CADTH

CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

Insulin glargine + lixisenatide (Soliqua)

(Sanofi-Aventis)

Indication: adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus inadequately controlled on basal insulin (less than 60 units daily) alone or in combination with metformin.

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CADTH

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.

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Abbreviations

A1C	glycated hemoglobin
AE	adverse event
BMI	body mass index
CDR	CADTH Common Drug Review
DDD	defined daily dose
DPP-4	dipeptidyl peptidase 4
GLP-1	glucagon-like peptide-1
ICUR	incremental cost-utility ratio
IDC	indirect comparison
iGlarLixi	fixed-ratio combination of insulin glargine and lixisenatide
ODB	Ontario Drug Benefit
QALY	quality-adjusted life-year
SE	standard error
SGLT2	sodium-glucose cotransporter-2
T2DM	type 2 diabetes mellitus
UKPDS-OM2	United Kingdom Prospective Diabetes Study – Outcomes Model version two
WHO	World Health Organization

Table 1: Summary of the Manufacturer's Economic Submission

Drug Product	Insulin glargine 100 units/mL + lixisenatide 33 mcg/mL
Study Question	What is the cost-effectiveness of insulin glargine and lixisenatide compared with a basal-prandial t.i.d. insulin therapy (both regimens with or without metformin), for the treatment of adults with type 2 diabetes mellitus (T2DM) inadequately controlled on basal insulin, with or without metformin?
Type of Economic Evaluation	Cost-utility analysis
Target Population	Adults with T2DM inadequately controlled on basal insulin (with or without metformin)
Treatment	Insulin glargine (100 units/mL) and lixisenatide (33 mcg/mL) (iGlarLixi) Dose: 47 units per day with or without metformin
Outcomes	QALYs, LYs
Comparator	Basal insulin once daily plus prandial insulin three times daily (basal-prandial t.i.d.), with or without metformin
Perspective	Canadian public health care payer
Time Horizon	Lifetime (25 years)
Results for Base Case	iGlarLixi is dominant (i.e., more effective and less expensive) than a basal-prandial t.i.d. insulin regimen
Key Limitations	• The manufacturer's analysis did not include all relevant comparators in Canada. Although a basal-prandial t.i.d. regimen has previously been the traditional approach, this is no longer in line with the 2018 Canadian Clinical Practice Guidelines. SGLT2, DPP-4 inhibitors, and other GLP-1 receptor agonists should have been included as comparators. • There is uncertainty regarding the size of the comparative treatment effects, as several limitations were found with the sources of evidence used by the manufacturer. This affects the reliability of the comparative analysis. • There is also uncertainty regarding the duration of iGlarLixi benefit. Surrogate outcomes, such as A1C and body weight, were used to estimate 25-year impact on micro- and macrovascular diabetic complications as well as survival. It is uncertain whether treatment effect and, in particular, the difference compared with the control arm will be maintained over the time horizon, and hence whether incremental benefits on micro- and macrovascular events and survival estimated by the model will, in fact, be realized. • The manufacturer's base case includes a disutility when the body mass index is above 25 kg/m^2. This approach does not align with CADTH therapeutic reviews for diabetes products and other single-drug diabetes reviews by CADTH. • The dose and costs for the basal-prandial t.i.d. regimen were overestimated. • The model has an extremely long run time (i.e., > 3 days), which limited CADTH's ability to run additional analyses.

CADTH Estimates	• CADTH could not address the limitations related to the data sources and the structure of the model (i.e., duration of benefit and impact on survival). • When assuming a dose of prandial insulin of 40 units (the World Health Organization's defined daily dose), using the least costly alternatives for basal and prandial insulin, removing the disutility when body mass index is above 25 kg/m^2, and correcting some errors identified in the data inputs, the incremental cost-utility ratio (ICUR) for iGlarLixi when compared with a basal-prandial t.i.d. insulin regimen, with or without metformin, was estimated at $170,875 per QALY. o A price reduction of 20% is required to achieve an ICUR of $50,000 per QALY. o A price reduction of approximately 25% is required to achieve an ICUR below $25,000 per QALY. • A series of scenario analyses were performed by varying inputs such as body weight change over time, disutility for hypoglycemic events or body mass index above 30 kg/m^2, vial and cartridge usage, cost of diabetic disposables (syringes/needles and lancets), and time horizon. In these scenario analyses, the ICUR was never less than $72,255 per QALY and most often more than $100,000 per QALY. • CADTH also undertook exploratory analyses comparing iGlarLixi with DPP-4 and SGLT2 inhibitors and with other GLP-1 receptor agonists. The analyses could only be conducted via pairwise analysis and resulted in ICURs above $100,000 per QALY for iGlarLixi against each comparator treatment.

A1C = glycated hemoglobin; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; ICUR = incremental cost-utility ratio; iGlarLixi = fixed-ratio combination of insulin glargine and lixisenatide; LY = life-year; QALY = quality-adjusted life-year; SGLT2 = sodium-glucose cotransporter-2; T2DM = type 2 diabetes mellitus; t.i.d. = three times daily.

Drug	Insulin glargine and lixisenatide injection (Soliqua)
Indication	An adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus inadequately controlled on basal insulin (less than 60 units daily) alone or in combination with metformin.
Reimbursement Request	As per indication
Dosage Form	Solution for injection in a pre-filled pen for subcutaneous injection
NOC Date	July 6, 2018
Manufacturer	Sanofi-Aventis Canada Inc.

Executive Summary

Background

Soliqua (insulin glargine and lixisenatide; iGlarLixi) is an antidiabetic drug containing a fixed-ratio combination of insulin glargine (100 units/mL), a basal insulin, and lixisenatide (33 mcg/mL), a glucose-like peptide-1 (GLP-1) receptor agonist. iGlarLixi is indicated as an adjunct to diet and exercise to improve glycemic control in type 2 diabetes mellitus (T2DM) inadequately controlled on less than 60 units/day of basal insulin, with or without metformin. It is administered as a once-daily subcutaneous injection via a pre-filled pen injector. The dose is individualized according to clinical response. The starting dose is selected according to the basal insulin dose in the previous regimen but should not exceed the recommend starting dose of lixisenatide (i.e., 10 mcg).[1] At the manufacturer's submitted price of $37.96 for a 3 mL pre-filled pen (equivalent to 300 units insulin glargine and 100 mcg lixisenatide), the annual treatment cost of iGlarLixi is estimated to vary between $693 and $2,770, depending on the dose administered.[2]

CADTH reviewed lixisenatide in 2017 and recommended reimbursement, provided lixisenatide cost does not exceed the cost of the least costly pharmacotherapy reimbursed for T2DM in combination with basal insulin (with or without metformin).[3] The manufacturer's insulin glargine formulation (Lantus) was first reviewed by CADTH in September 2005 and was not recommended for reimbursement.[4] A resubmission by the manufacturer resulted in a negative recommendation in March 2006 as well.[5] Since then, several public programs have included insulin glargine in their formulary. In March 2016, a subsequent entry biologic formulation of insulin glargine was recommended by CADTH to be reimbursed in a similar manner as Lantus.[6]

The manufacturer submitted a cost-utility analysis comparing iGlarLixi (47 units), with or without metformin, with a regimen containing basal insulin (47 units) once daily, together with rapid-acting insulin three times daily (88 units daily; basal-prandial three times daily), with or without metformin, from the perspective of the Canadian health care payer.[2] The manufacturer's model was based on the United Kingdom Prospective Diabetes Study – Outcomes Model version two (UKPDS-OM2) and assessed patients over a time horizon of 25 years (in individuals with an average age of 60). Patient data (demographics, baseline

characteristics, and cardiovascular and other diabetic complication risk factors) and iGlarLixi efficacy on glycated hemoglobin (A1C) and body weight were taken from the LixiLan-L study, while efficacy of the basal-prandial three times daily regimen came from an indirect comparison (IDC) sponsored by the manufacturer and supplemented with results from the GETGOAL DUO-2 study (a study comparing the individual components of iGlarLixi with an alternative insulin regimen in T2DM inadequately controlled on basal insulin with up to three oral antidiabetes drugs). Treatment effect on A1C and body weight was applied in the first year only. The incidence of microvascular (i.e., amputation, nephropathy, blindness, and leg/foot ulcers) and macrovascular (i.e., ischemic heart disease, myocardial infarction, heart failure, and stroke) diabetic complications as well as death were predicted by the model. The model also included treatment-related adverse events (i.e., hypoglycemic events and nausea). Costs and disutilities were associated to clinical events, including a disutility when the body mass index (BMI) was greater than 25 kg/m^2, and treatment-related adverse events. Costs and utilities were obtained from official sources such as provincial formularies and schedules of benefits or the medical literature. In the manufacturer's base case, iGlarLixi was estimated to be dominant (i.e., more effective, less expensive) over basal-prandial insulin three times daily, with lifetime savings of $17,898 and incremental quality-adjusted life-years (QALYs) of 0.10.

Summary of Identified Limitations and Key Results

CADTH Common Drug Review (CDR) identified several key limitations of the manufacturer's analysis. First, the manufacturer's analysis did not include all relevant comparators in Canada. The comparator chosen by the manufacturer (i.e., a basal-prandial three times daily regimen), while being the traditional approach, is no longer in line with the 2018 Canadian Clinical Practice Guidelines, which recommend adding prandial insulin only after a sodium-glucose cotransporter-2 (SGLT2), a dipeptidyl peptidase 4 (DPP-4) inhibitor, or a GLP-1 receptor agonist have been tried and glycemia is still uncontrolled.[7] Results are likely to be different with different comparators, as insulin is known to increase body weight and cause more hypoglycemic events than SGLT2 and DPP-4 inhibitors or GLP-1 receptor agonists.[7] Furthermore, there is uncertainty concerning the size of the effect of iGlarLixi and the comparator.[8] The CADTH clinical reviewers identified several limitations with the LixiLan-L trial that was used to provide efficacy and safety inputs for the iGlarLixi arm of the model, as well as with the manufacturer's IDC that was used to provide efficacy and safety inputs for the basal-prandial insulin three times daily arm of the model. There is also uncertainty regarding the duration of iGlarLixi benefit. Surrogate outcomes, such as A1C and body weight, were used to estimate the 25-year impact on micro- and macrovascular diabetic complications, as well as survival. It is uncertain, however, whether the treatment effect will be maintained over the 25-year period and hence whether benefits on micro- and macrovascular events and survival estimated by the model will, in fact, be realized. On the other hand, the 25-year time horizon chosen by the manufacturer might not capture the lifetime impact (recommended by CADTH for chronic conditions) of iGlarLixi in its entirety.[9] Furthermore, a disutility when the BMI is greater than 25 kg/m^2 has been included in the manufacturer's base case. This approach does not align with CADTH therapeutic reviews of diabetes products and other reviews undertaken by CADTH. In addition, the costs for the basal-prandial insulin three times daily regimen were overestimated on three aspects: the least costly alternative was not considered; the dose of prandial insulin used was higher than that reported in the literature; and a markup higher than allowed was applied. Last, the model has an extremely long run time (i.e., more than three days). This limited CADTH's ability to run additional analyses.

