed for patients with T2DM who have comorbid atherosclerotic cardiovascular (CV) disease. While some GLP-1 RAs have demonstrated CV benefits in these patient populations, there is no current evidence demonstrating that oral semaglutide improves CV outcomes in these patient populations. Antidiabetic agents with an established CV benefit should be prescribed for patients with T2DM with established or high risk of atherosclerotic cardiovascular disease. Patients who are at high risk of atherosclerotic cardiovascular disease can be defined as being over 60 years of age with at least 2 cardiovascular risk factors, which include tobacco use, dyslipidemia, hypertension, and central obesity.

Discussion Points

- Currently, 1 other GLP-1 RA (liraglutide) and 2 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. PIONEER 6 was an event-driven cardiovascular outcomes trial where time from randomization to first occurrence of a major cardiovascular event was the primary outcome; however, superiority of oral semaglutide compared to placebo was not demonstrated. The trial was designed to evaluate if there was an increased risk of CV events, rather than risk reduction. Further, oral semaglutide does not have a Health Canada indication for CV risk reduction or for specific use in patients with diabetes at higher CV risk. There is an ongoing trial to determine if oral semaglutide reduces CV events. However, the results of this trial were not available at the time of this review.
- Although Health Canada has approved oral semaglutide as a monotherapy in patients in whom metformin is contraindicated or who are intolerant to metformin, none of the PIONEER trials evaluated oral semaglutide as a monotherapy in this patient population. In PIONEER 1 and 9 where semaglutide was evaluated as monotherapy, patients were previously treated with diet and exercise, or an OAD (in PIONEER 9) that required a washout period.
- CDEC noted that the clinical benefit obtained by the 7 mg and 14 mg doses of oral semaglutide may differ. While 7 mg is the maintenance dose of oral semaglutide recommended by Health Canada, superiority in A1C reduction was consistently observed across the PIONEER studies with the 14 mg dose rather than the 7 mg dose. Further the benefit of oral semaglutide on body weight was inconsistent across trials depending on dose and comparator. In general, superiority was demonstrated with semaglutide 14 mg with all comparators (except empagliflozin), but semaglutide 7 mg did not consistently show benefit.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason
Initiation	
1. As an add-on therapy for adults with type 2 diabetes in either of the following: • In addition to metformin in patients who do not achieve adequate glycemic control with metformin alone • In addition to other antihyperglycemic agents	Results of PIONEER 2, 3, 4, 5, and 8 demonstrated that oral semaglutide provided reductions in A1C level in addition to metformin or when added to a background therapy of 1 or 2 antihyperglycemic agents (including metformin, sulfonylureas, SGLT-2 inhibitors, and/or insulin).
Prescribing	
1. Oral semaglutide should not be used in combination with any other GLP-1 RA or with DPP-4 inhibitors.	Semaglutide has a shared mechanism of action with GLP1-RAs and DPP-4 inhibitors, and the effects of combining semaglutide with other GLP1-RAs or DPP-4 inhibitors are unlikely to have therapeutic benefit.
Pricing	
1. The drug plan cost of treatment with oral semaglutide should not exceed the drug plan cost of treatment with the least costly GLP-1 RA, DPP-4 inhibitor, or SGLT-2 inhibitor currently reimbursed for the treatment of T2DM.	The effect of oral semaglutide on A1C levels was noninferior to the GLP-1 RA liraglutide in PIONEER 4. In addition, there are no data demonstrating that oral semaglutide is a benefit for CV outcomes, as with some other GLP-1 RA and SGLT-2 inhibitors.

A1C = glycated hemoglobin ; CV = cardiovascular; DPP-4 = dipeptidyl peptidase-4; GLP-1 RA = glucagon-like peptide-1 receptor agonists; SGLT-2 = sodium-glucose cotransporter-2; T2DM = type 2 diabetes mellitus.

