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CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

Semaglutide (Ozempic)

(Novo Nordisk Canada Inc.)

Indication: For the treatment of adults patients with type 2 diabetes mellitus to improve glycemic control, in combination with metformin (second-line treatment), and in combination with metformin and sulfonylurea (third-line treatment).

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Table of Contents

Tables

Figure

Abbreviations

BMI	body mass index
CDR	CADTH Common Drug Review
CHF	congestive heart failure
DBP	diastolic blood pressure
DPP-4	dipeptidyl peptidase-4
eGFR	estimated glomerular filtration rate
ER	extended release
GLP-1	glucagon-like peptide-1
A1C	glycated hemoglobin
HDL	high-density lipoprotein
HR	heart rate
ICER	incremental cost-effectiveness ratio
ICUR	incremental cost-utility ratio
IHE	Institute for Health Economics
LDL	low-density lipoprotein
MI	myocardial infarction
NI	not included
NMA	network meta-analysis
OAD	oral antidiabetic drug
PE	pharmacoeconomic
QALY	quality-adjusted life-year
RA	receptor agonist
SBP	systolic blood pressure
SE	standard error
SGLT2	sodium-glucose cotransporter-2
SMC	Scottish Medicines Consortium
SU	sulfonylurea
TC	total cholesterol
UKPDS	United Kingdom Prospective Diabetes Study
WBC	white blood cell

Table 1: Summary of the Manufacturer's Economic Submission

Drug Product	Semaglutide (Ozempic)
Study Question	Is semaglutide cost-effective compared with available treatments for type 2 diabetes mellitus in adults who are unable to achieve glycemic control with metformin alone or with metformin and sulfonylurea?
Type of Economic Evaluation	Cost-utility analysis
Target Population	• Patients who have not achieved adequate glycemic control with metformin alone (second-line treatment) • Patients who have not achieved adequate glycemic control with metformin in combination with sulfonylurea (third-line treatment)
Treatment	Semaglutide 0.5 mg/week in combination with metformin alone or with metformin and sulfonylurea Semaglutide 1 mg/week in combination with metformin alone or with metformin and sulfonylurea
Outcome	Quality-adjusted life-years (QALYs)
Comparators	Second-line treatment (all in combination with metformin) • Dulaglutide 1.5 mg/week, Exenatide extended release (ER) 2.0 mg/week, Liraglutide 1.2 mg/day, Liraglutide 1.8 mg/day, Lixisenatide 20 mcg/day, Sitagliptin 100 mg/day, Insulin glargine 0.53 IU/kg /day, Canagliflozin 300 mg/day, Dapagliflozin 10 mg/day, Empagliflozin 25 mg/day, Glyburide 15 mg/day Third-line treatment (all in combination with metformin and sulfonylurea) • Dulaglutide 1.5 mg/week, Exenatide ER 2.0 mg/week, Liraglutide 1.2 mg/day, Liraglutide 1.8 mg/day, Lixisenatide 20 mcg/day, Sitagliptin 100 mg/day, Insulin glargine 0.53 IU/kg/day, Canagliflozin 300 mg/day, Dapagliflozin 10 mg/day, Empagliflozin 25 mg/day
Perspective	Health care system perspective
Time Horizon	40 years (assumed to be close to lifetime)
Results for Base Case	• For both second- and third-line treatments, canagliflozin and semaglutide 1 mg resulted in highest QALYs and dominated all other treatments. • For second-line treatment, compared with glyburide (least costly treatment), the ICER for canagliflozin was $10,827, and ICER for semaglutide 1 mg versus canagliflozin was $714,488. • For third-line treatment, compared with canagliflozin (least costly treatment), the ICER for semaglutide 1 mg was $136,653.
Key Limitations	• The submitted model is non-transparent and there are conceptual problems in how disease progression with diabetes is modelled. • There are several issues with the clinical evidence with respect to the nature of the evidence; moreover, separate network meta-analyses (NMAs) were conducted for different outcomes rather than a single comprehensive NMA and the NMA did not cover all relevant outcomes which may bias the results. • The clinical review has raised significant concerns with respect to the appropriateness of the patient population within the NMAs which were used for the analysis of third-line treatment.
CDR Estimate(s)	• Given the lack of a comprehensive NMA and the selective choice of outcomes, the comparative clinical benefits of semaglutide compared with relevant compactors is uncertain. • With the lack of transparency and validity of the submitted model, it was not possible to conduct reanalyses that provide a suitable basis to answer the decision problem. • Semaglutide is more expensive than all treatment options, with the exception of liraglutide 1.8 mg/day. To justify a price greater than currently reimbursed second-line treatments, more robust information on cost-effectiveness is required.

Drug	Semaglutide (Ozempic)
Indication	The once-weekly treatment of adult patients with type 2 diabetes mellitus to improve glycemic control, in combination with: • Diet and exercise in patients for whom metformin is inappropriate due to contraindication or intolerance. • Metformin, when diet and exercise plus maximal tolerated dose of metformin do not achieve adequate glycemic control. • Metformin and a sulfonylurea, when diet and exercise plus dual therapy with metformin and a sulfonylurea do not achieve adequate glycemic control. • Basal insulin with metformin, when diet and exercise plus basal insulin with metformin do not achieve adequate glycemic control.
Reimbursement Request	• In combination with metformin for patients who have not achieved adequate glycemic control with metformin alone (second-line treatment). • In combination with metformin plus sulfonylurea for patients who have not achieved adequate glycemic control with metformin in combination with sulfonylurea (third-line treatment).
Dosage Form(s)	0.5 mg once weekly injection 1 mg once weekly injection
NOC Date	January 4, 2018
Manufacturer	Novo Nordisk Canada Inc.

Executive Summary

Background

Semaglutide is a once-weekly glucagon-like peptide-1 (GLP-1) receptor agonist injection, indicated for the treatment of adult patients with type 2 diabetes mellitus to improve glycemic control.[1] The manufacturer is seeking reimbursement of semaglutide: in patients with type 2 diabetes mellitus either in combination with metformin for patients who have not achieved adequate glycemic control with metformin alone (second-line treatment), or in combination with metformin plus sulfonylurea for patients who have not achieved adequate glycemic control with metformin in combination with sulfonylurea (third-line treatment).[2] The starting dose of semaglutide is 0.25 mg once weekly. After four weeks, the dose should be increased to 0.5 mg once weekly. After an additional week, the dose can be increased to 1 mg once weekly.

The manufacturer submitted a cost-utility analysis over a 40-year time horizon (the manufacturer suggests that this is essentially a lifetime 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 plus sulfonylurea (third-line treatment). The second-line treatment analysis compared both semaglutide 0.5 mg/week and 1 mg/week doses to dulaglutide 1.5 mg/ week, exenatide extended release (ER) 2.0 mg/week, liraglutide 1.2 mg/day, liraglutide 1.8 mg/day, lixisenatide 20 mcg/day, sitagliptin 100 mg/ day, insulin glargine 0.53 IU/kg/day, canagliflozin 300 mg/day, dapagliflozin 10 mg/day, empagliflozin 25 mg/day, and glyburide 15 mg/day. For third-line treatment, the same comparators are included with the exception of glyburide. The model incorporates a variety of health states relating to the important microvascular and macrovascular

complications associated with diabetes, the incidence of hypoglycemic events, and the associated impact of complications and events on mortality. Within the model, the annual probability of major diabetes-related macrovascular complications is derived from risk equations based on the United Kingdom Prospective Diabetes Study (UKPDS 82) study which is consistent with previous CADTH reports.[3,4] Microvascular complications are modelled based on previously published studies.[5,6] The risk of each complication is a function of a range of predictors including biomarkers such as glycated hemoglobin (A1C), systolic blood pressure (SBP), and low-density lipoprotein (LDL).

The clinical evidence base was focused on the SUSTAIN trial program, which comprised seven trials involving more than 8,000 patients. For the economic submission, the key trials were SUSTAIN-2 (versus sitagliptin), SUSTAIN-3 (versus exenatide ER), SUSTAIN-4 (versus insulin glargine), and SUSTAIN-7 (versus dulaglutide).[7-10] Trial duration varied from 30 weeks (SUSTAIN-4) to 56 weeks (SUSTAIN-2 and SUSTAIN-3). For SUSTAIN-2, 3, and 4 post-hoc subgroup analyses were conducted for second- and third-line treatment which were the principle analyses used to inform the economic model. In addition to the clinical trials, the manufacturer submitted five separate network meta-analyses (NMAs) to compare semaglutide to: other GLP-1 receptor agonists and sitagliptin as add-ons to one oral antidiabetic drug (OAD): sodium-glucose cotransporter-2 (SGL2) inhibitors as add-ons to one OAD; sulfonylurea as an add on to metformin; other GLP-1 receptor agonists and sitagliptin as add-ons to one or two OADs; and SGL2 inhibitors as add-ons to one or two OADs.[11-15]

The model incorporates the costs of treatment, which is obtained from reliable Canadian sources.[16] The costs of macrovascular complications are consistent with the previous CADTH therapeutic review.[4] The costs relating to microvascular complications are primarily based on US data, which is not appropriate.[17] Utility values were a function of age, gender, duration of disease, and body mass index (BMI),[18] and disutilities were applied for the prevalence of each of the modelled diabetes-related complications.[4,6]

For second-line treatment, the manufacturer reported that glyburide, canagliflozin, and semaglutide 1 mg were associated with higher quality-adjusted life-years (QALYs) and lower costs compared with other treatments – i.e. other treatments were dominated. The manufacturer reported the incremental cost per QALY gained (incremental cost-effectiveness ratio [ICER]) for canagliflozin versus glyburide was $10,827, and the ICUR for semaglutide 1 mg versus canagliflozin was $714,488. The manufacturer suggested that if semaglutide was lowered in price by 33%, the incremental cost-effectiveness ratio versus canagliflozin would be $50,000.