CADTH could not address the weaknesses pertaining to the clinical data inputs and was limited in its ability to change the duration of iGlarLixi benefit (and resulting survival benefit), owing to the model structure. However, CADTH attempted to address the other limitations, as possible, by adjusting the cost of the basal-prandial insulin three times daily regimen, both in terms of daily dose and the cost of each component; removing the disutility associated with BMI above 25 kg/m^2; varying the time horizon; and correcting errors identified in data inputs. A series of scenario analyses were also performed by varying inputs such as body weight change over time, disutility for hypoglycemic events, vial and cartridge usage, cost of diabetic disposables (i.e., syringes, lancets), etc. In addition, exploratory analyses were performed using three different comparators (i.e., SGLT-2 and DPP-4 inhibitors as well as other GLP-1 receptor agonists).

According to CADTH base case, the incremental cost-utility ratio (ICUR) of iGlarLixi, when compared with a basal-prandial insulin three times daily regimen, is estimated at $170,875 per QALY. The lowest ICUR ($72,255 per QALY) is observed with a scenario in which the costs of diabetic disposables are included in the analysis, while the highest ICUR ($19,420,053 per QALY) is observed when a different set of disutilities is used for hypoglycemic events. Furthermore, the ICUR is above $100,000 per QALY in the exploratory analyses comparing iGlarLixi with other GLP-1 receptor agonists, or with DPP-4 and SGLT2 inhibitors. A price reduction in the range of 20% to 25% would be needed to achieve an ICUR in the $25,000 to $50,000 per QALY range.

Conclusions

After accounting for alternative comparator costs, removing the disutility based on higher BMI, and correcting data input errors, the CADTH base-case ICUR for iGlarLixi (with or without metformin), compared with a basal-prandial three times daily insulin regimen (with or without metformin), was $170,875 per QALY. A price reduction of 20% would be needed to achieve an ICUR of $50,000 per QALY when comparing iGlarLixi with basal-prandial three times daily insulin regimen, while a price reduction of approximately 25% would be required to achieve an ICUR below $25,000 per QALY. However, these results should be viewed with caution, given the limitations in the manufacturer's inputs and model that could not be addressed by CADTH. In analyses undertaken by CADTH for the revised base case, no ICURs were lower than $72,255 per QALY. In addition, exploratory analyses comparing iGlarLixi with other GLP-1 receptor agonists or DPP-4 or SGLT2 inhibitors gave ICURs above $100,000 per QALY. However, a more complete economic analysis would need to be undertaken to better assess the cost-effectiveness of iGlarLixi in comparison with SGLT-2 and DPP-4 inhibitors as well as with other GLP-1 receptor agonists.

Information on the Pharmacoeconomic Submission

Summary of the Manufacturer's Pharmacoeconomic Submission

The manufacturer submitted a patient-level simulation model based on the United Kingdom Prospective Diabetes Study – Outcomes Model version two (UKPDS-OM2) comparing insulin glargine and lixisenatide (iGlarLixi) once daily with an insulin regimen consisting of a basal insulin once daily together with a rapid-acting insulin three times daily (basal-prandial three times daily), both regimens with or without metformin in type 2 diabetes mellitus (T2DM).[10] The perspective was that of the Canadian public health care payer. A 25-year time horizon in a 60-year-old individual was used, with a one-year cycle length.

A 10,000-patient cohort was developed using the baseline demographics and characteristics, cardiovascular complications, and physiological parameters that were stated to be representative of patients enrolled in the LixiLan-L clinical trial.

No direct comparison exists between iGlarLixi and the chosen comparator (i.e., basal-prandial insulin three times daily regimen). Therefore, the manufacturer opted for an approach in which the LixiLan-L trial was used to populate the iGlarLixi efficacy and safety parameters, while the results of an indirect comparison (IDC) and the GETGOAL DUO-2 trial (a study comparing insulin glargine and lixisenatide, with or without metformin, with insulin glargine and insulin glulisine once or three times daily, with or without metformin, in T2DM inadequately controlled on basal insulin, with or without up to three oral antidiabetes drugs) were used to populate the basal-prandial insulin three times daily arm.[11-13] Treatment effect was applied in the first year only as a one-time absolute impact on glycated hemoglobin (A1C; –1.11% for iGlarLixi and –1.17% for basal-prandial insulin) and body mass index (BMI; –0.24 for iGlarLixi and +0.71 for basal-prandial insulin three times daily). Microvascular (i.e., amputation, nephropathy, blindness, and leg/foot ulcers) and macrovascular (i.e., ischemic heart disease, myocardial infarction, heart failure, and stroke) events, as well as diabetes-related and all-cause deaths, were predicted by the model. Treatment-related adverse events (AEs), i.e., hypoglycemic events (severe, mild/moderate) and nausea were included, as long as the patient was alive. A disutility was applied when the BMI was above 25 kg/m^2. Utility values and Canadian public health care costs were taken from the medical literature and official sources, such as provincial formularies and schedules of benefits.[14]

The model base case was run probabilistically. Discounting (1.5% in the base case; 0% and 3% in sensitivity analyses) was applied to both costs and quality-adjusted life-years (QALYs). Several deterministic sensitivity analyses were performed. According to the manufacturer, 1,000 iterations of the 10,000-patient cohort were necessary to ensure convergence between the deterministic and the probabilistic results.[2,15]

Manufacturer's Base Case

The manufacturer reported that iGlarLixi, with or without metformin, was less expensive (savings of $17,898 over 25 years) and more effective (incremental QALYs of 0.10 over 25 years) than basal-prandial insulin three times daily, with or without metformin (Table 2), resulting in iGlarLixi being a dominant (i.e., more effective and less expensive) strategy in

74.6% of iterations. While iGlarLixi was less expensive in all iterations, a benefit in favour of the basal-prandial insulin three times daily regimen was observed in 25.4% of the iterations. The main driver of savings was medication cost (25-year costs: $52,226 for iGlarLixi and $70,368 for basal-prandial three times daily). The main drivers of QALY benefit were reduced hypoglycemic episodes (0.0633) and reduced BMI above 25 kg/m^2 (0.0276). There was also a smaller benefit from reduced heart failure (0.0008). These benefits compensated for iGlarLixi having a negative impact on other diabetes complications, in particular renal failure (–0.0074) and lixisenatide AEs, i.e., nausea (–0.0011). Overall, iGlarLixi was associated with a survival benefit of 0.018 years.

Table 2: Summary of Results of the Manufacturer's Base Case

	Total Costs ($)	Incremental Cost of iGlarLixi ($)	Total QALYs	Incremental QALYs of iGlarLixi	Incremental Cost per QALY
iGlarLixi	100,970	–17,898	12.12	0.0992	Dominant
Basal-prandial insulin	118,868		12.02		

iGlarLixi = fixed-ratio combination of insulin glargine and lixisenatide; QALY = quality-adjusted life-years.

Source: Manufacturer's pharmacoeconomic submission.[2]

Summary of Manufacturer's Sensitivity Analyses

Scenario analyses were performed on the manufacturer's base case using 0% and 3% discounting. The manufacturer's base case was also calculated deterministically, and a series of sensitivity analyses were performed on this manufacturer's deterministic base case. All scenario analyses gave similar results, i.e., iGlarLixi being dominant (more effective and less expensive), with the lowest incremental benefit (i.e., 0.04) observed when the disutility for a BMI above 25 kg/m^2 was removed, and the largest incremental benefit (i.e., 0.11) observed when the change in BMI was set to 1.080 kg/m^2 (i.e., a weight gain of approximately 3 kg) in the basal-prandial insulin three times daily treatment arm. The largest savings ($28,581) were observed when the iGlarLixi dose was reduced to 34.1 units (from 46.7 units in the manufacturer's base case), while the smallest savings ($3,750) were observed with a basal-prandial insulin three times daily therapy cost of $3,399.88 (i.e., assuming 40 units/day per the World Health Organization defined daily dose [WHO DDD]).[16]

Limitations of Manufacturer's Submission

CADTH identified the following key limitations of the manufacturer's pharmacoeconomic submission, which have notable implications for the economic analysis:

- The manufacturer's analysis did not include all relevant comparators in Canada. The comparator arm, a basal-prandial three times daily insulin regimen, with or without metformin, is considered the traditional approach in T2DM. This traditional approach has a known impact on body weight and resulting consequences on glycemic control and cardiovascular events.[17] The newly published 2018 Canadian Clinical Practice Guidelines suggests that sodium-glucose cotransporter-2 (SLGT2) or dipeptidyl peptidase 4 (DPP-4) inhibitors or other glucagon-like peptide-1 (GLP-1) receptor agonists should have been included as comparators.[7] However, as these guidelines have been only recently published, it is likely that there are still a fair number of T2DM patients on basal insulin in Canada. The risk of hypoglycemic events with insulin secretagogues such as sulfonylureas limits their use with insulin.[7] Thus, sulfonylureas

may not be considered a relevant option in patients already on basal insulin,[18] and hence not a relevant comparator to iGlarLixi.

- There is uncertainty concerning the size of iGlarLixi benefit. CADTH clinical reviewers identified several limitations of the LixiLan-L study used to populate the iGlarLixi arm of the model.[11] These include the open-label design; more patients in the insulin glargine treatment arm received the maximal dose of insulin glargine (60 units) than in the iGlarLixi arm, indicating possible suboptimal management of the comparator treatment (see CADTH Common Drug Review [CDR] Clinical Report for additional information); and the use of a titration algorithm different from what is used with insulin glargine in real life, according to the clinical expert involved in this review. Furthermore, there is no direct comparison available between iGlarLixi and basal-prandial insulin three times daily, and the manufacturer had to perform an IDC to provide the required data inputs. The manufacturer's report on the IDC concludes that the IDC was not considered appropriate to assess safety and efficacy.[12] CADTH clinical reviewers identified the following limitations of the manufacturer's IDC: the systematic review was not up to date, thus excluding several related trials published since their last search in 2016; the IDC used fixed-effects model results as the basis for interpretation, although random-effects model results would have been more appropriate for most end points (based on model fit); and the IDC did not address different study designs (i.e., open versus blinded) and different patient baseline characteristics (i.e., high baseline A1C levels) in sensitivity analyses.[8]
- There is also uncertainty concerning the duration of iGlarLixi benefit. The 30-week impact of iGlarLixi on surrogate markers, such as A1C and BMI, is used to estimate its long-term impact on micro- and macrovascular complications, as well as survival. Although control of blood glucose levels and management of cardiovascular risk factors (which include diet and body weight) are the mainstay of diabetes management, it is also recognized that treatment intensification is needed with time as the disease progresses.[7] Therefore, it is uncertain whether the effect of a 30-week treatment on a surrogate markers will be maintained over the lifetime, in particular versus the comparator, and hence, will translate into an impact on micro- and macrovascular events and survival. On the other hand, the manufacturer's chosen time horizon of 25 years led to 51% of the 10,000 individuals in the cohort being still alive at the end of the time horizon. A lifetime horizon (as recommended by CADTH Guidelines for the Economic Evaluation of Health Technologies in the case of chronic conditions) should have been tested.[9] For example, a CADTH therapeutic review published in 2017 on second-line T2DM agents included a 40-year horizon in its base case.[19]
- As noted in CADTH's therapeutic review of diabetes treatments in 2017, utilities associated with a BMI above 25 kg/m^2 have been derived from studies evaluating body weight interventions such as bariatric surgery, where the difference in weight was much larger than the change observed with some antidiabetic drugs.[19] It is unknown whether smaller effects on body weight would have a proportional effect on utility. Furthermore, as BMI is used to predict the impact on cardiovascular events, there is a potential for double-counting the long-term benefit of iGlarLixi on cardiovascular complications. In view of these, including a disutility for a BMI above 25 kg/m^2 should have been kept for sensitivity analyses. Removing this disutility reduces iGlarLixi benefit by 60%, as shown by one of the manufacturer's deterministic sensitivity analyses.
- The costs for the basal-prandial insulin three times daily regimen were overestimated. The manufacturer should have chosen the least costly alternative for both basal and prandial insulins (as recommended by CADTH Guidelines for the Economic Evaluation of Health Technologies), and the dose of prandial insulin should have been in line with

published literature.[9] Furthermore, a markup of 10% rather than the 8% allowed by the Ontario Drug Benefit (ODB) Formulary was used.[20] This overestimation favours iGlarLixi by overestimating the cost difference between the two regimens.