- Health-related quality of life was evaluated as an exploratory outcome in PIONEER 1 to 5 and 8 to 10 using a variety of generic and diabetes-specific scales. Overall, results were mixed regarding any potential benefit on health-related quality of life (HRQoL) with oral semaglutide compared to placebo or active comparators.
- There are numerous antihyperglycemic agents available for the treatment of T2DM, including 5 GLP-1 RAs. Semaglutide tablets are the first oral GLP-1 RA to be approved in Canada. However, semaglutide for subcutaneous (SC) injection has been available since 2018. The clinical expert described semaglutide tablets as an option for patients who are averse to injections; however, based on clinical experience, they could not describe a definitive benefit of oral semaglutide compared to SC semaglutide. It was noted that choice of treatment may be based on individual patient preferences as some patients may prefer a once-weekly as opposed to once-daily treatment. CDEC identified that a key evidence gap is the lack of comparative evidence for oral versus SC semaglutide formulations.
- There is uncertainty regarding benefits of oral semaglutide over the longer term in patients with T2DM. Primary and key secondary end points of the PIONEER trials were measured at 26 weeks, which is a short period of analysis for a chronic disease. Although this duration is sufficient to observe a treatment effect in terms of A1C and body weight, evidence for maintenance of effect is limited.

Background

Semaglutide has a Health Canada indication for use as an adjunct to diet and exercise to improve glycemic control in adults with T2DM, as monotherapy when metformin is considered inappropriate due to intolerance or contraindications, or in combination with other medicinal products for the treatment of diabetes. Semaglutide is a GLP-1 RA and is available as an oral tablet. The starting dose of oral semaglutide is 3 mg once daily. After 30 days, the dose should be increased to a maintenance dose of 7 mg once daily. If additional glycemic control is needed after at least 30 days on the 7 mg dose, the dose can be increased to a maintenance dose of 14 mg once daily.

Summary of Evidence

To make their recommendation, CDEC considered the following information:

- a systematic review of 9 randomized controlled trials in adult patients with T2DM
- patient perspectives gathered by 2 patient groups, Diabetes Canada (DC) and Type 2 Diabetes Experience Exchange (T2DXX)
- input from 1 clinical specialist with expertise diagnosing and treating patients with T2DM
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Summary of Patient Input

Two patient groups, DC and T2DXX, provided input for this submission. In the case of DC, patient perspectives were obtained from a series of online surveys, and T2DXXX obtained them through personal interviews and facilitated group discussions in their Experience Exchange forums and social media conversation threads. The following is a summary of key input from the perspective of the patient groups:

- Patients reported that the dealing with disease symptoms, monitoring and managing blood glucose levels and overall management of their diabetes required a high degree of self-management that represented a significant burden and a constant preoccupation. The stress of the disease and its potential complications was stated to be emotionally taxing for respondents, negatively influencing of social interactions, mental health, and, ultimately, the overall quality of life of patients.
- In several of the DC surveys some patients reported dissatisfaction with their current therapy citing side effects, difficulty with weight loss, and cost among the areas of concern.
- Patients expressed the desire for additional treatment options that would allow for individualized treatment. Patients hope that new treatments for T2DM will be safe, minimize side effects and damage to organs, improve overall health outcomes, and improve quality of life. Respondents reported a desire to reduce the pill burden associated with treatment, or to be off medication entirely; for treatments to help resume normal living, such as the ability to eat without restrictions; and for treatments to have with fewer unpleasant side effects. Some patients want treatments that are less physically invasive (i.e., do not require an injection) and can normalize or stabilize blood glucose levels, and improve A1C.

Clinical Trials

The systematic review included 9 randomized, parallel-group, multi-centre trials (PIONEER 1 to 6 and PIONEER 8 to 10). All included trials were double-blind except PIONEER 2 and 10, which were open-label and PIONEER 9, which was a combination of double-blind for semaglutide tablets and placebo, and open-label liraglutide. The trials evaluated the efficacy and safety of semaglutide tablets (3 mg, 7 mg, and 14 mg once daily) in adults with T2DM over 26 to 78 weeks of therapy. Although semaglutide 3 mg was evaluated as a maintenance dose in the trials and summarized as such, it is intended for use as a starting dose (for up to 30 days) as indicated in the product monograph. The trials were designed to assess semaglutide in comparison to a SGLT-2 inhibitor (empagliflozin, PIONEER 2), a DPP-4 inhibitor (sitagliptin, PIONEER 3), and subcutaneous GLP-1 RAs (liraglutide, PIONEER 4 and 9, and dulaglutide, PIONEER 10), as well as placebo (PIONEER 1, 4 to 6, 8, and 9). Of note, PIONEER 4 and 9 were both active- and placebo-controlled trials. Semaglutide was evaluated as monotherapy (PIONEER 1, 6 and 9), as an add-on to metformin (PIONEER 2), as an add-on to 1 to 2 OADs (PIONEER 3, 4, 10) or insulin with or without metformin (PIONEER 8). A total of 9,039 adult patients with T2DM were randomized in PIONEER 1 to 6 and 8 to 10. Across the PIONEER trials, 8% or less of patients discontinued from the studies, with the most common reasons being withdrawal by patient and lost to follow-up.