For third-line treatment, the manufacturer reported that canagliflozin and semaglutide 1 mg were associated with higher QALYs and lower costs compared with other treatments. The manufacturer reported that the ICUR for semaglutide 1 mg versus canagliflozin was $136,653. The manufacturer suggested that if semaglutide was lowered in price by 28%, the ICER versus canagliflozin would be $50,000.

Summary of Identified Limitations and Key Results

There were a number of major concerns with the analysis provided.

A major concern is the clinical data used to inform the economic model. A comprehensive NMA incorporating all treatment options and all clinical outcomes is required to fully assess the relative effectiveness of each treatment option considered. This was requested from the

manufacturer, but the manufacturer responded that including different classes of treatment would increase heterogeneity and that the comparators were not necessarily appropriate. This lack of a comprehensive NMA leads to inconsistency in the evidence for the various treatment options. For example, instead of providing a single NMA comparing all second-line treatments, three separate network meta-analyses were provided; covering different groups of second-line treatment. For certain treatments, data from single clinical trials were used, whereas for other treatments data from the NMA were used. Thus, a consistent base comparator is not available across the analyses and comparisons are de facto, based on naive indirect comparisons that are inappropriate. Furthermore, the range of clinical parameters incorporated varies by treatment. For some treatments, just A1C and BMI were used, while for other treatments A1C, BMI, and SBP, or A1C, BMI, SBP, diastolic blood pressure (DBP), total cholesterol (TC), LDL, high-density lipoprotein (HDL), triglycerides (TG), heart rate (HR), white blood cell count (WBC), and estimated glomerular filtration rate (eGFR) were used. In conclusion, the approach taken to modelling clinical effectiveness is not appropriate and likely leads to a degree of bias being introduced to the analysis, Hence, no reliable conclusions can be drawn from the submitted analysis.

The CADTH clinical review team found that the NMAs that were used for the economic analysis relating to third-line treatment were not representative of the patient population, as the study populations were not specific to patients who were not adequately controlled on metformin and sulfonylurea, and were therefore inappropriate for this analysis.

A further concern with respect to clinical effectiveness is that the analysis assumes no difference in hypoglycemia events between OADs except with insulin glargine, for which there was assumed to be greater rates of non-severe and severe hypoglycemic events. This is contrary to the values reported by the manufacturer in its economic submission (which were derived by the manufacturer from the SUSTAIN-4 trial).[19] The manufacturer reported a greater, though non-significant, rate of severe hypoglycemic events for semaglutide 1 mg versus insulin glargine.[9] The manufacturer assumed that patients treated with insulin after OAD would have a higher rate of hypoglycemic events if they were previously treated with insulin glargine compared with other OADs. CADTH requested a basis for this assumption. The evidence provided by the manufacturer involved a comparison of insulin-naive and insulin-experienced patients; however, those who were insulin-experienced need not have received insulin glargine. Thus, the appropriateness of this assumption is questionable.[20]

The manufacturer includes a disutility associated with BMI. A utility loss of 0.006 is applied for every additional BMI over 25. However, the basis for this assumption is questionable. The CADTH therapeutic review in this area has assumed no direct effect of BMI on utility.[4] It stated that “most widely cited studies derive such estimates [utility decrements] from much larger weight differences (i.e., 13 kg to 30 kg), and it is unclear whether these can be applied in a proportional manner to the smaller weight differences between drugs observed in the NMA of second-line therapies.”

The manufacturer contends that a cohort model for diabetes is preferred to the commonly adopted microsimulation models used in this disease area. This approach resulted in a model that was not fit for purpose in this context. In addition, the model lacks transparency, as data within the Excel model are hard coded with results generated by a series of Visual Basic macros. Verification of this code was not possible, and there were concerns given the inconsistency of results provided by the manufacturer. Furthermore, the cohort model does not accurately reflect the variability in disease progression and treatment response across the cohort, and requires the assumption of a linear relationship between biomarkers and

outcomes, although the risk equations adopted in the model suggest a non-linear relationship between biomarkers and the probability of events. Furthermore, modelling a fixed biomarker level for the entire patient population within the cohort rather than a variable level of biomarker across the population, ignores the impact of higher prevalence of complications in those at higher risk.

Given the above concerns, CADTH concluded that the model and analysis submitted by the manufacturer were not a suitable basis to assess the cost-effectiveness of semaglutide in this context. For this reason, no reanalysis was conducted.

Conclusions

The manufacturer's analysis suggests that the price of semaglutide 1 mg would need to be significantly reduced for semaglutide to be considered cost-effective (by at least 28% to 55%, based on the manufacturer's analysis).

CADTH noted significant limitations with the submitted economic analysis, and, as such, concluded that the model was not an appropriate basis to assess the cost-effectiveness of semaglutide in this context. Based on the clinical evidence provided, a conclusion could be reached that semaglutide appears to be at least as effective as other currently reimbursed second- and third-line OADs.

Information on the Pharmacoeconomic Submission

Summary of the Manufacturer's Pharmacoeconomic Submission

The manufacturer has submitted a cost-utility analysis over a 40-year time horizon (the manufacturer suggests that this is essentially a lifetime horizon, given that the average age of patients within the SUSTAIN trial program was 55). Analysis is conducted from the perspective of a Canadian public health care payer with long-term costs and outcomes discounted at 1.5% per annum. Analysis is 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 sulfonylurea (third-line treatment). For second-line treatment, the analysis compares both semaglutide 0.5 mg/week and 1 mg/week doses to GLP-1 receptor agonists (dulaglutide 1.5 mg/ week, exenatide extended release (ER) 2.0 mg/week, liraglutide 1.2 mg/day, liraglutide 1.8 mg/day, and lixisenatide 20 mcg/day); a dipeptidyl peptidase-4 (DPP-4) inhibitor (sitagliptin 100 mg/ day); insulin glargine 0.53 IU/kg/day; sodium-glucose cotransporter-2 (SGLT2) inhibitors (canagliflozin 300 mg/day, dapagliflozin 10 mg/day, and empagliflozin 25 mg/day); and glyburide 15 mg/day. For third-line treatment, the same comparators are included with the exception of glyburide.

The submission is based on the Institute for Health Economics (IHE) Cohort Model for Type 2 Diabetes; purportedly a Markov model within an Excel workbook.[21] However, the model is different from traditional Excel-based models. The progression of the cohort is hard coded as it is inputted through a series of Visual Basic macros that precludes examination of how patients move from state to state. Although a Markov trace for each treatment comparator is provided, the information is hard coded so it is not possible to follow how patients transition from one state to another. Furthermore, individuals do not transition from one state to another – instead, the model estimates the percentage of the cohort with different diabetes-related complications. Thus, there is not a finite list of potential health states, but rather a list of health states for each complication that are modelled, unconditional of other complications.

The model covers the important microvascular and macrovascular complications associated with diabetes, the incidence of hypoglycemic events, and the associated impact of complications and events on mortality. Microvascular complications incorporated into the model are: retinopathy (background diabetic retinopathy, macular edema, proliferative diabetic retinopathy, and severe visual loss); neuropathy (symptomatic neuropathy, peripheral vascular disease, and lower extremity amputation); and nephropathy (microalbuminuria, macroalbuminuria, and end-stage renal disease). Macrovascular complications that are included in the model are: ischemic heart disease (IHD), myocardial infarction (MI) (first and subsequent MI), stroke (first and subsequent strokes), and congestive heart failure (CHF).

Within the model, the annual probability of major diabetes-related macrovascular complications is derived from risk equations based on the United Kingdom Prospective Diabetes Study (UKPDS 82) study which is consistent with previous CADTH reports.[3,4] Thus, the risk of each complication is a function of a range of predictors including biomarkers such as glycated hemoglobin (A1C), systolic blood pressure (SBP), low-density

lipoprotein (LDL), high-density lipoprotein (HDL), and estimated glomerular filtration rate (eGFR), and as a function of other complications. The risk equations provide estimates of the probability of developing IHD and CHF and the probability of first and subsequent MIs and strokes. Microvascular complications are modelled based on previously published studies.[5,22] Probabilities relating to the progression of retinopathy and nephropathy are derived from the Eastman model of diabetes and are primarily a function of duration of diabetes and A1C.[5] Probabilities relating to progression of neuropathy are derived from both the Eastman and Bagust models of diabetes and are primarily a function of duration of diabetes, sex, and A1C.[5,22]

To model the impact of treatment on preventing complications within the models, given the absence of data relating to the impact of treatments on patient-related outcomes such as complications, quality of life, and mortality, it is necessary to rely on indirect evidence relating to the effects of treatment on the biomarkers that impact the probability of complications. From this, the model predicts the impact of treatment on patient-related outcomes. The manufacturer conducted a number of network meta-analyses (NMAs) purportedly relating to second- and third-line treatment. [11-15] For second-line treatment, NMAs were conducted for glucagon-like peptide-1 (GLP-1) receptor agonists (RAs) (and sitagliptin) versus semaglutide, SGLT2s versus semaglutide, and glyburide versus semaglutide. For third-line treatment, the NMAs related to GLP-1 RAs versus semaglutide and SGLT2s versus semaglutide.

