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CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

INSULIN DEGLUDEC (TRESIBA)

(Novo Nordisk Canada Inc.)

Indication: For once-daily treatment of adults with diabetes mellitus to improve glycemic control

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Table of Contents

List of Tables

List of Figure

Abbreviations

CDR	CADTH Common Drug Review
ICUR	incremental cost-utility ratio
IDeg	insulin degludec
IGlar	insulin glargine
NMA	network meta-analysis
NPH	neutral protamine Hagedorn
OAD	oral antidiabetes drug
QALY	quality-adjusted life-years
SMPG	self-measured plasma glucose
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus

Table 1: Summary of the Manufacturer's Economic Submission

Drug Product	Insulin degludec (Tresiba)
Study Question	To determine the cost-effectiveness of IDeg compared with IGlar for the treatment of adult patients with T1DM or T2DM
Type of Economic Evaluation	Cost-utility analysis
Target Population	• Population 1: T1DM patients on a basal + bolus insulin regimen (T1DM, basal + bolus) • Population 2: T2DM patients who are insulin starters on basal insulin and OADs (T2DM, basal + OAD) • Population 3: T2DM patients who are insulin-experienced on basal insulin and OADs (T2DM, basal + OAD EX) • Population 4: T2DM patients requiring insulin intensification, on a basal + bolus insulin regimen (T2DM, basal + bolus)
Treatment	IDeg administered once daily at any time of the day; dosing of IDeg should be individualized
Outcome	QALYs
Comparators	1. IGlar 2. NPH insulin
Perspective	Canadian Ministry of Health
Time Horizon	1 year
Results for Base Case	**IDeg vs. IGlar** T1DM, population 1: IDeg dominates IGlar T2DM, populations 2, 3, 4: $5,564/QALY, $20,887/QALY, and $95,155/QALY, respectively **IDeg vs. NPH** T1DM, population 1: IDeg dominates NPH T2DM, populations 2, 3, and 4: IDeg dominates NPH: $9,256/QALY for population 2 and $164,361/QALY for population 4
Key Limitations	CDR identified the following limitations: • **One-year economic model considers hypoglycemia:** The long-term relative risk of hypoglycemia and other clinical outcomes over a longer time horizon are unknown; the ICUR may be higher in subsequent years if the effects of IDeg on hypoglycemia change with time. • **Uncertainty over relative rates of hypoglycemia:** Relative efficacy related to hypoglycemic events in the model was derived from a manufacturer-sponsored meta-analysis and network meta-analysis. Limitations were noted for both analyses. • **Insulin doses:** The relative doses of IDeg and IGlar, as well as NPH, are highly uncertain where direct comparisons are generally unavailable. Many assumptions were made in the model that may favour IDeg. • **Baseline risk of hypoglycemia:** Trial-observed rates of hypoglycemia were derived from study populations that may be at greater risk of hypoglycemia than the population indicated by the reimbursement request.
CDR Estimates	**IDeg vs. IGlar** (using most likely RR of hypoglycemia, most likely relative insulin doses, and lowest cost of IGlar): T1DM, population 1: $92,850/QALY T2DM, populations 2, 3, and 4: $1,106,180/QALY, $73,122/QALY, and $150,351/QALY, respectively **IDeg vs. NPH** (using relative insulin dose of 1.2 and same frequency of SMPG tests): T1DM, population 1: IDeg dominates NPH T2DM, populations 2, 3, and 4: $25,677/QALY, $37,431/QALY, and $211,080/QALY, respectively

CDR = CADTH Common Drug Review; EX = experienced; ICUR = incremental cost-utility ratio; IDeg = insulin degludec; IGlar = insulin glargine; NPH = neutral protamine Hagedorn; OAD = oral antidiabetes drug; QALY = quality-adjusted life-year; RR = relative risk; SMPG = self-measured plasma glucose; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; vs. = versus.

Drug	Insulin Degludec (Tresiba)
Indication	Once daily subcutaneous injection in the treatment of adults with diabetes mellitus to improve glycemic control.
Listing Request	As per indication.
Dosage Form(s)	The recommended daily starting dose of IDeg in T2DM patients who are insulin-naive is 10 units followed by individual dosage adjustments. In T1DM patients, IDeg is to be used once daily with mealtime insulin and requires subsequent individual dosage adjustments.
NOC Date	August 25th, 2017
Manufacturer	Novo Nordisk Canada Inc.

Executive Summary

Background

Insulin degludec (Tresiba) is indicated for the treatment of adults with diabetes mellitus to improve glycemic control. The recommended daily starting dose of insulin degludec (IDeg) in type 2 diabetes mellitus (T2DM) patients who are insulin-naive is 10 units followed by individual dosage adjustments.1 In type 1 diabetes mellitus (T1DM) patients, IDeg is to be used once daily with mealtime insulin and requires subsequent individual dosage adjustments. IDeg is supplied in a 3 mL FlexTouch pen for subcutaneous administration at a submitted price of $125.28 per 1,500-unit pack.[1,2]

The manufacturer submitted a cost-utility analysis over a one-year time horizon from the perspective of the Canadian health care payer comparing IDeg with insulin glargine (IGlar) in four patient populations:

- Population 1: T1DM patients on a basal + bolus regimen (T1DM, basal + bolus)
- Population 2: T2DM patients who are insulin starters on basal insulin and oral antidiabetes drugs (OADs) (T2DM, basal + OADs)
- Population 3: T2DM patients who are insulin-experienced on basal insulin and OADs (T2DM, basal + OAD-experienced)
- Population 4: T2DM patients requiring insulin intensification, on a basal + bolus insulin regimen (T2DM, basal + bolus).

The economic model focused on short-term risks, costs, and quality-of-life impacts associated with hypoglycemia; glycated hemoglobin results were found not to differ between treatment regimens, and no other clinically important outcomes have yet been determined.[2] Trial-observed rates of hypoglycemia for patients receiving IGlar, with the corresponding rates for IDeg, were estimated based on the rate ratio observed in the clinical trials (SWITCH-1, SWITCH-2, and manufacturer-sponsored meta-analysis of phase IIIa trials).[3,4] Relative insulin doses for IDeg versus IGlar were obtained from the aforementioned clinical trials or meta-analysis.[2] Other inputs, such as costs and utility

values, were obtained from published literature. A secondary analysis was also performed comparing IDeg with neutral protamine Hagedorn (NPH) in the four patient populations. Efficacy data for IDeg versus NPH were obtained from the manufacturer-sponsored network meta-analysis (NMA).[2,5]

In its base case, the manufacturer reported that IDeg dominated IGlar (i.e., IDeg was more effective and less costly) in population 1 (T1DM), and resulted in an incremental cost-utility ratio (ICUR) of $5,564 to $95,155 per quality-adjusted life-year (QALY) in the other three T2DM populations. For IDeg versus NPH, IDeg dominated NPH in populations 1 and 2 and resulted in an ICUR of $9,256 to $164,361 per QALY in populations 3 and 4.

Summary of Identified Limitations and Key Results

The CADTH Common Drug Review (CDR) identified several key limitations with the submitted analysis. First, a short-term (one-year) decision model incorporating only hypoglycemic events was used by the manufacturer in its base case. The manufacturer assumed that the results could be extended to subsequent years; however, if differences in the risk of hypoglycemic events between IDeg and IGlar are reduced over time, the ICUR may increase. No long-term clinical data are currently available to inform this assumption. In addition, the relative efficacy of IDeg on hypoglycemic events was mostly derived from the manufacturer-sponsored meta-analysis (populations 2 and 4, IDeg versus IGlar, where population 4 was based on one trial) and from an NMA for IDeg versus NPH.[2,5] This meta-analysis has numerous identified limitations, and the results used by the manufacturer (i.e., lower risk of hypoglycemia with IDeg) are questionable, in that a "better fit" modelling approach shows no differences in risk of hypoglycemia. Third, there is uncertainty regarding the relative insulin dosage for IDeg versus IGlar for populations 2 and 4, derived from a manufacturer-sponsored meta-analysis. For IDeg versus NPH, the relative dose difference was based on a convenience sample of patients with T2DM from British Columbia, which might not be applicable to all patients. Finally, the baseline risk of hypoglycemia was obtained from SWITCH-1 and SWITCH-2 for many of the analyses; however, this patient population may have a greater baseline risk than the general patient population in which IDeg may be used.[2]

CDR attempted to address these limitations. In a plausible CDR base case (IDeg versus IGlar) that considers relative risk of hypoglycemic events from clinical trials of direct comparisons and meta-analyses (more details in Appendix 4) and that uses a dose ratio of 1 between IDeg and IGlar and the lowest-cost long-acting insulin analogue (Basaglar $94.06 per 1,500 IU), IDeg is dominant (i.e., less costly and more effective) in T1DM patients (population 1). In patients with T2DM, the ICUR ranged from $73,000 per QALY (population 3, basal + OAD-experienced) to more than $1 million (population 2, basal + OAD). The ICUR increased further when lower baseline hypoglycemia risks were used. The relative risk of hypoglycemic events had the greatest impact on the ICUR.

While long-acting insulin analogues are commonly used in most jurisdictions, insulin NPH is a valid comparator in light of CADTH guidance on the use of long-acting insulins.[6] For IDeg versus NPH, in a plausible CDR base case that considers a relative insulin dose of 1.2 and the same frequency of self-measured plasma glucose (SMPG) tests in populations 2 and 3 (not on bolus insulin), IDeg dominated NPH in T1DM (population 1), while for T2DM, the ICUR ranged from $26,000 per QALY (population 2, basal + OAD) to $211,000 per QALY (population 4, basal + bolus).

Conclusions

There is significant uncertainty in the true cost-effectiveness of IDeg due to a variety of factors, including the multiple patient populations in which IDeg may be used, the most relevant comparator, and uncertainty in the true relative difference of hypoglycemic events in patient populations where direct comparisons are absent (particularly given the numerous issues identified with the manufacturer-conducted NMA).