- The model run time is extremely long (i.e., more than three days) and therefore limits CADTH's ability to test other scenarios.

CADTH identified the following additional limitations with the manufacturer's pharmacoeconomic submission:

- The cost of metformin has not been included in the treatment and the comparator arms. This is inconsistent with the description of the comparison in the manufacturer's submission, but unlikely to make a significant difference in the results.[2]
- The standard error (SE) was approximated at 10% of average value for certain variables (e.g., disutility for renal failure, BMI above 25 kg/m^2, hypoglycemia, nausea). This is likely responsible for part of the large variability in the estimation of the QALYs observed at lower patient and iteration numbers with this model.
- All costs for diabetes-related complications are from old treatment patterns (1995 to 2005 for O'Reilly, 1994 to 1996 for O'Brien et al.).[21,22] It is very likely that patient management has changed since then, with an impact on costs that is difficult to estimate. Alternative costs — such as a combination of Ontario Case Costing Initiative values, values reported by O'Brien et al. for physician fees, and excess costs due to diabetes as reported by Goeree et al. — which would probably give values closer to the reality, could have been tested.[22-24]
- Errors, including typographic errors, are listed in Table 8.

CADTH Common Drug Review Reanalyses

CADTH was unable to address all of the limitations identified within the CADTH analyses (e.g., data quality of the IDC and the LixiLan-L study; duration of iGlarLixi benefit and subsequent impact on survival could not be varied owing to the structure of the model). CADTH undertook the following revisions to address the other limitations **(A)**:

- adjusting the costs of the basal-prandial three times daily insulin regimen in three ways:
  - reducing the dose of the prandial insulin to 40 units per day per the WHO DDD[16]
  - using the least costly alternative for both basal and prandial insulin, as described in Table 6
  - reducing the markup to 8% per ODB guidance.[20]
- removing the disutility associated with BMI above 25 kg/m^2
- correcting errors identified in data inputs.

In addition, some scenario analyses were conducted. These are:

- including an annual drift in body weight of approximately 0.5 kg per year, as observed in the first two years of the ELIXA trial[25] **(B)**
- testing alternative disutility values/scenarios in sensitivity analyses **(C)**:
  - disutility when BMI is above 30 kg/m^2 (per lixisenatide CDR)[3]
  - disutility for mild/moderate and severe hypoglycemic events.
- testing extreme assumptions for the use of insulin vials and cartridges **(D)**:
  - 100% cartridge use

  - 100% vial use.
- adding diabetes disposables costs (syringes/needles and lancets) **(E)**
- varying the time horizon **(F)**:
  - 100 years to capture the lifetime benefit
  - 5 years to reflect the uncertainty concerning the duration of iGlarLixi benefit.

Finally, exploratory analyses were performed using different comparator arms. The efficacy and safety inputs for these exploratory analyses were taken from the manufacturer's IDC when possible (despite its limitations described previously) or from targeted searches of the medical literature, and determined to be appropriate by the CADTH health economics reviewers. However, in view of the limited time available to perform these analyses, the limited amount of evidence identified, and the limitations of the quality of analyses identified, these results must be viewed with caution. These exploratory analyses included:

- basal insulin + SGLT2 inhibitors
- basal insulin + DPP-4 inhibitors
- basal insulin + other GLP-1 receptor agonists.

Note that the risk of hypoglycemic events with insulin secretagogues, such as sulfonylureas, limits their use with insulin.[7] Thus, sulfonylureas may not be considered a relevant option in patients already on basal insulin,[18] hence, they are not a relevant comparator to iGlarLixi. Detailed data inputs for the CADTH analyses can be found in Appendix 5, Table 14.

According to CADTH analyses, the incremental cost-utility ratio (ICUR) for iGlarLixi, with or without metformin, when compared with a basal-prandial three times daily insulin regimen, with or without metformin, is estimated at $170,875 per QALY (Table 3). iGlarLixi increases lifetime costs by $10,964, while the incremental benefit is 0.06416 QALY. The survival benefit remained at 0.018 life-year (LY), as this benefit is calculated by the model based on the impact on A1C and body weight (two parameters that were not changed in CADTH analyses).The lowest ICUR ($72,255 per QALY) is observed in a scenario that includes the costs of disposables (syringes/needles and lancets) in the analysis, while the highest ICUR ($19,420,053 per QALY) is observed when a different set of disutilities is used for hypoglycemic events. CADTH noted that the ICUR with alternative disutility values for hypoglycemic events varied notably over multiple model runs, indicating considerable uncertainty in the model associated with this parameter. However, all additional runs of this particular scenario gave ICURs well above $1,000,000 per QALY. Furthermore, the ICUR is above $100,000 per QALY in the exploratory analyses comparing iGlarLixi with other GLP-1 receptor agonists, or with DPP-4 or SGLT2 inhibitors. A price reduction of 20% would be needed to achieve an ICUR of $50,000 per QALY when comparing iGlarLixi with basal-prandial insulin three times daily, while a price reduction of approximately 25% would be required to achieve an ICUR below $25,000 per QALY. Additional results can be found in Appendix 5, Table 15.

Table 3: Results From CADTH Reanalyses

Scenario	Element		Total Costs	Total QALYs	ICUR
Manufacturer's base case		iGlarLixi	$100,970	12.1233	Dominant
		Basal-prandial	$118,868	12.0241	
		Incremental analysis	–$17,898	0.09917	
CADTH base case (A)		iGlarLixi	$101,064	12.0427	$170,875
		Basal-prandial	$90,100	11.9786	
		Incremental analysis	$10,964	0.06416	
CADTH scenario analysis (B)	Body weight drift over time	iGlarLixi	$101,092	12.0448	$155,769
		Basal-prandial	$90,192	11.9749	
		Incremental analysis	$10,900	0.06998	
CADTH scenario analysis (C)	BMI disutility	iGlarLixi	$101,119	11.9819	$117,401
		Basal-prandial	$90,203	11,8889	
		Incremental analysis	$10,916	0.01220	
	Disutility for hypoglycemic events	iGlarLixi	$101,223	12.2244	$19,420,053
		Basal-prandial	$90,211	12.2239	
		Incremental analysis	$10,896	0.00057	
CADTH scenario analysis (D)	100% cartridge use	iGlarLixi	$101,091	12.0512	$147,145
		Basal-prandial	$90,346	11.9782	
		Incremental analysis	$10,744	0.07302	
	100% vial use	iGlarLixi	$101,148	12.0476	$210,494
		Basal-prandial	86,398	11.9776	
		Incremental analysis	$14,750	0.07007	
CADTH scenario analysis (E)	Disposable costs	iGlarLixi	$103,662	12.0447	$72,255
		Basal-prandial	$98,555	11.9740	
		Incremental analysis	$5,106	0.07067	
CADTH scenario analysis (F)	100-year time horizon	iGlarLixi	$138,862	15.5793	$119,549
		Basal-prandial	$124,416	15.4584	
		Incremental analysis	$14,446	0.12083	
	5-year time horizon	iGlarLixi	$24,147	3.4808	$179,646
		Basal-prandial	$21,063	3.4637	
		Incremental analysis	$3,070	0.01717	
CADTH exploratory analyses	Additional comparator: basal insulin + GLP-1 receptor agonist	iGlarLixi	$101,133	12.0474	$100,580
		GLP-1+basal	$94,017	11.9766	
		Incremental analysis	$7,116	0.07075	
	Additional comparator: basal insulin + DPP-4 inhibitor	iGlarLixi	$101,166	12.0505	$768,362
		DPP-4 + basal	$76,520	12.0184	
		Incremental analysis	$24,646	0.03208	
	Additional comparator: basal insulin + SGLT2 inhibitor	iGlarLixi	$101,177	12.0403	$515,411
		SGLT2 + basal	$79,450	11.9982	
		Incremental analysis	$21,727	0.04216	

DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; ICUR = Incremental cost-utility ratio; iGlarLixi = fixed-ratio combination of insulin glargine and lixisenatide; QALY = quality-adjusted life-year; SGLT2 = sodium-glucose cotransporter-2.

In view of the ICUR, CADTH conducted price-reduction scenarios (Table 4). These analyses showed that a 20% to 25% reduction in iGlarLixi price would be needed to bring the ICUR in the $25,000 to $50,000 per QALY range.

Table 4: CADTH Reanalysis Price-Reduction Scenarios

ICURs of iGlarLixi Versus Basal-Prandial t.i.d. Insulin Regimen			
Price	**Annual Cost (15 to 60 units per day)**	**Base-Case Analysis Submitted by Manufacturer**	**Reanalysis by CADTH**
Submitted	$694 to $2,770	Dominant	$170,875
10% reduction	$674 to $2,695		$108,337[a]
15% reduction	$636 to $2,546		$79,199[a]
20% reduction	$599 to $2,396		$50,060[a]
24% reduction	$569 to $2,276		$26,749[a]
25% reduction	$562 to $2,246		$20,921[a]
30% reduction	$524 to $2,096		Dominant[a]

ICUR = incremental cost-utility ratio; t.i.d. = three times daily.

[a] Deterministic analysis.

Issues for Consideration

GLP-1 receptor agonists, including lixisenatide, have a coverage that is variable across the different provincial formularies. The same is true for SGLT-2 and DPP-4 inhibitors, which may also be accompanied by a therapeutic note indicating that they should be used in patients for whom insulin is not an option, hence, in theory, precluding their use in patients who are already on basal insulin.

Lixisenatide is considered to have a neutral effect on macro-cardiovascular outcomes, contrary to the effect of some other GLP-1 receptor agonists. Thus, lixisenatide may not be the preferred GLP-1 option when such impact is considered.[7]

Retitration of basal insulin might be necessary in patients who are on another basal insulin product when treatment is initiated, which may be a barrier to use for some patients, given the risks of hypoglycemia associated with any insulin treatment titration. Furthermore, as for any combination product, the fixed ratio may limit the use of the product.