Given the reliance on separate NMAs rather than comprehensive analyses, the source of clinical effects varies across treatments. For example, for the second-line treatment analysis, the effects for liraglutide and lixisenatide were derived from the NMA involving GLP-1 RAs; for canagliflozin, empagliflozin, dapagliflozin, and semaglutide 1 mg, they were derived from the SGLT2 NMA; and for glyburide and semaglutide 0.5 mg, they were derived from the glyburide NMA. Furthermore, for dulaglutide, exenatide ER, sitagliptin, and insulin glargine, the effects were derived from the single-arm results from the relevant SUSTAIN trials.[7-10] This derivation leads to different biomarkers being modelled for different treatments (e.g., the effect on SBP is modelled for some treatments but not all). Treatment is assumed to be given over a three-year period, after which patients are treated with insulin; biomarkers are assumed to return to either the previous level or close to that level. In the original submission, for second-line treatment, for all oral antidiabetic drugs (OADs) other than semaglutide 1 mg, A1C levels returned to 8.0. For semaglutide 1 mg, A1C returned to 7.93 after three years of treatment. No basis for this difference was provided and the manufacturer was requested to resubmit an analysis with similar assumptions for all OADs.

The manufacturer assumed no difference in hypoglycemic events between OADs except with insulin glargine, for which there were assumed to be greater rates of non-severe and severe hypoglycemic events. It was also assumed that patients treated with insulin after OAD would have different rates of hypoglycemic events depending on the OAD they received. Those previously treated with insulin glargine were assumed to have higher rates than those previously treated with other OADs.

The costs of treatment were obtained from the manufacturer (Novo Nordisk Canada Inc.), from McKesson Canada, and from the Ontario Drug Benefit Formulary.[16] Initial analysis provided by the manufacturer included the costs of prescription fees and markup and excluded the costs of metformin. This was rectified in a further analysis. Analysis incorporated the costs of complications. The costs related to macrovascular complications were consistent with a previous CADTH therapeutic review.[4] The costs related to

microvascular complications were obtained from a US study and converted to Canadian dollars.[17] Utility values within the model were based on an estimated utility value for a diabetic patient that was a function of age, gender, duration of disease, and body mass index (BMI), based on a previous analysis by Currie.[18] From here, disutilities were applied for each of the modelled diabetes-related complications.[4,6] The disutilities applied were consistent with previously used estimates.

Input parameters used in the model were assumed to be uncertain; where data on the uncertainty of parameters were unavailable it was assumed that the standard error was equivalent to 25% of the mean. Expected values of outcomes and costs associated with each treatment were obtained from randomly sampling parameter values 1,000 times.

Manufacturer's Base Case

Original Submission

For second-line treatment, in their original submission, the manufacturer reported that all therapies were subject to dominance (i.e., had higher costs and lower quality-adjusted life-years [QALYs]), other than glyburide, canagliflozin, and semaglutide 1 mg. The manufacturer reported the incremental cost per QALY gained (incremental cost-effectiveness ratio [ICER]) for canagliflozin versus glyburide (the least costly treatment) was $10,827, and the ICER for semaglutide 1 mg versus canagliflozin was $714,488. The manufacturer suggested that if semaglutide was lowered in price by 33%, the ICER versus canagliflozin would be $50,000. Furthermore, if the net price of canagliflozin was 50% of the list price, the price of semaglutide would need to be reduced by 53% for the ICER to be $50,000.

Note that the original submission involved two separate models for second-line treatment: one comparing semaglutide 1 mg to glyburide, canagliflozin, sitagliptin, lixisenatide, insulin glargine, and semaglutide 0.5 mg; while the other compared semaglutide 1 mg to empagliflozin, dapagliflozin, exenatide ER, dulaglutide, liraglutide 1.2 mg, and liraglutide 1.8 mg. Thus, a full sequential analysis comparing all treatments was not provided.

Table 2: Summary of Manufacturer's Base Case (Second-Line) — Original Submission

	Total Costs ($)	Total QALYs	ICER vs. Glyburide ($)	Sequential ICER ($)
Glyburide	121,992	12.245	–	–
Canagliflozin	123,398	12.375	10,827	10,827
Semaglutide 1.0 mg	126,483	12.379	33,461	714,488
Semaglutide 0.5 mg	129,650	12.310	118,678	Not provided

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Source: Manufacturer's Pharmacoeconomic Submission.[19]

For third-line treatment, the manufacturer reported in their original submission that all therapies were subject to dominance other than canagliflozin and semaglutide 1 mg. The manufacturer reported that the ICER for semaglutide 1 mg versus canagliflozin was $136,653. The manufacturer suggested that if semaglutide was lowered in price by 28%, the ICER versus canagliflozin would be $50,000. Furthermore, if the net price of canagliflozin was 50% of the list price, the price of semaglutide would need to be reduced by 55% for the ICER to be $50,000.

Note that the original submission involved two separate models for third-line treatment: one comparing semaglutide 1 mg to canagliflozin, sitagliptin, lixisenatide, liraglutide 1.2 mg, insulin glargine, and semaglutide 0.5 mg; while the other compared semaglutide 1 mg to empagliflozin, dapagliflozin, exenatide ER, dulaglutide, and liraglutide 1.8 mg. Thus, a full sequential analysis comparing all treatments was not provided.

Table 3: Summary of Manufacturer's Base Case (Third-Line) — Original Submission

	Total Costs ($)	Total QALYs	ICER vs. Canagliflozin ($)	Sequential ICER ($)
Canagliflozin	104,991	11.675	–	–
Semaglutide 1.0 mg	109,872	11.711	136,653	136,653
Semaglutide 0.5 mg	110,034	11.670	Dominated	Not provided

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Source: Manufacturer's Pharmacoeconomic Submission.[19]

Revised Submission

The manufacturer was requested to provide a revised submission.[23] The request related to removing the discrepancy on the effect of treatment at three years on A1C (second-line treatment only), incorporating the costs of metformin including combination therapies if cheaper, excluding prescription fees and markup, providing a full sequential analysis of all treatments and providing a rationale for not basing clinical effectiveness results on a comprehensive NMA incorporating all OADs. The manufacturer provided a reanalysis that addressed all of these concerns but did not provide a comprehensive NMA.

Given the requests that were incorporated, the CADTH reviewers expected that for third-line treatment, the costs of treatment would be different from that in the original submission for all comparators, but that the QALYs gained would be similar to the original submission. For second-line treatment there were similar expectations. It was expected that for semaglutide 1 mg, the requested change would reduce the QALYs gained relative to other OADs. However, in the revised submission for second-line treatment, costs for all OADs were lower than in the original submission and QALYs for all OADs were higher. The incremental QALY gain for semaglutide 1 mg increased from 0.004 to 0.017. Again, all therapies were subject to dominance other than glyburide, canagliflozin, and semaglutide 1 mg. The ICER for canagliflozin versus glyburide was $9,316 (compared with $10,827 in the original submission) and the ICER for semaglutide 1 mg versus canagliflozin was $245,441 (compared with $714,488 previously).

The manufacturer was asked to explain the results given that they were contrary to the expectations of the reviewer. The manufacturer responded as follows:

"The pharmacoeconomic reviewers are indeed correct that the changes requested by the reviewers on January 25, 2019 should not lead to changes in the QALYs in any other treatment arm aside from the semaglutide 1.0 mg arm where the post-treatment A1C value was to be adjusted.

The reason for the apparent impact on other treatment arms is that the original reference case model files submitted on November 23, 2018 contained results of a simulation where the hypoglycemia rates were incorrect. The actual hypoglycemia rates inputted in the input sheets are correct, but the output had not run on the correct inputs. If another simulation had

been performed, the correct set of outputs based on the inputs in the input sheets would have resulted."

Based on this response, and on the increasing concerns from the PE reviewer regarding the validity of the analysis, the manufacturer was requested to confirm the hypoglycemic rates that were used in the analysis as reported in the original submission, and to provide a justification for the changes made to the rates of hypoglycemia.

Table 4: Summary of Results of the Manufacturer's Base Case (Second-Line) — First Revised Submission

	Total Costs ($)	Total QALYs	ICER vs. Glyburide	Sequential ICER
Glyburide	108,765	12.326	–	–
Canagliflozin	109,962	12.455	9,316	9,316
Semaglutide 1.0 mg	114,227	12.472	37,458	245,441
Semaglutide 0.5 mg	115,469	12.400	90,997	Dominated by canagliflozin, empagliflozin, dapagliflozin, exenatide ER, semaglutide 1.0 mg, and dulaglutide.

ER = extended release; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Source: Manufacturer provided additional information.[23]

For third-line treatment, similar to second-line treatment, costs for all OADs were lower in the revised submission than in the original submission, and QALYs for all OADs were higher. As previously, all therapies were subject to dominance other than canagliflozin and semaglutide 1 mg. The ICER for semaglutide 1 mg versus canagliflozin was $95,452 (compared with $136,653 previously).