While the manufacturer analysis suggests that IDeg may be dominant compared with insulin analogues (great benefit and lower costs) in most patient populations, the CDR reanalyses that address the identified limitations with the manufacturer's economic analysis indicated that IDeg use is likely associated with incremental costs for several of the patient populations, particularly in patients with T2DM. In T2DM, where most of the use is likely to occur, the ICUR ranges between $73,000 per QALY and > $1 million per QALY, and price reductions of 10% to more than 25% would be required for IDeg to fall to $50,000 per QALY when compared with IGlar (and NPH).

In T1DM, IDeg dominated both IGlar (if the rate of hypoglycemia is truly lower with IDeg) and NPH.

Information on the Pharmacoeconomic Submission

Summary of the Manufacturer's Pharmacoeconomic Submission

The manufacturer submitted a cost-utility analysis comparing insulin degludec (IDeg) with insulin glargine (IGlar) in adult patients with type 1 or type 2 diabetes mellitus (T1DM or T2DM) when used as part of a basal plus bolus or basal and oral therapy regimen (four patient populations).[2] IDeg versus neutral protamine Hagedorn (NPH) insulin was also included as a secondary analysis. The time horizon was one year, and the analysis assumed that the short-term costs and outcomes represent an annual cost-effectiveness for the patients from the Canadian public payer perspective. The economic model focused only on the risk, costs, and quality-of-life impacts associated with hypoglycemia, as the glycated hemoglobin results were found not to differ between treatment regimens. The baseline hypoglycemia event rate (non-severe daytime, non-severe nocturnal, and severe) and the insulin dosage inputs for IGlar in the model were obtained from the SWITCH-1 and SWITCH-2 trials and manufacturer-sponsored meta-analyses of phase IIIa trials for IDeg versus IGlar. The relative efficacy for hypoglycemic events and relative dose ratios were also obtained from the SWITCH-1 and SWITCH-2 trials[3,4] and two manufacturers' meta-analyses (network meta-analysis [NMA] for relative risk of hypoglycemia and meta-analysis for relative dose).[5] A summary of the hypoglycemia rates and relative efficacy can be found in Appendix 4. For IDeg versus NPH, relative efficacy for hypoglycemic events was also obtained from the manufacturer's NMA, while relative dose ratios were obtained from a convenience sample of patients with T2DM in British Columbia.[7] Baseline utility and disutility for hypoglycemia events for each treatment arm were obtained from the literature.

In the phase IIIa trials,[2] hypoglycemia was confirmed by self-measured plasma glucose (SMPG) with a plasma glucose level < 3.1 mmol/L (56 mg/dL). These included episodes of severe hypoglycemia (episodes requiring external assistance) or episodes of hypoglycemia confirmed with a plasma glucose < 3.1 mmol/L (56 mg/dL) regardless of symptoms. A nocturnal episode was any confirmed episode with time of onset between 00:01 and 05:59 hours, inclusive. In the phase IIIb SWITCH trials, secondary end points included the number of treatment-emergent severe or blood glucose–confirmed symptomatic nocturnal hypoglycemic episodes during the maintenance period (weeks 16 to 32 and weeks 48 to 64), and the proportion of patients with one or more severe hypoglycemic episodes during the maintenance period (weeks 16 to 32 and weeks 48 to 64).

Drug costs of IDeg were obtained from the manufacturer based on a 1,500-unit 3 mL pack ($125.28). The cost of IGlar and bolus insulin were calculated based on the Ontario Drug Benefit/Comparative Drug Index list price and selected package size and format with the largest market share (Lantus Solostar pen 3 mL for IGlar and NovoRapid Penfill 3 mL for bolus). An 8% markup and a dispensing fee of $8.83 per prescription were also considered in the analysis. The cost of needles was calculated based on the Ontario Brogan private claims data average unit cost ($0.3321). Frequency of needle utilization was based on the pivotal trials (one basal injection per day for all treatment regimens and three bolus injections in addition to the basal injections). The cost of SMPG ($0.86 per test) was also included in the base case, assuming seven tests per week for basal and 28 tests per week for basal plus bolus. The model also assumed an additional 5.2 tests in T1DM and 1.9 tests in T2DM after a hypoglycemic event. Costs associated with a severe hypoglycemic

event were obtained from the 2016 CADTH pharmacoeconomic report for second-line therapies in T2DM ($2,142).[8] It was assumed that mild or moderate hypoglycemic events (daytime or nocturnal) did not require health care resource use ($0).

Manufacturer's Base Case

In the base case, the manufacturer reported that IDeg is the dominant strategy (more effective and less costly) in T1DM patients and has an incremental cost-utility ratio (ICUR) ranging from $5,564 to $95,155 per quality-adjusted life-year (QALY) in T2DM patients (Table 2). Detailed results are provided in Appendix 4 (Table 19 to Table 26).

Table 2: Summary of Results of the Manufacturer's Base Case — IDeg Versus IGlar

Population	Expected Incremental Cost ($)	Expected Incremental QALY	Mean ICUR ($/QALY)
T1DM			
1. Basal + bolus	−459	0.0181	Dominant
T2DM			
2. Basal + OAD	18	0.0032	5,564
3. Basal + OAD EX	121	0.0058	20,887
4. Basal + bolus	421	0.0044	95,155

EX = experienced; ICUR = incremental cost-utility ratio; IDeg = insulin degludec; IGlar = insulin glargine; OAD = oral antidiabetes drug; QALY = quality-adjusted life-year; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

Source: Manufacturer's pharmacoeconomic report.[2]

In the secondary analysis comparing IDeg with NPH, the manufacturer reported that IDeg is the dominant strategy (more effective and less costly) in populations 1 and 2, and has an ICUR of $9,256 per QALY in population 3 and $164,361 per QALY in population 4 (Table 3).

Table 3: Summary of Results of the Manufacturer's Base Case — IDeg Versus NPH

Population	Expected Incremental Cost ($)	Expected Incremental QALY	Mean ICUR ($/QALY)
T1DM			
1. Basal + bolus	−432	0.0224	Dominant
T2DM			
2. Basal + OAD	−15[a]	0.0103	Dominant
3. Basal + OAD EX	160	0.0173	9,256
4. Basal + bolus	727	0.0044	164,361

EX = experienced; ICUR = incremental cost-utility ratio; IDeg = insulin degludec; NPH = neutral protamine Hagedorn; OAD = oral antidiabetes drug; QALY = quality-adjusted life-year; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

a In the Manufacturer's Pharmacoeconomic Report, it is −$125 based on a dose ratio (IDeg:IGlar) of 0.83, but a dose ratio of 0.9 should be used according to the base case.

Source: Manufacturer's pharmacoeconomic report.[2]

Summary of Manufacturer's Sensitivity Analyses

Uncertainty was addressed using one-way deterministic sensitivity analyses that varied model parameters by using alternative values. A series of one-way sensitivity analyses was conducted by the manufacturer, including hypoglycemia rates per patient per year for IGlar from alternate sources (UK or Hypoglycemia Assessment Tool rates),[9,10] SMPG tests per week (one basal test per week for IDeg), cost of severe hypoglycemic events (± 20%), societal perspective, point estimates of hypoglycemia rate ratios including results that are not significant, number of insulin needles (two for IGlar and one for IDeg per day), time horizon (five or 10 years), alternate QALY decrements for hypoglycemia (0.047 severe, 0.014 non-severe), QALY gain for patients receiving IDeg (0.005), SMPG test disutility (0.0000221), and dosing flexibility utility (0.013).

For population 1 (T1DM), results were robust to changes to parameters. For T2DM, the results were sensitive to variations in hypoglycemia rates, dosing flexibility, SMPG frequency per week for IDeg, needle use for IGlar, and QALY decrements for hypoglycemic events. Variations in such parameters resulted in higher ICURs for IDeg when compared with IGlar in the T2DM population.

Probabilistic analyses

Based on the manufacturer's probabilistic sensitivity analyses for IDeg versus IGlar:

- Population 1: in 81.9% of simulations, the ICUR is less than $50,000 per QALY
- Population 2: in 96.5% of simulations, the ICUR is less than $50,000 per QALY
- Population 3: in 85.9% of simulations, the ICUR is less than $50,000 per QALY
- Population 4: in 14.2% of simulations, the ICUR is less than $50,000 per QALY.

No manufacturer's sensitivity analyses were performed on IDeg versus NPH.

Limitations of Manufacturer's Submission

A. *One-year economic model that considers only hypoglycemia:* A short-term (one-year) decision model incorporating only hypoglycemic events was used in the base case. The manufacturer assumed that the results could be extended to subsequent years; however, if differences in the risk of hypoglycemic events between IDeg and IGlar are reduced over time, the ICUR may increase. In addition, this model did not allow for consideration of potential benefits and harms from the treatment other than hypoglycemic events. A published Health Technology Assessment (HTA)[11] of IDeg criticized the appropriateness of the simplified model for diabetes (see Appendix 3). Although this simplified approach may be reasonable in the absence of data indicating differences in other clinically important outcomes, it does not allow for the assessment of clinical uncertainty.

B. *Uncertainty around relative effects on hypoglycemic events:* Relative effect on hypoglycemic events was derived from the manufacturer-sponsored meta-analysis for many analyses (populations 2 and 4, IDeg versus IGlar) and from an NMA for the analyses comparing IDeg with NPH due to lack of direct comparative evidence. All trials included in the meta-analysis were open-label studies; thus, subjective outcomes, such as hypoglycemia, may be prone to bias. The meta-analysis also did not provide data on study patient characteristics of the included studies. The main limitations of the NMA were (1) lack of information on how trials were selected, (2)

exclusion of insulin detemir as a comparator, and (3) selection of an analytic model that favoured IDeg (see clinical report, Appendix 6, for details). Use of a "better fit" model indicates that there may be no difference in hypoglycemia between comparators. If relative efficacy is lower than estimated, the cost-effectiveness of IDeg will be less favourable.

C. *Baseline risk of hypoglycemia:* SWITCH-1 and SWITCH-2 had a study population that may be at greater risk of hypoglycemia than the population for which the manufacturer is seeking a reimbursement request. As such, the absolute risk and absolute benefit of reducing the risk of hypoglycemia is likely to be lower in a real-world population. Further, it is not clear if the relative benefits observed in this patient population are what would be observed in a lower-risk patient population.

