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CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

Insulin degludec and liraglutide injection (Xultophy)

(Novo Nordisk Canada Inc.)

Indication: An adjunct to lifestyle modifications, for the once-daily treatment of adults with type 2 diabetes mellitus to improve glycemic control in combination with metformin, with or without sulfonylurea, when these combined with basal insulin (less than 50 U daily) or liraglutide (less than or equal to 1.8 mg daily) do not provide adequate glycemic control

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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

BMI	body mass index
CHF	congestive heart failure
eGFR	estimated glomerular filtration rate
GLP-1 RA	glucagon-like peptide 1 receptor agonist
ICER	incremental cost-effectiveness ratio
IDeg	insulin degludec
IDegLira	insulin degludec plus liraglutide in a fixed combination
IGlar	insulin glargine
iGlarLixi	insulin glargine and lixisenatide injection
ITC	indirect treatment comparison
LDL	low-density lipoprotein
NMA	network meta analysis
pCHF	probability of congestive heart failure
QALY	quality-adjusted life-year
SBP	systolic blood pressure
SU	sulfonylurea
T2DM	type 2 diabetes mellitus
VBA	Visual Basic for Applications
UKPDS	United Kingdom Prospective Diabetes Study

Table 1: Summary of the Manufacturer's Economic Submission

Drug product	IDegLira (Xultophy)
Study question	What is the cost-effectiveness of IDegLira compared with other available treatments for T2DM in Canada when used in patients as per the Health Canada–approved indication, and as per reimbursement request?
Type of economic evaluation	Cost-utility analysis
Target population	• Patients who have not achieved adequate glycemic control on basal insulin (basal insulin stratum) • Patients who have not achieved adequate glycemic control on liraglutide (liraglutide stratum) • Patients who have not achieved adequate glycemic control with oral glucose-lowering medications combined with basal insulin, or basal insulin alone (reimbursement request)
Treatment	IDegLira in combination with metformin, with or without a sulfonylurea
Outcome	QALYs
Comparators	All comparators were in combination with metformin, with or without a sulfonylurea. • Basal insulin stratum: Basal insulin (IGlar), basal insulin + bolus insulin (basal-bolus), iGLarLixi, IGlar + a GLP-1 RA ("loose combination"), pre-mixed insulin • Liraglutide stratum: Liraglutide, liraglutide + insulin degludec ("loose combination") • Reimbursement request: Basal-bolus
Perspective	Health care system perspective
Time horizon	40 years (assumed to be close to lifetime)
Results for base case	• Basal insulin stratum: For patients who have not achieved adequate glycemic control on basal insulin, IDegLira was cost-effective if the willingness to pay for a QALY was greater than $17,984. • Liraglutide stratum: For patients who have not achieved adequate glycemic control on liraglutide, liraglutide alone was more effective than IDegLira, interestingly. IDegLira was cost-effective if the willingness to pay for a QALY was less than $55,223 — otherwise, liraglutide alone is cost-effective. • Reimbursement request: IDegLira was cost-effective as it dominated basal-bolus (i.e., IDegLira is less costly and associated with greater QALYs).
Key limitations	• The long-term results forecasted by the manufacturer in the model with respect to hemoglobin A1C appear questionable as the benefit from IDegLira only begins in later years. • The liraglutide stratum has limited applicability given that liraglutide is not covered by most participating drug plans and that any QALY differences associated with IDegLira are as a result of assumptions relating to future treatments, not to IDegLira itself. • For the basal insulin stratum, a wide range of other therapeutic options should have been considered as comparators; as such, the relevance of the analysis is questionable. • The reimbursement scenario modelled does not reflect the reimbursement request as it does not cover patients who have not achieved adequate glycemic control with oral glucose-lowering medications in combination with basal insulin (beyond metformin and sulfonylureas). • It is unclear how the reimbursement request can be operationalized given that it would require certainty that patients uncontrolled on basal insulin alone would go on to receive bolus insulin and not other therapeutic options. • The submitted model is not transparent and there are conceptual problems in how disease progression with diabetes is modelled. • Several of the results submitted by the manufacturer appear questionable, and given the structure of the model, it was not possible to validate these results.
CADTH Common Drug Review estimate(s)	• Given the lack of transparency and validity of the submitted model, as well as concerns with the scenarios and comparators considered, it is not possible to conduct an analysis that provides a suitable basis upon which to answer the decision problem.

GLP-1 RA = glucagon-like peptide 1 receptor agonist; IDegLira = insulin degludec plus liraglutide in a fixed combination;
IGlar = insulin glargine; iGlarLixi = insulin glargine and lixisenatide injection; QALY = quality-adjusted life-year; T2DM = type 2 diabetes mellitus.

Drug	Insulin degludec and liraglutide injection (Xultophy)
Indication	An adjunct to lifestyle modifications, for the once-daily treatment of adults with type 2 diabetes mellitus to improve glycemic control in combination with metformin, with or without sulfonylurea, when these combined with basal insulin (less than 50 U daily) or liraglutide (less than or equal to 1.8 mg daily) do not provide adequate glycemic control
Reimbursement request	An adjunct to lifestyle modifications to improve glycemic control in adults with type 2 diabetes mellitus when oral glucose-lowering medications combined with basal insulin, or basal insulin alone, do not provide adequate glycemic control
Dosage form	Solution for subcutaneous injection in a pre-filled pen
Notice of compliance date	April 11, 2018
Manufacturer	Novo Nordisk Canada Inc.

Executive Summary

Background

Xultophy — insulin degludec and liraglutide injection (IDegLira) — is a fixed-ratio combination of a long-acting basal human insulin analogue, insulin degludec, and a glucagon-like peptide 1 receptor agonist (GLP-1 RA), liraglutide.[1] IDegLira is provided in a pre-filled pen containing 3 mL of solution equivalent to 300 U of insulin degludec and 10.8 mg of liraglutide.[1] IDegLira is administered in units: 1 U dispensed from the pen contains 1 U of insulin degludec and 0.036 mg of liraglutide. IDegLira is recommended for use as follows: as an adjunct to lifestyle modifications, for the once-daily treatment of adults with type 2 diabetes mellitus to improve glycemic control in combination with metformin, with or without sulfonylurea, when these combined with basal insulin (less than 50 U daily) or liraglutide (less than or equal to 1.8 mg daily) do not provide adequate glycemic control. The current submitted price for IDegLira is $60.80 per 3 mL pre-filled pen. Depending on the daily dose (16 U to 50 U), this would lead to a daily cost of $3.42 to $10.13, or $1,184 to $3,699 annually.[2]

Liraglutide was previously reviewed by the CADTH Common Drug Review in 2011. CADTH's Canadian Expert Drug Advisory Committee (CEDAC) recommended that liraglutide "not be listed at the submitted price".[3] The committee noted that a reduced price would increase the likelihood of a recommendation to "list with criteria" for patients with inadequate glycemic control on metformin and a sulfonylurea. In 2017, the CADTH Common Drug Review reviewed insulin degludec. The CADTH Canadian Drug Expert Committee recommended that insulin degludec be reimbursed similar to other long-acting insulin analogues that are reimbursed for the treatment of diabetes mellitus and that the overall drug plan cost should not exceed the treatment cost of the least costly long-acting insulin analogue.[4]

The manufacturer submitted a cost-utility analysis over a 40-year time horizon (referred to as a lifetime horizon).[5] The analysis was conducted from the perspective of a Canadian public health care payer. Analyses were conducted for three populations: patients who have not achieved adequate glycemic control on basal insulin (basal insulin stratum), patients who have not achieved adequate glycemic control on liraglutide (liraglutide stratum), and patients who have not achieved adequate glycemic control with oral glucose-lowering

medications combined with basal insulin, or basal insulin alone (reimbursement request). All comparators were assumed to be in combination with metformin, with or without a sulfonylurea. Based on the analysis, the treatments were as follows:

- Basal insulin stratum: IDegLira ([redacted] U daily, on average) compared with basal insulin ([redacted] U daily), basal-bolus ([redacted] U of insulin glargine [IGlar] and [redacted] U of bolus daily), IGlar and lixisenatide, (iGlarLixi, [redacted] U daily), "loose combination" comparator ([redacted] U daily of IGlar plus a GLP-1 RA, at an average price of $[redacted] daily), and pre-mixed insulin ([redacted] U daily).
- Liraglutide stratum: IDegLira ([redacted] U daily, on average) compared with liraglutide ([redacted] mg daily) and "loose combination" comparator (insulin degludec [redacted] U and [redacted] mg liraglutide daily).
- Reimbursement request: The analysis was restricted to patients who have not achieved adequate glycemic control with basal insulin alone and who would otherwise have gone on to receive bolus insulin. Thus, IDegLira [redacted] U daily was compared with basal-bolus ([redacted]U of IGlar and [redacted]U of bolus daily).

The submission is based on the IHE [Institute for Health Economics] Cohort Model for Type 2 Diabetes, purportedly a Markov model within an Excel workbook.[6] However, the model differs from traditional Excel-based models because the progression of the cohort is hard coded as it is inputted though a series of Visual Basic for Applications (VBA) macros, which precludes examination of how patients move from state to state. The model incorporated a variety of health states relating to the important microvascular and macrovascular complications associated with diabetes, the incidence of hypoglycemic events, and the associated impact of complications and events on mortality. Within the model, the annual probability of major diabetes-related macrovascular complications was derived from risk equations based on the United Kingdom Prospective Diabetes Study (UKPDS) 82 study,[7] a study that is consistent with previous CADTH reports.[8] Microvascular complications were modelled based on previously published studies.[9-11] Macrovascular complications were modelled based on the United Kingdom Prospective Diabetes Study 82 risk models.[7] Thus, the risk of each complication was a function of a range of predictors, including biomarkers such as hemoglobin A1C, systolic blood pressure, and low-density lipoprotein.