Table 5: Summary of Results of the Manufacturer's Base Case (Third-Line) — First Revised Submission

	Total Costs ($)	Total QALYs	ICER vs. Canagliflozin	Sequential ICER
Canagliflozin	93,228	11.709	–	–
Semaglutide 1.0 mg	97,367	11.752	95,452	95,452
Semaglutide 0.5 mg	97,704	11.709	Dominated	Dominated by canagliflozin and semaglutide 1.0 mg.

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Note: No price reduction scenarios were provided for the revised analysis.

Source: Manufacturer provided additional information.[23]

Summary of Manufacturer's Sensitivity Analyses

For both second- and third-line treatment, the only scenario analyses provided relate to the assumed price of semaglutide 1 mg and canagliflozin. These threshold analyses were provided only for the original submission and the results are detailed above. However, the manufacturer has subsequently stated that the original submission results are erroneous.

Limitations of Manufacturer's Submission

There were a number of major concerns with the analysis provided. There were fundamental concerns relating to the clinical evidence that formed the basis for estimating the incremental effects of OADs and the model used within the analysis. These are addressed in detail below.

Specific concerns with data employed in the model were as follows:

- In the model, the benefit of an OAD is provided through reduction of A1C level, though much of that benefit is lost after treatment is curtailed at three years. In the original submission for second-line treatment, for all OADs other than semaglutide 1 mg, A1C levels returned to 8.0%. For semaglutide 1 mg, A1C returned to 7.93% after three years of treatment. No basis for this difference was provided. After a request, the manufacturer did provide a revised analysis removing this anomaly. However, as described above, the results of this analysis were not as expected.
- A further concern with respect to clinical effectiveness is that the model assumes no difference in hypoglycemia events between OADs except with insulin glargine, for which there was assumed to be greater rates of non-severe and severe hypoglycemic events. This is contrary to the values reported by the manufacturer in their economic submission (which were derived by the manufacturer from the SUSTAIN-4 trial).[19] The manufacturer reported a greater, though non-significant, rate of severe hypoglycemic events for semaglutide 1 mg versus insulin glargine [9]. A more relevant analysis would incorporate hypoglycemic events within a comprehensive NMA. The model also assumed patients treated with insulin after OAD would have a higher rate of hypoglycemic events if they were previously treated with insulin glargine compared with other OADs. The manufacturer subsequently provided a published paper comparing hypoglycemic rates for those who are insulin-experienced and those who are insulin-naive [20]. However, the relevance of this paper is questionable as 'insulin experience' was not limited to those receiving insulin glargine.
- The manufacturer includes a disutility associated with BMI. A utility loss of 0.006 is applied for every additional unit of BMI greater than 25. A previous CADTH therapeutic review assumed no direct effect of BMI on utility[4]. It stated: "A utility decrement for weight gain in the primary economic analysis was not applied. Most widely cited studies derive such estimates from much larger weight differences (i.e., 13 kg to 30 kg), and it is unclear whether these can be applied in a proportional manner to the smaller weight differences between drugs observed in the NMA of second-line therapies." It is unclear in any final analysis what the impact of removing this assumption would be on the results.
- In the original submission, estimated costs included prescription fees and markup and excluded the costs of metformin. CADTH requires exclusion of fees and markup. Furthermore, for certain OADs, combination products with metformin are available and in one instance (empagliflozin) the combination product is cheaper than the constituent parts. Thus analysis should reflect this. This was rectified in the revised analysis provided by the manufacturer.

A major concern is the clinical data provided. The manufacturer conducted a number of NMAs purportedly relating to second- and third-line treatment. [11-15] For second-line treatment, NMAs were conducted for GLP-1 RAs versus semaglutide, SGLT2s versus semaglutide, and glyburide versus semaglutide. For third-line treatment, NMAs were conducted for GLP-1 RAs versus semaglutide and SGLT2s versus semaglutide. However, a comprehensive NMA incorporating all treatment options and all clinical outcomes is required

to fully assess the relative effectiveness of each treatment option considered. This was requested from the manufacturer but the manufacturer declined this request. They argued that a larger network may introduce bias and increase heterogeneity and would involve comparing treatments that are not directly of interest to the decision problem as recommended by the National Institute for Health and Care Excellence (NICE) Decision Support Unit. However, this is not the case here, as the manufacturer clearly compares all treatments concurrently within the economic analysis which emphasizes the need for all treatments to be compared concurrently within an NMA.

Without a comprehensive NMA, the evidence for the various treatments is inconsistent. For example, for the second-line treatment analysis, the effects for liraglutide and lixisenatide were derived from the NMA involving GLP-1 RAs; while for canagliflozin, empagliflozin, dapagliflozin, and semaglutide 1 mg the effects were derived from the SGLT2 NMA. For glyburide and semaglutide 0.5 mg the effects were derived from the glyburide NMA. Furthermore, for dulaglutide, exenatide ER, sitagliptin, and insulin glargine, the effects were not derived from NMAs but from the single-arm results from the SUSTAIN trials. This leads to different outcomes being modelled for different treatments: for liraglutide, lixisenatide, glyburide, and semaglutide 0.5 mg the model incorporates effects on A1C and BMI only; for canagliflozin, empagliflozin, dapagliflozin, and semaglutide 1 mg the model incorporates effects on A1C, BMI and SBP; and for sitagliptin, exenatide ER, dulaglutide, and insulin glargine, the model incorporates effects on A1C, BMI, SBP, DBP, TC, LDL, HDL, triglycerides, HR, WBC, and eGFR. For each treatment, if clinical data for the specific biomarker was not incorporated the model assumes the effect size for that treatment was 0.

Thus, given the multiple sources of data on treatment effectiveness for second-line treatment, a consistent base comparator is not available across these analyses and comparisons are de facto based on naive indirect comparisons, which is an inappropriate approach. Furthermore, the discrepancy across treatments in terms of which biomarkers for which effectiveness data are included within the model is also inappropriate and will lead to substantial bias in the estimated benefits from treatments.

In addition, the CADTH clinical review team found that the NMAs that were used for the economic analysis relating to third-line treatment were not representative of the desired patient population as they incorporated patients who had previously received either one or two OADs, and these were not necessarily a combination of sulfonylurea and metformin.

Thus, for both the second-line and third-line treatment analyses, the clinical effectiveness data employed were considered inappropriate and likely to lead to a degree of bias being introduced to the analysis, Hence, no reliable conclusions could be drawn from the submitted analysis.

Although the manufacturer contends that a cohort model for diabetes is preferred to the commonly adopted microsimulation models used in this disease area, CADTH concluded that this approach results in a model that is likely not fit for purpose in this context. The first concern raised is that the model lacks transparency. Data within the Excel model is hard coded with results generated by a series of 24 Visual Basic macros totalling approximately seventeen thousand lines of code. Given the complexity of the model, it was not possible in the time frame permitted to verify all of this code and assess how the data inputs generated the model outcomes. This concern was exacerbated by the inconsistencies between the first and second set of results provided by the manufacturer. This inconsistency heightens concerns regarding the validity of the model, given the inability to verify the link between input data and outcomes.

A further concern relates to how the model estimates the change in outcomes measures such as A1C over time and the related risk of events. The model does not permit any variance in clinical outcomes such as A1C or LDL across patients – rather each patient in the cohort is assumed to have the same value at each time point within the model. This is contrary to microsimulation models in diabetes, which plot the course of such markers on an individual patient basis, allowing for variation. [3]

The problem with the model arises partially because the risk equations used to estimate the probability of events are typically Weibull or exponential functions which specifically require a non-linear relationship between outcomes such as A1C, BMI, and LDL, and the probability of events. However, as the model assumes that there is no variability on the progression of markers and that this can be represented by the expected value, the model will give a biased estimate of the probability of events occurring. To illustrate this point consider the following scenario:

The patient cohort is representative of males currently aged 69 years of age, with a duration of diabetes of seven years, an LDL of 3.0 mmol/L, a BMI of 33, an eGFR of 50, microalbuminuria, and a history of amputation. Let's assume treatment will reduce BMI by 1, with a standard error of 0.5 and a standard deviation of 5.0. If we assume the patient cohort progresses solely based on the expected value of impact on BMI and all other parameters will remain the same, then after one year the patient cohort will be males currently aged 70 years of age, with a duration of diabetes of eight years, an LDL of 3.0 mmol/L, a BMI of 33, an eGFR of 50, microalbuminuria, and a history of amputation. For this, the probability of congestive heart failure (pCHF) in the following year will be:[3]

pCHF = 1-EXP (EXP(-12.332+62*0.068+3*10*0.012+32*0.072+50/10*-0.22
+0.771+0.658)*(81.514-91.514))

= 0.0267

However, if we allow for the variance in effect on BMI, we will get a different estimate of the probability. For example, for those whose BMI increases to 35 (an increase of three points versus the expected value) the probability of CHF would be 0.0331, while for those whose BMI decreased by three points versus the expected valued (to a BMI of 29) the probability will be 0.0216. The average of these values is greater than the forecasted probability (0.0273 versus 0.0267). Thus, the model is likely to overestimate the reduction in the probability of events associated with treatment. Focusing on one-year differences between treatments for only one clinical parameter may find small differences between a cohort approach and a microsimulation approach, although the estimate from a cohort approach will still be biased. However, the extent of bias that will be introduced is unclear, when considering both a long-term analysis and the interaction between clinical parameters in estimating event rates.