A key limitation of the included studies was that outcomes considered important to patients such as HRQoL, as well as lipid profile outcomes, and body mass index (BMI) were considered supportive and subject to type I error. Further, the demographic characteristics of patients may not adequately reflect the racial and ethnic diversity of Canadian patients.

Additionally, there was a lack of additional evidence for outcomes such as diabetes-related morbidity beyond the cardiovascular outcomes trial (PIONEER 6).

Outcomes

Outcomes were defined a priori in CADTH's systematic review protocol. Of these, CDEC discussed the following:

- Glycemic control was measured using a variety of measures in each of the included studies. For the purposes of this review, change from baseline in A1C (%) was reported. A1C was measured at every in-person study visit in the PIONEER trials, which typically occurred at week 0 (randomization), week 4, week 8, week 14, and then every 6 or 7 weeks until end of treatment.
- Mortality as an efficacy outcome was reported as all-cause deaths and CV-related deaths, which included undetermined cause of death (i.e., undetermined cause of death was assumed to be CV-related) and required adjudication by an event adjudication committee (EAC).
- Diabetes-related morbidity and mortality was assessed via the major adverse cardiovascular events (MACE) composite end point (defined as CV death, non-fatal myocardial infarction [MI], or non-fatal stroke) and an expanded MACE composite outcome, which included the same outcomes as the MACE in addition to unstable angina pectoris requiring hospitalization or heart failure requiring hospitalization. These outcomes were reported as the number of events and time to events.
- HRQoL was evaluated using a generic measure, the Short Form-36 version 2 (SF-36v2), 2 diabetes-specific measures, the Diabetes Treatment Satisfaction Questionnaire (DTSQ) and Diabetes Treatment Related-Quality of Life (DTR-QOL), and 2 generic or weight-management outcomes, the control of eating questionnaire (CoEQ) and the Impact of Weight on Quality of Life (IWQOL). Higher scores correspond to better health status, greater satisfaction with treatment, and improved quality of life for the SF-36v2, DTSQ, and DTR-QOL, respectively. The CoEQ is assessed using a visual analogue scale. For the IWQOL, a lower score indicates higher levels of functioning. Evidence of a minimal important difference (MID) was not identified for any of the HRQoL outcomes except the SF-36v2, for which a 1-point change was suggested for the MID for patients with T2DM, but the validity of this benchmark is unclear. Evidence of validity was identified for each of these outcomes except the CoEQ. The HRQoL outcomes were reported as a change from baseline to week 26 and end of study.

The change from baseline in A1C (%) at week 26 was the primary outcome in PIONEER 1 to 5, 8, and 9. In PIONEER 6, the primary outcome was time from randomization to first occurrence of a MACE, and in PIONEER 10 the primary outcome was the number of treatment emergent adverse events during exposure to treatment.

Efficacy

In active-controlled trials where semaglutide was evaluated as an add-on to 1 to 2 OADs, results of change from baseline in A1C at week 26 were as follows:

- SEM 14 mg was superior to empagliflozin with a between-group difference in A1C reduction of −0.4% (95% CI, −0.6 to −0.3, P < 0.0001) (PIONEER 2)

- SEM 14 mg and 7 mg were superior to sitagliptin with a between-group difference in A1C reduction of −0.3% (95% CI, −0.4 to −0.1, P < 0.0001) and −0.5% (95% CI, −0.6 to −0.4, P < 0.0001), respectively (PIONEER 3)
- SEM 3 mg failed to demonstrate non-inferiority to sitagliptin with a difference of 0.2% (95% CI, 0.1 to 0.3, P = 0.0856) in favour of sitagliptin (PIONEER 3)
- SEM 14 mg was noninferior to liraglutide 1.8 mg, the between-group difference in A1C reduction was −0.1% (95% CI, −0.3 to 0.0, P < 0.0001) (PIONEER 4).