For all treatment populations considered, the impact of treatment on preventing such complications was based on indirect evidence in that the model simulates the progression of biomarkers over time, incorporating the impact of treatment, which then impacts the probability of events occurring. This was necessary given that data from the clinical trials only cover a 26-week period and therefore assumptions relating to extrapolation beyond this period up to 40 years were necessary. Clinical data for the basal insulin stratum and the liraglutide stratum were derived from a manufacturer-submitted network meta-analysis,[12] given the limited number of comparators to which IDegLira has been compared.[9] For the reimbursement scenario, data from the DUAL VII clinical trial were used.[13]

The model incorporated the costs of treatment, which were obtained from reliable sources.[14] Similarly, the costs of macrovascular complications were consistent with the previous CADTH therapeutic review.[8] However, costs relating to microvascular complications were primarily based on US data converted to Canadian dollars, which is not appropriate.[14] Utility values were modelled based on an assumed utility value for an individual with diabetes, which is a function of age, gender, duration of disease, and body mass index.[8,15,16] In addition, a disutility was applied for each hypoglycemic event (severe and non-severe).[15]

For the basal insulin stratum, the manufacturer reported that the incremental cost-effectiveness ratio (ICER) — the incremental cost per quality-adjusted life-year (QALY) gained — for iGlarLixi versus pre-mixed insulin was $8,310 while the ICER for IDegLira versus iGlarLixi was $17,984. Basal insulin, basal-bolus, and the loose combination option were subject to dominance or extended dominance. For the liraglutide stratum, liraglutide was associated with highest estimated QALYs. The loose combination strategy was dominated by liraglutide and the ICER for liraglutide versus IDegLira was $55,223. For the reimbursement scenario, IDegLira dominated basal-bolus (i.e., IDegLira was associated with lower costs and greater QALYs).

Summary of Identified Limitations and Key Results

There were a number of major limitations identified with the manufacturer's analyses.

The manufacturer's indirect treatment comparison (ITC) for the population of patients that has not achieved adequate glycemic control on basal insulin (basal insulin stratum) considers all other GLP-1 RAs as a single treatment comparator — referred to as a "loose combination." This is not appropriate for inclusion in an economic evaluation as it would be relevant to consider all agents as potential comparator therapies in this patient group; all agents should have been incorporated individually. For both the basal insulin and liraglutide strata, the ITC adopted in the economic submission did not incorporate a full range of clinical parameters. The ITC did not cover important clinical markers such as [redacted]. The ITC does include data on [redacted] and therefore assumptions around the parsing of data between these needed to be made.

The clinical trial data were limited to 26 weeks' duration; as such, more than 90% of the incremental benefit suggested with IDegLira occurs after the clinical trial period. No assumption of differential waning of relative treatment effect is made.

There were concerns with the manufacturer's assumptions relating to the disutility associated with body mass index and hypoglycemic events. The results from the model with respect to the prevalence of hypoglycemic events do not match the clinical data inputted, which questions the validity of the model. This is especially important given that the model results are highly sensitive to the effect of treatment on hypoglycemia.

Within the liraglutide stratum analysis, it is unclear why liraglutide was forecasted to have significantly more treatment costs than IDegLira. It is also unclear why it is assumed that the loose combination of insulin degludec and liraglutide would involve much higher doses than IDegLira. This inconsistency results in concerns regarding the model logic. Further, within the reimbursement scenario, the model produces results with respect to hemoglobin A1C, that lack validity. The model suggests that there are no differences between basal-bolus and IDegLira for the first eight years of treatment and then subsequently there is a noticeable difference modelled for the following years. Thus, the QALY differences are not due to treatment with IDegLira itself but rather due to assumptions related to different future treatments for different comparators. The clinical data relating to this must be considered highly speculative. Furthermore, there is no guarantee that either the purported treatment algorithms would be held to or that they may still be in place in eight years' time. The assumption that IDegLira generates benefits purely because of different treatment options in the future raises significant cause for concern; it suggests analysis beyond eight years is

highly questionable and seriously undermines the validity of the analyses for the other patient strata.

While CADTH acknowledges that the manufacturer submitted a cohort model for diabetes with the purpose of increasing transparency (compared with microsimulation models), given the complexity of the condition, the accessibility of the model logic was affected and the model is not transparent — data within the Excel model was hard coded, with results generated by a series of Visual Basic macros. Verification of this code was not possible and there were concerns over the inconsistency of results provided by the manufacturer. Furthermore, a cohort model does not accurately reflect the variability in disease progression and treatment response across the cohort, and requires both the assumption of a linear relationship between biomarkers and outcomes, which is contrary to the risk equations adopted within the model, and ignores the impact of the higher prevalence of complications in those at higher risk.

Given these limitations, CADTH concluded that the model and analysis submitted by the manufacturer is not a suitable basis upon which to assess the cost-effectiveness of IDegLira. Thus, it was not possible for CADTH to provide meaningful reanalyses.

Conclusions

The manufacturer's analysis suggests that IDegLira is cost-effective in patients who have not achieved adequate glycemic control on basal insulin and/or oral glucose-lowering medications combined. However, CADTH identified a number of limitations with the submitted analysis, such that the cost-effectiveness of IDegLira could not be fully assessed.

Given that the ITC [redacted], it is difficult to conclude whether IDegLira represents a clinical benefit over all treatment alternatives. Based on the manufacturer's economic submission, the manufacturer's estimated treatments costs are generally higher for IDegLira relative to included comparators in all analyses. Given the lack of comparative clinical information for IDegLira and concerns with the submitted economic evaluation, it remains uncertain whether IDegLira represents a cost-effective treatment option.

Information on the Pharmacoeconomic Submission

Summary of the Manufacturer's Pharmacoeconomic Submission

The manufacturer has submitted a cost-utility analysis over a 40-year time horizon (referred to as a lifetime horizon).[5] The analysis, done from the perspective of a Canadian public health care payer, was conducted for three populations: patients who have not achieved adequate glycemic control on basal insulin (basal insulin stratum), patients who have not achieved adequate glycemic control on liraglutide (liraglutide stratum), and patients who have not achieved adequate glycemic control with oral glucose-lowering medications combined with basal insulin, or basal insulin alone (reimbursement request).

All comparators were assumed to be in combination with metformin, with or without a sulfonylurea.

- For patients who have not achieved adequate glycemic control on basal insulin, it was assumed that patients would receive insulin degludec plus liraglutide in a fixed combination (IDegLira) [redacted]daily (average). Comparators were basal insulin ([redacted]U daily), basal-bolus ([redacted]U daily of insulin glargine [IGlar] and [redacted]U daily of bolus), IGlar and lixisenatide (iGlarLixi [redacted]daily), a "loose combination" comparator ([redacted]U daily of IGlar plus a glucagon-like peptide 1 receptor agonist (GLP-1 RA), at an average price of $[redacted] daily), and pre-mixed insulin ([redacted]daily).(
- For patients who have not achieved adequate glycemic control on liraglutide, it was assumed that patients would receive IDegLira [redacted]U daily (average). Comparators were liraglutide ([redacted] mg daily), and a loose combination comparator (insulin degludec [redacted]U and [redacted]mg liraglutide daily).
- For the reimbursement scenario, analysis was restricted to patients who have not achieved adequate glycemic control with basal insulin alone and who would otherwise have gone on to receive bolus insulin. Thus, the comparators were IDegLira [redacted] U daily and basal-bolus ([redacted]U of IGlar and [redacted]U of bolus daily).

The submission is based on the IHE [Institute for Health Economics] Cohort Model for Type 2 Diabetes — purportedly a Markov model within an Excel workbook.[6] However, the model differs from traditional Excel-based models because the progression of the cohort is hard coded as it is inputted though a series of Visual Basic for Applications macros, which precludes examination of how patients move from state to state. Furthermore, individuals do not transition from one state to another; rather, the model estimates the percentage of the cohort with different diabetes-related complications. Thus, there is not a finite list of potential health states. Instead, there is a list of health states for each complication that are modelled unconditional of other complications.

The model covers the important microvascular and macrovascular complications associated with diabetes, the incidence of hypoglycemic events, and the associated impact of complications and events on mortality. Microvascular complications that were incorporated were retinopathy (background diabetic retinopathy, macular edema, proliferative diabetic retinopathy, and severe visual loss), neuropathy (symptomatic neuropathy, peripheral vascular disease, and lower extremity amputation), and nephropathy (microalbuminuria, macroalbuminuria, and end-stage renal disease). Macrovascular complications that were

included were ischemic heart disease, myocardial infarction (first and subsequent myocardial infarctions), stroke (first and subsequent strokes), and congestive heart failure (CHF).

Within the model, the annual probability of major diabetes-related macrovascular complications is derived from risk equations based on the United Kingdom Prospective Diabetes Study (UKPDS) 82,[7] a study that is consistent with previous CADTH reports.[8] Thus, the risk of each complication is a function of a range of predictors, including biomarkers such as hemoglobin A1C, systolic blood pressure, low-density lipoprotein (LDL), high-density lipoprotein, and estimated glomerular filtration rate (eGFR). and as a function of other complications. The risk equations provide estimates of the probability of developing ischemic heart disease and CHF, and the probability of first and subsequent myocardial infarctions and strokes. Microvascular complications are modelled based on previously published studies.[9-11] Probabilities relating to the progression of retinopathy and nephropathy are derived from the Eastman model of diabetes and the global diabetes model, and are primarily a function of the duration of diabetes and hemoglobin A1C.[10,11] Probabilities relating to the progression of neuropathy are derived from both the Eastman and Bagust models of diabetes, and are primarily a function of the duration of diabetes, sex, and hemoglobin A1C.[9-11]

To model the impact of treatment on preventing complications within the models, it is necessary to rely on indirect evidence relating to the effects of treatment on the biomarkers, which impact the probability of complications. This is due to the absence of data relating to the impact of treatments on patient-related outcomes such complications, quality of life, and mortality. The model predicts the impact of treatment on patient-related outcomes.