A related problem with the model is that it models the prevalence of events and the clinical markers independently. As a result, it ignores the fact that the clinical markers for patients with a history of event will necessarily be different than the clinical markers for those without an event. Consider the example above, given the probability of CHF. The equation predicts that those patients who experience CHF will be more likely to have a higher BMI than those who do not. As time progresses, the cohort of the model who do not have a history of CHF will be expected to have a lower BMI than those who have experienced CHF. Employing the average BMI of the whole cohort in the risk equation rather than the BMI for those not

having had CHF would give a biased upwards estimate of the probability of members of the cohort newly developing CHF.

The reviewer raises significant concerns regarding the adoption of a cohort model that does not accurately reflect the variability in disease progression and treatment response across the cohort, requiring the assumption of a linear relationship between biomarkers and outcomes that is contrary to the risk equations adopted within the model and models the progression of risk factors independent of the prevalence of history of events.

Thus, given the significant concerns both with the quality and appropriateness of the clinical data and with the design of the submitted model, there may be a significant degree of bias being introduced into the analysis. Hence, no reliable conclusions can be drawn from the submitted analysis.

CADTH Common Drug Review Reanalyses

Given that the CADTH reviewers identified significant problems with the submitted analysis in relation to both the quality of the clinical evidence provided and concerns with the nature of the model provided, it was not possible to conduct reanalysis to assess the cost-effectiveness of semaglutide in this context.

If the clinical evidence can be interpreted such that semaglutide is considered at least as effective as other OADs, then semaglutide could be compared with other OADs solely on the basis of annual treatment costs. However, as the actual prices of currently reimbursed OADs are unknown, CADTH is unable to provide such an analysis, but there is no evidence at the time to suggest that semaglutide warrants a higher price than treatment comparators.

Patient Input

Patient input was received from two patient groups: Diabetes Canada and Patient Commando. Respondents expressed a strong desire for medications that can stabilize blood glucose levels and improve A1C without causing weight gain or hypoglycemia.Overall, the manufacturer's economic submission captured outcomes of impor tance to patients such as changes in A1C and weight, and hypoglycemia, and their impact on costs and quality of life.

Patients noted semaglutide was the same or worse in terms of weight management properties and gastrointestinal side effects when compared with other therapies. The patient groups also noted that diabetes is a disease that requires intensive self-management, and highlighted the high cost and consequent distress associated with management of type 2 diabetes mellitus. Caregivers of patients with diabetes often experience anxiety and stress as they tend to serve as life-saving interventionists. As the economic analysis was based on the public health care payer perspective, the cost and quality-of-life impact on caregivers was not included and was not explored in scenario analysis.

Conclusions

The manufacturer's analysis suggests that the price of semaglutide 1 mg would need to be significantly reduced for semaglutide to be considered cost-effective (by at least 28% to 55%, based on the manufacturer's analysis).

CADTH noted significant limitations with the submitted analysis, and as such, concluded that the model was not an appropriate basis to assess the cost-effectiveness of semaglutide in this context. Based on the clinical evidence provided, a conclusion could be reached that semaglutide appears to be at least as effective as other currently reimbursed second- and third-line OADs.

Appendix 1: Cost Comparison

The comparators presented in Table 6 have been deemed to be appropriate by clinical experts. Comparators may be recommended (appropriate) practice, versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are manufacturer list prices, unless otherwise specified. Existing Product Listing Agreements are not reflected in the table and as such may not represent the actual costs to public drug plans.

Table 6: Cost Comparison Table for Non-Insulin Antidiabetic Agents

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Daily Drug Cost ($)	Average Annual Drug Cost ($)
Ozempic (semaglutide)	2 mg 4 mg	pre-filled pen (1.34 mg/mL)	195.06[a]	0.5 mg to 1.0 mg once weekly	6.97	2,544
GLP-1 Receptor Analogue						
Dulaglutide (Trulicity)	0.75 mg/0.5 mL 1.5 mg/0.5 mL	4 x 0.5 mL pre-filled pen	168.28[c]	0.75 mg to 1.5 mg once weekly	6.01	2,194
Exenatide (Byetta)	1.2 mL 2.4 mL	60-dose pre-filled pen (250 mcg/mL)	143.67[d]	5 mcg to 10 mcg twice daily	4.79	1,748
Liraglutide (Victoza)	2 x 3 mL 3 x 3 mL	pre-filled pen (6mg/mL)	136.98[c] 205.47[c]	1.2 mg to 1.8 mg daily	4.57 to 6.85	1,667 to 2,500
Lixisenatide (Adlyxin)	10 mcg 20 mcg	14-dose pre-filled pen (3 mL)	56.9800[d]	Starting dose of 10 mcg once daily for 14 days, after which the dose should be increased to 20 mcg once daily	4.07	1,486
Biguanides						
Metformin	500 mg 850 mg	tab	0.0247 0.2090	500 mg three to four times daily	0.07 to 0.36	27 to 130
Sulfonylureas						
Gliclazide (generics)	80 mg	tab	0.0931	80 mg to 320 mg daily (in divided doses if > 160 mg daily)	0.09 to 0.37	34 to 136
Gliclazide long-acting (Diamicron MR)	30 mg 60 mg	ER tab	0.1405 0.2529	30 mg to 120 mg daily	0.14 to 0.51	51 to 185
Glimepiride (generics)	1 mg 2 mg 4 mg	tab	0.4900	1 mg to 4 mg daily	0.49	179
Glyburide (generics)	2.5 mg 5.0 mg	tab	0.0321 0.0574	2.5 mg to 20 mg daily (in divided doses if > 10 mg daily)	0.03 to 0.23	12 to 84
DPP-4 Inhibitors						
Alogliptin (Nesina)	6.25 mg 12.5 mg 25 mg	tab	2.1000[c]	25 mg daily	2.10	767
Linagliptin (Trajenta)	5 mg	tab	2.6036	5 mg daily	2.60	950
Saxagliptin (Onglyza)	2.5 mg 5.0 mg	tab	2.4760 2.9680	5 mg daily	2.97	1,083

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Daily Drug Cost ($)	Average Annual Drug Cost ($)
Sitagliptin (Januvia)	25 mg 50 mg 100 mg	tab	3.0932	100 mg daily	3.09	1,129
DPP-4 Inhibitor Plus Metformin Fixed-Dose Combinations						
Alogliptin/ metformin (Kazano)	12.5/500 mg 12.5/850 mg 12.5/1,000 mg	tab	1.1450[c]	Two tabs daily	2.29	836
Linagliptin/ metformin (Jentadueto)	2.5 mg/500 mg 2.5 mg/850 mg 2.5 mg/1,000 mg	tab	1.3651	Two tabs daily	2.73	997
Saxagliptin/ metformin (Komboglyze)	2.5 mg/500 mg 2.5 mg/850 mg 2.5 mg/1,000 mg	tab	1.2700	Two tabs daily	2.54	927
Sitagliptin/ metformin (Janumet)	50 mg/500 mg 50 mg/850 mg 50 mg/1,000 mg	tab	1.6779	Two tabs daily	3.36	1,225
SGLT2 Inhibitors						
Canagliflozin (Invokana)	100 mg 300 mg	tab	2.7627	100 mg or 300 mg daily	2.76	1,008
Dapagliflozin (Forxiga)	5 mg 10 mg	tab	2.6750	5 mg or 10 mg daily	2.68	976
Empagliflozin (Jardiance)	10 mg 25 mg	tab	2.6727	10 mg or 25 mg daily	2.67	976
SGLT2 Inhibitors Plus Metformin Fixed-Dose Combinations						
Canagliflozin /metformin (Invokamet)	500/50 mg 850/50 mg 1,000/50 mg 500/150 mg 850/150 mg 1,000/150 mg	tab	1.5660[d]	Two tabs daily	3.13	1,143
Dapagliflozin /metformin (Xigduo)	5 mg/850 mg 5 mg/1,000 mg	tab	1.2250	Two tabs daily	2.45	894
Empagliflozin /metformin (Synjardy)	5 mg/500 mg 5 mg/850 mg 5 mg/1,000 mg 12.5 mg/500 mg 12.5 mg/850 mg 12.5 mg/1,000 mg	tab	1.3783	Two tabs daily	2.76	1,006

DPP-4 = dipeptidyl peptidase-4; ER = extended release; GLP-1 = glucagon-like peptide-1; MR = modified release; SGLT2 = sodium-glucose cotransporter-2; tabs = tablets.

[a] Manufacturer's submission price.

[b] Saskatchewan Drug Formulary (Accessed December 2018).[24]

[c] Quebec Drug Formulary (RAMQ) (Accessed December 2018).[25]

[d] Delta PA: IQVIA database (Accessed December 2018).[26]

Source: Ontario Drug Benefit (Accessed December 2018)[16] prices unless otherwise indicated.