Patient Input

Patient input gathered by Diabetes Canada was obtained from an online survey of 847 individuals (790 patients and 57 caregivers) conducted between October 2016 and April 2018. Approximately 70% of the respondents were more than 55 years of age, and 60% had been diagnosed for more than 10 years. Apart from curing the disease, patient expectations for new diabetes treatments included proven efficacy and safety without weight gain or hypoglycemia, affordable costs, timely coverage by public and private plans, ease of administration, and allowing flexibility with food intake and choices. They also prefer the least number of medications to be administered each day, and they prefer to avoid injections.

Efficacy, safety, weight, hypoglycemia, dosage, and costs were included in the manufacturer's model. While iGlarLixi does meet the patients' expectation of reducing the

number of daily administrations, it does not avoid injections. iGlarLixi seems to limit weight gain and hypoglycemic events when compared with a basal-prandial three times daily insulin regimen, but this advantage may not stand when compared with other regimens.

Conclusions

CADTH analyses could not address all identified limitations, due to the quality of the clinical data (e.g., IDC and LixiLan-L study), the structure of the model (e.g., duration of the iGlarLixi benefit and resulting impact on survival), and the extremely long model run time, which limited the number of scenario analyses that CADTH could perform. This means that results from CADTH analyses should be viewed with caution, as there is a lot of uncertainty concerning the benefit of iGlarLixi, and the extent of this uncertainty could not be fully tested by CADTH.

After accounting for alternative comparator costs, removing a disutility based on higher BMI, and correcting data input errors, the CADTH base-case ICUR for iGlarLixi (with or without metformin) compared with a basal-prandial insulin three times daily regimen (with or without metformin) was $170,875 per QALY. A price reduction of 20% would be needed to achieve an ICUR of $50,000 per QALY when comparing iGlarLixi with basal-prandial three times daily, while a price reduction of approximately 25% would be required to achieve an ICUR below $25,000 per QALY. In analyses undertaken by CADTH for the revised base case, no ICURs were lower than $72,255 per QALY.

In addition, exploratory analyses comparing iGlarLixi with other GLP-1 receptor agonists or DPP-4 or SGLT2 inhibitors gave ICURs above $100,000 per QALY. However, a more complete economic analysis would need to be undertaken to better assess the cost-effectiveness of iGlarLixi in comparison with SGLT-2 and DPP-4 inhibitors, as well as with other GLP-1 receptor agonists.

Appendix 1: Cost Comparison

The comparators presented in the Table 5 have been deemed appropriate by clinical experts. Comparators may be recommended (appropriate) practice, rather than actual practice. Comparators are not restricted to drugs but may include devices or procedures. Costs are manufacturer's list prices, unless otherwise specified. Existing Product Listing Agreements are not reflected in the table, and, as a result, Table 5 may not represent the actual costs to public drug plans.

Table 5: CADTH Cost Comparison for Insulin Glargine and Lixisenatide in Type 2 Diabetes Mellitus (Noninsulin Products)

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Daily Drug Cost ($)	Average Annual Drug Cost ($)
iGlarLixi; insulin glargine and lixisenatide (Soliqua)	**100 units/mL + 33 mcg/mL**	**3 mL pre-filled pen (SoloSTAR)**	**$37.9600[a]**	**15 to 60 units of insulin glargine and 5 to 20 mcg lixisenatide once daily. Starting dose must not exceed 10 mcg lixisenatide. Maximal daily dose: 60 units**	**$1.90 (15 units) to $7.59 (60 units)**	**$694 (15 units) to $2,770 (60 units)**
Glucagon-like peptide-1 (GLP-1) receptor agonist						
Lixisenatide (Adlyxine)	10 mcg 20 mcg	14-dose pre-filled pen (3 mL)	56.9800[b] per pen	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
Dulaglutide (Trulicity)	0.75 mg/0.5 mL 1.5 mg/0.5 mL	4 × 0.5 mL pre-filled pen	49.7900[b] per pen	0.75 mg – 1.5 mg once weekly	7.11	2,596
Exenatide (Byetta)	1.2 mL	60 × 5 mcg or 10 mcg-dose pre-filled pen (250 mcg/mL)	119.7250[b] per mL	5 to 10 mcg twice daily	4.79	1,748
	2.4 mL		49.8625[b] per mL			
Exenatide (Bydureon)	2 mg	2 mg pre-filled pen (extended release)	49.4850[b] per pen	2 mg once weekly	7.07	2,580
Liraglutide (Victoza)	2 × 3 mL 3 × 3 mL	Pre-filled pen (6 mg/mL)	29.0133[b] per mL	1.2 mg to 1.8 mg daily	5.80 to 8.70	2,118 to 3,177
Sulfonylureas						
Gliclazide (generics)	80 mg	Tablet	0.0931	80 to 320 mg daily (in divided doses if > 160 mg daily)	0.09 to 0.37	34 to 136
Gliclazide long-acting (generics)	30 mg	ER tablet	0.0931	30 mg to 120 mg daily	0.06 to 0.13	22 to 44
	60 mg		0.0632			
Glimepiride (generics)	1 mg 2 mg	Tablet	0.4900	1 mg to 4 mg daily	0.49	179

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Daily Drug Cost ($)	Average Annual Drug Cost ($)
	4 mg					
Glyburide (generics)	2.5 mg	Tablet	0.0321	2.5 mg to 20 mg daily (in divided doses if > 10 mg daily)	0.03 to 0.23	12 to 84
	5.0 mg		0.0574			
Thiazolidinediones (TZDs)						
Pioglitazone (generics)	15 mg	Tablet	0.3800[c]	15 mg to 45 mg daily	0.38 to 0.81	139 to 295
	30 mg		0.5360[c]			
	45 mg		0.8075[c]			
Rosiglitazone (generics)	2 mg	Tablet	1.1692	4 to 8 mg daily	1.83 to 2.62	670 to 958
	4 mg		1.8346			
	8 mg		2.6235			
Meglitinides						
Repaglinide (generics)	0.5 mg	Tablet	0.2083	0.5 mg to 2 mg daily	0.21 to 0.24	76 to 89
	1 mg		0.2165			
	2 mg		0.2441			
Alpha-glucosidase inhibitors						
Acarbose (Glucobay)	50 mg	Tablet	0.2695	50 to 100 mg three times daily	0.81 to 1.12	295 to 409
	100 mg		0.3732			
Sodium-glucose transport protein (SGLT2) inhibitors						
Empagliflozin (Jardiance)	10 mg 25 mg	Tablet	2.6177	10 or 25 mg daily	2.62	955
Canagliflozin (Invokana)	100 mg 300 mg	Tablet	2.7627	100 or 300 mg daily	2.76	1,008
Dapagliflozin (Forxiga)	5 mg 10 mg	Tablet	2.6750	5 or 10 mg daily	2.68	976
SGLT2 inhibitor plus metformin fixed-dose combinations						
Dapagliflozin and metformin (Xigduo)	5 mg/850 mg 5 mg/1,000 mg	Tablet	1.2250	One tablet twice daily	2.45	894
Canagliflozin and metformin (Invokamet)	50 mg and 500 mg, 850 mg, or 1,000 mg 150 mg and 500 mg, 850 mg, or 1,000 mg	Tablet	1.5660[b]	One tablet twice daily	3.13	1,143
Empagliflozin and metformin (Synjardy)	5 mg and 500 mg, 850 mg, or 1,000 mg 12.5 mg and 500 mg, 850 mg, or 1,000 mg	Tablet	1.3783[b]	One tablet twice daily	2.76	1,006
Dipeptidyl peptidase-4 (DPP-4) inhibitors						
Sitagliptin	25 mg	Tablet	3.0932	100 mg daily	3.09	1,129

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Daily Drug Cost ($)	Average Annual Drug Cost ($)
(Januvia)	50 mg 100 mg					
Saxagliptin (Onglyza)	2.5 mg	Tablet	2.4760	5 mg daily	2.48	904 to 1,083
	5.0 mg		2.9680		2.97	
Linagliptin (Trajenta)	5 mg	Tablet	2.5500	5 mg daily	2.55	931
Alogliptin (Nesina)	6.25 mg 12.5 mg 25 mg	Tablet	2.2000[b]	25 mg daily	2.20	803
DPP-4 inhibitor plus metformin fixed-dose combinations						
Alogliptin and metformin (Kazano)	12.5 mg and 500 mg, 850 mg, or 1,000 mg	Tablet	1.1950[c]	Two tablets daily	2.39	872
Linagliptin and metformin (Jentadueto)	2.5 mg and 500 mg, 850 mg, or 1,000 mg	Tablet	1.3337	Two tablets daily	2.67	974
Saxagliptin and metformin (Komboglyze)	2.5 mg and 500 mg, 850 mg, or 1,000 mg	Tablet	1.2700	Two tablets daily	2.54	927
Sitagliptin and metformin (Janumet and Janumet XR)	50 mg and 500 mg, 850 mg, or 1,000 mg	Tablet	1.6779	Twice daily. Maximal daily dose: 100 mg sitagliptin and 2,000 mg metformin	3.36	1,225
	50 mg and 500 mg or 50 mg and 1,000 mg	ER tablet	1.6779	Once daily. Maximal daily: 100 mg sitagliptin and 2,000 mg metformin	1.68 to 3.36	613 to 1,225
	100 mg and 1,000 mg		3.3557		3.36	1,225

ER = extended release; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; SGLT2 = sodium-glucose cotransporter-2; TZD = thiazolidinedione; XR = extended release.

Note: All prices are from the Ontario Drug Benefit Formulary (accessed June 2018) unless otherwise indicated and do not include dispensing fees.

[a] Manufacturer-submitted price.

[b] Delta PA: IQVIA (June 2018).[26]

[c] Saskatchewan Drug Formulary (June 2018).[27]

Table 6: CADTH Cost Comparison for Insulin Glargine and Lixisenatide in Type 2 Diabetes Mellitus (Insulin Products)

Drug/ Comparator	Strength	Dosage Form	Price ($) Per Package Unless Specified Otherwise	Recommended Dose[a]	Average Cost per Day ($)
Long-acting insulin analogues (basal)					
Insulin degludec (Tresiba)	100 units/mL	5 × 3 mL pre-filled pen	7.2593[b] per mL	40 units per day	2.90
	200 units/mL	3 × 3 mL pre-filled pen	14.5189[b] per mL		
Insulin glargine (Lantus)	100 units/mL	5 × 3 mL cartridge 5 × 3 mL disposable pen (SoloSTAR)	92.8500	40 units per day	2.47
		10 mL vial	61.6900		
Insulin glargine (Basaglar)	100 units/mL	5 × 3 mL cartridge 5 × 3 mL pre-filled pen	69.6375	40 units per day	1.86
Insulin detemir (Levemir)	100 units/mL	5 × 3 mL cartridge 5 × 3 mL disposable pen	108.8900	40 units per day	2.90
Rapid-acting insulins (prandial)					
Insulin aspart (NovoRapid)	100 units/mL	5 × 3 mL cartridge	60.6300	40 units per day	1.20 to 1.68
		5 × 3 mL disposable pen	63.1200		
		10 mL vial	29.9000		
Insulin glulisine (Apidra)	100 units/mL	5 × 3 mL cartridge	51.4500	40 units per day	1.04 to 1.38
		5 × 3 mL disposable pen	51.9500		
		10 mL vial	25.9600		
Insulin lispro (Humalog)	100 units/mL	5 × 3 mL cartridge	58.8800	40 units per day	1.19 to 1.57
		5 × 3 mL disposable	58.4600		
		10 mL vial	29.6400		
	200 units/mL	5 × 3 mL disposable pen	108.8200		
Regular human insulin (Humulin R)	100 units/mL	5 × 3 mL cartridge	48.3300	40 units per day	0.99 to 1.29
		10 mL vial	24.6300		
Regular human insulin (Novolin ge Toronto)	100 units/mL	5 × 3 mL cartridge	46.6100	40 units per day	0.95 to 1.24
		10 mL vial	23.7400		

All prices are from the Ontario Drug Benefit Formulary (accessed June 2018) unless otherwise indicated and do not include dispensing fees.