Data on the effect of comparators for both basal insulin stratum analysis and the liraglutide stratum analysis were derived from a manufacturer-submitted network meta-analysis, given the limited number of comparators with which IDegLira has been compared (see Table 10 and Table 11).[17] Data were collected when available for the following end points: [redacted]

Treatment continuation was modelled indirectly based on hemoglobin A1C. Treatment was assumed to have an immediate effect on hemoglobin A1C, but this effect dissipated over time due to drift in hemoglobin A1C; at one time point, it was assumed that all patients would move to an intensification treatment when the hemoglobin A1C reached 8.5%. Patients would then experience another hemoglobin A1C drop and once the hemoglobin A1C again reached 8.5%, patients would move to a final insulin treatment.

The model incorporated the costs of treatment, which were obtained from reliable sources: the manufacturer, McKesson, and the Ontario Drug Benefit Formulary (see Table 13, Table

14, and Table 15).[19] Initial analysis provided by the manufacturer included the costs of prescription fees and markup, and excluded the costs of metformin. This was rectified in a further analysis. Analysis incorporated the costs of complications (see Table 16). The costs relating to macrovascular complications were consistent with a previous CADTH therapeutic review.[8] The costs relating to macrovascular complications were obtained from a US study and converted to Canadian dollars.[14]

Utility values within the model were based on an assumed utility value for a diabetic patient. This was a function of age, gender, duration of disease, and body mass index (BMI) as per a previous analysis by Currie et al. (see Table 9).[15] From here, disutilities are applied for the prevalence of each of the modelled diabetes-related complications.[8,16] In addition, a disutility is applied for each hypoglycemic event (severe and non-severe) that occurs.[15] Then, quality-adjusted life-years (QALYs) are estimated by summing the baseline utility for diabetes and the disutilities that are applied for the prevalence of each of the modelled diabetes-related complications.

Relevant input parameters were assumed to be uncertain. Expected values of outcomes for each treatment were obtained from randomly sampling parameter values 1,000 times.

Manufacturer's Base Case

Original Submission

For the basal insulin stratum, basal-bolus had the lowest reported QALYs followed by pre-mixed insulin, basal insulin, iGlarLixi, the loose combination strategy and, finally, IDegLira (see Table 2). The manufacturer reported that basal insulin, basal-bolus, and the loose combination strategy were subject to dominance or extended dominance. The manufacturer reported that the incremental cost-effectiveness ratio (ICER) — the incremental cost per QALY gained — for iGlarLixi versus pre-mixed insulin was $8,310. The ICER for IDegLira versus iGlarLixi was $17,984. Thus, IDegLira would be considered cost-effective if a manufacturer's willingness to pay for a QALY were greater than $17,984.

At $50,000 per QALY, the probability that IDegLira is optimal was 97.8%.

Table 2: Summary of Results of the Manufacturer's Base Case for Basal Insulin Stratum

	Total Costs ($)	Total QALYs	ICER vs. Pre-Mixed Insulin	Sequential ICER
Pre-mixed insulin	163,279	10.651	reference	reference
iGlarLixi	168,768	11.326	$8,130	$8,130
IDegLira	173,646	11.597	$10,954	$17,984
Basal insulin	167,704	10.831	$24,492	Extended dominance through iGlarLixi
Basal-bolus	174,002	10.542	Dominated	Dominated by IDegLira
Loose combination	180,975	11.483	$21,265	Dominated by IDegLira

ICER = incremental cost-effectiveness ratio; IDegLira = insulin degludec plus liraglutide in a fixed combination; iGlarLixi = insulin glargine and lixisenatide injection; QALY = quality-adjusted life-year; vs. = versus.

Source: Manufacturer's pharmacoeconomic submission.[5]

For the liraglutide stratum, liraglutide was associated with the highest estimated QALYs (see Table 3). The loose combination strategy was associated with higher QALYs than IDegLira but was dominated by liraglutide. The ICER for liraglutide versus IDegLira was $55,223. At $50,000 per QALY, the probability that IDegLira is optimal was 57.4%.

Table 3: Summary of Results of the Manufacturer's Base Case for Liraglutide Stratum

	Total Costs ($)	Total QALYs	ICER vs. IDegLira	Sequential ICER
IDegLira	156,126	12.425	reference	reference
Liraglutide	170,637	12.688	$55,223	$55,223
Loose combination	178,270	12.661	$93,869	Dominated by liraglutide

ICER = incremental cost-effectiveness ratio; IDegLira = insulin degludec plus liraglutide in a fixed combination; QALY = quality-adjusted life-year; vs. = versus.

Source: Manufacturer's pharmacoeconomic submission.[5]

For the reimbursement scenario, IDegLira dominated basal-bolus (see Table 4).

Table 4: Summary of Results of the Manufacturer's Base Case for Reimbursement Scenario

	Total Costs ($)	Total QALYs	ICER vs. Basal-Bolus
IDegLira	151,648	12.206	Dominant
Basal-bolus	162,196	10.849	-

ICER = incremental cost-effectiveness ratio; IDegLira = insulin degludec plus liraglutide in a fixed combination; QALY = quality-adjusted life-year; vs. = versus.

Source: Manufacturer's pharmacoeconomic submission.[5]

Requested Revisions

The manufacturer was asked to provide a revised submission. This required excluding markup and pharmacy fees and using only the cost of Basaglar for the cost of IGlar in the submission. The manufacturer provided this reanalysis. The revised results did not differ significantly from those reported above from the original submission.

Summary of Manufacturer's Sensitivity Analyses

The manufacturer provided a wide range of scenario analyses for each patient stratum considered. Scenario analyses primarily related to choice of perspective (societal), discount rate (0% and 3%), hemoglobin A1C threshold, time horizon, real-world test strip utilization, and revised utility values. Results were generally consistent across all scenarios.

Limitations of Manufacturer's Submission

There were a number of major limitations identified with the manufacturer's analysis. These can be categorized in terms of decision problems considered, data inputs, and the model adopted.

- **Appropriate comparator:** Analysis for the basal insulin stratum considered a loose combination therapeutic option, which was a combination of all other GLP-1 RAs as a single treatment comparator. This is not appropriate for inclusion in an economic evaluation as it would be relevant to consider all agents as separate potential comparator therapies in this patient group. All agents should have been incorporated individually. Similarly, for this stratum, consideration of other classes of drugs would have been warranted.

  The liraglutide stratum may have limited applicability, given that liraglutide is not covered by most participating drug plans and treatment with liraglutide was an integral part of each comparator considered. It was also unclear why it is assumed that the loose combination of insulin degludec and liraglutide would involve much higher doses than IDegLira.

The reimbursement scenario modelled does not reflect the reimbursement request. The request is for patients who have not achieved adequate glycemic control with oral glucose-lowering medications combined with basal insulin, or basal insulin alone. The analysis submitted for the reimbursement scenario, however, was restricted to patients who have not achieved adequate glycemic control with basal insulin alone and who would otherwise have gone on to receive bolus insulin. Thus, it is unclear how the reimbursement request can be operationalized given that it would require certainty that patients uncontrolled on basal insulin alone would go on to receive bolus insulin, not other therapeutic options.

- **Generalizability of the clinical studies:** IDegLira has been studied as part of the DUAL clinical trial program in two phase IIIa trials (DUAL I and II) and six phase IIIb trials (DUAL III, DUAL IV, DUAL V, DUAL VI, DUAL VII, and DUAL IX).[13,20-26] However, only three trials relate to the scenarios covered within this submission (DUAL III, DUAL V, and DUAL VII)[17,19,21] and none compared IDegLira explicitly with other GLP-1 RA therapeutic options. All three trials are randomized, two-arm studies limited to only 26 weeks' duration. In DUAL III, the efficacy of IDegLira was assessed in adults with type 2 diabetes mellitus (T2DM) uncontrolled on GLP-1 RA therapy. IDegLira was assessed in comparison with unchanged GLP-1 RA therapy, not with other combinations of insulin plus GLP-1 RA. In DUAL V, the efficacy of IDegLira was assessed in adults with T2DM uncontrolled on basal insulin. IDegLira was assessed in comparison with basal intensification. In DUAL VII, IDegLira was assessed in patients uncontrolled on basal insulin and was compared with intensification through bolus.

  The base populations for the economic evaluations were based on the clinical trial populations. This may not be relevant for the Canadian context. For example, all three populations considered assumed a high proportion of Hispanics: 23.1% in the basal insulin stratum, 9.6% in the liraglutide stratum, and 25.2% in the reimbursement scenario.[5]

- **Comparative clinical information:** The indirect treatment comparison (ITC) [redacted] For both the basal insulin and the liraglutide strata, the ITC adopted in the economic submission did not incorporate a full range of clinical parameters. The ITC did not cover important clinical markers such as [redacted].

  The ITC does include data on [redacted] and therefore assumptions around the parsing of data between these needed to be made. This led to inconsistencies in [redacted] across the three study populations, which was difficult to interpret.

- **Availability of longer-term information on IDegLira:** Clinical trial data were limited to 26 weeks' duration. Thus, generally more than 90% of the incremental benefit predicted with IDegLira occurs after the clinical trial time period. No assumption of differential waning of relative treatment effect was made.