Table 7: Cost Comparison of Insulin Agents

Drug / Comparator	Strength	Dosage Form	Price ($)	Cost per mL ($)
Short-Acting Insulins				
Insulin aspart (NovoRapid)	100 U/mL	5 x 3 mL cartridge 5 x 3 mL disposable pen 10 mL vial	60.63 63.12 29.90	4.04 4.21 2.99
Insulin glulisine (Apidra)	100 U/mL	5 x 3 mL cartridge 5 x 3 disposable pen 10 mL vial	51.45 51.95 25.96	3.43 3.46 2.60
Insulin lispro (Humalog)	100 U/mL	5 x 3 mL cartridge 5 x 3 mL disposable pen 10 mL vial	58.88 58.46 29.64	3.93 3.90 2.96
Regular human insulin (Humulin R)	100 U/mL	5 x 3 mL cartridge 10 mL vial	48.33 24.63	3.22 2.46
Regular human insulin (Novolin ge Toronto)	100 U/mL	5 x 3 mL cartridge 10 mL vial	46.61 23.74	3.11 2.37
Long-Acting Insulin Analogues				
Insulin glargine (Basaglar)	100 U/mL	5 x 3 mL cartridge 5 x 3 disposable pen	69.64 69.64	4.64 4.64
Insulin glargine (Lantus)	100 U/mL	5 x 3 mL cartridge 5 x 3 disposable pen 10 mL vial	92.85 92.85 61.69	6.19 6.19 6.17
Insulin detemir (Levemir)	100 U/mL	5 x 3 mL disposable pen	108.89	7.26
Insulin NPH				
Humulin N	100 U/mL	5 x 3 mL cartridge 10 mL vial	48.33 24.63	3.22 2.46
Novolin ge NPH	100 U/mL	5 x 3 mL cartridge 10 mL vial	47.73 24.28	3.18 2.43
Pre-Mixed Insulins				
Biphasic insulin aspart 30/70 (NovoMix 30)	100 U/mL	5 x 3 mL cartridge	56.14	3.74
Lispro/lispro protamine 25/75 (Humalog Mix 25)	100 U/mL	5 x 3 mL cartridge 5 x 3 mL disposable pen	59.58 59.14	3.97 3.94
Lispro/lispro protamine 50/50 (Humalog Mix 50)	100 U/mL	5 x 3 mL cartridge 5 x 3 mL disposable pen	58.68 58.16	3.91 3.88
Humulin 30/70	100 U/mL	5 x 3 mL cartridge 10 mL vial	48.33 24.63	3.22 2.46
Novolin ge 30/70	100 U/mL	5 x 3 mL cartridge 10 mL vial	47.18 24.41	3.15 2.44
Novolin ge 40/60	100 U/mL	5 x 3 mL cartridge	47.52	3.17
Novolin ge 50/50	100 U/mL	5 x 3 mL cartridge	47.52	3.17

Source: Ontario Drug Benefit prices unless otherwise indicated (accessed December 2018)[16].

Appendix 2: Summary of Key Outcomes

Table 8: When Considering Only Costs, Outcomes, and Quality of Life, How Attractive is Semaglutide Relative to Other OADs?

Semaglutide vs. Other OADs	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	N/A
Costs (total)						Uncertain given lack of appropriate basis to assess cost-effectiveness
Drug treatment costs alone					X	
Clinical outcomes			X			
Quality of life						Uncertain given lack of appropriate basis to assess cost-effectiveness
Incremental CE ratio or net benefit calculation	Uncertain given lack of appropriate basis to assess cost-effectiveness					

CE = cost-effectiveness; N/A = not applicable; OAD = oral antidiabetic drug.

Appendix 3: Additional Information

Table 9: Submission Quality

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?			X
Comments Reviewer to provide comments if checking “no”	The model lacks transparency and is not possible to validate		
Was the material included (content) sufficient?			X
Comments Reviewer to provide comments if checking “poor”	A comprehensive NMA is required		
Was the submission well organized and was information easy to locate?		X	
Comments Reviewer to provide comments if checking “poor”	None		

NMA = network meta-analysis.

Table 10: Authors information

Authors of the Pharmacoeconomic Evaluation Submitted to CDR

☐ Adaptation of Global model/Canadian model done by the manufacturer

☒ Adaptation of Global model/Canadian model done by a private consultant contracted by the manufacturer

☐ Adaptation of Global model/Canadian model done by an academic consultant contracted by the manufacturer

☐ Other (please specify)

	Yes	No	Uncertain
Authors signed a letter indicating agreement with entire document		X	
Authors had independent control over the methods and right to publish analysis		X	

CDR = CADTH Common Drug Review.

Appendix 4: Summary of Other HTA Reviews of Drug

Neither the National Institute for Health and Care Excellence (NICE) or the Australian Pharmaceutical Benefits Advisory Committee (PBAC) had published a completed HTA review for semaglutide at the time of this review.

The Scottish Medicines Consortium (SMC) reviewed a manufacturer's economic analysis for semaglutide.[27] The analysis was a cost-utility analysis comparing semaglutide to dulaglutide, liraglutide, exenatide, and exenatide extended release (ER) in patients with type 2 diabetes mellitus. Three subpopulations were considered; two of these were similar to the submission to CADTH Common Drug Review (CDR):

- Patients with inadequate glycemic control on oral antidiabetic drugs (OADs) as part of dual therapy
- Patients with inadequate glycemic control on OADs as part of triple therapy

Unlike with the submission to CDR, the analysis reviewed by the SMC was based on the use of the CORE diabetes model.[28] The analysis modelled the impact of treatment on only two biomarkers – glycated hemoglobin (A1C) and body mass index (BMI). Similar assumptions to the current submission were made in relation to the duration of treatment and sustaining of treatment effect. Similar to the current submission, the clinical data consisted of a combination of direct trial evidence and indirect comparisons. The manufacturer's submission suggested that semaglutide was dominant over all other comparators for both treatment populations. SMC concluded that despite uncertainties with the submission, an economic case had been demonstrated.

It should be noted that in the SMC report, the manufacturer's submitted analysis compared semaglutide only to other glucagon-like peptide-1 (GLP-1) receptor agonists (dulaglutide, exenatide ER, exenatide, and liraglutide). These drugs are not covered by all Canadian public drug plans.

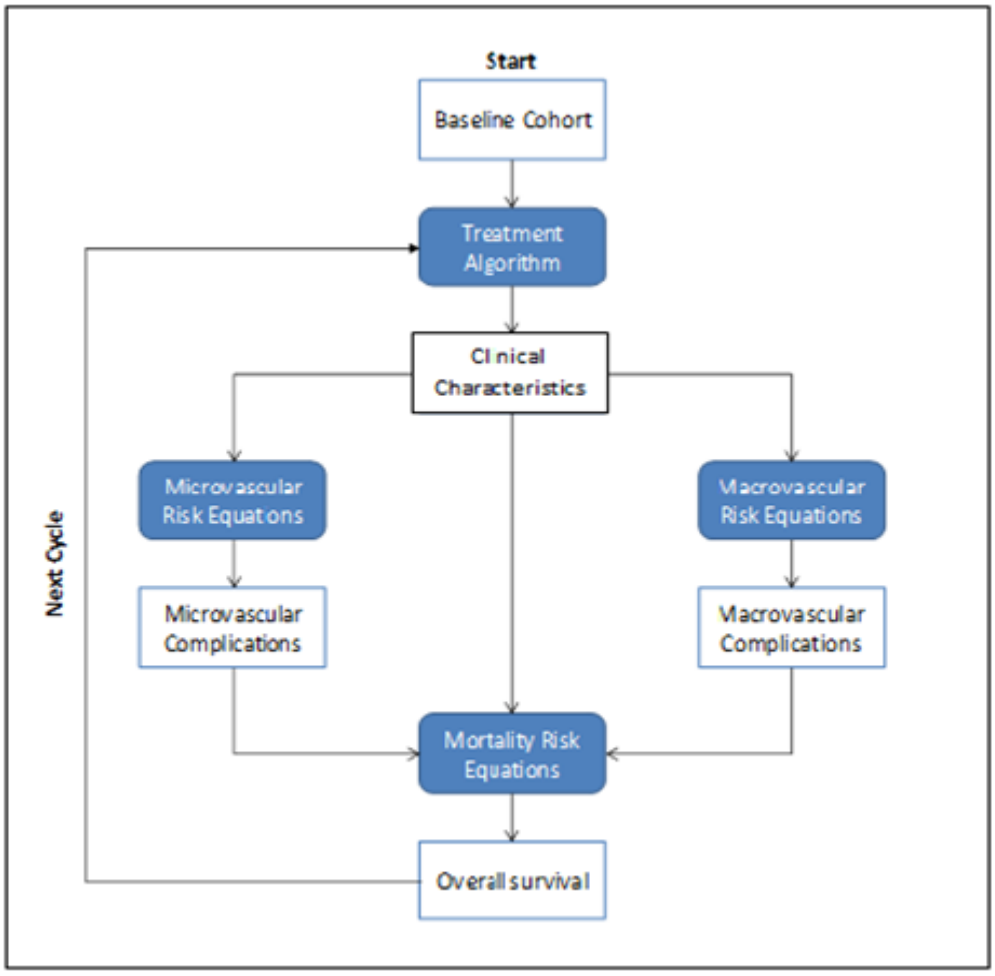
It should also be noted that in the SMC report semaglutide had an equal or lower annual cost than liraglutide, exenatide ER, and dulaglutide, which is contrary to the Canadian context as evidenced in the Cost Comparison Table (Appendix 1).

The Institut national d'excellence en santé et en services sociaux, Quebec (INESSS) reviewed a cost-utility analysis comparing semaglutide to dulaglutide based on efficacy results from the SUSTAIN-7 trial.[29] INESSS concluded that semaglutide has similar safety and efficacy to dulaglutide and liraglutide, and recommended on the basis of redacted drug costs that semaglutide be reimbursed for patients with diabetes who have: inadequate glycemic control, a BMI greater than 30 kg/m^2, and for whom a dipeptidyl peptidase-4 (DPP-4) inhibitor is contraindicated, not tolerated, or ineffective.

