CADTH

CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

Lixisenatide (Adlyxine)

(Sanofi-aventis Canada Inc.)

Indication: As an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus in combination with:

- metformin
- a sulfonylurea (alone or with metformin)
- pioglitazone (alone or with metformin)
- a basal insulin (alone or with metformin).

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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

CDR	CADTH Common Drug Review
DDD	defined daily dose
A1C	glycated hemoglobin
ICUR	incremental cost-utility ratio
NICE	National Institute for Health and Care Excellence
QALY	quality-adjusted life-year
UKPDS	United Kingdom Prospective Diabetes Study
WHO	World Health Organization

Table 1: Summary of the Manufacturer's Economic Submission

Drug Product	Lixisenatide injection (Adlyxine)
Study Question	To assess the cost-effectiveness of lixisenatide compared with prandial insulin, when used in adult patients with type 2 diabetes mellitus who are failing to reach optimal glycemic control despite being treated with basal insulin (with or without metformin and/or a sulfonylurea).
Type of Economic Evaluation	Cost-utility analysis
Target Population	Adult patients with type 2 diabetes mellitus to achieve glycemic control in combination with basal insulin alone or in combination with metformin and/or a sulfonylurea.
Treatment	Lixisenatide
Outcome	Quality-adjusted life-years (QALYs)
Comparators	Prandial insulin (89 IU per day in manufacturer's base case)
Perspective	Canadian Ministry of Health
Time Horizon	Lifetime (25 years)
Results for Base Case	Lixisenatide dominates (i.e., is less expensive and more effective than) prandial insulin.
Key Limitations	CDR identified the following limitations: • Surrogate outcomes of A1C and BMI from the GETGOAL – DUO 2 trial were used to predict long-term microvascular and macrovascular complications. • The relative efficacy and safety (hypoglycemia) was determined from a trial in patients naive to both prandial insulin and lixisenatide. It is accepted that the dose of prandial insulin is typically increased over time to control blood sugar. It is unclear if the relative efficacy and safety in a prandial-naive population observed over 26 weeks in this patient population persists over a lifetime. • The dose of prandial insulin examined in GETGOAL – DUO 2 is much lower than the dose used in the model, which was taken from cross-sectional data that would include patients experienced on insulin. The model assumes efficacy and harms from the GETGOAL – DUO 2 study (prandial naive), but uses doses from observational data (prandial experienced), which is not appropriate and favours lixisenatide. • The lowest cost regular human insulin (recommended by CADTH) was not used in the base case.
CDR Estimates	Assuming an average daily prandial dose of 40 IU (the World Health Organization's defined daily dose) and using the lowest cost of human insulin (Novolin ge Toronto), the incremental cost-utility ratio (ICUR) for lixisenatide was $63,818 per QALY. Using alternate disutility values for hypoglycemia increased the ICUR to > $100,000 per QALY.

A1C = glycated hemoglobin; CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

Drug	Lixisenatide (Adlyxine)
Indication	Treatment of adult patients with type 2 diabetes mellitus to achieve glycemic control who are not controlled on existing therapy, in combination with the following oral antidiabetics: metformin, a sulfonylurea, a thiazolidinedione, or a combination of these agents; or in combination with a basal insulin alone or in combination with metformin and/or a sulfonylurea.
Reimbursement Request	Use of once-daily lixisenatide in combination with basal insulin with or without metformin for the treatment of adult patients with type 2 diabetes mellitus who are not controlled on existing therapy.
Dosage Form(s)	The stating dose is 10 mcg once daily for 14 days, then increased to 20 mcg once daily. It is supplied as a solution for injection in a pre-filled injector pen for subcutaneous administration.
NOC Date	10-05-2017
Manufacturer	Sanofi-aventis Canada Inc.

Executive Summary

Background

Lixisenatide (Adlyxine) is a glucagon-like peptide-1 receptor agonist indicated for the treatment of type 2 diabetes mellitus in patients uncontrolled on basal insulin with or without oral glucose-lowering agents. The starting dose is 10 mcg once daily for 14 days, then increased to 20 mcg once daily.[1] It is supplied as a solution in a pre-filled injector pen for subcutaneous administration in strengths of 0.05 mg/mL and 0.1 mg/mL, delivering 14 doses of 10 mcg per dose or 20 mcg per dose. The submitted price of lixisenatide is $56.98 per injector pen (regardless of strength) or $1,486 annually.[1,2]

The manufacturer submitted a cost-utility analysis, from the perspective of the Canadian health care payer, comparing lixisenatide with prandial insulin in patients failing to reach optimal glycemic control despite being treated with basal insulin (with or without metformin) over a lifetime time horizon (i.e., 25 years).[2] The economic model used by the manufacturer was based on the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model,[3] and was populated by patient data from the UKPDS and the GETGOAL – DUO 2 trial.[4] The model predicted the incidence of specific diabetes-related complications and mortality as health state outcomes using the UKPDS 82 health outcomes risk equations,[5] after treatment effect estimates were applied for the first year after treatment initiation. The model also incorporated hypoglycemic events (disutility and cost) as well as changes in quality of life with changes in BMI. The treatment effects and safety (adverse events) of basal plus lixisenatide and basal plus prandial (bolus) were taken from the GETGOAL – DUO 2 study.[2] Other inputs, such as costs and utility values, were obtained from published literature.[2]

In its base case, the manufacturer reported that lixisenatide dominated (i.e., was more effective and less costly than) prandial insulin, with a cost savings of $8,331 and an incremental quality-adjusted life-year (QALY) of 0.0793.2

Summary of Identified Limitations and Key Results

CADTH Common Drug Review (CDR) identified several key limitations with the submitted analysis. First, while surrogate outcomes such as glycated hemoglobin and BMI were used to predict long-term microvascular and macrovascular complications, the GETGOAL – DUO 2 study had a relatively short-term follow-up period (26 weeks).[4] Second, the manufacturer used an average daily prandial insulin dose of 89 IU per day, which is much greater than the dose used in the trial to establish efficacy and safety (20 IU per day).[2] This dose is higher than expected (according to the clinical expert consulted by CADTH) and is greater that the World Health Organization's defined daily dose. This assumption favours lixisenatide given the greater cost of higher doses of prandial insulin. Further, the comparator of prandial insulin was based on IMS Brogan data, not on drug plan reimbursement or CADTH recommendations on using regular human insulin,[6] and did not consider the lowest cost alternative. Finally, there is uncertainty over the disutility of hypoglycemia used in the manufacturer's model that is reflective of the heterogeneity between studies on the impact of hypoglycemia on quality of life.