- **Disutilities associated with BMI and hypoglycemia:** The manufacturer included a disutility associated with BMI. A utility loss of 0.006 was applied for every extra BMI over 25. The CADTH therapeutic review assumed no direct effect of BMI on utility.[8] It stated, "A utility decrement for weight gain in the primary economic analysis was not applied. Most widely cited studies derive such estimates from much larger weight differences (i.e., 13 kg to 30 kg), and it is unclear whether these can be applied in a proportional manner to the smaller weight differences between drugs observed in the ITC of second-line therapies." As such, the appropriateness of the disutility for BMI is unclear.

The manufacturer adopted a disutility of 0.014 for non-severe hypoglycemia and 0.047 for severe hypoglycemia. However, as noted in previous National Institute for Health and Care Excellence (NICE) technology assessments, the decrement is based on a three-month period. Therefore, the utility decrement must be divided by four to obtain the annual utility decrement. A further concern is that the network meta-analysis and the analysis of the DUAL VII trial considered all non-severe hypoglycemic events, many of which were asymptomatic. The assignment of a disutility to an asymptomatic event is unlikely to be appropriate. These limitations are especially important given that the model results are highly sensitive to the effect of treatment on hypoglycemia.

Removing the disutility associated with BMI and non-severe hypoglycemia and dividing the disutility for severe hypoglycemia by four leads to a significant change in the estimate of QALY gains. For example, for the reimbursement scenario, under a deterministic analysis, the QALY gains for IDegLira versus basal-bolus fall from 1.334 to 0.223.

- **Model approach:** While CADTH acknowledges that the manufacturer submitted a cohort model for diabetes with the purpose of increasing transparency (compared with microsimulation models), given the complexity of T2DM, the accessibility of the model logic was affected.

  The first concern raised is that the model lacks transparency. Data within the Excel model is hard coded with results generated by a series of 24 Visual Basic macros totalling approximately 17,000 lines of code. Given the complexity of the model, it was not possible within the review time frame to verify all the code and assess how the data inputs generated the model outcomes. This concern is exacerbated by the inconsistencies between the first and second set of results provided by the manufacturer. This inconsistency heightens concerns over the validity of the model, given the inability to verify the link between input data and outcomes.

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

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

  To illustrate this point, consider the following scenario:

  > The patient cohort is representative of males currently aged 69 years of age, with seven years of diabetes, an LDL of 3.0 mmol/L, a BMI of 33, an eGFR of 50, with microalbuminuria, and a history of amputation. Let's assume treatment will reduce BMI by one, with a standard error of 0.5 and a standard deviation of five. If we assume the patient cohort progresses solely based on the expected value of impact on BMI and all other parameters remain the same, after one year, the patient cohort will be males currently aged 70 years of age, with eight years of diabetes, an LDL of 3.0 mmol/L, a BMI of 33, an eGFR of 50, with microalbuminuria, and a history of amputation. For this, the probability of congestive heart failure (pCHF) in the following year will be:[5]

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

= 0.0267

However, if we allow for the variance in effect on BMI, we will get a different estimate of the probability. For example, for those whose BMI increases to 35 (an increase of three versus the expected value), the probability of CHF would be 0.0331 while for those whose BMI decreased by three versus the expected value (29), the probability will be 0.0216. The average of these values is greater than the forecasted probability –0.0273 versus 0.0267. Thus, the model is likely to overestimate the reduction in the probability of events associated with treatment.

A related problem with the model is that it predicts the prevalence of events and the clinical markers independently. Thus, it ignores the fact that the clinical markers for patients with a history of events will necessarily be different than the clinical markers for those without an event.

Consider the previous example given pCHF. The equation predicts that those patients who experience CHF will be more likely to have BMI than those who do not. As time progresses, the cohort of the model who do not have a history of CHF will be expected to have a lower BMI than those who have experienced CHF. Thus, employing the average BMI of the whole cohort in the risk equation rather than the BMI for those who have not had CHF would give a biased upward estimate of the probability of members of the cohort newly developing CHF.

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

The concerns over the lack of transparency with the submitted model are exacerbated by the inability to explain certain results provided by the manufacturer.

The results from the model with respect to the prevalence of hypoglycemic events do not match the clinical data inputted. This questions the validity of the model. For example, the annual number of non-severe hypoglycemic events with basal-bolus in the reimbursement scenario is entered into the model as 10.91; yet, the estimated number the model generates for the first year is 13.69. The manufacturer suggests that this is done to a correction factor that adjusts the hypoglycemic event by the current hemoglobin A1C versus the baseline value. This approach is incorrect as the hypoglycemic rates observed in the trials are already factoring the change in hemoglobin A1C over the trial's duration. Thus, the correction should be based on the change from the observed hemoglobin A1C at the end of the trial, not on the baseline value. This will result in a consistent overestimation of hypoglycemic events and, more importantly, an overestimation of differences in hypoglycemic events between treatments. This is, again, especially important given that the model results are highly sensitive to the effect of treatment on hypoglycemia.

Within the reimbursement scenario, the model produces results with respect to hemoglobin A1C that are not explainable. There are no differences between basal-bolus and IDegLira for the first eight years of treatment and then, subsequently, there is a noticeable difference modelled for subsequent years. This suggests that the results of analysis beyond eight years might be dependent not on the initial treatment option but on assumptions relating to treatments further down the treatment pathway. Thus, the QALY

differences are not due to treatment with IDegLira itself but rather due to assumptions related to different future treatments for different comparators. The clinical data relating to this must be considered highly speculative. Furthermore, there is no guarantee that either the purported treatment algorithms would be held to or that they may still be in place in eight years' time. In further analysis for the reimbursement scenario, the incremental QALYs gained (incorporating the revised disutilities for hypoglycemia and BMI) for IDegLira versus basal-bolus fell from 0.223 for 40 years to 0.002 at eight years. Thus, consideration of a long-term time horizon may be questionable.

Finally, there may be face validity concerns with the model. For the reimbursement scenario analysis, more than 20% of patients receiving either basal-bolus or IDegLira were alive at the end of the 40-year time horizon. If this were realistic, then it would question the suitability of 40 years as a choice of time horizon. However, the likelihood that more than 20% of a population cohort that were aged 58 and had an average BMI of more than 31 and more than 11 years' history of diabetes being alive at age 98 is questionable. Following the opportunity to comment on the CADTH pharmacoeconomic report, the manufacturer attempted to address this issue with a revised report and accompanying models. However, this new information did not change the concerns raised by CADTH. A discussion of this new information and its implications are contained in Appendix 5.

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

CADTH Common Drug Review Reanalyses

Given the concerns identified by CADTH with the submitted analysis in relation to both the data used and the nature of the model provided, it was not possible to conduct reanalysis to assess the cost-effectiveness of IDegLira.

Patient Input

Two patient groups, Diabetes Canada and Type 2 Diabetes Experience Exchange (T2DXX), provided patient input for this submission. Diabetes Canada collected patient input through online surveys conducted in October 2016 and in January and February 2019, using a self-administered questionnaire targeting people living with T2DM and their caregivers across Canada. The T2DXX group indicated the following sources of data for their submission: personal interviews and facilitated group discussion in T2DXX forums and social media conversation threads.

The patient groups highlighted that diabetes is a chronic, progressive disease without cure. T2DM is very complex and has a striking burden on the physical, emotional, social, and economic status of the person. The common symptoms of diabetes include extreme fatigue, unusual thirst, frequent urination, and weight change (gain or loss). The goal of diabetes management is to keep glucose levels within a target range to minimize symptoms and avoid or delay complications. Most patients surveyed talked about the adverse effect diabetes has had on their lives. Patients who responded to the surveys indicated that they experienced the following symptoms or comorbidities: hyperglycemia; hypoglycemia; high blood pressure; high cholesterol; heart problems; mental health problems; kidney symptoms

or disease; foot problems; eye problems; nerve damage; damage to blood vessels, heart, or brain; liver disease; weight gain; and sexual dysfunction. These elements were captured within the manufacturer's economic model.

Both the Diabetes Canada and T2DXX groups indicated the wish for new treatments to enhance weight loss and improve health outcomes at an affordable cost. They want treatments that are easily administered, cause the least amount of disruption to lifestyle, and allow for flexibility with food intake and choices. They also want medications that will help avoid polypharmacy and eliminate the need for injections while minimizing the risk of any short-term medication-related side effects or long-term disease-related side effects. Given the ITC provided by the manufacturer, it is unclear how IDegLira compares with other treatments in some of these patient-important outcomes. IDegLira is an injection, which does not address the desire for eliminating injections.

Conclusions

The manufacturer's analysis suggests that IDegLira is cost-effective in patients who have not achieved adequate glycemic control on basal insulin and/or oral glucose-lowering medications combined. However, CADTH identified a number of limitations with the submitted analysis, such that the cost-effectiveness of IDegLira could not be fully assessed.

Given that the ITC [redacted], it is difficult to conclude whether IDegLira represents a clinical benefit over all treatment alternatives. Based on the manufacturer's economic submission, the estimated treatment costs by the manufacturer are generally higher for IDegLira relative to included comparators in all analyses. Given the lack of comparative clinical information for IDegLira and concerns with the submitted economic evaluation, it remains uncertain whether IDegLira represents a cost-effective treatment option.

Appendix 1: Cost Comparison

The comparators presented in Table 5 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 list prices, unless otherwise specified. Existing product listing agreements are not reflected in the table and as such may not represent the actual costs to public drug plans.