Appendix 5: Reviewer Worksheets

Model Structure

Figure 1: Overview of IHE Cohort Model



Source: Manufacturer's Pharmacoeconomic submission.[19]

Table 11: Utility Data

	Mean	SE
QoL Baseline	1.027	0.027
Microvascular Complications	QoL Decrements	
Retinopathy		
Background Diabetic Retinopathy	–0.040	–0.010
Proliferative Diabetic Retinopathy	–0.070	–0.018
Macular Edema	–0.040	–0.010
Proliferative Diabetic Retinopathy and Macular Edema	–0.070	–0.018
Severe Visual Loss	–0.050	–0.012
Neuropathy		
Symptomatic	–0.084	0.014
Peripheral Vascular Disease	–0.061	0.015
Lower Extremity Amputation Event	–0.272	0.029
History of Lower Extremity Amputation	–0.272	0.029
Nephropathy		
Microalbuminuria	0.000	0.000
Macroalbuminuria	–0.048	0.022
End-Stage Renal Disease	–0.263	–0.066
Macrovascular Complications		
Ischemic Heart Disease	–0.041	–0.010
Myocardial Infarction (MI)		
First MI Event	–0.041	–0.010
History of First MI	–0.012	–0.003
Subsequent MI Events	–0.041	–0.010
History of Subsequent MIs	–0.012	–0.003
Stroke		
First Stroke Event	–0.052	–0.013
History of First Stroke	–0.040	–0.010
Subsequent Strokes Events	–0.052	–0.013
History of Subsequent Strokes	–0.040	–0.010
Congestive Heart Failure	–0.064	–0.016
Demographic Factors		
Age (per 10 years)	–0.024	0.000
Female	–0.093	0.009
Diabetes Duration (per 10 years)	–0.016	0.001
Obesity (per 1 BMI over 25)	–0.006	0.001
Hypoglycemia		
Non-severe	–0.014	–0.004
Severe	–0.047	–0.012

BMI = body mass index; MI = myocardial infarction; QoL = quality of life; SE = standard error.

Source: Manufacturer's Pharmacoeconomic submission.[19]

Table 12: Annual Treatment Costs

	Annual Treatment Cost ($)
Semaglutide 1.0 mg	2,554
Semaglutide 0.5 mg	2,554
Glyburide	81
Lixisenatide	1,504
Sitagliptin	1,147
Canagliflozin	1,026
Insulin Glargine	995
Dulaglutide 1.5 mg	2,554
Liraglutide 1.2 mg	2,327
Liraglutide 1.8 mg	3,412
Exenatide ER 2.0 mg	2,538
Empagliflozin	994
Dapagliflozin	912

ER = extended release.

Source: Manufacturer's Pharmacoeconomic submission.[19]

Table 13: Cost of Complications

	Event Cost ($)		State Cost ($)	
	Mean	SE	Mean	SE
Microvascular Complications				
Retinopathy				
Background Diabetic Retinopathy	643	161	73	18
Proliferative Diabetic Retinopathy (PDR)	643	161	73	18
Macular Edema (ME)	835	209	73	18
PDR & ME	835	209	73	18
Severe Visual Loss	3,314	828	2,362	590
Neuropathy				
Symptomatic	919	230	1,152	288
Peripheral Vascular Disease	132	33	132	33
Lower Extremity Amputation	41,850	10,463		
Nephropathy				
Microalbuminuria	83	21	0	0
Macroalbuminuria	114	29	0	0
End-Stage Renal Disease	50,323	12,581	58,983	14,746
Macrovascular Complications				
Ischemic Heart Disease	6,199	1,550	3,579	895
Myocardial Infarction (MI)				
First MI	19,807	4,952	3,097	774
Subsequent MIs	3,097	774	3,097	774
Stroke				
First Stroke	26,979	3,372	3,743	936
Subsequent Stroke	3,743	936	3,743	936
Congestive Heart Failure	18,119	4,530	5,080	1,270
Hypoglycemia (Per Episode)				
Non-Severe	2	0		
Severe	2,179	545		

ME = macular edema; MI = myocardial infarction; PDR = proliferative diabetic retinopathy; SE = standard error.

Source: Manufacturer's Pharmacoeconomic submission.[19]

Table 14: Sources of Clinical Effectiveness Data

Intervention	Comparator	Class	Second-line treatment	Third-line treatment	Source
Semaglutide 1.0 mg	Exenatide ER 2.0 mg	GLP-1 RA	✓*	✓†	SUSTAIN 3[34]
Semaglutide 0.5 and 1.0 mg	Dulaglutide 1.5 mg	GLP-1 RA	✓		SUSTAIN 7[30]
Semaglutide 0.5 and 1.0 mg	Dulaglutide 1.5 mg	GLP-1 RA		✓	NMA
Semaglutide 0.5 and 1.0 mg	Liraglutide 1.2 and 1.8 mg	GLP-1 RA	✓	✓	NMA
Semaglutide 0.5 and 1.0 mg	Lixisenatide 20 µg	GLP-1 RA	✓	✓	NMA
Semaglutide 0.5 and 1.0 mg	Sitagliptin 100 mg	DPP-4	✓*	✓§	SUSTAIN 2[28]
Semaglutide 0.5 and 1.0 mg	Insulin glargine	Basal insulin	✓*	✓†	SUSTAIN 4[29]
Semaglutide 0.5 and 1.0 mg	Canagliflozin 300 mg	SGLT-2	✓	✓	NMA
Semaglutide 0.5 and 1.0 mg	Empagliflozin 25 mg	SGLT-2	✓	✓	NMA
Semaglutide 0.5 and 1.0 mg	Dapagliflozin 10 mg	SGLT-2	✓	✓	NMA
Semaglutide 0.5 and 1.0 mg	Glyburide 15 mg	SU	✓		NMA

ER = extended release; GLP-1 = glucagon-like peptide-1; NMA = network meta-analysis; RA = receptor agonist; SGLT2 = sodium-glucose cotransporter-2; SU = sulfonylurea.

Source: Manufacturer's Pharmacoeconomic submission.[19]

Table 15: Treatment Effects — Second-Line

	A1C	SBP	DBP	TC	LDL	HDL	TG	BMI	HR	WBC	eGFR	Hypo events (non-severe)	Hypo events (severe)
Semaglutide 1.0 mg	–1.42 (0.09)	–7.28 (–1.37)	NI	NI	NI	NI	NI	–1.48 (0.14)	NI	NI	NI	0.04 (0.01)	0.01 (0.003)
Semaglutide 0.5 mg	–1.11 (0.14)	NI	NI	NI	NI	NI	NI	–0.94 (0.49)	NI	NI	NI	0.04 (0.01)	0.01 (0.003)
[redacted]													
[redacted]													
[redacted]													
Canagliflozin	–0.76 (0.07)	–6.61 (0.98)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	–0.91 (0.1)	NI	NI	NI	0.04 (0.01)	0.01 (0.003)
[redacted]													
[redacted]													
[redacted]													
[redacted]													
[redacted]													
Empagliflozin	–0.62 (0.07)	–4.8 (0.99)	NI	NI	NI	NI	NI	–0.74 (0.08)	0 (0)	NI	NI	0.04 (0.01)	0.01 (0.003)
Dapagliflozin	–0.37 (0.06)	–3.94 (1.29)	NI	NI	NI	NI	NI	–0.74 (0.09)	0 (0)	NI	NI	0.04 (0.01)	0.01 (0.003)

A1C = glycated hemoglobin; BMI = body mass index; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; HR = heart rate; Hypo = hypoglycemic; LDL = low-density lipoprotein; NI = not included; SBP = systolic blood pressure; TC = total cholesterol; TG = triglycerides; WBC = white blood cells.

Note: Figures represent mean effect with standard errors in parenthesis.

Source: Manufacturer's Pharmacoeconomic submission.[19]

Table 16: Treatment Effects — Third-Line

	A1C	SBP	DBP	TC	LDL	HDL	TG	BMI	HR	WBC	eGFR	Hypo events (non-severe)	Hypo events (severe)
Semaglutide 1.0 mg	–1.47 (0.12)	–6.28 (1.52)	NI	NI	NI	NI	NI	–1.35 (0.1)	NI	NI	NI	0.21 (0.05)	0.09 (0.022)
Semaglutide 0.5 mg	–1.24 (0.11)	–2.8 (1.42)	NI	NI	NI	NI	NI	–0.89 (0.18)	NI	NI	NI	0.21 (0.05)	0.09 (0.022)
[redacted]													
[redacted]													
[redacted]													
Liraglutide 1.2 mg	–0.87 (0.12)	–4.45 (1.39)	NI	NI	NI	NI	NI	–0.64 (0.1)	NI	NI	NI	0.21 (0.05)	0.09 (0.022)
Lixisenatide	–0.56 (0.2)	–3 (1.53)	NI	NI	NI	NI	NI	–0.32 (0.1)	NI	NI	NI	0.21 (0.05)	0.09 (0.022)
[redacted]													
[redacted]													
Dulaglutide 1.5 mg	–1.12 (0.15)	–4.32 (1.56)	NI	NI	NI	NI	NI	–0.42 (0.11)	NI	NI	NI	0.21 (0.05)	0.09 (0.022)
[redacted]													
Liraglutide 1.8 mg	–1.11 (0.1)	–4.21 (1.36)	NI	NI	NI	NI	NI	–0.73 (0.09)	NI	NI	NI	0.21 (0.05)	0.09 (0.022)
Semaglutide 1.0 mg	–1.47 (0.12)	–6.28 (1.52)	NI	NI	NI	NI	NI	–1.35 (0.1)	NI	NI	NI	0.21 (0.05)	0.09 (0.022)

A1C = glycated hemoglobin; BMI = body mass index; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; HR = heart rate; Hypo = hypoglycemic; LDL = low-density lipoprotein; NI = not included; SBP = systolic blood pressure; TC = total cholesterol; TG = triglycerides; WBC = white blood cells.