CDR attempted to address these issues through a plausible base case that assumes an average prandial dose of 40 IU and using the lowest cost of human insulin. The incremental cost-utility ratio (ICUR) for lixisenatide was $63,818 per QALY when compared with prandial insulin. A scenario analysis on the CDR base case using alternate values for disutility of hypoglycemia resulted in an ICUR of > $100,000 per QALY when compared with prandial insulin.

The limitation that had a significant impact on results was prandial insulin dose. There is significant uncertainty on the actual dose of prandial insulin over time, and how relative efficacy and safety of prandial insulin and lixisenatide may be altered over time. Additional scenario analyses on the CDR base case were undertaken; when the average daily prandial dose from the trial was used (20.24 IU), the ICUR increased to $112,093 per QALY.

Conclusions

The key limitations of this submission were the assumption of relative efficacy and safety from a short-term trial (26 weeks), the extrapolation of the short-term effects to a lifetime time horizon, and the use of relative and efficacy data from a trial that included patients naive to prandial insulin while using dose of prandial insulin reported from insulin-experienced patients. Further, the estimates of utility for both hypoglycemia and BMI differences may have overestimated the benefits of lixisenatide, resulting in an ICUR that makes lixisenatide appear more attractive.

CDR re-analyses to address the identified limitations with the manufacturer's economic analysis showed that results were sensitive to prandial insulin dose and price, as well as utility decrements for hypoglycemic events. In the CDR plausible base case, the ICUR was more than $63,000 per QALY if a 40 IU daily dose of prandial insulin and the lowest price of human insulin were assumed. The ICUR was greater (> $100,000 per QALY) when the trial-based prandial insulin dose was used and alternate values for the disutility of hypoglycemia were considered.

Information on the Pharmacoeconomic Submission

Summary of the Manufacturer's Pharmacoeconomic Submission

The manufacturer submitted a cost-utility analysis, from the perspective of the Canadian health care payer, comparing lixisenatide with prandial insulin thrice daily in patients with type 2 diabetes mellitus who have failed to reach optimal glycemic control, despite being treated with basal insulin alone or in combination with metformin and/or a sulfonylurea. The time horizon was a patient lifetime (i.e., 25 years) with a one-year cycle length. The economic model was based on the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model, and was populated by patient data from the UKPDS and the GETGOAL – DUO 2 trial.[4] The manufacturer's model used annual cycles, in which the patient cohort entered the model with a set of baseline characteristics and modifiable risk factors to predict long-term health outcomes and complications. The modifiable risk factors that differed by treatment comparator were glycated hemoglobin (A1C) and BMI from GETGOAL – DUO 2; other inputs (e.g., low-density lipoprotein cholesterol, systolic blood pressure) were the same for each group.[4] The value of A1C and systolic blood pressure variables changed as the model simulation progressed, reflecting treatment effects and natural progression (modelled using UKPDS 68 risk equations).[3] The model predicted eight diabetes complications when using the UKPDS 82 health outcomes risk equations.[5]

The following health states were included in the manufacturer's model:

- type 2 diabetes mellitus without complications
- type 2 diabetes mellitus with one or more diabetes-related complications: ischemic heart disease (nonfatal), myocardial infarction (fatal or nonfatal), congestive heart failure (fatal or nonfatal), stroke (fatal or nonfatal), amputation (fatal or nonfatal), blindness (nonfatal), end stage renal disease (nonfatal), or ulcer (nonfatal)
- death (non-specific, not caused by diabetes-related complications).

At the end of the first annual cycle, the UKPDS 82 risk equations determined the occurrence of the fatal and nonfatal complications, as well as non-cardiovascular (all-cause) and direct diabetes deaths.[5] If the patients survived beyond the first cycle, they transitioned to the next cycle whereby they remained at risk of treatment-related adverse events and long-term complications. The base case result was based on the average costs and utilities generated from a simulated population of 15,000 patients.

The model incorporated treatment-related adverse events (major or minor hypoglycemic events and nausea) as well as utility decrements per unit increase in BMI for patients whose BMI exceeded 25 kg/m^2. Rates for major and minor hypoglycemic events, as well as rates for nausea events, were derived from the GETGOAL – DUO 2 clinical trial.[4] There was no major hypoglycemia reported and zero events were assumed in the model. For minor hypoglycemia, lixisenatide was assigned a rate of 0.72 events per patient year versus 1.52 events for the basal-prandial arm. Patients were assumed to remain on the same treatment over the lifetime of the model.

Health state utilities and decrements for diabetes-related complications were obtained from the literature, mostly non-Canadian studies that were also used in the 2013 CADTH report

on optimal use.[7] The annual utility decrement of –0.00195 for each unit increase in BMI more than 25 kg/m^2) was also obtained from that CADTH report. For treatment-related adverse events, the annual utility decrement on hypoglycemic events (–0.014 for mild and –0.047 for severe) and nausea (–0.02) were obtained from two UK studies.[8,9] The utility decrements on hypoglycemic events from one of those UK studies (the 2006 report by Currie et al.) were used in the base case, while the lower utility decrements from the CADTH 2013 report (–0.000004767 for mild and –0.01 for severe) were used in the sensitivity analysis.[7,8]

Drug costs of lixisenatide were obtained from the manufacturer based on a daily dose of 20 mcg (annual cost of $1,635). The weighted average cost of prandial insulin was calculated (from cross-sectional data) based on a daily dose of 89 IU from a 2008 report by the Canadian Optimal Medication Prescribing and Utilization Service (COMPUS).[6] According to IMS Brogan market share data, 9.8% patients were on vials (1,000 IU) and the other 90.2% were on cartridge (1,500 IU).[2] The prandial insulins used in Canada included Apidra, Humalog, Humulin R, Novolin ge Toronto, and NovoRapid, resulting in an average annual cost of $1,298. A 10% markup and a dispensing fee of $8.83 per three months' supply were also considered in the analysis. The cost of needles and syringes were included in the base-case analysis ($0.29 each from Diabetes Depot).[2] Patients using basal plus lixisenatide were assumed to need two injections per day, while patients using basal plus prandial were assumed to need four needles. The cost of self-monitoring blood glucose ($0.88 per test) was also included in the base case. Patients treated with basal plus lixisenatide were assumed to use two test strips per day versus four tests for patients treated with basal plus prandial. The costs associated with managing long-term diabetes-related complications were obtained from the Ontario Ministry of Health and Long-Term Care's Ontario Diabetes Economic Model.[10] It was assumed that mild or moderate hypoglycemic events did not require health care resource use ($0), meaning only the most severe hypoglycemia-incurred costs (i.e., glucagon usage, hospital admission, and health care consultation) were included in the base case.[2]

Manufacturer's Base Case

In the base case, the manufacturer reported that lixisenatide compared with prandial insulin is associated with an additional 0.0793 quality-adjusted life-year (QALY). Treatment with lixisenatide also resulted in lower total health care costs (–$8,332) than prandial insulin. As shown in Table 2, lixisenatide is the dominant (i.e., more effective and less costly) strategy.