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

Drug / Comparator	Strength	Dose Form	Price ($)	Recommended Dosage	Average Daily Drug Cost ($)	Average Annual Drug Cost ($)
Insulin and GLP-1 RA Combinations						
Insulin degludec/ liraglutide (Xultophy)	**100 U/mL and 3.6 mg/mL**	**3 mL pre-filled pen**	**60.8000[a]**	**16 U to 50 U IDeg and 0.58 mg to 1.8 mg liraglutide once a day Max. daily dose: 50 U**	**3.42 (16 U) to 10.13 (50 U)**	**1,184 (16 U) to 3,699 (50 U)**
iGlarLixi (Soliqua)	100 U/mL and 33 mcg/mL	3 mL pre-filled pen (SoloStar)	37.9600[b]	15 U to 60 U IGlar and 5 mcg to 20 mcg lixisenatide once a day. Starting dose not > 10 mcg lixisenatide Max. daily dose: 60 U	1.90 (15 U) to 7.59 (60 U)	694 (15 U) to 2,770 (60 U)
GLP-1 RAs						
Dulaglutide (Trulicity)	0.75 mg/0.5 mL 1.5 mg/0.5 mL	4 x 0.5 mL pre-filled pen	49.7900[c] per pen	0.75 mg to 1.5 mg once weekly	7.11	2,596
Exenatide (Byetta)	1.2 mL 2.4 mL	60 x 5 mcg dose or 10 mcg dose pre-filled pen (250 mcg/mL)	119.7250[c] per mL 49.8625[c] per mL	5 mcg to 10 mcg twice daily	4.79	1,748
Exenatide (Bydureon)	2 mg	2 mg pre-filled pen (extended release)	49.4850[c] per pen	2 mg once weekly	7.07	2,580
Liraglutide (Victoza)	2 x 3 mL 3 x 3 mL	Pre-filled pen inj (6 mg/mL)	29.7367[c] per mL	1.2 mg to 1.8 mg daily	5.95 to 8.92	2,170 to 3,256
Lixisenatide (Adlyxine)	10 mcg 20 mcg	14 dose pre-filled pen (3 mL)	56.9800[c] 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
Semaglutide (Ozempic)	2 mg 4 mg	Pre-filled pen (1.34 mg/mL)	195.06[e]	0.5 mg to 1.0 mg once weekly	6.97	2,544
Metformin						
Metformin (generics)	500 mg 850 mg	Tab	0.0247 0.0339	500 mg 3 to 4 times daily, or 850 mg 2 to 3 times daily	0.07 to 0.10	25 to 36
Sulfonylureas						
Gliclazide	80 mg	Tab	0.0931	80 mg to 320 mg daily	0.09 to 0.37	34 to 136

Drug / Comparator	Strength	Dose Form	Price ($)	Recommended Dosage	Average Daily Drug Cost ($)	Average Annual Drug Cost ($)
(generics)				(in divided doses if > 160 mg daily)		
Gliclazide, long-acting (generics)	30 mg 60 mg	ER tab	0.0931 0.0632	30 mg to 120 mg daily	0.06 to 0.13	22 to 44
Glimepiride (generics)	1 mg 2 mg 4 mg	Tab	0.4900	1 mg to 4 mg daily	0.49	179
Glyburide (generics)	2.5 mg 5.0 mg	Tab	0.0321 0.0574	2.5 mg to 20 mg daily (in divided doses if > 10 mg daily)	0.03 to 0.23	12 to 84
TZDs						
Pioglitazone (generics)	15 mg 30 mg 45 mg	Tab	0.3800[d] 0.5360[d] 0.8075[d]	15 mg to 45 mg daily	0.38 to 0.81	139 to 295
Rosiglitazone (generics)	2 mg 4 mg 8 mg	Tab	1.0316[d] 1.6188[d] 2.3150[d]	4 mg to 8 mg daily	1.62 to 2.32	591 to 845
Meglitinides						
Repaglinide (generics)	0.5 mg 1 mg 2 mg	Tab	0.2083 0.2165 0.2441	0.5 mg to 2 mg daily	0.21 to 0.24	76 to 89
Alpha-Glucosidase Inhibitors						
Acarbose (Glucobay)	50 mg 100 mg	Tab	0.2695 0.3732	50 mg to 100 mg 3 times daily	0.81 to 1.12	295 to 409
SGLT2 Inhibitors						
Empagliflozin (Jardiance)	10 mg 25 mg	Tab	2.6727	10 mg or 25 mg daily	2.67	976
Canagliflozin (Invokana)	100 mg 300 mg	Tab	2.8100	100 mg or 300 mg daily	2.81	1,026
Dapagliflozin (Forxiga)	5 mg 10 mg	Tab	2.6750	5 mg or 10 mg daily	2.68	976
SGLT2 Inhibitor Plus Metformin Fixed-Dose Combinations						
Dapagliflozin + metformin (Xigduo)	5 mg/850 mg 5 mg/1,000 mg	Tab	1.2250	1 tablet twice a day	2.45	894
Canagliflozin + metformin (Invokamet)	50 mg + 500 mg, 850 mg, or 1,000 mg 150 mg + 500 mg, 850 mg or 1,000 mg	Tab	1.5800[c]	1 tablet twice a day	3.16	1,153
Empagliflozin + metformin (Synjardy)	5 mg + 500 mg, 850 mg or 1,000 mg 12.5 mg + 500 mg, 850 mg or 1,000 mg	Tab	1.3783	1 tablet twice a day	2.76	1,006

Drug / Comparator	Strength	Dose Form	Price ($)	Recommended Dosage	Average Daily Drug Cost ($)	Average Annual Drug Cost ($)
DPP-4 Inhibitors						
Sitagliptin (Januvia)	25 mg 50 mg 100 mg	Tab	3.0932	100 mg daily	3.09	1,129
Saxagliptin (Onglyza)	2.5 mg	Tab	2.4760	5 mg daily	2.48	904 to 1,083
	5.0 mg		2.9680		2.97	
Linagliptin (Trajenta)	5 mg	Tab	2.6036	5 mg daily	2.60	950
Alogliptin (Nesina)	6.25 mg 12.5 mg 25 mg	Tab	2.2000[c]	25 mg daily	2.20	803
DPP-4 Inhibitor Plus Metformin Fixed-Dose Combinations						
Alogliptin + metformin (Kazano)	12.5 mg + 500 mg, 850 mg or 1,000 mg	Tab	1.1950[c]	2 tablets daily	2.39	872
Linagliptin + metformin (Jentadueto)	2.5 mg + 500 mg, 850 mg or 1,000 mg	Tab	1.3651	2 tablets daily	2.73	997
Saxagliptin + metformin (Komboglyze)	2.5 mg + 500 mg, 850 mg or 1,000 mg	Tab	1.2700	2 tablets daily	2.54	927
Sitagliptin + metformin (Janumet + Janumet XR)	50 mg + 500 mg, 850 mg or 1,000 mg	Tab	1.6779	Twice daily. Maximal daily dose: 100 mg sitagliptin + 2,000 mg metformin	3.36	1,225
	50 mg + 500 mg or 50 mg + 1,000 mg	ER tab	1.6779	Once a day. Maximal daily: 100 mg sitagliptin + 2,000 mg metformin	1.68 to 3.36	613 to 1,225
	100 mg + 1,000 mg		3.3557		3.36	1,225

DPP-4 = dipeptidyl peptidase-4; ER=extended release; GLP-1 RA = glucagon-like peptide 1 receptor agonist; IDeg = insulin degludec; IGlar = insulin glargine; iGlarLixi = insulin glargine and lixisenatide injection; max. = maximum; SGLT2 = sodium-glucose cotransporter-2; TZD = thiazolidinediones.

Note: All prices are from the Ontario Drug Benefit Formulary (accessed February 2019) unless otherwise indicated and do not include dispensing fees.

[a] Manufacturer-submitted price.

[b] Soliqua CADTH Common Drug Review pharmacoeconomic report.[27]

[c] Delta, PA, IQVIA, wholesale price (February 2019).[28]

[d] Saskatchewan formulary list price (February 2019).[29]

[e] Semaglutide CADTH Canadian Drug Expert Committee recommendation.[30]

Table 6: CADTH Cost Table for Insulin Products

Drug / Comparator	Strength	Dose Form	Price ($) Per Package Unless Specified Otherwise	Recommended Dosage[a]	Average Cost per Day ($)
Long-Acting Insulin Analogues (Basal)					
Insulin degludec (Tresiba)	100 U/mL	5 x 3 mL pre-filled pen	130.6701	40 U per day	2.42 to 3.48
	200 U/mL	3 x 3 mL pre-filled pen	108.8895		
Insulin glargine (Lantus)	100 U/mL	5 x 3 mL cartridge 5 x 3 mL disposable pen (SoloStar)	92.8500	40 U per day	2.47
		10 mL vial	61.6900		
Insulin glargine (Basaglar)	100 U/mL	5 x 3 mL cartridge 5 x 3 mL pre-filled pen	69.6375	40 U per day	1.86
Insulin detemir (Levemir)	100 U/mL	5 x 3 mL cartridge 5 x 3 mL disposable pen	108.8900	40 U per day	2.90
Rapid-Acting Insulins (Prandial)					
Insulin aspart (NovoRapid)	100 U/mL	5 x 3 mL cartridge	60.6300	40 U per day	1.20 to 1.68
		5 x 3 mL disposable pen	63.1200		
		10 mL vial	29.9000		
Insulin glulisine (Apidra)	100 U/mL	5 x 3 mL cartridge	51.4500	40 U per day	1.04 to 1.38
		5 x 3 mL disposable pen	51.9500		
		10 mL vial	25.9600		
Insulin lispro (Humalog)	100 U/mL	5 x 3 mL cartridge	58.8800	40 U per day	1.19 to 1.57
		5 x 3 mL disposable pen	58.4600		
		10 mL vial	29.6400		
	200 U/mL	5 x 3 mL disposable pen	108.8200		
Regular human insulin (Humulin R)	100 U/mL	5 x 3 mL cartridge	48.3300	40 U per day	0.99 to 1.29
		10 mL vial	24.6300		
Regular human insulin (Novolin ge Toronto)	100 U/mL	5 x 3 mL cartridge	46.6100	40 U per day	0.95 to 1.24
		10 mL vial	23.7400		