When compared to placebo, semaglutide 3 mg, 7 mg, and 14 mg (unless otherwise noted) demonstrated superiority based on the following:

- a between-group difference in A1C reduction of −0.6% (95% CI, −0.8 to −0.4, P < 0.0001) to −1.1% (95% CI, −1.3 to −0.9, P < 0.0001) when used as monotherapy in treatment-naive patients (PIONEER 1)
- a between-group difference in A1C reduction of −0.8% (95% CI, −1.0 to −0.6, P < 0.0001) (SEM 14 mg only) as an add-on to metformin (MET) alone, a sulfonylurea (SU)
- with or without MET, and basal insulin with or without MET, in patients with moderate renal impairment (PIONEER 5)
- a between-group difference in A1C reduction of−0.5% (95% CI, −0.7 to −0.3, P < 0.0001) to −1.2% (95% CI, −1.4 to −1.0, P < 0.0001) as an add-on to insulin with or without MET (PIONEER 8)
- a between-group difference in A1C reduction of −1.1% (95% CI, −1.2 to −0.9, P < 0.0001) (SEM 14 mg only) as an add-on to MET with or without a SGLT2 inhibitor (PIONEER 4).

Additionally, between-groups differences ranging from −0.8% to −1.4% were reported for semaglutide 3 mg, 7 mg, and 14 mg compared to placebo, and 0.2% to −0.4% compared to liraglutide 0.9 mg in PIONEER 9. In PIONEER 10, between-groups differences ranging from 0.4% to −0.4% was reported for semaglutide 3 mg, 7 mg, and 14 mg compared to dulaglutide. The clinical expert indicated a reduction of 0.5% in A1C or achievement of A1C between 8 and 8.5% or lower was clinically meaningful, 1 of which was achieved by all treatment groups in the PIONEER studies.

In terms of a reduction in body weight from baseline to week 26, semaglutide as an add-on to 1-2 OADs in active-controlled trials:

- demonstrated superiority to sitagliptin with a between-groups difference of −1.6 kg (95% CI, −2.0 to −1.1, P < 0.0001) and −2.5 kg (95% CI, −3.0 to −2.0, P < 0.0001) for SEM 7 mg and 14 mg, respectively (PIONEER 3)
- demonstrated superiority to liraglutide with a between-groups difference of −1.2 kg (95% CI, −1.9 to −0.6, P = 0.0003) for SEM 14 mg (PIONEER 4)
- reported a between-groups difference of −0.6 kg (95% CI, −1.1 to −0.1, P = 0.02) for SEM 3 mg compared to sitagliptin (PIONEER 3); however, the analysis was conducted following a failure in the statistical testing hierarchy and therefore must be interpreted nominally
- reported a between-groups difference of −0.1 kg (95% CI, −0.7 to 0.5, P = 0.7593) for SEM 14 mg compared to empagliflozin, which corresponded to no difference in treatment effect (PIONEER 2).

In placebo-controlled trials, the change in body weight at week 26 was evaluated compared to placebo, where:

- SEM 14 mg demonstrated superiority as monotherapy in treatment-naive patients with a between-groups difference of −2.3 kg (95% CI, −3.1 to −1.5, P < 0.0001) compared to placebo (PIONEER 1)
- SEM 14 mg demonstrated superiority in patients with renal impairment with a between-groups difference of −2.5 kg (95% CI, −3.2 to −1.8, P < 0.0001) compared to placebo (PIONEER 5)
- SEM 3 mg, 7 mg, and 14 mg demonstrated superiority as an add-on to insulin with or without MET in patients with a between-groups difference of −0.9 kg (95% CI, −1.8 to −0.0, P = 0.0392), −2.0 kg (95% CI, −3.0 to −1.0, P < 0.0001), and −3.3 kg (95% CI, −4.2 to −2.3, P < 0.0001) (PIONEER 8)
- A between-groups difference of −0.1 kg (95% CI, −0.9 to 0.8, P = 0.87) for SEM 3 mg and 7 mg −0.9 (95% CI, −1.9 to 0.1, P = 0.09) did not demonstrate a difference in treatment effect (PIONEER 1).

The clinical expert consulted for this review suggested a change in weight of at least 2 kg over 26 weeks would be a meaningful change in clinical practice. This was achieved by patients treated with semaglutide 7 mg and 14 mg in PIONEER 1 to 8, and patients treated with semaglutide 14 mg in PIONEER 10. Of note, patients in PIONEER 9 and 10 weighed less at baseline compared to patients in PIONEER 1 to 6 and 8.