Table 2: Results of the Manufacturer's Base Case

	Basal Plus Lixisenatide	Basal Plus Prandial	Difference
QALY	**11.9332**	**11.8539**	**0.0793**
Cost ($)			
Treatment costs (drug, injection, monitoring)	**61,512**	**69,913**	**–8,401**
Diabetes-related complications	**53,975**	**53,906**	**70**
Adverse event costs	**0**	**0**	**0**
Total costs ($)	**115,487**	**123,819**	**–8,332**
ICUR ($/QALY)			**Lixisenatide is dominant**

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-years.

Source: Manufacturer's pharmacoeconomic report.[2]

Summary of Manufacturer's Sensitivity Analyses

Uncertainty was addressed using one-way deterministic sensitivity analyses, which varied model parameters by using alternative values. A series of one-way sensitivity analyses were conducted by the manufacturer, including time horizon (five years to 10 years); discount rates (3% and 0%); markup and dispensing (excluded); injection supplies (excluded); self-monitoring glucose testing frequency (zero tests per day to four tests per day); insulin cost ($1,030 for prandial and $587 for basal); daily dose of prandial insulin (20 IU per day to 69 IU per day); prandial vial versus cartridge usage (4.8% cartridge, 7.2% vial); A1C efficacy (95% confidence interval); change in BMI (95% confidence interval); utility for BMI (0); and utility for hypoglycemia (–0.01 to 0).

The base case result is that lixisenatide dominates prandial insulin. The results were robust except for the following parameters:

- **Excluding self-monitoring glucose testing cost:** The cost per QALY gained for lixisenatide is $27,442.
- **Daily dose of prandial insulin reduced to 20 IU per day and 40 IU per day:** The cost per QALY gained for lixisenatide is $41,838 (40 IU per day) and $100,798 (20 IU per day).

Limitations of Manufacturer's Submission

A. Use of surrogate outcomes: Surrogate outcomes of A1C and BMI from the GETGOAL – DUO 2 trial were used to predict long-term microvascular and macrovascular complications (using the UKPDS 82 health outcomes risk equations) as well as a utility gain with difference in BMI.[4] Given that the GETGOAL – DUO 2 study demonstrated that lixisenatide is noninferior to prandial insulin in A1C reduction,[4] this does not have a major impact on the model's results. However, differences that may occur in long-term clinical outcomes by treatment have not yet been determined. Further, it is not definitively established that changes in BMI with alternate diabetes treatment strategies lead to differences in clinically important outcomes, and there is uncertainty if changes in BMI alone lead to clinically important differences in quality of life.

B. **Assumption of relative long-term benefits and harms:** The efficacy and safety observed for lixisenatide from the 26-week GETGOAL – DUO 2 trial were assumed to last for the patient's lifetime (25 years in the model). If relative efficacy wanes or the differences in the risk of hypoglycemia attenuate overt time, the incremental cost-utility ratio (ICUR) may be higher. Further, relative efficacy and harms were determined in patients naive to prandial insulin and lixisenatide, but increases in prandial insulin are typically required over time in adult patients with type 2 diabetes mellitus. It is unclear if the relative efficacy and safety determined in this patient population persist over time.

C. **Overestimates prandial insulin dose:** The dose of prandial insulin examined in the GETGOAL – DUO 2 trial (which was used to examine clinical outcomes) is much lower (20 IU per day) than the dose used in the manufacturer's model (89 IU per day). The average daily dose of prandial insulin in the model was based on estimates from the COMPUS[6] report that are much higher (89 IU per day) than those of GETGOAL – DUO 2 because they include patients who have been on insulin for a long time and therefore require higher doses. There are significant evidence gaps and modelling assumptions that are challenging to definitely establish. First, patients initiating prandial insulin start on a lower dose of insulin (as evidenced by GETGOAL – DUO 2), but the dose is typically increased to maintain efficacy over time. Second, relative efficacy of prandial insulin and lixisenatide is established over 26 weeks in the GETGOAL – DUO 2 trial, but no data are provided indicating that lixisenatide maintains similar absolute or relative efficacy and harms over time. An ideal model would allow prandial insulin dose to change over time instead of assuming that doses observed in a cross-sectional population persist from year 1 indefinitely. It would also incorporate changes in relative efficacy and harms of lixisenatide (compared with prandial insulin) over time; however, these data are not available. Assuming efficacy and harms from the GETGOAL – DUO 2 trial but using insulin doses from observational data may impart bias favouring lixisenatide.

D. **Cost of insulin:** The average cost of prandial insulin was derived from observational data from IMS Brogan. The price of the lowest cost alternative may be a more appropriate comparator as CADTH recommends most patients requiring short-acting insulin be started on regular human insulin.[6] While insulin analogues may be a more appropriate comparator for patients with significant hypoglycemia on short-acting insulin, this is not the requested indication for lixisenatide.

E. **Utility decrements with hypoglycemic events:** Utility decrements for hypoglycemic events from the 2006 UK report by Currie et al.[8] were used in the manufacturer's base case.[2] There is considerable uncertainty with the available evidence on how hypoglycemia would affect quality of life mainly due to the heterogeneity between quality of life studies and the uncertainty around the elicited utility values. As such, utility decrements from the 2013 CADTH report as well as values from the 2016 National Institute for Health and Care Excellence (NICE) report were tested in the sensitivity analyses of both the manufacturer and CADTH Common Drug Review (CDR).[7,11]

F. **Utility decrements on BMI:** Utility decrements for BMI more than 25 kg/m^2 were applied in the manufacturer's base case; this cut-off value was lower than the cut-off used in the 2013 and 2016 CADTH diabetes reports as the threshold for defining obesity (30 kg/m^2).[7,12,13] According to the clinical expert consulted by CADTH, a 0.23

BMI reduction is likely not of clinical significance (average BMI of 32 kg/m^2 in GETGOAL DUO 2 trial) for differences in quality of life. In addition, the manufacturer used BMI to predict diabetes-related complications such as heart failure, which might overestimate the benefits from BMI reduction from lixisenatide.[2]

CADTH Common Drug Review Re-Analyses

CDR considered the following re-analyses, which apply to the comparison of lixisenatide with prandial insulin, to address the above-mentioned limitations. Additional details on the results of these re-analyses are provided in Table 14 of Appendix 5.