[a] WHO-defined daily dose.

[b] Delta PA: IQVIA (June 2018).[26]

Appendix 2: Summary of Key Outcomes

Table 7: When Considering Only Costs, Outcomes, and Quality of Life, How Attractive Is iGlarLixi Relative to the Basal-Prandial Insulin Regimen?

iGlarLixi Versus Basal-Prandial Insulin t.i.d.	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)				X		
Drug treatment costs alone					X	
Clinical outcomes		X				
Quality of life		X				
Incremental CE ratio or net benefit calculation (CADTH base case)	$170,875 per QALY $888,493 per life-year gained					

CE = cost-effectiveness; NA = not applicable; QALY = quality-adjusted life-year; t.i.d. = three times daily.

Appendix 3: Additional Information

Table 8: Submission Quality

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?		X	
Comments	There are several important typographic and other errors that made the review more laborious. For example: • Table 8.4 of Manufacturer's pharmacoeconomic report: numbers for the differences are off by one line, starting at "ulcer decrement." • Baseline values from the iGlarLixi group of the LixiLan-L trial were used to generate the model's patient cohort. A more representative approach would have been to use the values for both groups together. This would have avoided underestimation or overestimation of some characteristics. For example, [redacted]% of the entire cohort had a history of stroke (ischemic, hemorrhagic, unknown, or transient ischemic attack) versus [redacted]% in the iGlarLixi group.[11] Furthermore, values were not accurately taken from the LixiLan-L trial (see below). This will likely impact both groups similarly, with likely more cardiovascular events and mortality, which may or may not result in different incremental results. • The presence of ischemic heart disease at baseline was underestimated. In Table 16.2.4.3.2 (Medical history of cardiovascular and cerebrovascular events at screening) of the LixiLan-L study report, [redacted]% of iGlarLixi patients ([redacted]% of the entire study cohort) are reported to have had angina pectoris, with [redacted]% ([redacted]% of the entire cohort) having unstable angina.[11] The manufacturer used the [redacted]% value for ischemic coronary artery disorder from the medical or surgical history at screening table (16.2.4.3.1), while an additional [redacted]% in that same table had coronary artery disorder. Although there are discrepancies between the 2 tables, ischemic heart disease was present in at least [redacted]% of patients and possibly [redacted]% of patients on iGlarLixi. • The presence of albuminuria at baseline was also underestimated. Table 16.2.4.2.1 of the LixiLan-L study report shows that 20.2% of patients had microalbuminuria and 6.0% had macroalbuminuria, compared with [redacted]% used by the manufacturer in the model.[11] • The presence of renal insufficiency at baseline was also underestimated. Table 16.2.4.2.1 (page 14) of the LixiLan-L study report states that [redacted]% of iGlarLixi patients had moderate to severe renal insufficiency, compared with [redacted]% used by the manufacturer in the model.[11] • A value of 1.11 for iGlarLixi efficacy on A1C was used, rather than 1.13, as reported in the LixiLan-L study report.[11]		
Was the material included (content) sufficient?	X		
Comments	None		
Was the submission well organized and was information easy to locate?		X	
Comments	See comments on typographic and other errors		

Table 9: Author Information

Authors of the Pharmacoeconomic Evaluation Submitted to CADTH Common Drug Review
☐ 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	

Appendix 4: Reviewer Worksheets

Manufacturer's Model Structure and Data Inputs

Model Structure

The manufacturer submitted a type 2 diabetes mellitus (T2DM) patient-level simulation model based on the United Kingdom Prospective Diabetes Study – Outcomes Model version 2 (UKPDS-OM2) comparing iGlarLixi once daily with a basal-prandial insulin regimen, i.e., basal insulin once daily plus rapid-acting insulin three times daily (basal-prandial three times daily) — both regimens with or without metformin. The choice of the comparator was based on opinion from one clinical expert.

A 10,000-patient cohort was built with baseline demographics/characteristics (i.e., age at diagnosis, years since diagnosis at entry in model, gender, ethnicity, current smoker, albuminuria, peripheral vascular disease, atrial fibrillation), complications (i.e., ischemic heart disease, myocardial infarction, heart failure, stroke, amputation, blindness, renal failure), and physiological parameters (i.e., glycated hemoglobin [A1C], body mass index [BMI], high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, heart rate, estimated glomerular filtration rate, white blood cell count, hemoglobin, systolic blood pressure) representative of patients enrolled in the LixiLan-L clinical trial according to the manufacturer. A1C and systolic blood pressure were allowed to drift over time, according to the UKPDS 68 risk equations. All other variables were kept static over time.

Parameter uncertainty was addressed in two ways. First, each of the 10,000 patients in the cohort had his/her baseline characteristics and cardiovascular risk factors randomly selected from defined distribution parameters. This was used to estimate future clinical events and adverse events as well as related costs and quality-adjusted life-years (QALYs). In addition, these calculations were iterated 1,000 times by varying utilities, costs, efficacy, and safety parameters according to defined distribution parameters. Discounting was applied to both costs and QALYs (1.5% in the base case; 0% and 3% in sensitivity analyses). Sensitivity analyses performed by the manufacturer are listed in Table 10.

Table 10: Manufacturer's Sensitivity Analyses

Parameter	Value(s) Tested	Type of Analysis
Time horizon	5 and 10 years	Deterministic
Discounting rates	0% and 3%	Probabilistic
Markup and dispensing fees	Excluded	Deterministic
Injection supplies	Excluded	Deterministic
Self-monitoring glucose testing frequency	iGlarLixi 1 per day; basal-prandial insulin 4 per day	Deterministic
Self-monitoring glucose testing costs	Excluded	Deterministic
Insulin costs	Lowest cost basal-prandial insulin regimen ($3,399.98)	Deterministic
iGlarLixi dose	34.1 units and 59.3 units	Deterministic
Daily dose of prandial insulin	40 units; 65.9 units; 69 units	Deterministic
Vial use for prandial insulin	14.2% vial; 21.3% vial	Deterministic
iGlarLixi efficacy on A1C	–1.222; –0.998	Deterministic
Basal-prandial insulin efficacy on A1C	–1.006; –1.334	Deterministic
BMI change with iGlarLixi	–3.66; –0.112	Deterministic

Parameter	Value(s) Tested	Type of Analysis
BMI change with basal-prandial insulin	0.347; 1.080	Deterministic
Utility for BMI	Excluded	Deterministic
Utility for hypoglycemic events	–0.000004767	Deterministic
Utility for severe hypoglycemia	–0.01	Deterministic

A1C = glycated hemoglobin; BMI = body mass index; iGlarLixi = fixed-ratio combination of insulin glargine and lixisenatide.

Data Inputs

The LixiLan-L trial was used to populate iGlarLixi efficacy and safety.[11] The methods and results of this study are provided in the CADTH Common Drug Review (CDR) Clinical Report.[8] According to the clinical expert involved with this review, transferability of the study results to Canada is acceptable.

An indirect comparison (IDC) was used to estimate efficacy and safety of the basal-prandial regimen in relation to iGlarLixi.[12] The IDC included three patient populations: 1) insulin-naive inadequately controlled on two oral antidiabetes drugs; 2) insulin-naive inadequately controlled on one ± two oral antidiabetes drugs; and 3) insulin-exposed (inadequately controlled on insulin therapy). Only the insulin-exposed population was of interest for the economic analysis. Outcomes of interest included a) A1C change from baseline; b) body weight change from baseline; c) A1C < 6.5%; d) A1C < 7.0%; and e) hypoglycemic events. Three basal-prandial insulin regimens were analyzed:

- basal insulin once daily + rapid-acting insulin three times daily
- basal insulin once daily + rapid-acting insulin once daily + one oral antidiabetes drug
- basal insulin once daily + rapid-acting insulin three times daily + one oral antidiabetes drug (basal-prandial insulin three times daily, considered the most relevant for the economic evaluation)

The GETGOAL DUO-2 trial was used to populate the rate of severe hypoglycemic events and the rate of nausea in the control arm.[13] The GETGOAL DUO-2 trial was a randomized controlled study comparing lixisenatide plus insulin glargine (iGlarLixi) with insulin glulisine either as a basal-plus (insulin glargine + insulin glulisine once daily) or basal-bolus (insulin glargine + insulin glulisine three times daily) regimen, with or without metformin, in 893 T2DM patients. The basal-bolus arm was of interest for the model. Table 11 gives a description of the data sources used by the manufacturer.

Table 11: Data Sources

Data Input	Description of Data Source	Comment
Baseline characteristics	From the iGlarLixi arm of the LixiLan-L trial[11]	Study population similar to the Canadian population who would be candidates for iGlarLixi treatment, according to clinical expert involved in this review
Efficacy	**iGlarLixi:** LixiLan-L trial[11]	The change in A1C, as reported in the LixiLan-L study report (Table 16, p. 87) is –1.13 (versus –1.11 as used by the manufacturer).[11] Change observed at 30 weeks in the LixiLan-L study is assumed to be sustained over time and for the entire modelling horizon; however, A1C is allowed to drift over time per UKPDS 68 risk equations.[10] BMI change was estimated from change in weight and average height.
	Basal-prandial: manufacturer's IDC[12]	The IDC result of a +0.06% change from baseline (iGlarLixi versus control) was used to estimate the absolute change from baseline for the control arm (i.e., –1.11 + –0.06= –1.17).[12] The same process was applied to body weight and hence BMI.
Natural history	UKPDS 82 risk equations, with all risk factors static over time except A1C and systolic blood pressure[10]	Best data available, despite being outdated
Utilities	Baseline utility: 0.785 (SE 0.0051)[28]	Mirroring value from CADTH therapeutic review of 2017, although correct reference should be Clarke et al. (2002).[19,29] SE value was not reported in original paper, and it is unknown how the manufacturer obtained the 0.0041 value.
	Disutility value for IHD, MI, HF, stroke, and blindness from Sullivan et al.[30,31] Disutility for amputation and renal failure from Clarke et al.[28]	Mirroring value in CADTH therapeutic review of 2017.[19] However, for renal failure, CADTH reference was indeed the default value from UKPDS-OM at the time the model was run (now value is –0.33).[32] Disutility for renal failure was not reported in Clarke et al. (2002) or Clarke et al. (2004).[28,29] SE was assumed by the manufacturer to be 10% of average. A set of disutility values in diabetic patients has been published recently; however, EQ-5D values directly collected from patients were supplemented with SF-12 values mapped to EQ-5D.[33]
	Disutility for diabetic ulcer from Redekop et al.[34]	Disutility obtained by subtracting "active uninfected ulcer" from "no active ulcer." SD is computed from the SE of each average, but transforming into SE has been forgotten. SE should have been 0.0026. All utilities obtained from TTO (vignette) in 96 individuals from the general population. TTO method usually gives higher estimates than EQ-5D. For example, ICD9-707 (chronic ulcer of the skin) was associated with a disutility of –0.0272 in Sullivan's catalogue.[31] Foot ulcer was not specifically mentioned in CADTH therapeutic review of 2017, but is an outcome of the UKPDS-OM, with a default value of –0.210[19,32]
	Disutility for BMI above 25 kg/m^2 per CADTH therapeutic review of 2017[19]	CADTH therapeutic review 2017 is cited by the manufacturer for this value. However, this value was only used by CADTH in the sensitivity analysis. CADTH base case in this particular therapeutic review did not include a