Mortality (as an efficacy outcome) and diabetes-related morbidity were only reported in PIONEER 6, and time from randomization to first EAC-confirmed MACE was the primary outcome in the trial. The hazard ratio for semaglutide 14 mg compared to placebo was 0.79 (95% CI, 0.57 to 1.11), therefore demonstrating non-inferiority by the pre-specified non-inferiority margin; however, the analysis for superiority was not confirmed. EAC-confirmed all-cause deaths were reported for 23 patients (1.4%) in the semaglutide 14 mg treatment group and 45 patients (2.8%) in the placebo treatment group of the cardiovascular outcome trial (CVOT). Ten of the 23 deaths in the semaglutide 14 mg treatment group, and 23 of the 45 deaths in the placebo treatment group were caused by CV events.

HRQoL was evaluated in PIONEER 1-5, and 8-10 using the SF-36v2, DTSQ, DTR-QOL, CoEQ, and the IWQOL. These outcomes were exploratory and measured as a change from baseline. Overall, semaglutide did not show benefit in terms of HRQoL when evaluated against active and placebo comparators.

Pre-specified subgroup analyses on the primary analysis in PIONEER 6 were conducted by: sex, age (younger than 65 years or 65 years or older), region, race, BMI, A1C (8.5% or less, greater than 8.5%), renal function (less than 60 mL/min/1.73m^2 or 60 mL/min/1.73m^2 or greater), and evidence of CV disease at screening. The treatment effect may be greater for patients that weight less (BMI of 30 or less), without a history of MI or stroke prior to randomization, and for patients exhibiting CV risk factors; however, the latter is limited by a wide confidence interval. Subgroup analyses by A1C, renal function or for patients with a BMI greater than 30, prior MI or stroke, and presence of CV disease do not appear to have a differential treatment effect. Subgroup analyses by background therapy on the change in A1C and body weight in PIONEER 3 and PIONEER 4 were also reported, and were consistent with the primary analysis.

Harms (Safety)

In the active-controlled trials, adverse events (AEs) were reported by 71% to 80% of patients treated with semaglutide, 70% to 83% of patients treated with active comparators (all:

empagliflozin, sitagliptin, liraglutide, and dulaglutide), and 67% of patients in the placebo group of PIONEER 4. In placebo-controlled trials, between 53 and 58% of patients in the semaglutide groups and 56% of patients in the placebo group of PIONEER 1 reported AEs. In PIONEER 5 and 8, between 74% and 83% of patients in semaglutide treatment groups and 65% to 76% of patients in the placebo treatment groups reported AEs. In PIONEER 9 and 10, between 71% and 85% of patients in semaglutide treatment groups, 67% to 82% of patients in the active comparator groups (liraglutide and dulaglutide), and 80% of patients in the placebo treatment group reported AEs. Overall AEs were not reported in PIONEER 6. In all studies, AEs were largely driven by gastrointestinal disorders: nausea, vomiting, and diarrhea in particular. In general, gastro-intestinal-related AEs were higher in patients treated with semaglutide compared to placebo, as well as active comparators with the exception of other GLP-1 RAs. Of note, feedback from patient groups indicated that GI upset was something patients disliked about current treatments for T2DM.

In PIONEER 1 to 5, and 8 to 10, serious adverse events (SAEs) were reported by 0% to 14% of patients across all treatment groups and the frequency of SAEs was similar between treatment groups in all trials. Serious AEs were a key focus of PIONEER 6; 18.9% and 22.5% of patients in the semaglutide 14 mg and placebo treatment groups, respectively, reported a SAE. Individual SAEs were infrequently reported. In PIONEER 1 to 5, and 8 to 10, withdrawal due to adverse events (WDAEs) ranged from 2% to 15% in semaglutide treatment groups, 0% to 9% of active comparator groups (empagliflozin, sitagliptin, and liraglutide), and 0% to 5% of placebo groups. Gastrointestinal disorders were the most commonly reported reasons for WDAEs in all studies. In PIONEER 6, 11.6% of patients in the semaglutide 14 mg treatment group and 6.5% of patients in the placebo treatment group permanently WDAE, with the most common reasons for WDAE attributed to gastrointestinal disorders.

Few deaths were reported in the PIONEER trials. A total of 16 deaths were reported in semaglutide treatment groups across PIONEER 1 to 5 and 8 to 10, 8 deaths were reported in active treatment groups (all), and 3 deaths were reported in placebo groups. No deaths were reported in PIONEER 1, 9, or 10. Deaths for PIONEER 6 were reported in the efficacy section under mortality outcomes.