D. *Uncertainty in relative insulin dosage:* Relative insulin dosages for IDeg versus IGlar for populations 2 and 4 were derived from a meta-analysis conducted by the manufacturer.[2] As noted in the CADTH Common Drug Review (CDR) clinical review for IDeg, the meta-analysis did not account for within-trial clustering and correlation, likely leading to a less conservative estimate for insulin dosage. Further, there was no exploration of heterogeneity. As such, it is not clear that reported results are robust. For IDeg versus NPH, the relative dose difference was based on a convenience sample of patients with T2DM from British Columbia, which might not be applicable to all patients. The CDR clinical expert has indicated that the dose ratio of 1.42 for NPH to IGlar is likely greater than what would be observed in a real-world setting.

E. *Utility decrements for hypoglycemic events:* Utility decrements for hypoglycemic events were obtained from literature. 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 different sources (CADTH 2013 and 2016 reports and National Institute for Health and Care Excellence [NICE] 2016 Guidance)[8,12] were tested in the CDR sensitivity analyses.

F. *Cost of insulin:* For IGlar, the package size and format with the largest market share (Lantus pen 3 mL) was used in the base case. However, there were lower-cost alternatives (e.g., Basaglar). The price of lowest-cost alternative was tested in the CDR analyses.

CADTH Common Drug Review Reanalyses

CDR considered the following analyses to address the limitations identified above. The following considerations and reanalyses apply to the comparison of IDeg versus IGlar. Details on the IDeg versus NPH comparison are provided in Appendix 4 (Table 29 to Table 32).

1. **Use of more likely relative risk for hypoglycemic events:** To address the limitations with the manufacturer's meta-analysis, as identified in B above, where there was uncertainty in the relative risk of hypoglycemia (relative risk crossed unity in direct comparisons or non-robust findings from indirect comparisons), a relative risk of 1.0 was used. A summary of RRs used in the CDR plausible case can be found in Appendix 4 (Table 28).

2. **Baseline risk of hypoglycemia:** To address the generalizability of the populations in the SWITCH trials, as described in C above, 10% to 50% reductions of the baseline hypoglycemia rates were tested in the sensitivity analysis (in models where the relative risk of hypoglycemia was not equal to 1). In addition, alternate values from the CADTH 2013 report on severe hypoglycemia (0.0053) for T2DM were evaluated.[12]
3. **Relative insulin dosage to align with more plausible values:** To address the uncertainty with relative insulin doses, as described in D above, a dose ratio of 1 was tested in the sensitivity analysis. For populations 2 and 4, insulin dose was based on a meta-analysis of four phase IIIa trials; as such, the relative dose of insulin was set to 1.0.
4. **Alternate estimates of utility decrements for hypoglycemic events:** Values from the CADTH 2013 report (0.000004767 mild and 0.01 severe) were used, as well as from National Institute for Health and Clinical Excellence (NICE) guidance (0.0052 mild and 0.01 severe) to address limitation E.
5. **Cost of IGlar (for comparison of IDeg versus IGlar only):** The lowest-cost alternative (Basaglar $94.06 per 1,500 IU including 8% markup and dispensing fee) was used to address limitation F.
6. **Plausible CDR base case:** The CDR base case used a more likely relative risk of hypoglycemia events, a relative dose of one for indirect comparisons, and the lowest IGlar cost:
    a. Scenario analysis with 10% reduction in baseline severe hypoglycemia if RR severe was not = 1
    b. Scenario analysis with 25% reduction in baseline severe hypoglycemia if RR severe was not = 1
    c. Others

In population 1 (T1DM, basal + bolus), the total cost per patient per year in the IDeg group is $310 lower than that in the IGlar group. The results of the CDR base-case analysis show that IDeg is dominant when compared with IGlar (Table 4).

Table 4: CDR Reanalysis, IDeg Versus IGlar — Plausible Base Case, Population 1 (T1DM, Basal + Bolus)

	Description	IDeg Versus IGlar		
		Incremental Cost ($)	Incremental QALYs	ICUR ($/QALY)
	Manufacturer base case	−459	0.0181	Dominant
1	**RR severe hypoglycemia = 1 (Dawoud)[13]**	**119**	**0.0029**	**41,256**
2	**Baseline hypoglycemia events (RR mild daytime = 1 in base case)**			
	Severe events −10%	−401	0.0166	Dominant
	All −10%	−401	0.0165	Dominant
	Severe events −25%	−315	0.0143	Dominant
	All −25%	−314	0.014	Dominant
	Severe events −50%	−170	0.0105	Dominant
	All −50%	−168	0.0099	Dominant
3	**Relative insulin dosage (dose ratio = 1)**	−422	0.0181	Dominant
4	**Utility decrements for hypoglycemic events**			
4a	0.000004767 mild and 0.01 severe	−459	0.0027	Dominant
4b	0.0052 mild and 0.01 severe	−459	0.0069	Dominant
5	**Lower IGlar cost**	−310	0.0181	Dominant
6	**Plausible base case** Cost IGlar $94.06	**−310**	**0.0181**	**Dominant**
6a	Scenario analysis of CDR base case Severe events −10%	−253	0.0166	Dominant
6b	Scenario analysis of CDR base case Severe events −25%	−253	0.0143	Dominant
6c	Scenario analysis of CDR base case (RR severe =1)	268	0.0029	**92,850**

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; IDeg = insulin degludec; IGlar = insulin glargine; QALY = quality-adjusted life-year; RR = relative risk; T1DM = type 1 diabetes mellitus.

Note: Dominant means IDeg is more effective and less costly.

In population 2 (T1DM, basal + oral antidiabetes drug [OAD]), the incremental cost per patient per year in the IDeg group is $380, which is more than the incremental cost reported by the manufacturer at $18 for IDeg. This is attributed to the lower unit costs for IGlar and the reduced dose ratio of IDeg to IGlar. The incremental QALYs associated with IDeg in the CDR base case reduced to 0.0003 compared with 0.0032 in the manufacturer's base case due to varying the relative risk of nocturnal hypoglycemia. The differences in incremental costs and QALYs resulted in an ICUR of more than $1.1 million per QALY for IDeg when compared with IGlar (Table 5).

Table 5: CDR Reanalysis, IDeg Versus IGlar — Plausible Base Case, Population 2 (T2DM, Basal + OAD)

	Description	IDeg Versus IGlar		
		Incremental Cost ($)	Incremental QALYs	ICUR ($/QALY)
	Manufacturer base case	18	0.0032	5,564
1	**RR hypoglycemia**			
1a	DEVOTE (RR severe = 0.6)	33	0.0028	11,801
1b	RR nocturnal = 1 (Freemantle)	18	0.0007	24,141
2	**Baseline hypoglycemia events (RR mild daytime = 1 in base case)**			
	Severe events −10%	20	0.0031	6,595
	All −10%	20	0.0030	6,785
	Severe events −25%	25	0.0030	8,273
	All −25%	25	0.0027	8,953
	Severe events −50%	32	0.0028	11,340
	All −50%	32	0.0023	13,830
	CADTH rate 0.0053	36	0.0027	13,403
3	**Relative insulin dosage (dose ratio = 1)**	175	0.0032	55,623
4	**Utility decrements for hypoglycemic events**			
4a	0.000004767 mild and 0.01 severe	18	0.0001	133,225
4b	0.0052 mild and 0.01 severe	18	0.0011	16,188
5	**Lower IGlar cost**	207	0.0032	65,700
6	**Plausible base case** RR severe hypo = 0.6; RR nocturnal hypo = 1; dose ratio = 1; cost IGlar = $94.06	**380**	**0.0003**	**1,106,180**
6a	Scenario analysis of CDR base case Severe events −10%	381	0.0003	1,231,448
6b	Scenario analysis of CDR base case Severe events −25%	383	0.0003	1,487,552
6c	Scenario analysis of CDR base case Relative dose = 0.90	222	0.0003	647,067

CDR = CADTH Common Drug Review; hypo = hypoglycemic event; ICUR = incremental cost-utility ratio; IDeg = insulin degludec; IGlar = insulin glargine; OAD = oral antidiabetes drug; QALY = quality-adjusted life-year; RR = relative risk; T2DM = type 2 diabetes mellitus.

In population 3 (T1DM, basal + OAD-experienced]), the incremental costs per patient per year in the IDeg group increased to $446 compared with the incremental costs reported by the manufacturer at $121 for IDeg. This is attributed to the lower unit costs for IGlar. The incremental QALYs associated with IDeg in the CDR base case reduced to 0.0052 compared with 0.0058 in the manufacturer's base case due to varying the relative risk of severe hypoglycemia. The differences in incremental costs and QALYs resulted in an ICUR of $85,487 per QALY for IDeg when compared with IGlar (Table 6).

Table 6: CDR Reanalysis, IDeg Versus IGlar — Plausible Base Case, Population 3 (T2DM, Basal + OAD-Experienced)

	Description	IDeg Versus IGlar		
		Incremental Cost ($)	Incremental QALYs	ICUR ($/QALY)
	Manufacturer base case	121	0.0058	20,887
1	**DEVOTE (RR severe = 0.6)**	143	0.0052	27,435
2	**Baseline hypoglycemia events**			
	Mild daytime events −25%	121	0.0057	21,345
	Mild nocturnal events −25%	121	0.0056	21,512
	Severe events −25%	147	0.0051	28,655
	All −25%	147	0.0048	30,374
	Mild daytime events −50%	121	0.0055	21,941
	Mild nocturnal events −50%	121	0.0054	22,349
	Severe events −50%	172	0.0044	38,737
	All −50%	173	0.0038	45,334
	CADTH rate 0.0053	218	0.0032	67,069
3	**Relative insulin dosage (dose ratio = 1)**	222	0.0058	38,280
4	**Utility decrements for hypoglycemic events**			
4a	0.000004767 mild and 0.01 severe	121	0.0005	251,745
4b	0.0052 mild and 0.01 severe	121	0.0034	35,157
5	**Lower IGlar cost**	424	0.0058	73,122
6	**Plausible base case** Cost IGlar $94.06	**424**	**0.0058**	**73,122**
6a	Scenario analysis of CDR base case Severe events −10%	454	0.0050	90,725
6b	Scenario analysis of CDR base case Severe events −25%	466	0.0047	99,472
6c	Scenario analysis of CDR base case RR severe hypo = 0.6	446	0.0052	85,487

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; IDeg = insulin degludec; IGlar = insulin glargine; OAD = oral antidiabetes drug; QALY = quality-adjusted life-year; RR = relative risk; T2DM = type 2 diabetes mellitus.