- **Prandial insulin daily dose:** The doses observed in trials used to inform relative efficacy and harms (analysis 1a), as well as the World Health Organization (WHO) daily defined dose (DDD) of 40 IU (analysis 1b), were examined instead of the doses taken from the cross-sectional sample used in the manufacturer's base case. There is uncertainty in the exact dose trajectory over time, as well as uncertainty in relative efficacy and harms over time. Given the absence of data on long-term relative efficacy and harms, trial-based data (from a naive patient population that requires a lower dose of prandial insulin) have the least uncertainty, although the CDR clinical expert commented that the daily dose of 20.14 IU might be lower than used in practice.
- **Prandial insulin cost:** Limitation D was addressed by using the price of the lowest cost alternative (Novolin ge Toronto), which has an annual drug cost of $4,047.
- **BMI disutility cut-off:** Limitation F was addressed by exploring a disutility starting at a BMI of 30 kg/m2 (instead of 25 kg/m2), congruent with the 2013 CADTH report.
- **Disutility from hypoglycemic events:** Limitation E was addressed by assessing the utility decrements associated with hypoglycemic events from the 2013 CADTH report and 2016 NICE report.[7,11]
- **CDR base case:** A plausible CDR base case assumed a dose of 40 IU prandial insulin per day (aligned with the WHO DDD and greater than the trial-reported dose) and used the lowest cost prandial insulin alternative (analyses 1b and 2). Scenario analyses were also performed to assess the impact of uncertainty in other parameters on this CDR base case.

Table 3: CDR Re-Analysis of Plausible Base Case

	Description	Basal + Lixisenatide Versus Basal + Prandial		
		Incremental Cost	Incremental QALY	ICUR
	Manufacturer base case	–$8,331	0.0793	Dominant
1	**Prandial insulin daily dose**			
1a	20.24 IU ($3,288 annual drug cost)	$7,992	0.0793	$100,787 per QALY
1b	40 IU ($3,577 annual drug cost)	$3,281	0.0793	$41,383 per QALY
2	**Prandial insulin cost**			
	Novolin ge Toronto ($4,047 annual drug cost)	–$4,379	0.0793	Dominant
3	**BMI disutility cut-off**			
	Disutility applied after BMI of 30 kg/m^2 and above	–$8,331	0.0737	Dominant
4	**Utility decrements on hypoglycemic events**			
	0.000004767 mild, 0.01 severe (CADTH, 2013)[7]	–$8,331	0.0251	Dominant

	Description	Basal + Lixisenatide Versus Basal + Prandial		
		Incremental Cost	Incremental QALY	ICUR
	0.0052 mild, 0.01 severe (NICE, 2016)[11]	–$8,331	0.0485	Dominant
5	**Plausible base case (1b, 2)**	**$5,060**	**0.0793**	**$63,818 per QALY**
5a	Scenario analysis of CDR base case with daily prandial insulin dose of 20.14 IU ($3,233 annual drug cost)	$8,888	0.0793	$112,093 per QALY
5b	Scenario analysis of CDR base case with daily prandial insulin dose of 60 IU ($3,706 annual drug cost)	$1,179	0.0793	$14,867 per QALY
5c	Scenario analysis of CDR base case with daily lixisenatide dose of 10 mcg for 17% patients	$2,793	0.0793	$35,222 per QALY
5d	Scenario analysis of CDR base case with BMI disutility cut-off of 30 kg/m^2	$5,060	0.0793	$68,677 per QALY
5e	Scenario analysis of CDR base case with CADTH 2013 utility decrements	$5,060	0.0251	$202,028 per QALY
5f	Scenario analysis of CDR base case with NICE 2016 utility decrements	$5,060	0.0485	$104,247 per QALY

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; NICE = National Institute for Health and Care Excellence; QALY = quality-adjusted life-year.
Note: Annual drug costs include costs of basal insulin, lixisenatide/prandial insulin, dispensing fees, needles, and self-monitoring.

In the new CDR base-case analysis using the WHO DDD of 40 IU prandial insulin per day, the ICUR is $63,818 per QALY. Given inherent uncertainty, additional sensitivity analysis was performed, indicating that the results vary between lixisenatide being dominant to having an ICUR of $202,028 per QALY. The dose and cost of insulin was a major driver of results. A series of price-reduction analyses were undertaken based on the CDR base case (Table 4) and sensitivity analyses of CDR base case, indicating that a price reduction of between 6% and 19% may be required to lead to an ICUR < $50,000 per QALY.

Table 4: CDR Re-Analysis of Price-Reduction Scenarios Based on CDR Base Case

ICUR of Basal + Lixisenatide Versus ICUR of Basal + Prandial		
Price	**Base-Case Analysis Submitted by Manufacturer**	**Re-Analysis by CDR (Based on Plausible Base Case)**
Submitted	Dominant	63,818
4% reduction	Dominant	50,446
5% reduction	Dominant	46,948

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio.

Table 5: Threshold Analyses Based on the Sensitivity Analyses of CDR Base Case

ICUR of Basal + Lixisenatide Versus ICUR of Basal + Prandial				
Price	**CDR Base Case With 20.14 IU**	**CDR Base Case With BMI Cut-Off of 30 kg/m^2**	**CDR Base Case With CADTH 2013 Utility Decrements[7]**	**CDR Base Case With NICE 2016 Utility Decrements[11]**
Submitted	112,093	68,677	202,028	104,247
Discount to Bring ICUR to < $50,000	19% reduction	6% reduction	15% reduction	10% reduction

BMI = body mass index; CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; NICE = National Institute for Health and Care Excellence.