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

[a] World Health Organization defined daily dose.[31]

Appendix 2: Additional Information

Table 7: Submission Quality

	Yes or Good	Somewhat or Average	No or Poor
Are the methods and analysis clear and transparent?			X
Comments Reviewer to provide comments if checking “no”	The model lacks transparency and is not possible to validate — as detailed in other sections of the report		
Was the material included (content) sufficient?		X	
Comments Reviewer to provide comments if checking “poor”			
Was the submission well organized and was information easy to locate?		X	
Comments Reviewer to provide comments if checking “poor”			

Table 8: Authors Information

Authors of the Pharmacoeconomic Evaluation Submitted to CADTH Common Drug Review

☐ Adaptation of global model or Canadian model done by the manufacturer

☒ Adaptation of global model or Canadian model done by a private consultant contracted by the manufacturer

☐ Adaptation of global model or 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	

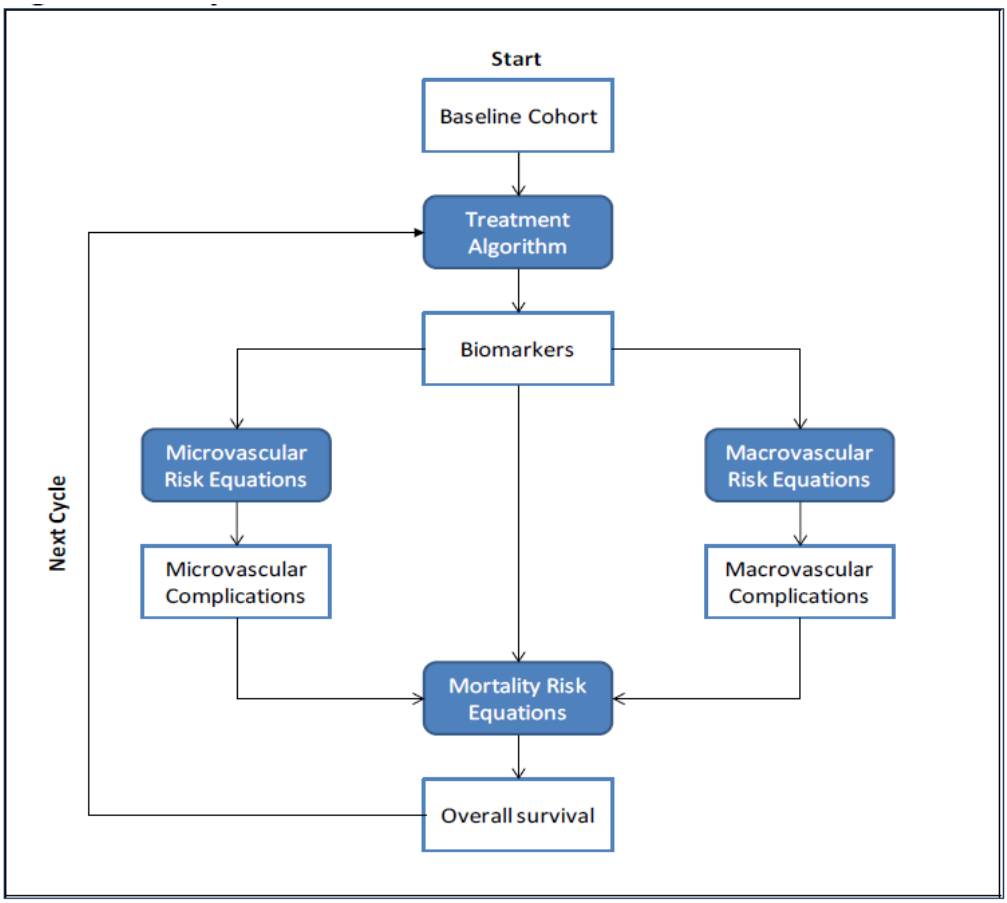
CADTH

Appendix 3: Summary of Other Health Technology Assessment Reviews of Drug

There were no Health Technology Assessment reviews for IDegLira conducted by Health Technology Assessment organizations available at the time of this review.

Appendix 4: Reviewer Worksheets

Figure 1: Model Structure



Source: Manufacturer's pharmacoeconomic submission.[5]

Table 9: Utility Data

	Mean	SE
QoL Baseline	1.027	0.027
Microvascular Complications	QoL decrements	
Retinopathy		
BDR	−0.040	−0.010
PDR	−0.070	−0.018
ME	−0.040	−0.010
PDR + ME	−0.070	−0.018
SVL	−0.050	−0.013
Neuropathy		
Symptomatic	−0.084	0.014
PVD	−0.061	0.015
LEA event and subsequent years	−0.272	0.029
Nephropathy		
Microalbuminuria	0.000	0.000
Macroalbuminuria	−0.048	0.022
ESRD	−0.263	−0.066
Macrovascular Complications		
IHD	−0.041	−0.010
MI event	−0.041	−0.010
History of MI	−0.012	−0.003
Stroke event	−0.052	−0.013
History of stroke	−0.040	−0.010
CHF	−0.064	−0.016
Demographic Factors		
Age (per 10 years)	−0.024	0.002
Female	−0.093	0.009
Diabetes duration (per 10 years)	−0.016	0.001
Obesity (per 1 BMI over 25)	−0.006	0.001
Hypoglycemia		
Non-severe	−0.014	−0.004
Severe	−0.047	−0.012

BDR = background diabetic retinopathy; BMI = body mass index; CHF = congestive heart failure; ESRD = end-stage renal disease; IHD = ischemic heart disease; LEA = lower extremity amputation; ME = macular edema; MI = myocardial infarction; PDR = proliferative diabetic retinopathy; PVD = peripheral vascular disease; QoL = quality of life; SE = standard error; SVL = severe visual loss.

Source: Manufacturer's pharmacoeconomic submission.[5]

Table 10: Treatment Effects — Basal Insulin Stratum

Parameter	[redacted]						DUAL VII Trial
	Basal Insulin	Basal-Bolus	IDegLira	iGlarLixi	Loose Combination	Pre-Mixed Insulin	Intensification Treatment
Daily Dose (Mean, End of Trial)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment Effects (Mean Change From Baseline [SE])							
Hemoglobin A1C (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	−1.46 (0.05)
SBP (mm Hg)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	−0.90 (0.72)
DBP (mm Hg)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	−0.18 (0.05)
TC (mmol/L)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.01 (0.06)
LDL (mmol/L)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.06 (0.05)
HDL (mmol/L)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.04 (0.01)
Triglycerides (mmol/L)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	−0.27 (0.05)
BMI (kg/m^2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.96 (0.08)
HR (bpm)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.06 (0.11)
WBC (1 x 10^6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.13 (0.01)
eGFR (mL/min/1.73 m^2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0 (0)
Adverse Event Rates (Mean per Patient-Year [SE])							
Non-severe hypoglycemic events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	10.91 (2.7275)
Severe hypoglycemic events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.0011 (0.0003)

BMI = body mass index; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; HR = heart rate; IDegLira = insulin degludec plus liraglutide in a fixed combination; iGlarLixi = insulin glargine and lixisenatide injection; LDL = low-density lipoprotein; SBP = systolic blood pressure; SE = standard error; TC = total cholesterol; WBC = white blood cell.

Note: Doses are weighted average doses from studies within the NMA.

Source: Manufacturer's pharmacoeconomic submission.[5]

Table 11: Treatment Effects — Liraglutide Stratum

Parameter	[redacted]			DUAL VII Trial
	Liraglutide	IDegLira	[redacted]	Intensification Treatment
Daily Dose (Mean, End of Trial)	[redacted]	[redacted]	[redacted]	[redacted]
Treatment Effects (Mean Change From Baseline [SE])				
Hemoglobin A1C (%)	[redacted]	[redacted]	[redacted]	−1.46 (0.05)
SBP (mm Hg)	[redacted]	[redacted]	[redacted]	−0.90 (0.72)
DBP (mm Hg)	[redacted]	[redacted]	[redacted]	−0.18 (0.05)
TC (mmol/L)	[redacted]	[redacted]	[redacted]	0.01 (0.06)
LDL (mmol/L)	[redacted]	[redacted]	[redacted]	0.06 (0.05)
HDL (mmol/L)	[redacted]	[redacted]	[redacted]	0.04 (0.01)
Triglycerides (mmol/L)	[redacted]	[redacted]	[redacted]	−0.27 (0.05)
BMI (kg/m^2)	[redacted]	[redacted]	[redacted]	0.96 (0.08)
HR (bpm)	[redacted]	[redacted]	[redacted]	1.06 (0.11)
WBC (1 x 10^6)	[redacted]	[redacted]	[redacted]	0.13 (0.01)
eGFR (mL/min/1.73 m^2)	[redacted]	[redacted]	[redacted]	0 (0)
Adverse Event Rates (Mean per Patient-Year [SE])				
Non-severe hypoglycemic events	[redacted]	[redacted]	[redacted]	10.91 (2.7275)
Severe hypoglycemic events	[redacted]	[redacted]	[redacted]	0.0011 (0.0003)

BMI = body mass index; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; HR = heart rate; IDegLira = insulin degludec plus liraglutide in a fixed combination; LDL = low-density lipoprotein; SBP = systolic blood pressure; SE = standard error; TC = total cholesterol; WBC = white blood cell.

Note: Doses are weighted average doses from studies within the NMA.