In population 4 (T1DM, basal + bolus), the incremental costs per patient per year in the IDeg group increased to $669 compared with the incremental costs reported by the manufacturer at $421 for IDeg. This is attributed to the lower unit costs for IGlar. The CDR base case did not result in incremental QALYs between IDeg and IGlar, thereby resulting in IDeg being dominated by IGlar for being costlier than IGlar but equally effective (Table 7).

Table 7: CDR Reanalysis, IDeg Versus IGlar — Plausible Base Case, Population 4 (T2DM, Basal + Bolus)

	Description	IDeg Versus IGlar		
		Incremental Cost ($)	Incremental QALYs	ICUR ($/QALY)
	Manufacturer base case	421	0.0044	95,155
1	**RR hypoglycemia (Not available from other source)**			
2	**Baseline hypoglycemia events (RR severe = 1 in base case)**			
	Mild daytime events −25%	421	0.0042	99,515
	Mild nocturnal events −25%	421	0.0042	100,141
	All −25%	422	0.0040	104,968
	Mild daytime events −50%	422	0.0040	105,499
	Mild nocturnal events −50%	421	0.0039	107,193
	All −50%	423	0.0035	120,424
3	**Relative insulin dosage (dose ratio = 1)**	258	0.0044	58,398
4	**Utility decrements for hypoglycemic events**			
4a	0.000004767 mild and 0.01 severe	421	0	35,948,573
4b	0.0052 mild and 0.01 severe	421	0.0128	32,955
5	**Lower IGlar cost**	665	0.0044	150,351
6	**Plausible base case** Cost IGlar $94.06	**665**	**0.0044**	**150,351**
6a	Scenario analysis (NA as RR severe = 1)	NA		

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; IDeg = insulin degludec; IGlar = insulin glargine; NA = not applicable; QALY = quality-adjusted life-year; RR = relative risk; T2DM = type 2 diabetes mellitus.

The CDR base case for IDeg versus NPH is shown in Table 8 using a dose ratio of 1.2 for NPH versus IGlar (suggested by the CDR clinical expert) and the same frequency of SMPG tests for both comparators in populations 2 and 3. Other details of the CDR sensitivity analysis of IDeg versus NPH can be found in Appendix 4 (Table 29 to Table 32).

Table 8: CDR Reanalysis, IDeg Versus NPH — Plausible Base Case

	Description	IDeg Versus NPH		
		Incremental Cost ($)	Incremental QALYs	ICUR ($/QALY)
	Population 1: T1DM, basal + bolus			
	Manufacturer base case	−432	0.0224	Dominant
	Plausible base case	**−306**	**0.0224**	**Dominant**
	Population 2: T2DM, basal + OAD			
	Manufacturer base case	−15	0.0103	Dominant
	Plausible base case	**266**	**0.0103**	**25,677**
	Population 3: T2DM, basal + OAD EX			
	Manufacturer base case	160	0.0173	9,256
	Plausible base case	**648**	**0.0173**	**37,431**
	Population 4: T2DM, basal + bolus			
	Manufacturer base case	727	0.0044	164,361
	Plausible base case	**933**	**0.0044**	**211,080**

CDR = CADTH Common Drug Review; EX = experienced; ICUR = incremental cost-utility ratio; IDeg = insulin degludec; NPH = neutral protamine Hagedorn; OAD = oral antidiabetes drug; QALY = quality-adjusted life-year; RR = relative risk; T2DM = type 2 diabetes mellitus.
Note: Dominant means IDeg is more effective and less costly.

A series of price reduction analyses were undertaken based on the CDR base case.

Table 9: CDR Reanalysis, Price Reduction Scenarios — Population 1 (T1DM, Basal + Bolus) — Based on the CDR Base Case

ICURs of IDeg Versus IGlar or NPH				
Price	**Base-Case Analysis Submitted by Manufacturer IDeg vs. IGlar**	**Base-Case Analysis Submitted by Manufacturer IDeg vs. NPH**	**Reanalysis by CDR IDeg vs. IGlar**	**Reanalysis by CDR IDeg vs. NPH**
Submitted	Dominant	Dominant	Dominant	Dominant

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; IDeg = insulin degludec; IGlar = insulin glargine; NPH = neutral protamine Hagedorn; T1DM = type 1 diabetes mellitus; Vs. = versus.
Note: Dominant means IDeg is more effective and less costly.

Table 10: CDR Reanalysis, Price Reduction Scenarios — Population 2 (T2DM, Basal + OAD) — Based on the CDR Base Case

ICURs of IDeg Versus IGlar or NPH				
Price	**Base-Case Analysis Submitted by Manufacturer IDeg vs. IGlar**	**Base-Case Analysis Submitted by Manufacturer IDeg vs. NPH**	**Reanalysis by CDR IDeg vs. IGlar**	**Reanalysis by CDR IDeg vs. NPH**
Submitted	$5,564	Dominant	$1,106,180	$25,677
10% reduction	Dominant	Dominant	$646,994	$6,708
15% reduction	Dominant	Dominant	$417,584	Dominant
20% reduction	Dominant	Dominant	$187,808	Dominant
23% reduction	Dominant	Dominant	$50,382	Dominant
25% reduction	Dominant	Dominant	Dominant	Dominant

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; IDeg = insulin degludec; IGlar = insulin glargine; NPH = neutral protamine Hagedorn; OAD = oral antidiabetes drug; T2DM = type 2 diabetes mellitus; vs. = versus.
Note: Dominant means IDeg is more effective and less costly.

Table 11: CDR Reanalysis, Price Reduction Scenarios — Population 3 (T2DM, Basal + OAD-Experienced) — Based on the CDR Base Case

ICURs of IDeg versus IGlar or NPH				
Price	**Base-Case Analysis Submitted by Manufacturer IDeg vs. IGlar**	**Base-Case Analysis Submitted by Manufacturer IDeg vs. NPH**	**Reanalysis by CDR IDeg vs. IGlar**	**Reanalysis by CDR IDeg vs. NPH**
Submitted	$20,887	$9,256	$73,122	$37,431
10% reduction	Dominant	Dominant	$31,373	$16,469

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; IDeg = insulin degludec; IGlar = insulin glargine; NPH = neutral protamine Hagedorn; OAD = oral antidiabetes drug; QALY = quality-adjusted life-year; T2DM = type 2 diabetes mellitus; vs. = versus.
Note: Dominant means IDeg is more effective and less costly.

Table 12: CDR Reanalysis, Price Reduction Scenarios — Population 4 (T2DM, Basal + Bolus) — Based on the CDR Base Case

ICURs of IDeg Versus IGlar or NPH				
Price	**Base-Case Analysis Submitted by Manufacturer IDeg vs. IGlar**	**Base-Case Analysis Submitted by Manufacturer IDeg vs. NPH**	**Reanalysis by CDR IDeg vs. IGlar**	**Reanalysis by CDR IDeg vs. NPH**
Submitted	$95,155	$164,361	$150,351	$211,080
10% reduction	$45,525	$114,730	$100,721	$161,448
15% reduction	$20,730	$89,934	$75,926	$136,652
20% reduction	Dominant	$65,099	$51,091	$111,817
25% reduction	Dominant	$40,303	$26,296	$87,021
30% reduction	Dominant	$15,507	$1,501	$62,225
35% reduction	Dominant	Dominant	Dominant	$37,390

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; IDeg = insulin degludec; IGlar = insulin glargine; NPH = neutral protamine Hagedorn; T2DM = type 2 diabetes mellitus; vs. = versus.
Note: Dominant means IDeg is more effective and less costly.

Issues for Consideration

- According to the clinical expert, there is a possibility that IDeg might be used off-label in T1DM patients under age 18 when hypoglycemia is a particular concern. The cost-effectiveness of IDeg in this population is unknown at this time.
- Previous CADTH reviews had recommended that insulin NPH be added for most adults with T2DM inadequately controlled on metformin and a sulfonylurea;12 therefore, it was included as a comparator in this report. Arguably it may be considered the most appropriate comparator, although its use is waning in many jurisdictions.
- The incremental QALYs among comparisons are very small — between 0.0044 and 0.0181, equivalent to an additional 1.1 to 6.6 days of perfect health in one year. This can lead to instability in the ICUR, where small changes in cost can lead to larger changes in the ICUR.
- IDeg is indicated for use in patients with both T1DM and T2DM. While ICURs are presented for each patient population, the vast majority of use is likely to occur in patients with T2DM, given the frequency of this disease (90%).14 As such, the ICUR in this patient population may be the most relevant. It is not clear which T2DM population would experience the greatest use if IDeg were reimbursed.

Patient Input

Patients had many expectations for IDeg, including (1) improved blood glucose control without weight gain; (2) avoidance of side effects (hypoglycemia), symptoms (high blood pressure), long-term complications, and organ damage; (3) improvement in treatment adherence; (4) improvement in the predictability of an individual's daily response to insulin; (5) reduction in dependence on insulin or other medications; (6) reduction in the demands and requirements of disease management; and (7) affordability. Only the side effect of hypoglycemia and reduction in insulin dosage were incorporated into the economic analysis base case. Benefits of dosing flexibility were also tested in the manufacturer's sensitivity analysis (an increased utility of 0.013).