Issues for Consideration

- Pre-mixed insulin might be a possible comparator in adult patients with type 2 diabetes mellitus; however, the current model was not able to assess the cost-effectiveness of lixisenatide versus pre-mixed insulin. Given that the price of pre-mixed insulin is a bit higher than that of prandial insulin, the ICUR would be lower when comparing lixisenatide with pre-mixed insulin and when the same effectiveness is assumed.
- According to the clinical expert, there is a possibility that lixisenatide might be used off-label as an insulin-preventing drug or to control a patient's body weight.
- The approved dose is 20 mcg once daily for lixisenatide; however, some patients (17%) received a lower dose of 10 mcg in the trial. This difference is unlikely to affect the analyses as both doses are priced similarly.

Patient Input

Patients expected the use of a glucagon-like peptide-1 receptor agonist to lead to satisfactory control of diabetes as well as the avoidance of hypoglycemia and weight loss, all of which reported in the economic analysis. Several side effects were also reported, including extreme nausea, gastrointestinal effects, and thirst or dehydration, with nausea modelled as a side effect in the base case.

Conclusions

The key limitations of this submission were the assumption of relative efficacy and safety from a short-term trial (26 weeks), the extrapolation of the short-term effects to a lifetime time horizon, and the use of relative and efficacy data from a trial that included patients naive to prandial insulin while using a dose of prandial insulin reported from insulin-experienced patients. Further, the estimates of utility for both hypoglycemia and BMI differences may have overestimated the benefits of lixisenatide, resulting in an ICUR that makes lixisenatide appear more attractive.

CDR re-analyses to address the identified limitations with the manufacturer's economic analysis showed that results were sensitive to prandial insulin dose and price, as well as utility decrements for hypoglycemic events. In the CDR plausible base case, the ICUR was more than $63,000 per QALY if a 40 IU daily dose of prandial insulin and the lowest price of human insulin were assumed. The ICUR was greater (> $100,000 per QALY) when the trial-based prandial insulin dose was used and alternate values for the disutility of hypoglycemia were considered.

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: they may also be devices or procedures. Costs are manufacturer reimburse prices, unless otherwise specified. Existing product reimbursement agreements are not reflected in this table and as such may not represent the actual costs to public drug plans.

Table 6: Cost Comparison of Non-Insulin Antidiabetic Drugs

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Daily Drug Cost ($)	Average Annual Drug Cost ($)
Glucagon-Like Peptide-1 (GLP-1) Receptor Analogues						
Lixisenatide (Adlyxine)	**10 mcg 20 mcg**	**14-dose pre-filled pen (3 mL)**	**56.9800**	**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	168.2800[b]	0.75 mg to 1.5 mg once weekly	6.01	2,188
Exenatide (Bydureon)	2 mg	2 mg pre-filled pen	48.4675[b]	2 mg once weekly	6.92	2,520
Exenatide (Byetta)	1.2 mL 2.4 mL	60-dose pre-filled pen (250 mcg/mL)	119.7250[b]	5 mcg to 10 mcg twice daily	3.99	1,457
Liraglutide (Victoza)	2 × 3 mL 3 × 3 mL	Pre-filled pen (6 mg/mL)	136.9800[b] 205.4700[b]	1.2 mg to 1.8 mg daily	4.57 to 6.85	1,667 to 2,500
Biguanides						
Metformin	500 mg 850 mg	tab	0.0444 0.0610[d]	500 mg three to four times daily	0.18 to 0.23	49 to 65
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	0.0931 0.2150	30 mg to 120 mg daily	0.09 to 0.43	34 to 157
Glimepiride (generics)	1 mg 2 mg 4 mg	tab	0.3857[c]	1 mg to 4 mg daily	0.39	142
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
Dipeptidyl Peptidase-4 (DPP-4) Inhibitors						
Alogliptin (Nesina)	6.25 mg 12.5 mg 25 mg	tab	2.1000[c]	25 mg daily	2.10	767

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Daily Drug Cost ($)	Average Annual Drug Cost ($)
Linagliptin (Trajenta)	5 mg	tab	2.5500	5 mg daily	2.55	931
Saxagliptin (Onglyza)	2.5 mg 5.0 mg	tab	2.4261 2.9070	5 mg daily	2.91	1,062
Sitagliptin (Januvia)	25 mg 50 mg 100 mg	tab	3.0296	100 mg daily	3.03	1,106
DPP-4 Inhibitors Plus Metformin (Fixed-Dose Combinations)						
Alogliptin/ metformin (Kazano)	12.5 mg/500 mg 12.5 mg/850 mg 12.5 mg/1,000 mg	tab	1.1450[c]	Two tablets daily	2.29	836
Linagliptin/ metformin (Jentadueto)	2.5 mg/500 mg 2.5 mg/850 mg 2.5 mg/1,000 mg	tab	1.3337	Two tablets daily	2.67	974
Saxagliptin/ metformin (Komboglyze)	2.5 mg/500 mg 2.5 mg/850 mg 2.5 mg/1,000 mg	tab	1.2700	Two tablets daily	2.54	927
Sitagliptin/ metformin (Janumet)	50 mg/500 mg 50 mg/850 mg 50 mg/1,000 mg	tab	1.6434	Two tablets daily	3.29	1,200
Subtype 2 Sodium-Glucose Transport Protein (SGLT2) Inhibitors						
Canagliflozin (Invokana)	100 mg 300 mg	tab	2.7203	100 mg or 300 mg daily	2.72	993
Dapagliflozin (Forxiga)	5 mg 10 mg	tab	2.6200	5 mg or 10 mg daily	2.62	956
Empagliflozin (Jardiance)	10 mg 25 mg	tab	2.6177	10 mg or 25 mg daily	2.62	956

ER = extended release; tab = tablet.