Source: Manufacturer's pharmacoeconomic submission.[5]

Table 12: Treatment Effects — Reimbursement Scenario

Parameter	DUAL VII Trial		
	IDegLira	Basal-Bolus	Intensification Treatment
Daily Dose (Mean, End of Trial)	[redacted]U	[redacted] U IGlar U100 + [redacted]U IAsp	[redacted]U IGlar U100 + [redacted]U IAsp
Treatment Effects (Mean Change From Baseline [SE])			
Hemoglobin A1C (%)	−1.41 (0.05)	−1.39 (0.05)	−1.46 (0.05)
SBP (mm Hg)	−4.45 (0.71)	−0.75 (0.72)	−0.90 (0.72)
DBP (mm Hg)	0.02 (0.50)	−0.03 (0.50)	−0.18 (0.05)
TC (mmol/L)	−0.18 (0.05)	0.01 (0.06)	0.01 (0.06)
LDL (mmol/L)	−0.03 (0.05)	0.06 (0.05)	0.06 (0.05)
HDL (mmol/L)	−0.01 (0.01)	0.04 (0.01)	0.04 (0.01)
Triglycerides (mmol/L)	−0.36 (0.05)	−0.27 (0.05)	−0.27 (0.05)
BMI (kg/m^2)	−0.35 (0.05)	0.96 (0.08)	0.96 (0.08)
HR (bpm)	3.55 (0.35)	1.06 (0.11)	1.06 (0.11)
WBC (1 x 10^6)	0.19 (0.02)	0.13 (0.01)	0.13 (0.01)
eGFR (mL/min/1.73 m^2)	0 (0)	0 (0)	0 (0)
Adverse Event Rates (Mean per Patient-Year [SE])			
Non-severe hypoglycemic events	2.28 (0.57)	10.91 (2.73)	10.91 (2.73)
Severe hypoglycemic events	0.0003 (0.0001)	0.001 (0.0003)	0.0011 (0.0003)

BMI = body mass index; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; HR = heart rate; IAsp= insulin aspart; IDegLira = insulin degludec plus liraglutide in a fixed combination; IGlar U100 = insulin glargine 100 U/mL; LDL = low-density lipoprotein; SBP = systolic blood pressure; SE = standard error; TC = total cholesterol; WBC = white blood cell.

Note: Doses are from the DUAL VII trial.

Source: Manufacturer's pharmacoeconomic submission.[5]

Table 13: Annual Treatment Costs — Basal Insulin Stratum

	Cost per Unit ($)	Units per Day	Cost per Day ($)	Cost per Year ($)
Basal Insulin (Reference Treatment)				
IGlar U100	[redacted]	[redacted]	[redacted]	[redacted]
Needles	0.4966	1 needle	0.50	181.40
Test strips	0.8173	1 strip	0.82	298.52
Total				[redacted]
Basal-Bolus				
IGlar U100	[redacted]	[redacted]	[redacted]	[redacted]
Needles	0.4966	1 needle	0.50	181.40
Test strips	0.8173	1 strip	0.82	298.52
Bolus insulin	0.0468§	[redacted]	[redacted]	[redacted]
Needles	0.4966	3 needles	1.49	544.20
Test strips	0.8173	3 strips	2.45	895.56
Total				[redacted]
IDegLira				
IDegLira	[redacted]	[redacted]	[redacted]	[redacted]
Needles	0.4966	1 needle	0.50	181.40
Test strips	0.8173	1 strip	0.82	298.52
Total				[redacted]
iGlarLixi				
iGlarLixi	[redacted]	[redacted]	[redacted]	[redacted]
Needles	0.4966	1 needle	0.50	181.40
Test strips	0.8173	1 strip	0.82	298.52
Total				[redacted]
Loose Combination				
IGlar U100	[redacted]	[redacted]	[redacted]	[redacted]
Needles	0.4966	1 needle	0.50	181.40
Test strips	0.8173	1 strip	0.82	298.52
GLP-1 RA	NR	NR	[redacted]	[redacted]
Needles	0.4966	1 needle	0.50	181.40
Total				**4,672.75**
Pre-Mixed Insulin				
Pre-mixed insulin	[redacted]	[redacted]	[redacted]	[redacted]
Needles	0.4966	2 needles	0.99	362.80
Test strips	0.8173	2 strips	1.63	597.04
Total				[redacted]
Intensification (Based on Treatments Used in DUAL VII				
IGlar U100	[redacted]	[redacted]U	[redacted]	[redacted]
Needles	0.4966	1 needle	0.50	181.40
Test strips	0.8173	1 strip	0.82	298.52
IAsp	[redacted]	[redacted]U	[redacted]	[redacted]
Needles	0.4966	3 needles	1.49	544.20
Test strips	0.8173	3 strips	2.45	895.56
Total				**3,749.38**

GLP-1 RA = glucagon-like peptide 1 receptor agonist; IAsp = insulin aspart; IDegLira = insulin degludec plus liraglutide in a fixed combination; IGlar U100 = insulin glargine 100 U/mL; iGlarLixi = insulin glargine and lixisenatide injection; NR = not reported/

Note: Doses are weighted average doses from studies within the NMA.

Source: Manufacturer's pharmacoeconomic submission.[5]

Table 14: Annual Treatment Costs — Liraglutide Stratum

	Cost per Unit ($)	Units per Day	Cost per Day ($)	Cost per Year ($)
IDegLira				
IDegLira	[redacted]	[redacted]U	[redacted]	[redacted]
Needles	0.4966	1 needle	0.50	181.40
Test strips	0.8173	1 strip	0.82	298.52
Total				[redacted]
Lira				
Liraglutide	[redacted]	[redacted]mg	[redacted]	[redacted]
Needles	0.4966	1 needle	0.50	181.40
Total†				[redacted]
Loose Combination				
IDeg	[redacted]	[redacted]	[redacted]	[redacted]
Needles	0.4967	1 needle	0.50	181.40
Test strips	0.8173	1 strip	0.82	298.52
Total IDeg cost				[redacted]
Liraglutide	[redacted]	[redacted]	[redacted]	[redacted]
Needles	0.4966	1 needle	0.50	181.40
Total liraglutide cost				[redacted]
Total Loose Combination				**5,911.72**
Intensification				
IGlar U100	[redacted]	[redacted]U	[redacted]	[redacted]
Needles	0.4966	1 needle	0.50	181.40
Test strips	0.8173	1 strip	0.82	298.52
IAsp	[redacted]	[redacted]U	[redacted]	[redacted]
Needles	0.4966	3 needles	1.49	544.20
Test strips	0.8173	3 strips	2.45	895.56
Total				**3,749.38**

IAsp = insulin aspart; IDeg = insulin degludec; IDegLira = insulin degludec plus liraglutide in a fixed combination; IGlar U100 = insulin glargine 100 U/mL.
Note: Doses are weighted average doses from studies within the NMA.
Source: Manufacturer's pharmacoeconomic submission.[5]

Table 15: Annual Treatment Costs — Reimbursement Scenario

	Cost per Unit ($)	Units per Day	Cost per Day ($)	Cost per User ($)
IDegLira				
IDegLira	[redacted]	[redacted]U	[redacted]	[redacted]
Needles	0.4966	1 needle	0.50	181.40
Test strips	0.8173	1 strip	0.82	298.52
Total				[redacted]
Basal-Bolus				
IGlar U100	[redacted]	[redacted]U	[redacted]	[redacted]
Needles	0.4966	1 needle	0.50	181.40
Test strips	0.8173	1 strip	0.82	298.52
IAsp	[redacted]	[redacted]U	[redacted]	[redacted]
Needles	0.4966	3 needles	1.49	544.20
Test strips	0.8173	3 strips	2.45	895.56
Total				**3,749.38**

IAsp = insulin aspart; IDegLira = insulin degludec plus liraglutide in a fixed combination.
Note: Doses are from the DUAL VII trial.
Source: Manufacturer's pharmacoeconomic submission.[5]

Table 16: Cost of Complications

	Event Cost ($)		State Cost ($)	
	Mean	SE	Mean	SE
Microvascular Complications				
Retinopathy				
BDR	643	161	73	18
PDR	643	161	73	18
ME	835	209	73	18
PDR + ME	835	209	73	18
SVL	3,314	828	2,362	590
Neuropathy				
Symptomatic	919	230	1,152	288
PVD	132	33	132	33
LEA	41,850	10,463		
Nephropathy				
Microalbuminuria	83	21	0	0
Macroalbuminuria	114	29	0	0
ESRD	50,323	12,581	58,983	14,746
Macrovascular Complications				
IHD	6,199	1,550	3,579	895
MI				
First MI	19,807	4,952	3,097	774
Subsequent MIs	19,807	4,952	3,097	774
Stroke				
First stroke	26,979	6,745	3,743	936
Subsequent strokes	26,979	6,745	3,743	936
CHF	18,119	4,530	5,080	1,270
Hypoglycemia (Per Episode)				
Non-severe	1.55	0.39		
Severe	2,179	545		

BDR = background diabetic retinopathy; CHF = congestive heart failure; ESRD = end-stage renal disease; IHD = ischemic heart disease; LEA = lower extremity amputation; ME = macular edema; MI = myocardial infarction; PDR = proliferative diabetic retinopathy; PVD = peripheral vascular disease; SE = standard error; SVL = severe visual loss.

Source: Manufacturer's pharmacoeconomic submission.[5]

Appendix 5: CADTH Comment on Updated Manufacturer's Economic Report (Received July 10, 2019)

Issue

In the CADTH pharmacoeconomic report sent to the manufacturer for comment, CADTH highlighted face validity concerns with the model. For the reimbursement scenario analysis, more than 20% of patients receiving either basal-bolus or insulin degludec plus liraglutide in a fixed combination (IDegLira) were alive at the end of the 40-year time horizon. If this were realistic, then it would question the suitability of 40 years as a choice of time horizon. However, the likelihood that more than 20% of a population cohort that were aged 58 and had an average BMI of more than 31 and more than 11 years' history of diabetes being alive at age 98 is questionable.