Conclusions

There is significant uncertainty in the true cost-effectiveness of IDeg due to a variety of factors, including multiple patient populations in which IDeg may be used, the most relevant comparator, and uncertainty in the true relative difference of hypoglycemic events in patient populations where direct comparisons are absent (particularly given the numerous issues identified with the manufacturer-conducted meta-analysis and NMA).

While the manufacturer's analysis suggests that IDeg may be dominant compared with insulin analogues (greater benefit and lower costs) in most patient populations, the CDR reanalyses that address the identified limitations with the manufacturer's economic analysis indicated that IDeg use is likely associated with incremental costs for several of the patient populations, particularly in patients with T2DM. In T2DM, where most of the use is likely to occur, the ICUR ranges between $73,000 per QALY and > $1 million per QALY; price reductions of 10% to more than 25% would be required for IDeg to fall to $50,000 per QALY when compared with IGlar (and NPH).

In T1DM, IDeg dominated both IGlar (if the rate of hypoglycemia is truly lower with IDeg) and NPH.

Appendix 1: Cost Comparison

The comparators presented in Table 13 have been deemed appropriate by clinical experts. Comparators may be recommended (appropriate) practice versus actual practice. Comparators are not restricted to drugs but may be devices or procedures. Costs are manufacturer list prices, unless otherwise specified. Existing product listing agreements are not reflected in the table; as such, they may not represent the actual costs to public drug plans.

Table 13: Cost Comparison of Insulins

Drug/Comparator	Strength	Dosage Form	Price ($)	Cost Per mL ($)
Long-Acting Insulin Analogues				
Insulin degludec (Tresiba)	**100 U/mL** **200 U/mL**	**5 × 3 mL pre-filled pen** **3 x 3 mL pre-filled pen**	**107.8200[a]** **129.3840[a]**	**7.188** **14.376**
Insulin glargine (Lantus)	100 U/mL	5 × 3 mL cartridge 5 × 3 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 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
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 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
Insulin NPH				
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
Premixed 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 Mix 25)	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 Mix 50)	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

Drug/Comparator	Strength	Dosage Form	Price ($)	Cost Per mL ($)
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

NPH = neutral protamine Hagedorn.
[a] Manufacturer's submission price.[2]
[b] IMS Delta PA, IMS Brogan (July 2017).[16]
Source: Ontario Drug Benefit (July 2017) prices unless otherwise indicated.[15]

Appendix 2: Additional Information

Table 14: Submission Quality

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?	X		
Comments Reviewer to provide comments if checking “no”	None		
Was the material included (content) sufficient?	X		
Comments Reviewer to provide comments if checking “poor”	None		
Was the submission well organized and was information easy to locate?	X		
Comments Reviewer to provide comments if checking “poor”	None		

Table 15: Authors’ Information

Authors of the pharmacoeconomic evaluation submitted to CDR
☐ Adaptation of Global model/Canadian model done by the manufacturer ☒ Adaptation of Global model/Canadian model done by a private consultant contracted by the manufacturer ☐ Adaptation of Global model/Canadian model done by an academic consultant contracted by the manufacturer ☐ Other (please specify)

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

CDR = CADTH Common Drug Review.

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

Table 16: Other Health Technology Assessment Findings

	NCPE (Ireland), November 2014[11]
Treatment	Insulin degludec (Tresiba)
Price	Confidential
Similarities With CDR Submission	A one-year model compared with insulin glargine; main efficacy outcome was hypoglycemic event.
Differences With CDR Submission	Only two patient groups were considered: (1) patients with T1DM who used a basal + bolus regimen; (2) patients with T2DM who used a basal oral therapy regimen. Patients under age 18 were also considered.
Manufacturer's Results	T1DM: €6,284/QALY T2DM: €3,010/QALY
Issues Noted by the Review Group	The review group considered that the model, which mainly models the benefit in terms of hypoglycemia, may be overly simplistic for a multi-faceted condition such as diabetes mellitus.
Results of Reanalyses by the Review Group	Based on alternative estimates for hypoglycemic event rates and the proportion that occurred at night, costs associated with a hypoglycemic episode and disutility estimates for a hypoglycemic episode: T1DM: €50,697/QALY T2DM: €108,203/QALY In addition, assuming dose equivalence: T1DM: €101,532/QALY T2DM: €161,372/QALY
Recommendation	Insulin degludec is not considered cost-effective vs. insulin glargine for the treatment of diabetes mellitus in adults, adolescents, and children older than one year. Therefore, it is not recommended for reimbursement at the submitted price. In December 2015, the HSE approved reimbursement following confidential price negotiations.

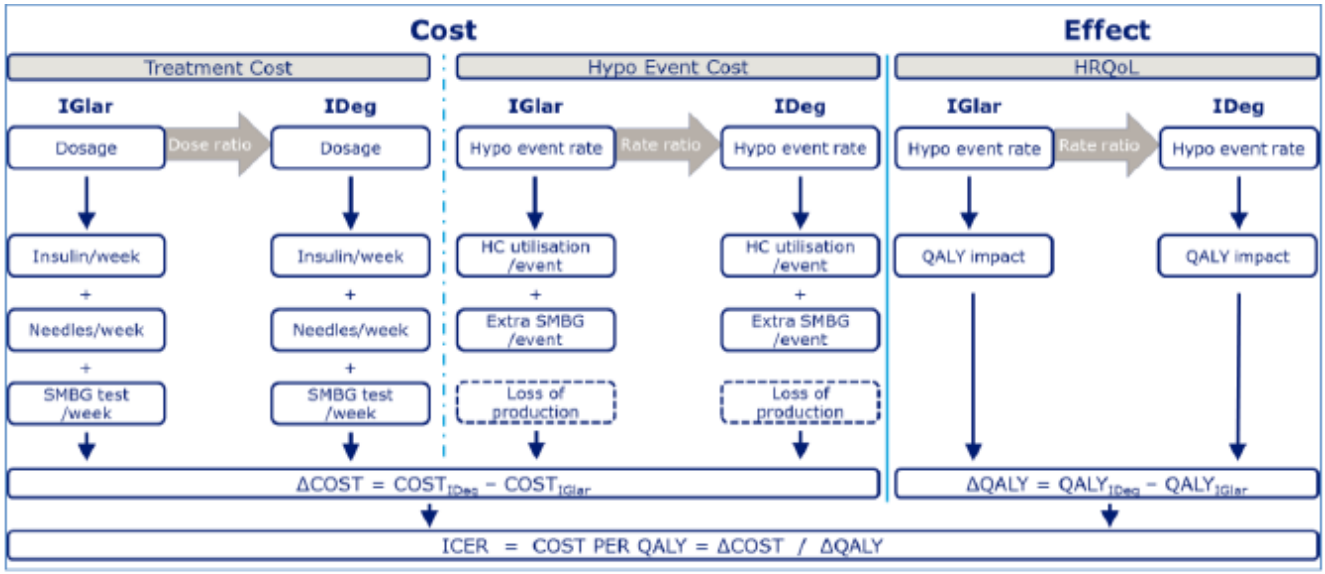
CDR = CADTH Common Drug Review; HSE = Health Service Executive; HTA = Health Technology Assessment; NCPE = National Centre for Pharmacoeconomics; QALY = quality-adjusted life-years; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; vs. = versus.

Appendix 4: Reviewer Worksheets

Manufacturer's Model Structure

The short-term (one-year) economic model focused only on risk, costs, and quality-of-life impacts associated with hypoglycemia. An overview of the cost-effectiveness analysis is shown in Figure 1.

Figure 1: Cost-Effectiveness Analysis Overview (Base Case)



Δ, change in; HC, healthcare; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; IDeg, insulin degludec; IGlar, insulin glargine; QALY, quality-adjusted life year; SMBG, self-monitored blood glucose

Source: Manufacturer's pharmacoeconomic report.[2]

Table 17 and Table 18 report the relevant data sources and assumptions incorporated by the manufacturer.

Table 17: Data Sources

Data Input	Description of Data Source	Comment
Efficacy	Trial-observed rates of hypoglycemia for patients receiving IGlar, with the corresponding rates for IDeg estimated based on the rate ratio observed in the clinical trials (SWITCH-1, SWITCH-2, and manufacturer-sponsored meta-analysis of phase IIIa trials).[3-5]	Uncertain. Trial-determined rate ratios are appropriate; however, there were several limitations associated with the manufacturer-sponsored meta-analysis that may favour IDeg.
Natural History	No other elements of diabetes complications (such as A1C or other harms) were modelled. The baseline risk of hypoglycemia is from SWITCH-1 and SWITCH-2.[3,4]	Uncertain. The model was unable to evaluate the effects of A1C or other potential harms. However, absence of data about differences in other outcomes suggests this may not introduce bias. May not be appropriate. The populations included in these trials may include patients at greater risk of hypoglycemia than patients indicated by the

Data Input	Description of Data Source	Comment
		reimbursement criteria.
Utilities	The baseline QALY was assumed to be 0.753, obtained from the 2010 CADTH report.[7] The disutilities of hypoglycemic events were obtained from published literature (Evan 2013, Lauridsen 2014, CADTH report).[17,18]	Appropriate, although there is uncertainty around the true disutility of the various hypoglycemic events (with its range of severities and definitions).
Resource Use	Insulin dose ratio (IDeg:IGlar) was obtained from the meta-analysis at end of trial. Insulin dose ratio (IDeg:NPH) was obtained from a convenience sample of patients with T2DM in British Columbia.[2]	The manufacturer's meta-analysis was subject to several limitations (see clinical report for details). Also, according to the CDR clinical expert, the insulin dose ratio for IDeg vs. NPH was likely too high.
Adverse Events	See efficacy.	
Mortality	Not modelled. Model duration is only 1 year.	
Costs		
Drug	The manufacturer provided the costs for IDeg. The insulin unit cost of basal insulin IGlar (Lantus) and bolus treatment (NovoRapid) were obtained from the Ontario Drug Benefit/Comparative Drug Index.[15] The package size and format with the largest market share was selected. Costs of OAD were excluded in the model. All drug costs included an 8% markup fee and a $8.83 dispensing fee.[2]	The lowest-cost alternative (Basaglar) is arguably the most relevant comparator of the insulin analogues. However, NPH insulin is also arguably a relevant comparator based on previous CADTH guidance.
Administration and Monitoring	The costs of needles and syringes, as well as the SMPG test, were included in the base-case analysis.	According to the CDR clinical expert, the SMPG test for patients not on bolus insulin should be the same for IDeg as for NPH; no evidence was provided to counter this.
AEs (Hypoglycemia)	It was assumed that mild/moderate hypoglycemic events had no impact on health care resource use ($0 cost). The cost of severe hypoglycemia was based on the CADTH optimal use reports.	Appropriate.