[a] Manufacturer's submission price.[2]

[b] IMS Delta PA. IMS Brogan (July 2017).[14]

[c] Régie de l'assurance maladie du Québec (July 2017).[15]

[d] Alberta Drug Formulary (July 2017).[16]

Source: Ontario Drug Benefit (July 2017) prices unless otherwise indicated.[17]

Table 7: Cost Comparison of Insulin Drugs

Drug/Comparator	Strength	Dosage Form	Price ($)	Cost ($/mL)
Short-Acting Insulins				
Insulin aspart (NovoRapid)	100 U/mL	5 × 3 mL cartridge 5 × 3 mL disposable pen 10 mL vial	59.80 62.25 29.49	3.99 4.15 2.95
Insulin glulisine (Apidra)	100 U/mL	5 × 3 mL cartridge 5 × 3 mL disposable pen 10 mL vial	51.45 51.95 25.95	3.43 3.46 2.60
Insulin lispro (Humalog)	100 U/mL	5 × 3 mL cartridge 5 × 3 mL disposable pen 10 mL vial	56.62 56.21 28.50	3.77 3.75 2.85
Regular human insulin (Humulin R)	100 U/mL	5 × 3 mL cartridge 10 mL vial	46.47 23.68	3.10 2.37
Regular human insulin (Novolin ge Toronto)	100 U/mL	5 × 3 mL cartridge 10 mL vial	45.48 23.17	3.03 2.32
Long-Acting Insulin Analogues				
Insulin glargine (Lantus)	100 U/mL	5 × 3 mL cartridge 5 × 3 mL disposable pen 10 mL vial	92.85 92.85 61.69	6.19 6.19 6.17
Insulin glargine (Basaglar)	100 U/mL	5 × 3 mL cartridge 5 × 3 mL pre-filled pen	78.92[b] 78.92[b]	5.26 5.26
Insulin detemir (Levemir)	100 U/mL	5 × 3 mL cartridge 5 × 3 mL disposable pen	106.76 107.29	7.12 7.15
NPH Insulins				
Humulin N	100 U/mL	5 × 3 mL cartridge 10 mL vial	46.47 23.68	3.10 2.37
Novolin ge NPH	100 U/mL	5 × 3 mL cartridge 10 mL vial	46.57 23.69	3.10 2.37
Pre-Mixed Insulins				
Biphasic insulin aspart 30/70 (NovoMix 30)	100 U/mL	5 × 3 mL cartridge	55.37	3.69
Lispro/lispro protamine 25/75 (Humalog Mix25)	100 U/mL	5 × 3 mL cartridge 5 × 3 mL disposable pen	57.29 56.87	3.82 3.79
Lispro/lispro protamine 50/50 (Humalog Mix50)	100 U/mL	5 × 3 mL cartridge 5 × 3 mL disposable pen	56.42 55.92	3.76 3.73
Humulin 30/70	100 U/mL	5 × 3 mL cartridge 10 mL vial	46.47 23.68	3.10 2.37
Novolin ge 30/70	100 U/mL	5 × 3 mL cartridge 10 mL vial	46.03 23.82	3.07 2.38
Novolin ge 40/60	100 U/mL	5 × 3 mL cartridge	46.37	3.09
Novolin ge 50/50	100 U/mL	5 × 3 mL cartridge	46.37	3.09

Source: Ontario Drug Benefit (July 2017) prices, unless otherwise indicated.[17]

Appendix 2: Summary of Key Outcomes

The summary provided in Table 8 is based on the CADTH Common Drug Review base case.

Table 8: When Considering Only Costs, Outcomes and Quality of Life, How Attractive Is Lixisenatide Relative to the Prandial Insulin?

Basal + Lixisenatide vs. Basal + Prandial	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)				X		
Drug treatment costs alone				X		
Clinical outcomes		X				
Quality of life			X			
ICER or net benefit calculation	CDR base case: $63,818 per QALY					

CDR = CADTH Common Drug Review; ICER = incremental cost-effectiveness ratio; NA = not applicable; QALY = quality-adjusted life-year.

Appendix 3: Additional Information

Table 9: Submission Quality

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?	X		
Comments	None		
Was the material included (content) sufficient?	X		
Comments	None		
Was the submission well organized and was information easy to locate?	X		
Comments	None		

Table 10: Authors 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: Summary of Other CADTH Health Technology Assessment Reviews

Table 11: Other CADTH Health Technology Assessment Findings

	PBAC, July 2014[18]
Treatment	Lixisenatide injection (10 mcg or 20 mcg dose)
Price	Annual drug cost per patient: $1,132.52 lixisenatide versus $957.41 for bolus versus $829.57 for pre-mixed insulin
Similarities with CDR submission	The outcome is a reduction in glycated hemoglobin.
Differences with CDR submission	A cost-minimization analysis was performed, comparing lixisenatide with basal-bolus regimen and pre-mixed insulin.
Manufacturer's results	Confidential
Issues noted by the review group	The appropriateness of the approach was dependent on the acceptance of the clinical claim of equivalence despite the limitations of the presented evidence. The estimates of equi-effective doses were unreasonable.
Results of re-analyses by the review group (if any)	Not applicable
Recommendation	The PBAC rejected the request to reimburse lixisenatide for use in combination with insulin. Because the clinical place of glucagon-like peptide-1 drugs in patients with type 2 diabetes mellitus who require insulin therapy has yet to be established, titrated insulin is not the only appropriate comparator. The basis for the cost-minimization analysis of lixisenatide compared with up-titrated insulin was therefore not accepted.

CDR = CADTH Common Drug Review; PBAC = Pharmaceutical Benefits Advisory Committee.