Data Input	Description of Data Source	Comment
		disutility for weight gain, as the disutility values reported with weight gain have been derived from much greater weight differences (i.e., 13 kg to 30 kg).[19] This particular value was calculated from the weighted averages for men and women with a BMI between 28 and 31, as reported in NICE Clinical Guideline 43 (Obesity prevention) and considering 56% of women, which is consistent with LixiLan-L patient characteristics.[11,35] SE was not reported in the original reference and had been assumed to be equal to 10% of average.
	Disutility for mild/moderate and severe hypoglycemia from Currie et al.[36]	Mirroring value in CADTH therapeutic review of 2017.[19] No SE reported in original paper. SE estimated by manufacturer at 10% of average. CADTH therapeutic review of 2017 performed a sensitivity analysis with alternative values from NICE guidance on insulin glargine, i.e., 0.0052 for mild/moderate and 0.01 for severe.[19]
	Disutility for nausea, per Matza et al.[37]	Matza et al. assessed utilities in 129 individuals with T2DM using the standard gamble method.[37] Value for nausea/vomiting is –0.04 (SD 0.07). Manufacturer applied this value to the first 6 months only and estimated SE at 10% of value rather than using published SD. SE value should have been 0.003. Furthermore, value was applied to nausea only (not to vomiting). Per manufacturer, NICE assumed nausea was present only for 6 weeks; hence, manufacturer's approach is more conservative. No utility decrement was included in CADTH therapeutic review of 2017.[19]
Adverse events	**iGlarLixi:** Minor/moderate and severe hypoglycemia as well as nausea from LixiLan-L trial[11]	All adverse events are add-on to UKPDS-OM2. Of note, 29 of the 367 iGlarLixi patients discontinued treatment (12, due to AEs) versus 10 in the control arm (3, due to AEs).
		Per LixiLan-L trial, the rate of minor/moderate hypoglycemic events per patient-year was 3.02 for iGlarLixi and 4.19 per patient-year for iGlar.[11] According to the manufacturer, the model cannot discriminate treatment difference if the annual rate is larger than 1 per patient-year; the rate was adjusted to maintain the relative difference between iGlarLixi and iGlar, i.e., 100% for iGlar and 72.08% (i.e., 3.02/4.19) for iGlarLixi. Note: the presence of minor/moderate hypoglycemia in the model is a binary variable based on a random draw being lower than a proportion of events; hence, if both proportions are above 100%, no difference between treatments can be seen. This, however, underestimates the impact of the adverse event.
		Nausea AEs from the LixiLan-L trial (i.e., [redacted] per patient-year) were considered to have all occurred during the first 6 months, in view of the transient nature of the event, giving a rate of [redacted]% of individuals experiencing nausea.[11] Vomiting was not considered.

Data Input	Description of Data Source	Comment
	Basal-prandial: Minor (moderate) hypoglycemia annual rate from the manufacturer's IDC[12] Severe hypoglycemia and nausea annual rates from the GETGOAL DUO-2 trial[13]	Minor (moderate) hypoglycemia: same method as for other parameters in which the IDC was used. Severe hypoglycemia was not an end point of the IDC.[12] The GETGOAL DUO-2 trial was used to populate this parameter.[13] No difference in severe hypoglycemic events was observed in the GETGOAL DUO-2 trial; hence, the same rate of major hypoglycemic events was used for both groups. The GETGOAL DUO-2 trial showed that nausea in control arm was [redacted] that of iGlarLixi.[13] Note that nausea was higher in the iGlarLixi arm of the GETGOAL DUO-2 trial compared with the LixiLan-L trial ([redacted] versus [redacted] events per patient-year).[11,13]
Mortality	UKPDS 86 risk equations[10]	These are based on UK individuals newly diagnosed with T2DM in 1977 to 1991. Since then, T2DM and cardiovascular disease management has changed significantly, which has likely affected survival. However, CADTH recognized that the UKPDS represents the longest survey of a population with diabetes.
Resource use and costs		
Drug (annual)	Acquisition costs, dispensing fees, and glucose strips from ODB formulary. Costs of syringes/needles and lancets from Internet.	Manufacturer's price for iGlarLixi, ODB for basal-prandial insulin regimen and supplies. Basal-prandial insulin acquisition costs are largely overestimated: • A weighted average, based on supplied market data, was used for insulin products, rather than considering the least costly alternative. This has a greater impact on basal insulin than prandial insulin. Eli Lilly product (insulin glargine – Basaglar) and Humulin N and NPH are much less expensive than the weighted average used by the manufacturer ($0.0246 to $0.0464 per unit versus $0.06227). For prandial insulin, the less costly alternative would be 0.0237 per unit, compared with $0.03861 used by the manufacturer. • The manufacturer used a 10% markup on manufacturer's price and ODB price and cites the CADTH therapeutic review of 2017as the source. CADTH used 8%, per ODB rules.[19,20] • Daily dose of prandial insulin was assumed to be 1.00 units/kg for vials and 0.98 units/kg for cartridges (86.47 units per day), per CADTH 2008.[38] Studies included in the IDC should have been used as a source for this parameter, as they represent more recent and true usage rather than experts' opinion, as in the CADTH analysis published in 2008.[12,38] For example, in the GETGOAL DUO-2 trial, the average daily insulin glulisine dose was 20 units (SD 13) for an average of 0.22 units/kg.[13] In the 4B study, the average dose of insulin lispro was 42.1 units (SD 30.8) or 0.47 units/kg.[39] These values are less than 50% of the values used by the manufacturer.

Data Input	Description of Data Source	Comment
		Daily dose of iGlarLixi was assumed to be 46.7 units per week 30 dose in the LixiLan-L trial.[40] All patients were assumed to use the 15-60 SoloSTAR pen (price: $37.96). Daily dose of basal insulin was assumed to be 46.7 units based on week 30 daily dose of insulin glargine in LixiLan-L trial.[40] OAD not included in costs. This is not consistent with the indication, but OAD costs are likely to be the same in both groups. Dispensing fees ($8.83) were incurred 4 times per year, consistent with ODB Program rules, in particular for dispensing medications for chronic use.[20,41] CADTH was unable to verify costs for syringes/needles and lancets. Glucose monitoring assumption: 4 per day for basal-prandial regimen, 2 per day for iGlarLixi
Administration		Not applicable: medication is self-administered. Supplies are included in drug costs.
Event	Costs for IHD, MI, HF, stroke, amputation, blindness, and renal failure from O'Reilly.[21]	O'Reilly (2006) CADTH therapeutic review of 2017 The values from O'Reilly, collected between 1995 and 2005, and used by CADTH in its therapeutic review of 2017, were those for a 63-year-old man.[19,21] Furthermore, costs were inflated with the health component of the consumer price index, which is no longer believed to be the most appropriate index for health care services.[19,42] SEs were not published in the sources. The manufacturer assumed the SEs to be equal to 10% of average.
	Costs for diabetic ulcers from O'Brien et al. (2003)[22]	SE assumed to be 10% of average
	Costs for hypoglycemia from CADTH 2017 therapeutic review[19]	No SE published; SE assumed to be 10% of average
AEs	Nausea not costed	
Health state	Per UKPDS-OM2	

A1C = glycated hemoglobin; AE = adverse event; BMI = body mass index; BW = body weight; EQ-5D = EuroQol 5-Dimensions; HF = heart failure; ICD9 = International Classification of Diseases, ninth revision; IDC = indirect comparison; iGlarLixi = fixed-ratio combination of insulin glargine and lixisenatide; IHD = ischemic heart disease; MI = myocardial infarction; NICE = National Institute for Health and Care Excellence; NPH = neutral protamine Hagedorn; OAD = oral antidiabetes drug; ODB = Ontario Drug Benefit; SE = standard error; SD = standard deviation; SF-12 = Short-Form (12) Health Survey; T2DM = type 2 diabetes mellitus; TTO = time trade off; UKPDS-OM2 = United Kingdom Prospective Diabetes Study – Outcome Measures version 2.

Table 12: Manufacturer's Key Assumptions

Assumption	Comment
Patients remain on the same treatment over the 25-year horizon of the model.	In view of the uncertainty of treatment post-treatment failure, this simplifying assumption was made (in line with CADTH therapeutic review of 2017).[19]
Efficacy observed in the LixiLan-L trial at week 30 is assumed to have continued throughout year 1 and to have been maintained throughout the entire model horizon.	Impact of iGlarLixi was gradual over the 30-week period, and it is unknown whether its impact would remain the same beyond the first 30 weeks of treatment. This assumption was applied similarly in both groups. This would overestimate treatment impact in both groups. This would also favour iGlarLixi if, in reality, there is a decrease in efficacy as time goes on.
A1C levels and BMI after 30 weeks of treatment are good surrogate markers of the long-term development of micro- and macrovascular complications in diabetes.	Although it is generally accepted that keeping A1C levels below 6.5% to 7.0% and BMI below 25 kg/m^2 will prevent/reduce diabetes complications, it is also recognized that treatment will need to be intensified with time, and, hence, the short-term impact on surrogate markers may not result in expected reduction of complications without treatment intensification.[7]
A 25-year horizon is appropriate to capture the difference in treatment benefit.	Approximately 51% of the cohort was still alive at the end of the 25-year horizon. If the benefit is to remain for the patient's lifetime, a 25-year time horizon might underestimate the benefit and is not in line with CADTH recommendations for chronic conditions.[9] On the other hand, in view of the use of surrogate markers, this might be an acceptable compromise.
Nausea is assumed to occur only during the first 6 months of treatment.	Per NICE review of 2016[35]
The weight difference observed at week 30 of the LixiLan-L trial is assumed to have been observed throughout the entire year 1 and to have remained the same for the entire 25-year analysis.	In the LixiLan-L trial, there was a weight gain early on (during the first 9 weeks) with iGlarLixi. This has not been taken into consideration in the model. Furthermore, it is unknown how long the weight difference observed at week 30 had lasted.
Dispensing fees: 4 per year × 1 product in the iGlarLixi group and 2 products in the basal-prandial group.	Using the drug 4 times per year versus 12 times per year is conservative and favours the basal-prandial insulin group over the iGlarLixi group.