A1C = glycated hemoglobin; AE = adverse event; CDR = CADTH Common Drug Review; IDeg = insulin degludec; IGlar = insulin glargine; OAD = oral antidiabetes drug; NPH = neutral protamine Hagedorn; QALY = quality-adjusted life-year; SMPG = self-measured plasma glucose; T2DM = type 2 diabetes mellitus; vs. = versus.

Table 18: Manufacturer's Key Assumptions

Assumption	Comment
Natural History and Efficacy	
The outcomes represented the average annual cost-effectiveness in a steady state.	The trials were short (mostly 26 weeks to 52 weeks) and longer-term differences in the risk of hypoglycemia are unknown. If any difference in the risk of hypoglycemia with IDeg attenuates over time, the ICUR will increase.
Efficacy and relative dosage for population 2 and population 4 were derived from manufacturer-sponsored meta-analysis.	The manufacturer-sponsored meta-analysis was subject to several significant limitations (see clinical report, Appendix 6, for details); the results of this meta-analysis likely favour IDeg.
Efficacy and relative dosage derived from the manufacturer-sponsored meta-analysis were applied to the comparison between IDeg and NPH.	There is currently no direct trial that compares IDeg against NPH.

ICUR = incremental cost-utility ratio; IDeg = insulin degludec; NPH = neutral protamine Hagedorn.

Detailed Manufacturer's Results

Manufacturer's Base Case (Insulin Degludec Versus Insulin Glargine)

In the base case, the manufacturer reported that insulin degludec (IDeg) compared with insulin glargine (IGlar) is associated with an additional 0.0032 to 0.0180 quality-adjusted life-years (QALYs), depending on the patient population. Treatment with IDeg resulted in lower total health care costs of –$459 in patients with type 1 diabetes mellitus (T1DM), and higher total health care costs of $18 to $421 in patients with type 2 diabetes mellitus (T2DM). IDeg is the dominant strategy (more effective and less costly) in T1DM patients. The incremental cost-utility ratio (ICUR) of IDeg ranged from $5,564 per QALY to $95,155 per QALY in T2DM patients.

Table 19: Manufacturer's Base-Case Results — Type 1 Diabetes Mellitus, Basal + Bolus

Population 1 (T1DM, Basal + Bolus)	IDeg	IGlar	Difference
QALYs	0.6416	0.6235	0.0181
Total costs ($) Basal insulin cost Bolus insulin cost Needle cost Routine SMPG test cost Non-severe daytime hypoglycemia cost Non-severe nocturnal hypoglycemia cost Severe hypoglycemia cost	5,262 1,201 562 485 1,253 77 12 1,672	5,721 1,078 562 485 1,253 77 15 2,250	−459
ICUR ($/QALY)			IDeg dominates

ICUR = incremental cost-utility ratio; IDeg = insulin degludec; IGlar = insulin glargine; QALY = quality-adjusted life-year; SMPG = self-measured plasma glucose; T1DM = type 1 diabetes mellitus.

Source: Manufacturer's pharmacoeconomic report.[2]

Table 20: Manufacturer's Base-Case Results — Type 2 Diabetes Mellitus, Basal + OAD

Population 2 (T2DM, Basal + OAD)	IDeg	IGlar	Difference
QALYs	0.7212	0.7181	0.0032
Total costs ($) Basal insulin cost Bolus insulin cost Needle cost Routine SMPG test cost Non-severe daytime hypoglycemia cost Non-severe nocturnal hypoglycemia cost Severe hypoglycemia cost	1,862 1,419 0 121 313 3 1 5	1,844 1,374 0 121 313 3 1 33	18
ICUR ($/QALY)			5,564

ICUR = incremental cost-utility ratio; IDeg = insulin degludec; IGlar = insulin glargine; OAD = oral antidiabetes drug; QALY = quality-adjusted life-year; SMPG = self-measured plasma glucose; T2DM = type 2 diabetes mellitus.

Source: Manufacturer's pharmacoeconomic report.[2]

Table 21: Manufacturer's Base-Case Results — Type 2 Diabetes Mellitus, Basal + OAD-Experienced

Population 3 (T2DM, Basal + OAD EX)	IDeg	IGlar	Difference
QALYs	0.7152	0.7094	0.0058
Total costs ($) Basal insulin cost Bolus insulin cost Needle cost Routine SMPG test cost Non-severe daytime hypoglycemia cost Non-severe nocturnal hypoglycemia cost Severe hypoglycemia cost	2,957 2,421 0 121 313 2 1 99	2,836 2,196 0 121 313 3 1 201	121
ICUR ($/QALY)			20,887

ICUR = incremental cost-utility ratio; IDeg = insulin degludec; IGlar = insulin glargine; OAD = oral antidiabetes drug; QALY = quality-adjusted life-year; SMPG = self-measured plasma glucose; T2DM = type 2 diabetes mellitus.

Source: Manufacturer's pharmacoeconomic report.[2]

Table 22: Manufacturer's Base-Case Results — Type 2 Diabetes Mellitus, Basal + Bolus

Population 4 (T2DM, Basal + Bolus)	IDeg	IGlar	Difference
QALYs	0.6949	0.6905	0.0044
Total costs ($) Basal insulin cost Bolus insulin cost Needle cost Routine SMPG test cost Non-severe daytime hypoglycemia cost Non-severe nocturnal hypoglycemia cost Severe hypoglycemia cost	5,344 2,194 1,281 485 1,253 16 2 112	4,923 1,769 1,281 485 1,253 19 3 112	421
ICUR ($/QALY)			95,155

ICUR = incremental cost-utility ratio; IDeg = insulin degludec; IGlar = insulin glargine; QALY = quality-adjusted life-year; SMPG = self-measured plasma glucose; T2DM = type 2 diabetes mellitus.

Source: Manufacturer's pharmacoeconomic report.[2]

Manufacturer's Secondary Analysis (Insulin Degludec Versus Neutral Protamine Hagedorn)

In the base case, the manufacturer reported that IDeg compared with neutral protamine Hagedorn (NPH) insulin is associated with an additional 0.0044 to 0.0224 QALYs, depending on the patient population. Treatment with IDeg resulted in lower total health care costs of −$432 in T1DM patients and −$15 in T2DM oral antidiabetes drug (OAD) patients, and higher total health care costs of $160 to $727 in other T2DM patients. IDeg is the dominant strategy (more effective and less costly) in patients with T1DM and T2DM on oral antidiabetes drugs, and the ICUR of IDeg ranged from $9,256 per QALY to $164,361 per QALY in other T2DM patients.

Table 23: Manufacturer's Base-Case Results — Type 1 Diabetes Mellitus, Basal + Bolus

Population 1 (T1DM, Basal + Bolus)	IDeg	NPH	Difference
QALYs	0.6416	0.6192	0.0224
Total costs ($) Basal insulin cost Bolus insulin cost Needle cost Routine SMPG test cost Non-severe daytime hypoglycemia cost Non-severe nocturnal hypoglycemia cost Severe hypoglycemia cost	5,262 1,201 562 485 1,253 77 12 1,672	5,693 813 562 550 1,420 77 22 2,250	−578
ICUR ($/QALY)			IDeg dominates

ICUR = incremental cost-utility ratio; IDeg = insulin degludec; NPH = neutral protamine Hagedorn; QALY = quality-adjusted life-year; SMPG = self-measured plasma glucose; T1DM = type 1 diabetes mellitus.

Source: Manufacturer's pharmacoeconomic report.[2]

Table 24: Manufacturer's Base-Case Results — T2DM, Basal + Oral Antidiabetes Drug

Population 2 (T2DM, Basal + OAD)	IDeg	NPH	Difference
QALYs	0.7212	0.7109	0.0103
Total costs ($) Basal insulin cost Bolus insulin cost Needle cost Routine SMPG test cost Non-severe daytime hypoglycemia cost Non-severe nocturnal hypoglycemia cost Severe hypoglycemia cost	1,862 1,419 0 121 313 3 1 5	1,877 1,035 0 211 545 3 2 81	−15[a]
ICUR ($/QALY)			IDeg dominates

ICUR = incremental cost-utility ratio; IDeg = insulin degludec; NPH = neutral protamine Hagedorn; OAD = oral antidiabetes drug; QALY = quality-adjusted life-year; SMPG = self-measured plasma glucose; T2DM = type 2 diabetes mellitus.
[a] Based on a dose ratio (IDeg:IGlar) of 0.9 from the base case.[2]
Source: Manufacturer's pharmacoeconomic report.[2]

Table 25: Manufacturer's Base-Case Results — Type 2 Diabetes Mellitus, Basal + OAD-Experienced

Population 3 (T2DM, Basal + OAD EX)	IDeg	NPH	Difference
QALYs	0.7152	0.6979	0.0173
Total costs ($) Basal insulin cost Bolus insulin cost Needle cost Routine SMPG test cost Non-severe daytime hypoglycemia cost Non-severe nocturnal hypoglycemia cost Severe hypoglycemia cost	2,957 2,421 0 121 313 2 1 99	2,797 1,655 0 121 545 4 3 380	160
ICUR ($/QALY)			9,256

EX = experienced; ICUR = incremental cost-utility ratio; IDeg = insulin degludec; NPH = neutral protamine Hagedorn; OAD = oral antidiabetes drug; QALY = quality-adjusted life-year; SMPG = self-measured plasma glucose; T2DM = type 2 diabetes mellitus.
Source: Manufacturer's pharmacoeconomic report.[2]