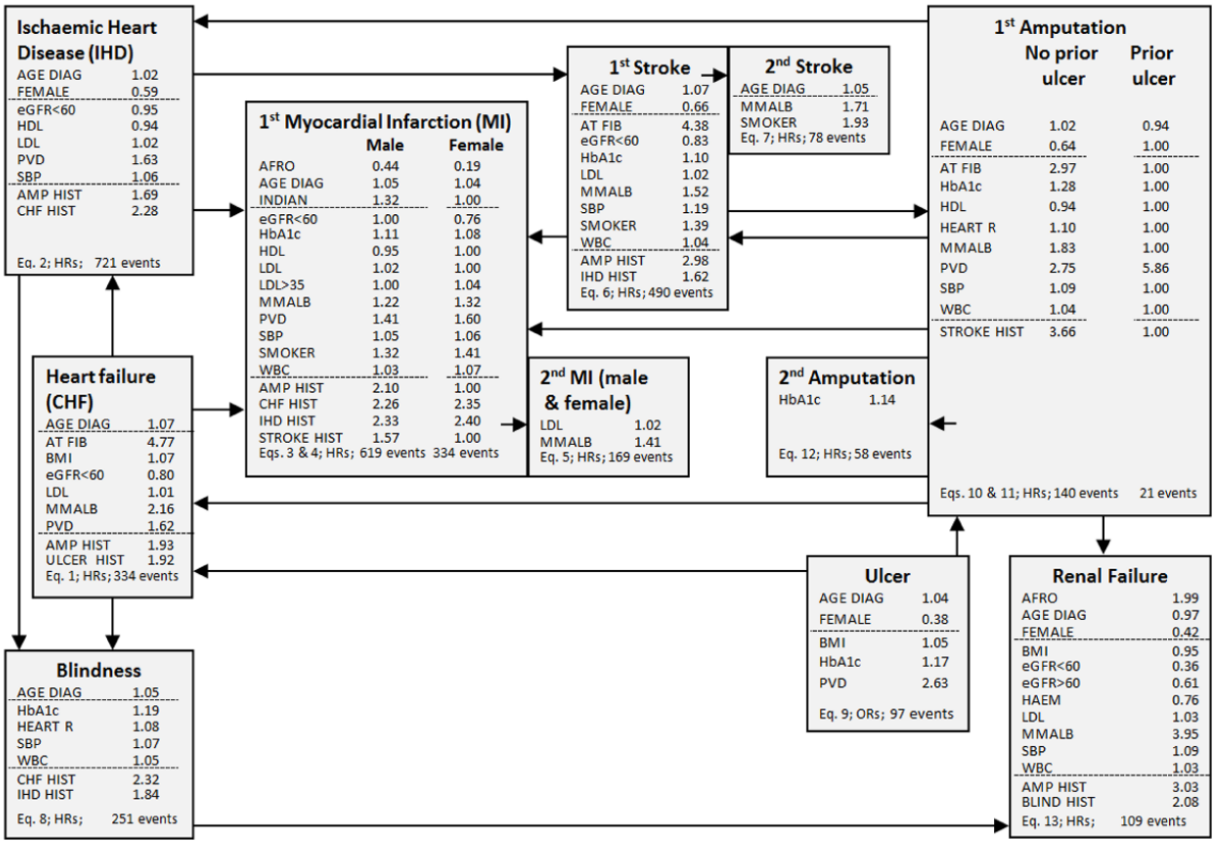
Appendix 5: Reviewer Worksheets

Manufacturer's Model Structure

The manufacturer's economic model was based on the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model, and was populated by patient data from the UKPDS and the GETGOAL – DUO 2 trial.[3,4] The UKPDS is a patient-level simulation model that runs stochastic simulations on disease progression and the occurrence of disease-related complications and mortality. These simulations were also used in the 2013 CADTH report on second-line pharmacotherapy for type 2 diabetes mellitus.[7]

Details of the complications and risk-factor coefficients are shown in Figure 1.

Figure 1: United Kingdom Prospective Diabetes Study Model Algorithm



KEY: AGE DIAG = age at diagnosis; AFRO = Afro-Caribbean; AMP HIST = amputation history; AT FIB = atrial fibrillation; BLIND HIST = blindness history; BMI = body mass index; CHF HIST = congestive heart failure history; eGFR = estimated glomerular filtration rate; HbA1C = Hemoglobin A1c ; HAEM = hemoglobin; HDL = high-density lipoprotein; HEART R = heart rate; IHD HIST = Ischemic heart disease history; LDL = low-density lipoprotein; MMALB = microalbuminuria; PVD = peripheral vascular disease; SBP = systolic blood pressure; STROKE HIST = stroke history; ULCER HIST = ulcer history; WBC = white blood cell count

Source: Manufacturer's pharmacoeconomic report.[2]

Health state utilities in the manufacturer's submission were adopted based on the utilities used in the 2013 CADTH report, with the exception of the disutility of hypoglycemic events; these values are congruent with the draft 2016 CADTH report on second-line drugs for diabetes management.[13]

Table 12 and Table 13 report the relevant data sources and assumptions incorporated by the manufacturer.

Table 12: Data Sources

Data Input	Description of Data Source	Comment
Patient characteristics	Baseline characteristics were informed by the UKPDS and the GETGOAL – DUO 2 trial.[3,4]	Appropriate. However, the manufacturer did not specify the precise source of each parameter.
Efficacy	Efficacy on A1C and BMI were taken from the GETGOAL – DUO 2 trial (a randomized, open-label, three-arm, 26-week, multicenter study).[4]	Both outcomes are surrogate outcomes. (See the following row on "Natural history" for issues around the use of A1C and predicting clinical outcomes.) There is uncertainty in how changes in BMI may affect quality of life.
Natural history	The UKPDS 82 health outcomes risk equations were used to predict incidence of diabetes-related complications.[5]	Uncertain. It is not definitely established that surrogate outcomes (i.e., A1C) are valid for predicting clinical outcomes (e.g., cardiovascular disease). Mechanisms other than control of diabetes may lead to differences in long-term clinical outcomes. However, this has no appreciable impact given noninferiority in A1C between comparators
Utilities	Health state utilities and decrements for diabetes-related complications and treatment-related adverse events were obtained from the literature. Disutilities on hypoglycemic events from the 2006 publication by Currie et al.[8] were used in the base case (0.014 mild; 0.047 severe), which were higher than those in the 2013 CADTH report or the 2016 NICE report (0.000004767 or 0.0052 mild; 0.01 severe).[7,11]	Appropriate, but most studies used to inform the model were non-Canadian. However, these studies were also used in CADTH reports as studies on Canadian populations were unavailable.
Resource use	See "Costs" section.	
Adverse events (indicate the specific adverse events considered in the model)	Rates for major and minor hypoglycemic events as well as nausea events were derived from the GETGOAL – DUO 2 trial.[4]	Appropriate.
Mortality	Fatal diabetes-related complications, non-cardiovascular (all-cause), and direct diabetes deaths were estimated based on UKPDS 82 risk equations.[5]	Appropriate, but might not be applicable to the Canadian population.
Costs		
Drug (lixisenatide)	The manufacturer provided the costs for lixisenatide. The average daily dose was obtained from project monograph.	Appropriate.
Drug (prandial insulin)	The average unit cost of prandial or basal insulin was calculated based on a weighted average for all prandial insulin using 2016	Inappropriate insulin dosage: the using dose from cross-sectional studies includes patients with a longer history of insulin use and higher

Data Input	Description of Data Source	Comment
	market share data observed in Ontario by IMS Brogan.[2] The average daily dose was based on estimates from physicians and pharmacists on the Canadian Optimal Medication Prescribing and Utilization Service expert review committee.[6] All drug costs included a 10% markup fee and a $8.83 dispensing fee.[2]	insulin requirements. While this may be reasonable in specific contexts, the efficacy and harms data are from trials in patients who are naive to prandial insulin or lixisenatide, and where a much lower dose of prandial insulin is used. It is not appropriate to use efficacy and harms data from the trial while using dose from cross-sectional data (and not trial-based dose).
Administration and monitoring	The frequency of self-monitoring blood glucose testing and the costs of needles were included in the base-case analysis (two tests per day for basal + lixisenatide versus four tests per day for basal + prandial).	Reasonable, although it is not clearly established that the self-monitoring of blood glucose would be half as frequent for patients on lixisenatide.
Adverse events	It was assumed that mild and moderate hypoglycemic events do not require health care resource use ($0 cost). The cost of severe hypoglycemia was based on CADTH optimal use reports.[7]	Appropriate.
Health state (cost of diabetes-related complications)	Costs associated with managing long-term diabetes-related complications were obtained from the 2013 CADTH report and the Ontario Ministry of Health and Long-Term Care's Ontario Diabetes Economic Model.[10] Costs associated with ulcer-related complications were taken from another Canadian study (O'Brien, Patrick, & Caro).[19]	Appropriate.