A1C = glycated hemoglobin; BMI = body mass index; iGlarLixi = fixed-ratio combination of insulin glargine and lixisenatide; NICE = National Institute for Health and Care Excellence.

Manufacturer's Results

The manufacturer's analysis showed that iGlarLixi, with or without metformin, was less expensive (1.5% lifetime discounted savings of $17,898) and more effective (1.5% discounted lifetime incremental QALYs of 0.10) than basal-prandial insulin three times daily, with or without metformin, resulting in iGlarLixi being a dominant strategy in 74.6% of iterations. A negative benefit was observed in 25.4% of the iterations. The main saving driver was medication costs (lifetime 1.5% discounted costs: $52,226 for iGlarLixi and $70,368 for basal-prandial insulin therapy). The main drivers of benefits were reduced hypoglycemia episodes (0.0633) and less frequent BMI above 25 kg/m^2 (0.0276). There was also a smaller benefit for heart failure (0.0008). These benefits compensated for iGlarLixi's negative impact on other diabetes complications, in particular renal failure (–0.0074) and adverse events due to lixisenatide, i.e., nausea (–0.0011). All scenario analyses gave similar results, with the lowest incremental benefit (i.e., 0.04) observed when the disutility for a BMI above 25 kg/m^2 was removed and the largest incremental benefit (i.e., 0.11) observed when the change in BMI was set to 1.080 (or approximately 3 kg weight gain) in the basal-prandial insulin treatment arm. The largest savings ($28,581) were observed when the iGlarLixi dose was reduced to 34.1 units (from 46.7 units in the manufacturer's base case), while the smallest savings ($3,750) were observed with a basal-prandial insulin therapy cost of

$3,399.88 (i.e., assuming 40 units/day per the World Health Organization defined daily dose).[16]

The breakdown of the cost and benefit components from the manufacturer's base case is provided in Table 13.

Table 13: Cost and QALY Breakdown From Manufacturer's Base-Case Probabilistic Analysis

Cost Items	iGlarLixi	Basal-Prandial Insulin	LYG and QALY Items	iGlarLixi	Basal-Prandial Insulin
Drug acquisition	$52,226	$70,368	**LYG**	16.53	16.51
Congestive heart failure	$8,844	$9,085	**Utility**	12.973703	12.957068
Ischemic heart disease	$5,531	$5,527	**Congestive heart failure decrement**	–0.031203	–0.032019
Myocardial infarction	$12,266	$12,208	**Ischemic heart disease decrement**	–0.036954	–0.036886
Stroke	$6,437	$6,402	**Myocardial infarction decrement**	–0.040043	–0.039898
Blindness	$1,293	$1,286	**Stroke decrement**	–0.047633	–0.047471
Ulcer	$35	$35	**Blindness decrement**	–0.026186	–0.026173
Amputation	$1,147	$1,146	**Ulcer decrement**	–0.002283	–0.002308
Renal failure	$12,321	$11,942	**Amputation decrement**	–0.028739	–0.028465
Minor hypoglycemia	$0	$0	**Renal failure decrement**	–0.249001	–0.241558
Severe hypoglycemia	$870	$868	**Minor hypoglycemia decrement**	–0.168065	–0.231368
Nausea	$0	$0	**Nausea decrement**	–0.001141	–0.000051
Total	$100,970	$118,868	**BMI disutility**	–0.200461	–0.228038
			QALYs	12.12	12.02

BMI = body mass index; iGlarLixi = fixed-ratio combination of insulin glargine and lixisenatide; LYG = life-years gained; QALY = quality-adjusted life-years.

CADTH Common Drug Review Reanalyses

Values included in CADTH base-case and sensitivity analyses are listed in Table 14, together with the manufacturer's values that they replace.

Table 14: Values Used for CADTH Reanalyses

Parameter	Manufacturer's Values Average (SE or SD)	CADTH's Value Average (SE or SD)	Reason/Source
CADTH base case			
iGlarLixi change in A1C from baseline	–1.11 (SE 0.057)	–1.13 (SE 0.057)	Correct value from LixiLan-L study report (Table 16, page 87)[11]
Basal-prandial insulin change in A1C from baseline	–1.17 (SE 0.084)	–1.19 (SE 0.084)	In view of the correction to the value for iGlarLixi
Age at diagnosis (years)	47.5 (SD 9.6)	47.8 (SD 9.3)	Per Table 13 of LixiLan-L study report (all patients)[11]
Years since diagnosis (years)	12.02 (SD 6.64)	12.08 (SD 6.74)	Per Table 13 of LixiLan-L study report (all patients)[11]
Gender (% men)	45.0%	46.7%	Per Table 12 of LixiLan-L study report (all patients)[11]

Parameter	Manufacturer's Values Average (SE or SD)	CADTH's Value Average (SE or SD)	Reason/Source
Ethnicity (% black; % Asian)	4.6%; 3.3%	5.2%; 2.7%	Per Table 12 of LixiLan-L study report (all patients)[11]
A1C level (%)	8.07 (SD 0.68)	8.08 (SD 0.71)	Per Table 14 of LixiLan-L study report (all patients)[11]
Systolic blood pressure (mm Hg)	131 (SD 13.9)	131.8 (SD 14.25)	Per Table 16.2.7.1.2.1 (page 1) of LixiLan-L study report (weighted average of iGlarLixi and iGlar)[11]
Body mass index (kg/m^2)	31.33 (SD 4.25)	31.14 (SD 4.20)	Per Table 12 of LixiLan-L study report (all patients)[11]
HDL-cholesterol (mmol/L)	1.332 (SD 0.355)	1.310 (SD 0.338)	Per Table 16.2.8.4.2.9 (page 1) of LixiLan-L study report (weighted average of iGlarLixi and iGlar)[11]
LDL-cholesterol (mmol/L)	2.624 (SD 0.991)	2.603 (SD 0.976)	Per Table 16.2.8.4.2.13 (page 1) of LixiLan-L study report (weighted average of iGlarLixi and iGlar)[11]
Heart rate (beats per minute)	72.9 (SD 8.9)	73.0 (SD 8.8)	Per Table 16.2.7.1.2.7 (page 1) of LixiLan-L study report (weighted average of iGlarLixi and iGlar)[11]
eGFR (mL/min/1.73 m^2)	82.84 (SD23.04)	83.80 (SD 23.37)	Corrected according to corrected demographic parameter inputs on eGFR calculation model sheet[2]
WBC count (1 × 10^6/mL)	6.89 (SD 1.89)	6.95 (SD 1.88)	Per Table 16.2.8.3.2.1 (page 1) of LixiLan-L study report (weighted average of iGlarLixi and iGlar)[11]
Hb (g/dL)	13.83 (SD 1.26)	13.85 (SD 1.24)	Per Table 16.2.8.2.2.3 (page 1) of LixiLan-L study report (weighted average of iGlarLixi and iGlar)[11]
% current smokers	13.4%	12.8%	Per Table 16.2.4.3.5 of LixiLan-L study report (all patients)[11]
% with albuminuria	8.2%	10.6%	Per Table 13 of LixiLan-L trial (micro and overt proteinuria – all patients)[11]
% with PVD	5.2%	5.0%	Per Table 16.2.4.3.2 of LixiLan-L report (all patients)[11]
% atrial fibrillation	3.3%	3.7%	Per Table 16.2.4.3.2 of LixiLan-L study report (all patients)[11]
% ischemic heart disease	4.4%	10.1%	Per Table 16.2.4.3.2 of LixiLan-L study report (angina pectoris – all patients)[11]
% myocardial infarction	6.3%	5.8%	Per Table 16.2.4.3.2 of LixiLan-L study report (all patients)[11]
% heart failure	7.6%	5.8%	Per Table 16.2.4.3.2 of LixiLan-L study report (all patients)[11]
% stroke	2.8%	4.0%	Per Table 16.2.4.3.2 of LixiLan-L study report (ischemic stroke, stroke of unknown origin, transient ischemic attack, hemorrhagic stroke – all patients)[11]
% amputation	0.3%	0.1%	Per Table 16.2.4.3.2 of LixiLan-L study report (all patients)[11]
% renal failure	2.5%	3.7%	Per Table 16.2.4.2.1 (page 14, creatinine clearance ≤ 60 mL/min)[11]

Parameter	Manufacturer's Values Average (SE or SD)	CADTH's Value Average (SE or SD)	Reason/Source
% ulcer	0.3%	1.1%	Per Table 16.2.4.3.1 (skin and subcutaneous tissue ulcerations – all patients)[11]
BMI disutility	–0.00195 (SE 0.0002) per unit above 25	0	Per CADTH therapeutic review (2017), CADTH Optimal Use Report (2013), and Lixisenatide CDR (2017), in view of the uncertainty of the benefit of a small weight loss and possible double-counting[3,19,43]
Prandial insulin dose	86 units	40 units	Per WHO DDD[16]
Acquisition cost of short-acting insulin	$0.03861 per unit	$0.02317 (vial) and $0.03032 (cartridge) per unit	Per least expensive product
Acquisition cost of basal insulin	$0.06227	$0.02368 (vial) and $0.03098 (cartridge) per unit	Per least expensive product
Markup	10%	8%	Per ODB rules[20]
Disutility for renal failure	0.263	0.330	Per latest default value of UKPDS-OM2[32]
Disutility for diabetic ulcer – first year	0.09	0.210	Per latest default value of UKPDS-OM2[32]
Costs of syringes and needles removed	iGlarLixi: $105.52 Basal-prandial insulin: $422.08	$0	CADTH unable to verify costs
Cost of syringes, needles, and lancets removed	iGlarLixi: $125.75 Basal-prandial insulin: $939.05	$0	CADTH unable to verify costs
SE for nausea disutility	0.002	0.003	Computed from reported standard deviation[37]
Scenario analyses on CADTH base case			
Full PSA	Most baseline characteristics, including risk factors for cardiovascular disease, are not included in the PSA	All parameters included in the PSA	Manufacturer's base case does not comply with CADTH economic guidelines.[9] However, including all parameters in the PSA doubles the run time of the model.
Body weight drift over time	0	0.6%	Equivalent to 0.5 kg per year, as observed in lixisenatide long-term safety study (over the first 2 years only, as the sample size at year 3 was much smaller and hence less representative)[25]
BMI disutility	–0.00195 (SE 0.0002) per unit above 25	–0.00195 (SE 0.0002) per unit above 30	Per Lixisenatide CDR (2017)[3]
Disutility for hypoglycemia	Mild/moderate: –0.0142 (SE 0.00142) Severe: –0.0470 (SE 0.0047)	Mild/moderate: –0.000004767 Severe: –0.01	Per CADTH Optimal Use Report (2013) and lixisenatide CDR (2017)[3,43]
Cartridge 100%	Basal insulin: 99.2% Prandial insulin: 92.89%	Basal insulin: 100% Prandial insulin: 100%	Daily costs with cartridges are higher. CADTH could not verify the per cent use of cartridges versus vials suggested by the manufacturer.
Vial 100%	Basal insulin: 0.8% Prandial insulin: 7.11%	Basal insulin: 100% Prandial insulin: 100%	Daily costs with vials are lower. CADTH could not verify the per cent use of cartridges versus vials