Table 26: Manufacturer's Base-Case Results — Type 2 Diabetes Mellitus, Basal + Bolus

Population 4 (T2DM, Basal + Bolus)	IDeg	NPH	Difference
QALYs	0.6949	0.6905	0.0044
Total costs ($) Basal insulin cost Bolus insulin cost Needle cost Routine SMPG test cost Non-severe daytime hypoglycemia cost Non-severe nocturnal hypoglycemia cost Severe hypoglycemia cost	5,344 2,194 1,281 485 1,253 16 2 112	4,617 1,334 1,281 521 1,347 19 3 112	727
ICUR ($/QALY)			164,361

ICUR = incremental cost-utility ratio; IDeg = insulin degludec; NPH = neutral protamine Hagedorn; QALY = quality-adjusted life-year; SMPG = self-measured plasma glucose; T2DM = type 2 diabetes mellitus.
Source: Manufacturer's pharmacoeconomic report.[2]

Efficacy Estimates Used in the Manufacturer's Base Case and CADTH Common Drug Review Reanalyses

Baseline hypoglycemia rates used in the manufacturer model are listed in Table 27. The event rates for IDeg were calculated by applying the relative risk in Table 27 to the rates of hypoglycemia with IGlar. As the patient populations included in SWITCH-1 and SWITCH-2 may be at greater risk of hypoglycemia than the average patient, alternate values were tested by CADTH Common Drug Review (CDR), including rates from other sources provided by the manufacturer (UK and Hypoglycemia Assessment Tool), 10% and 25% lower risk of hypoglycemia, and a baseline event rate of 0.0053 for severe hypoglycemia for patients with T2DM (CADTH 2013 report).

Table 27: Baseline Hypoglycemia Rates for Insulin Glargine and Insulin Degludec (per Patient Year)

Manufacturer's Base Case	Source	IGlar			IDeg		
		Non-severe Daytime	Non-severe Nocturnal	Severe	Non-severe Daytime	Non-severe Nocturnal	Severe
Population 1: T1DM, basal + bolus	SWITCH-1 trial results	17.18	3.45	1.05	17.18	2.62	0.78
Population 2: T2DM, basal + OAD	Manufacturer's meta-analysis of phase IIIa trials	1.54	0.51	0.02	1.54	0.33	0.002
Population 3: T2DM, basal + OAD EX	SWITCH-2 trial results	1.79	0.86	0.09	1.43	0.65	0.05
Population 4: T2DM, basal + bolus	Manufacturer's meta-analysis of phase IIIa trials	11.75	1.83	0.05	9.75	1.37	0.05

EX = experienced; IDeg = insulin degludec; IGlar = insulin glargine; OAD = oral antidiabetes drug; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.
Source: Manufacturer's pharmacoeconomic report.[2]

The following tables show the different estimates used for relative risk of hypoglycemia in the CDR reanalyses. The numbers highlighted in red were different from the manufacturer's base case due to the following:

a) Population 1: Relative risk of severe hypoglycemia was changed to 1 in the scenario analysis due to the meta-analysis by Dawoud et al.[13] Other values from the trial SWITCH-1 remained as is.[2,3]

b) Population 2: Values from the manufacturer's meta-analysis on the relative risk of non-severe hypoglycemia were changed to 1 due to the limitations identified in the clinical report (see Appendix 6). Relative risk of severe hypoglycemia was changed to 0.60 as per the results from the DEVOTE trial.[19]

c) Population 3: Relative risk of severe hypoglycemia of 0.6 from the DEVOTE trial was tested in the scenario analysis.[19] Other values from the trial SWITCH-2 remained as is.[2,4]

d) Population 4: Values from phase IIIa trial 3582 were used.

Table 28: Relative Risk of Hypoglycemia, Insulin Degludec Versus Insulin Glargine

	Source	Manufacturer's Base Case			CDR Plausible Case		
		Non-severe Daytime	Non-severe Nocturnal	Severe	Non-severe Daytime	Non-severe Nocturnal	Severe
Population 1: T1DM, basal + bolus	SWITCH-1 trial results	1	0.758	0.743	1	0.758	0.743
Population 2: T2DM, basal + OAD	Manufacturer's meta-analysis of phase IIIa trials	1	0.640	0.14	1	1	0.60
Population 3: T2DM, basal + OAD EX	SWITCH-2 trial results	0.798	0.758	0.49	0.798	0.758	0.49

	Source	Manufacturer's Base Case			CDR Plausible Case		
		Non-severe Daytime	Non-severe Nocturnal	Severe	Non-severe Daytime	Non-severe Nocturnal	Severe
Population 4: T2DM, basal + bolus	Manufacturer's meta-analysis of phase IIIa trials (based on one phase IIIa trial 3582)	0.830	0.750	1	0.830	0.750	1

CDR = CADTH Common Drug Review; EX = experienced; IDeg = insulin degludec; IGlar = insulin glargine; OAD = oral antidiabetes drug; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

Manufacturer's Sensitivity Analyses

Type 1 Diabetes Mellitus

In population 1 (T1DM, basal + bolus), the base-case result for IDeg versus IGlar is IDeg being the dominant strategy (less costly and more effective). This conclusion remained the same in the sensitivity analysis.

Type 2 Diabetes Mellitus

In population 2, (T2DM, basal + OAD), the ICUR in the base case was $5,564 per QALY. The following parameters changed the base-case result or increased or decreased the incremental cost per QALY gained by more than 25%:

- using UK or Hypoglycemia Assessment Tool hypoglycemia rates: IDeg dominates
- one basal self-measured plasma glucose (SMPG) test per week for IDeg: IDeg dominates
- two needles for 1Glar: IDeg dominates
- cost of severe hypoglycemic events −20%: $8,360 per QALY
- dosing flexibility utility: $1,224 per QALY.

In population 3 (T2DM, basal + OAD-experienced), the ICUR in the base case was $20,887 per QALY. The following parameters changed the base-case result or increased or decreased the incremental cost per QALY gained by more than 25%:

- using Hypoglycemia Assessment Tool hypoglycemia rates: IDeg dominates
- one basal SMPG test per week for IDeg: IDeg dominates
- two needles for 1Glar: $442 per QALY
- QALY decrements for hypoglycemic events: $12,542 per QALY
- dosing flexibility utility: $6,897 per QALY.

In population 4 (T2DM, basal + bolus), the ICUR in the base case was $95,155 per QALY. The following parameters changed the base-case result or increased or decreased the incremental cost per QALY gained by more than 25%:

- using UK hypoglycemia rates: $292,644 per QALY
- using Hypoglycemia Assessment Tool hypoglycemia rates: $376,736 per QALY
- one basal SMPG test per week for IDeg: $36,030 per QALY

- two needles for 1Glar: $67,597 per QALY
- QALY decrements for hypoglycemic events: $12,656 per QALY
- dosing flexibility utility: $24,513 per QALY.

CADTH Common Drug Review Reanalyses (Insulin Degludec Versus Neutral Protamine Hagedorn)

The manufacturer's pharmacoeconomic submission included a secondary cost-effectiveness analysis that compared IDeg with NPH insulin to align with the CADTH recommendation of NPH as the cost-effective third-line therapy in patients with T2DM.[12] However, since the manufacturer had noted the low utilization of NPH as a long-acting insulin in Canada and the potential severe consequences of nocturnal hypoglycemia, especially in T1DM patients, as reasons to include NPH insulin as a secondary analysis, no additional sensitivity analyses were conducted by the manufacturer for this treatment option.[2] CDR conducted sensitivity analyses on the secondary analysis of NPH as follows:

1. Baseline risk of hypoglycemia: The SWITCH-1 and SWITCH-2 trials enrolled patients who may be at greater risk of hypoglycemia than the population indicated for the reimbursement status. Ten per cent to 25% reductions in the baseline hypoglycemia rates were tested in the sensitivity analysis (in populations where the relative risk was not equal to 1). In addition, alternate values from the CADTH 2013 report on severe hypoglycemia (0.0053) for T2DM were evaluated.
2. Relative insulin dosage to align with more plausible values: According to the CDR clinical expert, dose ratios of 1.2 or 1 for IDeg versus NPH are more likely values; these are used in the sensitivity analysis.
3. Alternate estimates of utility decrements for hypoglycemic events: Values from the CADTH 2013 report (0.000004767 mild and 0.01 severe) were used, as well as those from National Institute for Health and Clinical Excellence (NICE) guidance (0.0052 mild and 0.01 severe) in the sensitivity analysis.
4. SMPG frequency and costs: The same SMPG test frequency was assumed for both comparators in patient populations 2 and 3; no evidence was provided that SMPG frequency differs, and equal use was recommended as appropriate by the CDR clinical expert.
5. Plausible CDR base case: The CDR base case assumes a relative dose of 1.2 and the same SMPG tests for populations 2 and 4.
6. Scenario analysis: Since indirect comparisons were used in the model (IDeg versus IGlar and NPH versus IGlar), the manufacturer's meta-analysis informed efficacy values for both comparisons. Due to the limitations previously identified for IDeg versus IGlar, the relative risks for hypoglycemic events for IDeg versus IGlar were changed to CDR base-case values.

Table 29: CDR Reanalysis, IDeg Versus NPH — Population 1 (T1DM, Basal + Bolus)

	Description	IDeg Versus NPH		
		Incremental Cost ($)	Incremental QALYs	ICUR ($/QALY)
	Manufacturer base case	−432	0.0224	Dominant
1	**Baseline hypoglycemia events**			
	Severe events −25%	−287	0.0186	Dominant
	Severe events −50%	−143	0.0148	Dominant
2	**Dose ratio: insulin dosage**			
2a	1.2	−306	0.0224	Dominant
2b	1	−191	0.0224	Dominant
3	**Utility decrements for hypoglycemic events**			
3a	0.000004767 mild and 0.01 severe	−432	0.0027	Dominant
3b	0.0052 mild and 0.01 severe	−432	0.0151	Dominant
4	**Same SMPG costs (NA for bolus)**			
5	**Plausible base case (2a)**	−306	0.0224	Dominant
5a	**Scenario analysis of CDR base case (RR severe hypo = 1 for IDeg versus IGlar)**	272	0.0072	37,952

CDR = CADTH Common Drug Review; hypo = hypoglycemic event; ICUR = incremental cost-utility ratio; IDeg = insulin degludec; IGlar = insulin glargine; NA = not available; NPH = neutral protamine Hagedorn; QALY = quality-adjusted life-year; RR = relative risk; SMPG = self-measured plasma glucose; T1DM = type 1 diabetes mellitus.