A1C = glycated hemoglobin; NICE = National Institute for Health and Care Excellence; UKPDS = United Kingdom Prospective Diabetes Study.

Table 13: Manufacturer's Key Assumptions

Assumption	Comment
Natural History and Efficacy	
The patients' characteristics from the GETGOAL – DUO 2 trial were assumed to be representative to the target population.[4]	Uncertain, but reasonable. Note that the population was naive to prandial insulin and lixisenatide (not patients who were already treated with prandial insulin).
Risk factors besides A1C and systolic blood pressure were assumed to be static because no time-progression equations were available.	Uncertain, but unlikely to modify results as no differences between comparators are noted.
The UKPDS 82 health outcome risk equations were used to predict incidence of specific diabetes-related complications.[5]	Uncertain, but unlikely to modify results as no differences between comparators are noted.
Non-Canadian utilities and decrements were used in the model.	Uncertain. The model may not represent the Canadian patients' population quality of life.
Patients were assumed to remain on the same treatment over the lifetime of the model.	Not a real-world scenario, but reasonable in that it allows comparison between two strategies (as opposed to a sequence of treatment), similar in approach to previous CADTH reports. Note that the model cannot account for alterations in relative efficacy and harms or dose over time (nor is this information known).

Assumption	Comment
Mortality	
Fatal diabetes-related complications, non-cardiovascular (all-cause), and direct diabetes deaths were estimated based on UKPDS 82 risk equations.[5]	Uncertain. A small mortality benefit was predicted by the model based on the drug efficacy (BMI reduction or lower hypoglycemic rates); however, the model was unable to assess the origin of this benefit.

A1C = glycated hemoglobin; UKPDS = United Kingdom Prospective Diabetes Study.

CADTH Common Drug Review Re-Analyses (Lixisenatide Versus Bolus)

Table 14: CADTH Common Drug Review Re-Analysis of Plausible Base Case

	Description	Treatment	Costs	QALY	Incremental Costs	Incremental QALY	ICUR
	Manufacturer base case	Lixisenatide	$115,486	11.9332	–$8,331	0.0793	Dominant
		Basal-bolus	$123,818	11.8539			
1	**Prandial insulin daily dose**						
1a	20.24 IU ($3,288 annual drug cost)	Lixisenatide	$115,486	11.9332	$7,992	0.0793	$100,787/QALY
		Basal-bolus	$107,495	11.8539			
1b	40 IU ($3,577 annual drug cost)	Lixisenatide	$115,486	11.9332	$3,281	0.0793	$41,383/QALY
		Basal-bolus	$112,205	11.8539			
2	**Prandial insulin cost**						
	Novolin ge Toronto ($4,047 annual drug cost)	Lixisenatide	$115,486	11.9332	–$4,379	0.0793	Dominant
		Basal-bolus	$119,865	11.8539			
3	**BMI disutility cut-off**						
	Disutility applied after BMI of 30 kg/m^2 and above	Lixisenatide	$115,486	12.0648	–$8,331	0.0737	Dominant
		Basal-bolus	$123,818	11.9911			
4	**Utility decrements on hypoglycemic events**						
	0.000004767 mild, 0.01 severe (CADTH, 2013)[7]	Lixisenatide	$115,486	12.0720	–$8,331	0.0251	Dominant
		Basal-bolus	$123,818	12.0469			
	0.0052 mild, 0.01 severe (NICE, 2016)[11]	Lixisenatide	$115,486	12.0119	–$8,331	0.0485	Dominant
		Basal-bolus	$123,818	11.9633			
5	**Plausible base case (analyses 1b, 2)**	Lixisenatide	$115,486	11.9332	**$5,060**	**0.0793**	**$63,818/QALY**
		Basal-bolus	$110,428	11.8539			
5a	Scenario analysis of CDR base case with daily prandial insulin dose of 20.14 IU ($3,233 annual drug cost)	Lixisenatide	$115,486	11.9332	$8,888	0.0793	$112,093/QALY
		Basal-bolus	$106,598	11.8539			
5b	Scenario analysis of CDR base case with daily prandial insulin dose of 60 IU ($3,706 annual drug cost)	Lixisenatide	$115,486	11.9332	$1,179	0.0793	$14,867/QALY
		Basal-bolus	$114,307	11.8539			
5c	Scenario analysis of CDR base case with daily lixisenatide dose of 10 mcg for 17% patients	Lixisenatide	$113,221	11.9332	$2,793	0.0793	$35,222/QALY
		Basal-bolus	$110,428	11.8539			

	Description	Treatment	Costs	QALY	Incremental Costs	Incremental QALY	ICUR
5d	Scenario analysis of CDR base case with BMI disutility cut-off of 30 kg/m^2	Lixisenatide	$115,489	11.9332	$5,060	0.0793	$68,677/QALY
		Basal-bolus	$110,428	11.8539			
5e	Scenario analysis of CDR base case with CADTH 2013 utility decrements	Lixisenatide	$115,489	12.072	$5,060	0.0251	$202,028/QALY
		Basal-bolus	$110,428	12.0469			
5f	Scenario analysis of CDR base case with NICE 2016 utility decrements	Lixisenatide	$115,489	12.0119	$5,060	0.0485	$104,247/QALY
		Basal-bolus	$110,428	11.9633			

BMI = body mass index; CDR = CADTH Common Drug Review; dominant = lixisenatide more effective and less costly; NICE = National Institute for Health and Care Excellence; QALY = quality-adjusted life-year.

Note: Annual drug costs include costs of basal insulin, lixisenatide/prandial insulin, dispensing fees, needles, and self-monitoring.

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