Manufacturer's Response

The manufacturer responded to the concerns raised by CADTH by providing a revised report with annotated changes and revised models.[32] The response from the manufacturer stated that mortality had been corrected within the model, but the response did not detail how that correction was made. Furthermore, CADTH noted that survival at age 98 was still approximately 5%, which appeared high for this population (i.e., age 58 with an average BMI of more than 31 and more than 11 years history of diabetes).

CADTH requested that the manufacturer both provide details on how the correction was made and a justification for the 5% survival at age 98.

For the first issue, the manufacturer provided a detailed technical response as follows:

The model has two parallel Markov traces, one for microvascular complications and one for macrovascular complications. The mortality risk is calculated individually for each combination of microvascular and macrovascular health state. The mortality is then applied separately to both the microvascular Markov trace and the macrovascular Markov trace.

When the mortality was applied to a macrovascular health states, the mortality risks were summarized across all microvascular health states by multiplying each risk by the prevalence in the corresponding microvascular health state. As the Markov traces are parallel and not multiplicative this resulted in a double counting of the proportion alive, as the proportion in the macrovascular health states were multiplied by the proportion in the microvascular health states. That is, the mortality was multiplied by the proportion alive twice instead of once. Consequently, the mortality was underestimated by a factor inversely related to proportion alive (i.e., if 90% were alive, the mortality was underestimated by 10%).

The same error occurred in the microvascular Markov trace by multiplying each risk by the prevalence in the corresponding macrovascular health state.

As the proportion alive grows smaller, the error grows larger. Meaning that the impact is larger at the end of simulation than at the start. More specifically: In the VBA macro code shown in the bullet points below, function Trace_Mort in the module MortalityB applies the calculated mortality to the parallel traces of micro- and macrovascular health states. Here, Prev_Macro and Prev_Micro denote the surviving proportion of the cohort in each of the

micro- and macrovascular health states. That is, both sum(Prev_Macro) and sum(Prev_Micro) equal the proportion alive at that cycle, and they partition the surviving cohort into the set of micro and macrovascular health states.

In the faulty code version, Mort_Micro, that is, the total amount of mortality to be applied to Prev_Micro (and likewise for Mort_Macro and Prev_Macro), was calculated by multiplying the mortality in each combination of micro- and macrovascular health state (p_Mort_Tot) with both prevalences: Prev_Macro and Prev_Micro. But because both Prev_Macro and Prev_Micro sum to Proportion Alive, this effectively resulted in multiplying by proportion alive twice, in error. The error was fixed by dividing the calculated mortality by survival (i.e., proportion alive), which cancels one of the multiplications by proportion alive. i.e.,:

- *Faulty version: mortality = Sum(p_Mort_Tot * Prev_Macro * Prev_Micro), which equals Sum(p_Mort_Tot * partition of macro * Survival * partition of Micro * Survival)*
- *Corrected version: mortality = Sum(p_Mort_Tot * Prev_Macro * Prev_Micro /Survival), which equals Sum(p_Mort_Tot * partition of macro * partition of Micro* Survival)*

For the second issue, the manufacturer provided the following response:

Although we did not find comprehensive T2DM life tables through literature search, we were able to compare the survival results in the model with survival rates in the general population. Using general population life tables (StatCan, 2015/2017)i and the age/sex cohort in the reimbursement scenario base case, the proportion alive at 98 (starting age 58) is expected to be 6.06% (5,667 / 93,524). Adjusting for sex (55% female), it is 6.03%. The corresponding survival in the model is 4.3% (basal-bolus treated cohort) or 4.7% (IDegLira treated cohort), which does seem feasible for a T2DM population with blood glucose controlled using antihyperglycemic therapy.

We agree that the survival may be slightly higher in the model simulations than in reality due to limitations of the UKPDS study, the source for the mortality equations in the model. The UKPDS cohort included patients aged 25-65 at baseline, and a follow-up that was limited to 20 years and therefore no enrolled patients reached ages beyond 85 years. Consequently, if there is a sharp increase in mortality at very advanced ages in the T2DM population, this would not be reflected in the UKPDS mortality equations used in the model.

However, we further suggest that slightly higher survival rates in the later cycles of the model would have very little impact on the conclusions of the model due to the effects of discounting.

Revised Results

Table 17, Table 18, and Table 19 provide a comparison of the results from the updated report with the original submitted results.

Table 17: Comparison of the Results of the Manufacturer's Original Analysis and Revised Analysis for Basal Insulin Stratum

Sequential ICER ($ per QALY)		
	Initial Submission	Revised Analysis
Pre-mixed insulin	reference	reference
iGlarLixi	$8,130	$6,980
IDegLira	$17,984	$22,997

Sequential ICER ($ per QALY)		
	Initial Submission	Revised Analysis
Basal insulin	Extended dominance through iGlarLixi	Extended dominance through iGlarLixi
Basal-bolus	Dominated by IDegLira	Dominated by IDegLira
Loose combination	Dominated by IDegLira	Dominated by IDegLira

ICER = incremental cost-effectiveness ratio; IDegLira = insulin degludec plus liraglutide in a fixed combination; iGlarLixi = insulin glargine and lixisenatide injection; QALY = quality-adjusted life-year.

Source: Manufacturer's pharmacoeconomic submission[5] and manufacturer's revised analysis.[32]

Table 18: Comparison of the Results of the Manufacturer's Original Analysis and Revised Analysis for Liraglutide Stratum

Sequential ICER ($ per QALY)		
	Initial Submission	Revised Analysis
IDegLira	reference	reference
Liraglutide	$55,223	$47,056
Loose combination	Dominated by liraglutide	Dominated by liraglutide

ICER = incremental cost-effectiveness ratio; IDegLira = insulin degludec plus liraglutide in a fixed combination; QALY = quality-adjusted life-year.

Source: Manufacturer's pharmacoeconomic submission[5] and manufacturer's revised analysis.[32]

Table 19: Comparison of the Results of the Manufacturer's Original Analysis and Revised Analysis for Reimbursement Scenario

ICER vs. Basal-Bolus ($ per QALY)		
	Initial Submission	ICER vs. Basal-Bolus Revised Analysis
IDegLira	Dominant	Dominant
Basal-bolus	-	-

ICER = incremental cost-effectiveness ratio; IDegLira = insulin degludec plus liraglutide in a fixed combination; QALY = quality-adjusted life-year; vs. = versus.

Source: Manufacturer's pharmacoeconomic submission[5] and manufacturer's revised analysis.[32]

CADTH acknowledges that the manufacturer's correction did not lead to major changes from the original results. The one result of note is that in the liraglutide stratum, it appears that IDegLira is no longer cost-effective compared with liraglutide alone if the threshold for cost-effectiveness is at least $47,056 per QALY. This is as a result of liraglutide alone being found to be more effective than IDegLira, interestingly.

The other results appear generally consistent in terms of cost-effectiveness, with estimates of expected costs and quality-adjusted life-years for all treatments beginning lower than in the original submitted analysis.

Critique of Manufacturer's Response

CADTH notes four concerns arising from the revised analysis provided by the manufacturer.

1. Due to the lack of transparency within the submitted models, the explanation of what changes were required due to errors within the original models is not in itself transparent. This is primarily due to the reliance on VBA macros within the submitted models. As noted previously, data within the Excel model is hard coded with results generated by a series of 24 Visual Basic macros, with extensive lines of code. Thus, it is not possible to verify that there are not other similar errors in the model.

2. The explanation potentially highlights a further major concern with the modelling framework. The explanation suggests that mortality is applied as a weighted average to all states equally rather than higher mortality in states associated with conditions that increase mortality. Furthermore, it highlights that microvascular and macrovascular conditions are modelled separately, not allowing for interaction with respect to mortality effects. This is inappropriate.
3. If, in the model, increased mortality is not applied to the proportion of the patient population that has events associated with increased mortality, this would result in the model exacerbating the benefits of treatments, which have small incremental effects in reducing events associated with increased mortality. This would be because patients with such events are not dying at a faster rate than patients without these conditions, thus exacerbating the effects on long-term costs of these conditions and resulting in the absolute mortality difference between treatments remaining artificially large in the long-term. Estimates of incremental effects in such analyses are likely biased.
4. However, given the concerns with model transparency and the reliance on hard coding of the Markov trace, it is not possible to determine if the concerns noted here are an issue.
5. The results relating to survival within the modelled population at age 98 are still a concern. Based on the Statistics Canada life tables from 2015 to 2017, CADTH finds that survival in the *general population* at 98 years from age 58 is 5.16%. This compares with the estimated survival for IDegLira in the liraglutide stratum of 5.29%. Similar rates of mortality between the modeled population and the general Canadian population would seem unlikely. The explanation that this is due to the reliance on the UKPDS study is not valid; it is not acceptable in modelling to argue that results which appear inappropriate are justified because of the data employed. If there are concerns that KPDSUKPDS might overestimate survival in older individuals with diabetes, then this should be addressed during the calibration phase of model development.
6. It is unclear whether the errors identified within the original version of the model submitted by the manufacturer have always been inherent within the model used. If the error is inherent in the model, it suggests that previous validation studies of the model may no longer be applicable and that previous analyses with this model may also be questionable, Furthermore, it brings up concerns over the likelihood there may be other errors within the model that have not yet been identified, given the non-transparent approach adopted.

Summary

Given these issues, the updated report provided by the manufacturer does not alleviate the concerns raised by CADTH, but instead potentially increases the concerns previously raised. As such, the conclusions to the review remain unchanged. Whether IDegLira represents a cost-effective treatment option remains highly uncertain, but the results provided by the manufacturer are likely biased in favour of IDegLira.

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