Indirect Evidence

One sponsor-submitted indirect treatment comparison (ITC) was considered in the review of semaglutide. The ITC assessed change in A1C and change in body weight, explored through semaglutide as a second-line treatment added to metformin and through semaglutide as a third-line treatment added to metformin and a SU. Forty-three studies were included in network meta-analysis (NMA) for second-line therapies, with 10 of the trials compared to placebo. Nine studies were included in the network for third-line therapies with 1 of the trials compared to placebo. A Bayesian-based framework was used to conduct multiple network meta-analyses and both fixed and random-effects models were conducted with all models reporting the change from baseline for both outcomes. Analyses were conducted using a Markov Chain Monte Carlo (MCMC) method using the WINBUGS software package.

Overall, the results of the submitted ITC indicate semaglutide is likely better than placebo both as second- and third-line therapy and the results suggest potential superiority to other treatment classes, specifically SGLT-2 inhibitors, DPP-4 inhibitors, TZD, and SUs. However, the applicability of the sponsor's ITC is affected by the limited scope of the analysis and minimalistic analysis conducted. The ITC included an extensive systematic review, but was limited to only 2 outcomes, which significantly limited the utility and the robustness of the

results. Importantly, no exploration of baseline differences between studies was included. However, no conclusions can be made for efficacy or safety outcomes beyond glycemic reduction and weight loss since these outcomes were not evaluated.

Cost and Cost-Effectiveness

Semaglutide is available as 3 mg, 7 mg, and 14 mg tablets at a submitted price of $6.97 per tablet. The starting dose of oral semaglutide is 3 mg once daily, which should be increased to a maintenance dose of 7 mg once daily after 30 days. The dose can be increased to a maintenance dose of 14 mg once daily if additional glycemic control is needed. The annual cost of treatment is $2,543 per patient.

The sponsor submitted 2 cost-utility analyses (CUAs): 1 for oral semaglutide in combination with metformin as second-line treatment; and 1 for oral semaglutide in combination with metformin and a SU as third-line treatment. When considered as second-line treatment, oral semaglutide was compared with canagliflozin 300 mg, empagliflozin 25 mg, dapagliflozin 10 mg, liraglutide 1.8 mg, lixisenatide 20 mcg, dulaglutide 1.5 mg, injectable semaglutide 1.0 mg, SU, saxagliptin 5 mg, sitagliptin 100 mg, and linagliptin 5 mg. When considered as third-line treatment, oral semaglutide was compared with canagliflozin 300 mg, empagliflozin 25 mg, dapagliflozin 10 mg, and sitagliptin 100 mg. These CUAs were based on the Swedish Institute of Health Economics Diabetes Cohort Model, which captures important micro- and macrovascular complications associated with diabetes, the incidence of hypoglycemic events and the associated impact of complications and events on mortality. The model incorporates risk equations from a variety of sources. Data from PIONEER 2 and PIONEER 3 were used to inform baseline characteristics, while NMAs incorporating data from PIONEER 2, PIONEER 3 and PIONEER 4 were used to inform the comparative effectiveness for oral semaglutide with the included comparators in each line of therapy. The sponsor reported that oral semaglutide was associated with an incremental cost-effectiveness ratio of $29,000 per quality-adjusted life-year compared to canagliflozin 300 mg when used as second-line treatment, and was dominant (i.e., less costly and more effective) than all third-line treatments.

CADTH identified limitations with the submitted economic evaluation. The sponsor's model uses predictive risk equations based on surrogate outcomes (A1C and BMI) to predict morbidity and mortality outcomes. The outcomes predicted by the model suggest that oral semaglutide has CV and mortality benefits compared with several treatments, including those that have a Health Canada indication to reduce the incidence of CV death in patients with T2DM, which oral semaglutide does not currently have. In addition to this limitation, CADTH noted limitations with the sponsor-submitted NMAs, application of utility values, and transparency of the model. Furthermore, the CADTH clinical review concluded that based on the currently available evidence, there was no strong evidence to suggest a quality of life benefit for oral semaglutide compared to other antidiabetic treatments. After considering the totality of the limitations, CADTH determined the output of the sponsor's model to be uncertain. CADTH noted that a key driver of the model was an assumption of a disutility due to the route of administration for weekly injectable treatment, compared with daily oral treatments.

At a submitted price of $6.97 per tablet (daily cost of $6.97), oral semaglutide is more costly than all SGLT-2 based products ($2.45 to $3.24), DPP-4 based products ($2.20 to $3.47), and some GLP-1 RAs, depending on dose ($3.55 to $9.34).

CDEC Members

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.

Meeting date: April 21, 2021

Regrets: One expert committee member did not attend.

Conflicts of interest: None