Note: Dominant means IDeg is more effective and less costly.

Table 30: CDR Reanalysis, IDeg Versus NPH — Population 2 (T2DM, Basal + OAD)

	Description	IDeg Versus NPH		
		Incremental Cost ($)	Incremental QALYs	ICUR ($/QALY)
	Manufacturer base case	−15	0.0103	Dominant
1	**Baseline hypoglycemia events**			
	Severe events −25%	−107	0.0098	Dominant
	Severe events −50%	−88	0.0093	Dominant
	CADTH rates 0.0053	−76	0.0090	Dominant
2	**Dose ratio: insulin dosage**			
2a	1.2	34	0.0103	3,303
2b	1	180	0.0103	17,393
3	**Utility decrements for hypoglycemic events**			
3a	0.000004767 mild and 0.01 severe	−15	0.0004	Dominant
3b	0.0052 mild and 0.01 severe	−15	0.0058	Dominant
4	**Same SMPG costs**	216	0.0103	20,875
5	**Plausible base case (2a, 4)**	**266**	**0.0103**	**25,677**
5a	**Scenario analyses (RR hypoglycemic events and dose ratio from CDR plausible case IDeg versus IGlar)**	549	0.0075	72,848

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; IDeg = insulin degludec; IGlar = insulin glargine; NPH = neutral protamine Hagedorn; OAD = oral antidiabetes drug; QALY = quality-adjusted life-year; RR = relative risk; SMPG = self-measured plasma glucose; T2DM = type 2 diabetes mellitus.
Note: Dominant = IDeg more effective and less costly.

Table 31: CDR Reanalysis, IDeg Versus NPH — Population 3 (T2DM, Basal + OAD-Experienced)

	Description	IDeg Versus NPH		
		Incremental Cost ($)	Incremental QALYs	ICUR ($/QALY)
	Manufacturer base case	160	0.0173	9,256
1	**Baseline hypoglycemia events**			
	Severe events −25%	231	0.0155	14,916
	Severe events −50%	301	0.0136	22,083
	CADTH rates 0.0053	426	0.0103	41,211
2	**Dose ratio: insulin dosage**			
2a	1.2	417	0.0173	24,064
2b	1	650	0.0173	37,521
3	**Utility decrements for hypoglycemic events**			
3a	0.000004767 mild and 0.01 severe	160	0.0013	121,401
3b	0.0052 mild and 0.01 severe	160	0.0110	14,585
4	**Same SMPG costs**	392	0.0173	22,623
5	**Plausible base case (2a, 4)**	648	0.0173	37,431
5a	**Scenario analyses (RR hypoglycemic events and dose ratio from CDR plausible case IDeg versus IGlar)**	671	0.0167	40,059

CDR = CADTH Common Drug Review; EX = experienced; ICUR = incremental cost-utility ratio; IDeg = insulin degludec; IGlar = insulin glargine; NPH = neutral protamine Hagedorn; OAD = oral antidiabetes drug; QALY = quality-adjusted life-year; RR = relative risk; SMPG = self-measured plasma glucose; T2DM = type 2 diabetes mellitus.

Table 32: CDR Reanalysis, IDeg Versus NPH — Population 4 (T2DM, Basal + Bolus)

	Description	IDeg Versus NPH		
		Incremental Cost ($)	Incremental QALYs	ICUR ($/QALY)
	Manufacturer base case	727	0.0044	164,361
1	**Baseline hypoglycemia events (NA as RR severe = 1)**	**NA**		
2	**Dose ratio: insulin dosage**			
2a	1.2	933	0.0044	211,080
2b	1	1,121	0.0044	253,557
3	**Utility decrements for hypoglycemic events**			
3a	0.000004767 mild and 0.01 severe	727	0	62,093,753
3b	0.0052 mild and 0.01 severe	727	0.0128	56,923
4	**Same SMPG costs (NA for bolus)**	**NA**		
5	**Plausible base case (2a)**	933	0.0044	211,080

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; IDeg = insulin degludec; IGlar = insulin glargine; NA = not applicable; NPH = neutral protamine Hagedorn; QALY = quality-adjusted life-year; RR = relative risk; SMPG = self-measured plasma glucose; T2DM = type 2 diabetes mellitus.

References

1. Tresiba (insulin degludec): TRESIBA® Penfill® 100 U/mL, Solution for injection in a cartridge; TRESIBA® FlexTouch® 100 U/mL, Solution for injection in a pre-filled pen; TRESIBA® FlexTouch® 200 U/mL, Solution for injection in a pre-filled pen [product monograph]. Mississauga (ON): Novo Nordisk; 2016 Sep 1.
2. Cost-effectiveness analysis of insulin degludec for the treatment of adults with diabetes mellitus to improve glycemic control. In: CDR submission: Tresiba (insulin degludec). Company: Novo Nordisk. [**CONFIDENTIAL** manufacturer's submission]. Mississauga (ON): Novo Nordisk; 2017 May 17.
3. Lane W, Bailey TS, Gerety G, Gumprecht J, Philis-Tsimikas A, Hansen CT, et al. Effect of Insulin Degludec vs Insulin Glargine U100 on Hypoglycemia in Patients With Type 1 Diabetes: The SWITCH 1 Randomized Clinical Trial. JAMA. 2017 Jul 4;318(1):33-44.
4. Wysham C, Bhargava A, Chaykin L, de la RR, Handelsman Y, Troelsen LN, et al. Effect of Insulin Degludec vs Insulin Glargine U100 on Hypoglycemia in Patients With Type 2 Diabetes: The SWITCH 2 Randomized Clinical Trial. JAMA. 2017 Jul 4;318(1):45-56.
5. Allen F. Network meta-analysis of degludec, glargine and NPH. Bicester (GB): Abacus International; 2012 Oct 15.
6. Optimal therapy recommendations for the prescribing and use of insulin analogues [Internet]. Ottawa: CADTH; 2009 May. (CADTH optimal therapy report; vol.2, no. 7). [cited 2017 Aug 30]. Available from: https://www.cadth.ca/sites/default/files/pdf/compus_IA_OT_rec_report.pdf
7. Economic evaluation: third-line therapy for patients with type 2 diabetes inadequately controlled with metformin and sulfonylurea combination therapy [Internet]. Ottawa: CADTH; 2010 Aug. [cited 2017 Aug 25]. (CADTH Therapeutic review). Available from: https://www.cadth.ca/sites/default/files/pdf/Diabetes_TR_Economic_Evaluation_Final_e.pdf
8. New drugs for type 2 diabetes: second-line therapy - science report [forthcoming]. Ottawa: CADTH; 2017. (CADTH therapeutic review; vol.4, no. 1b).
9. Aronson R, Goldenberg R, Boras D, Skovgaard R, Bajaj H. The Canadian Hypoglycemia Assessment Tool Program: Insights Into Rates and Implications of Hypoglycemia From an Observational Study. Can J Diabetes. 2017 May 17.
10. UK Hypoglycaemia Study Group. Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. Diabetologia. 2007 Jun;50(6):1140-7.
11. Cost effectiveness of insulin degludec (Tresiba) for the treatment of diabetes mellitus in adults, adolescents and children aged grater than one year [Internet]. Dublin: National Centre for Pharmacoeconomics; 2015 May 4. [cited 2017 Aug 28]. Available from: http://www.ncpe.ie/wp-content/uploads/2015/05/Summary.pdf
12. Optimal use recommendations for second and third-line therapy for patients with type 2 diabetes [Internet]. Ottawa: CADTH; 2013 Jul. [cited 2017 Aug 25]. (Optimal use report; vol.3, issue 1D). Available from: https://www.cadth.ca/media/pdf/OP0512_Diabetes_RecsReport_2nd_3rd-line_e.pdf
13. Dawoud D, O'Mahony R, Wonderling D, Cobb J, Higgins B, Amiel SA. Basal insulin regimens for adults with type 1 diabetes mellitus: a systematic review and network meta-analysis. Value Health. 2017.
14. Cost-effectiveness of blood glucose test strips in the management of adult patients with diabetes mellitus [Internet]. Ottawa: CADTH; 2009 May. [cited 2017 Aug 25]. (Optimal therapy report; vol.3, issue 3). Available from: https://www.cadth.ca/sites/default/files/pdf/BGTS_Consolidated_Economic_Report.pdf
15. Ontario drug benefit formulary / comparative drug index [Internet]. Version 2.4. Toronto: Ministry of Health and Long-Term Care; 2016 Apr 10. [cited 2017 Jan 19]. Available from: https://www.formulary.health.gov.on.ca/formulary/
16. IMS DeltaPA®. Kanata (ON): QuintilesIMS; 2017.
17. Evans M, Khunti K, Mamdani M, Galbo-Jorgensen CB, Gundgaard J, Bogelund M, et al. Health-related quality of life associated with daytime and nocturnal hypoglycaemic events: a time trade-off survey in five countries. Health Qual Life Outcomes. 2013 Jun 3;11:90. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3679729
18. Lauridsen JT, Lonborg J, Gundgaard J, Jensen HH. Diminishing marginal disutility of hypoglycaemic events: results from a time trade-off survey in five countries. Qual Life Res. 2014 Nov;23(9):2645-50.
19. Marso SP, McGuire DK, Zinman B, Poulter NR, Emerson SS, Pieber TR, et al. Efficacy and Safety of Degludec versus Glargine in Type 2 Diabetes. N Engl J Med [Internet]. 2017 Jun 12 [cited 2017 Jul 12]. Available from: http://www.nejm.org/doi/pdf/10.1056/NEJMoa1615692