Note: Figures represent mean effect with standard errors in parenthesis.

Source: Manufacturer's Pharmacoeconomic submission.[19]

Manufacturer's Results

Table 17: Summary of Manufacturer's Base Case (Second-Line) — Original Submission

	Total Costs ($)	Total QALYs	ICER Versus Glyburide ($)	Sequential ICER ($)
Glyburide	121,992	12.245	–	–
Canagliflozin	123,398	12.375	10,827	10,827
Semaglutide 1.0 mg	126,483	12.379	33,461	714,488
Sitagliptin	124,076	12.295	41,563	Not provided
Lixisenatide	126,205	12.275	141,630	Not provided
Insulin Glargine	129,236	10.566	Dominated	Not provided
Semaglutide 0.5 mg	129,650	12.310	118,678	Not provided
Empagliflozin	123,523	12.360	Not provided	Not provided
Dapagliflozin	123,829	12.339	Not provided	Not provided
Exenatide ER 2.0 mg	128,090	12.330	Not provided	Not provided
Dulaglutide 1.5 mg	128,994	12.345	Not provided	Not provided
Liraglutide 1.2 mg	129,335	12.293	Not provided	Not provided
Liraglutide 1.8 mg	133,251	12.292	Not provided	Not provided

ER = extended release; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Source: Manufacturer's Pharmacoeconomic submission.[19]

Table 18: Summary of Manufacturer's Base Case (Third-Line) — Original Submission

	Total Costs ($)	Total QALYs	ICER versus Canagliflozin ($)	Sequential ICER ($)
Canagliflozin	104,991	11.675	–	–
Semaglutide 1.0 mg	109,872	11.711	136,653	136,653
Sitagliptin	106,107	11.627	Dominated	Not provided
Lixisenatide	107,652	11.618	Dominated	Not provided
Liraglutide 1.2 mg	109,311	11.663	Dominated	Not provided
Semaglutide 0.5 mg	110,034	11.670	Dominated	Not provided
Insulin Glargine	110,534	9.922	Dominated	Not provided
Empagliflozin	105,079	11.651	Not provided	Not provided
Dapagliflozin	105,198	11.647	Not provided	Not provided
Exenatide ER 2.0 mg	110,011	11.636	Not provided	Not provided
Dulaglutide 1.5 mg	110,154	11.661	Not provided	Not provided
Liraglutide 1.8 mg	112,575	11.673	Not provided	Not provided

ER = extended release; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Source: Manufacturer's Pharmacoeconomic submission.[19]

Table 19: Summary of Manufacturer's Base Case (Second-Line) — First Revised Submission

	Total Costs ($)	Total QALYs	ICER versus Glyburide ($)	Sequential ICER ($)
Glyburide	108,765	12.326	–	–
Canagliflozin	109,962	12.455	9,316	9,316
Semaglutide 1.0 mg	114,227	12.472	37,458	245,441
Empagliflozin	110,253	12.436	13,612	Dominated by canagliflozin.
Dapagliflozin	110,581	12.408	22,149	Dominated by canagliflozin and empagliflozin.
Sitagliptin	110,924	12.369	50,957	Dominated by canagliflozin, empagliflozin, and dapagliflozin. Extended dominance through glyburide and semaglutide 1.0 mg; and glyburide and dulaglutide.
Lixisenatide	113,110	12.344	243,083	Dominated by canagliflozin, empagliflozin, dapagliflozin, and sitagliptin. Extended dominance through glyburide and exenatide ER; glyburide and semaglutide 1.0 mg; glyburide and dulaglutide; glyburide and liraglutide 1.2 mg; glyburide and semaglutide 0.5 mg.; and glyburide and liraglutide 1.8 mg.
Insulin Glargine	113,415	10.686	Dominated	Dominated by glyburide, canagliflozin, empagliflozin, dapagliflozin, sitagliptin, and lixisenatide.
Exenatide ER 2.0 mg	114,089	12.416	59,495	Dominated by canagliflozin and empagliflozin. Extended dominance through glyburide and semaglutide 1.0 mg; glyburide and dulaglutide; dapagliflozin and semaglutide 1.0 mg; dapagliflozin and dulaglutide; sitagliptin and semaglutide 1.0 mg; sitagliptin and dulaglutide; lixisenatide and semaglutide 1.0 mg; lixisenatide and dulaglutide.
Dulaglutide 1.5 mg	114,463	12.444	48,431	Dominated by canagliflozin and semaglutide 1.0 mg.
Liraglutide 1.2 mg	114,999	12.389	98,527	Dominated by canagliflozin, empagliflozin, dapagliflozin, exenatide ER, semaglutide 1.0 mg, and dulaglutide. Extended dominance through sitagliptin and semaglutide 0.5 mg.
Semaglutide 0.5 mg	115,469	12.400	90,997	Dominated by canagliflozin, empagliflozin, dapagliflozin, exenatide ER, semaglutide 1.0 mg, and dulaglutide.
Liraglutide 1.8 mg	118,256	12.396	136,025	Dominated by canagliflozin, empagliflozin, dapagliflozin, exenatide ER, semaglutide 1.0 mg, dulaglutide, and semaglutide 0.5 mg.

ER = extended release; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Source: Manufacturer's Pharmacoeconomic submission.[19]

Table 20: Summary of Manufacturer's Base Case (Second-Line) — First Revised Submission

	Total Costs ($)	Total QALYs	ICER versus Glyburide ($)	Sequential ICER ($)
Glyburide	108,765	12.326	-	-
Canagliflozin	109,962	12.455	9,316	9,316
Semaglutide 1.0 mg	114,227	12.472	37,458	245,441
Semaglutide 0.5 mg	115,469	12.400	90,997	Dominated by canagliflozin, empagliflozin, dapagliflozin, exenatide ER, semaglutide 1.0 mg, and dulaglutide.

ER = extended release; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Source: Manufacturer provided additional information.[23]

For third-line treatment, similar to second-line treatment, costs for all OADs were lower than in the original submission and QALYs for all OADs were higher. As previously, all therapies were subject to dominance other than canagliflozin and semaglutide 1 mg. The ICER for semaglutide 1 mg versus canagliflozin was $95,452 (compared with $136,653 previously).

Table 21: Summary of Manufacturer's Base Case (Third-Line) — First Revised Submission

	Total Costs ($)	Total QALYs	ICER versus Canagliflozin ($)	Sequential ICER ($)
Canagliflozin	93,228	11.709	-	-
Semaglutide 1.0 mg	97,367	11.752	95,452	95,452
Dapagliflozin	93,372	11.677	Dominated	Dominated by canagliflozin.
Empagliflozin	93,449	11.682	Dominated	Dominated by canagliflozin.
Sitagliptin	95,048	11.657	Dominated	Dominated by canagliflozin, dapagliflozin, and empagliflozin.
Lixisenatide	95,981	11.648	Dominated	Dominated by canagliflozin, dapagliflozin, empagliflozin, and sitagliptin.
Insulin Glargine	96,098	9.993	Dominated	Dominated by canagliflozin, dapagliflozin, empagliflozin, sitagliptin, and lixisenatide.
Liraglutide 1.2 mg	97,277	11.696	Dominated	Dominated by canagliflozin. Extended dominance through dapagliflozin and semaglutide 1.0 mg; dapagliflozin and semaglutide 0.5 mg; empagliflozin and semaglutide 1.0 mg; empagliflozin and semaglutide 0.5 mg; empagliflozin and liraglutide 1.8 mg; sitagliptin and semaglutide 1.0 mg; sitagliptin and semaglutide 0.5 mg; and lixisenatide and semaglutide 1.0 mg.
Semaglutide 0.5 mg	97,704	11.709	Dominated	Dominated by canagliflozin and semaglutide 1.0 mg.
Dulaglutide 1.5 mg	97,890	11.698	Dominated	Dominated by canagliflozin, semaglutide 1.0 mg, and semaglutide 0.5 mg. Extended dominance through empagliflozin and liraglutide 1.8 mg; liraglutide 1.2 mg and liraglutide 1.8 mg; and semaglutide 0.5 mg and liraglutide 1.8 mg.
Exenatide ER 2.0 mg	97,928	11.670	Dominated	Dominated by canagliflozin, dapagliflozin, empagliflozin, liraglutide 1.2 mg, semaglutide 1.0 mg, semaglutide 0.5 mg, dulaglutide 1.5 mg. Extended dominance through sitagliptin and liraglutide 1.8 mg; and lixisenatide and liraglutide 1.8 mg.
Liraglutide 1.8 mg	100,045	11.709	11,814,015	Dominated by semaglutide 1.0 mg.

ER = extended release; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Source: Manufacturer provided additional information.[23]

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