Parameter	Manufacturer's Values Average (SE or SD)	CADTH's Value Average (SE or SD)	Reason/Source
			suggested by the manufacturer.
Disposable costs	Per CADTH base case: iGlarLixi: $0 Basal-prandial insulin: $0	iGlarLixi: $125.75 Basal-prandial insulin: $939.05	The costs suggested by the manufacturer that were removed in CADTH base case were added in this sensitivity analysis.
Exploratory analyses on CADTH base case			
Additional comparator: Basal insulin + GLP-1 receptor agonist	Basal-prandial insulin effect on: A1C: –1.17 (SE 0.084) BMI: +0.714 (SE 0.187) Mild/moderate hypoglycemia: 257.42% Severe hypoglycemia: 2.5% Nausea: 0.01%	A1C: –1.44% BMI: –1.30 kg/m^2 Mild/moderate hypoglycemia: 118% Severe hypoglycemia: 2.5% Nausea: 0.4%	Manufacturer's NMA sensitivity analysis pooling by class for effect on A1C, BMI, and mild/moderate hypoglycemia. Literature for severe hypoglycemia and nausea.[44-46]
Additional comparator: Basal insulin + DPP-4 inhibitor		A1C: –1.26% BMI: +1.61 kg/m^2 Mild/moderate hypoglycemia: 86.2% Severe hypoglycemia: 0.63% Nausea: 0.01%	Manufacturer's NMA sensitivity analysis pooling by class for DPP-4 effect on A1C and BMI; DPP-4 RCT against insulin for hypoglycemia and nausea[47,48]
Additional comparator: Basal insulin + SGLT2		A1C: –0.38% BMI: –0.53 kg/m^2 Mild/moderate hypoglycemia: 110% Severe hypoglycemia:0.6% Nausea:0.01%	Medical literature for all parameters[49,50]

A1C = glycated hemoglobin; BMI = body mass index; CDR = CADTH Common Drug Review; DPP-4 = dipeptidyl peptidase-4; eGFR = estimated glomerular filtration rate; GLP-1 = glucagon-like peptide-1; Hb = hemoglobin; HDL = high-density lipoprotein; iGlar = insulin glargine; iGlarLixi = fixed-ratio combination of insulin glargine and lixisenatide; LDL = low-density lipoprotein; NMA = network meta-analysis; ODB = Ontario Drug Benefit; PVD = peripheral vascular disease; PSA = probabilistic sensitivity analysis; RCT = randomized controlled trial; SD = standard deviation; SE = standard error; SGLT2 = sodium-glucose cotransporter-2; UKPDS-OM2 = United Kingdom Prospective Diabetes Study – Outcomes Model version 2; WBC = white blood cell; WHO DDD = World Health Organization defined daily dose.

Source: Manufacturer's pharmacoeconomic submission.

Table 15: Additional Results From CADTH Reanalyses

Scenario	Element		Total Costs	Total QALY	ICUR
To form CADTH base case	Manufacturer's base case (probabilistic)	iGlarLixi	$100,970	12.1233	Dominant
		Basal-prandial insulin	$118,868	12.0241	
		Incremental analysis	–$17,898	0.09917	
	Corrected iGlarLixi efficacy on A1C	iGlarLixi	$100,864	12.1267	Dominant
		Basal-prandial insulin	$118,877	12.0268	
		Incremental analysis	–$18,013	0.09991	
	Corrected age at diagnosis	iGlarLixi	$100,586	12.1049	Dominant
		Basal-prandial insulin	$118,546	12.0077	
		Incremental analysis	–$17,961	0.09715	
	Corrected years since diagnosis	iGlarLixi	$100,528	12.1012	Dominant
		Basal-prandial insulin	$118,505	12.0055	
		Incremental analysis	–$17,978	0.09568	
	Corrected % men	iGlarLixi	$100,644	12.1043	Dominant
		Basal-prandial insulin	$118,620	12.0090	
		Incremental analysis	–$17,976	0.09532	
	Corrected ethnicity	iGlarLixi	$100,694	12.1056	Dominant
		Basal-prandial insulin	$118,675	12.0102	
		Incremental analysis	–$17,981	0.09535	
	Corrected A1C level	iGlarLixi	$100,702	12.1026	Dominant
		Basal-prandial insulin	$118,627	12.0067	
		Incremental analysis	–$17,925	0.09590	
	Corrected systolic blood pressure	iGlarLixi	$100,670	12.0943	Dominant
		Basal-prandial insulin	$118,586	11.9991	
		Incremental analysis	–$17,917	0.09515	
	Corrected body mass index	iGlarLixi	$100,672	12.0997	Dominant
		Basal-prandial insulin	$118,597	12.0004	
		Incremental analysis	–$17,925	0.0933	
	Corrected HDL-cholesterol (probabilistic)	iGlarLixi	$100,892	12.1034	Dominant
		Basal-prandial insulin	$118,786	12.0032	
		Incremental analysis	–$17,894	0.10026	
	Corrected LDL-cholesterol (probabilistic)	iGlarLixi	$100,839	12.1156	Dominant
		Basal-prandial insulin	$118,740	12.0167	
		Incremental analysis	–$17,902	0.09891	
	Corrected heart rate	iGlarLixi	$100,847	12.1161	Dominant
		Basal-prandial insulin	$118,770	12.0171	
		Incremental analysis	–$17,924	0.09904	
	Corrected eGFR	iGlarLixi	$100,784	12.1166	Dominant
		Basal-prandial insulin	$118,775	12.0180	
		Incremental analysis	–$17,991	-$17,991	
	Corrected WBC	iGlarLixi	$100,726	12.1114	Dominant
		Basal-prandial insulin	$118,717	12.0137	
		Incremental analysis	–$17,989	0.09775	
	Corrected Hb	iGlarLixi	$100,718	12.1156	Dominant
		Basal-prandial insulin	$118,672	12.0162	
		Incremental analysis	–$17,953	0.09945	

Scenario	Element		Total Costs	Total QALY	ICUR
	Corrected % smokers	iGlarLixi	$100,798	12.1228	Dominant
		Basal-prandial insulin	$118,754	12.0232	
		Incremental analysis	–$17,956	0.09961	
	Corrected % albuminuria	iGlarLixi	$100,912	12.0861	Dominant
		Basal-prandial insulin	$118,862	11.9888	
		Incremental analysis	–$17,951	0.09732	
	Corrected % PVD	iGlarLixi	$100,955	12.0914	Dominant
		Basal-prandial insulin	$118,910	11.9939	
		Incremental analysis	–$17,956	0.09745	
	Corrected % atrial fibrillation	iGlarLixi	$100,847	12.0801	Dominant
		Basal-prandial insulin	$118,786	12.9826	
		Incremental analysis	–$17,939	0.09750	
	Corrected % ischemic heart disease	iGlarLixi	$103,323	11.9776	Dominant
		Basal-prandial insulin	$121,189	11.8822	
		Incremental analysis	–$17,866	0.09541	
	Corrected % MI	iGlarLixi	$103,187	11.9836	Dominant
		Basal-prandial insulin	$121,065	11.8882	
		Incremental analysis	–$17,878	0.09548	
	Corrected % HF	iGlarLixi	$102,174	12.0307	Dominant
		Basal-prandial insulin	$120,122	11.9349	
		Incremental analysis	–$17,947	0.09582	
	Corrected % stroke	iGlarLixi	$102,652	12.0071	Dominant
		Basal-prandial insulin	$120,565	11.9112	
		Incremental analysis	–$17,913	0.09586	
	Corrected % amputation	iGlarLixi	$102,683	12.0223	Dominant
		Basal-prandial insulin	$120,613	11.9264	
		Incremental analysis	–$17,931	0.09596	
	Corrected % renal failure	iGlarLixi	$104,415	11.9551	Dominant
		Basal-prandial insulin	$122,312	11.8592	
		Incremental analysis	–$17,897	0.09584	
	Corrected % ulcer	iGlarLixi	$104,304	11.9311	Dominant
		Basal-prandial insulin	$122,167	11.8359	
		Incremental analysis	–$17,862	0.09514	
	BMI disutility	iGlarLixi	$104,304	12.1231	Dominant
		Basal-prandial insulin	$122,167	12.0561	
		Incremental analysis	–$17,862	0.06698	
	Prandial insulin dose	iGlarLixi	$104,304	12.1231	Dominant
		Basal-prandial insulin	$110,593	12.0561	
		Incremental analysis	–$6,289	0.06698	
	Acquisition cost of short-acting insulin	iGlarLixi	$104,304	12.1231	Dominant
		Basal-prandial insulin	$108,473	12.0561	
		Incremental analysis	–$4,169	0.06698	
	Acquisition cost of basal insulin	iGlarLixi	$104,304	12.1231	$79,755
		Basal-prandial insulin	$98,963	12.0561	
		Incremental analysis	$5,342	0.06698	
	Markup	iGlarLixi	$103,599	12.1231	$73,916

Scenario	Element		Total Costs	Total QALY	ICUR
		Basal-prandial insulin	$98,648	12.0561	
		Incremental analysis	$4,951	0.06698	
	Disutility value for renal failure	iGlarLixi	$103,599	12.0480	$75,823
		Basal-prandial insulin	$98,648	11.9827	
		Incremental analysis	$4,951	0.06529	
	Disutility for diabetic ulcer	iGlarLixi	$103,599	12.0451	$75,703
		Basal-prandial insulin	$98,648	11.9797	
		Incremental analysis	$4,951	0.06540	
	Cost of needles and syringes removed	iGlarLixi	$101,873	12.0451	$154,770
		Basal-prandial insulin	$91,752	11.9797	
		Incremental analysis	$10,121	0.06540	
	Cost of syringes, needles, and lancets removed	iGlarLixi	$101,098	12.0451	$166,615
		Basal-prandial insulin	$90,202	11.9797	
		Incremental analysis	$10,896	0.06540	
	SE of nausea disutility corrected	iGlarLixi	$101,098	12.0451	$166,615
		Basal-prandial insulin	$90,202	11.9797	
		Incremental analysis	$10,896	0.06540	
	CADTH base case	iGlarLixi	$103,555	10.9966	$199,924
		Basal-prandial insulin	$92,112	10.9421	
		Incremental analysis	$10,903	0.05449	
	CADTH base case (probabilistic)	iGlarLixi	$101,064	12.0427	$170,875
		Basal-prandial insulin	$90,100	11.9786	
		Incremental analysis	$10,964	0.06416	

A1C = glycated hemoglobin; BMI = body mass index; eGFR = estimated glomerular filtration rate; Hb = hemoglobin; HDL = high-density lipoprotein; HF = heart failure; ICUR = incremental cost-utility ratio; iGlarLixi = fixed-ratio combination of insulin glargine and lixisenatide; LDL = low-density lipoprotein; MI = myocardial infarction; PVD = peripheral vascular disease; QALY = quality-adjusted life-year; SE = standard error; WBC = white blood cell.

Note: Results are deterministic unless otherwise stated.

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