CADTH

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

Insulin Icodec (Awiqli)

Indication: the once-weekly treatment of adults with diabetes mellitus to improve glycemic control

Sponsor: Novo Nordisk Canada Inc.

Recommendation: Reimburse with Conditions

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Single Technology

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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.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that insulin icodec be reimbursed for the once weekly treatment of adults with type 2 diabetes (T2D) to improve glycemic control only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Five randomized controlled trials (RCTs) (ONWARDS 1 [n = 984], ONWARDS 2 [n = 582], ONWARDS 3 [n = 526], ONWARDS 4 [n = 1,085], and ONWARDS 5 [n = 588]) demonstrated that in patients with T2D who were insulin-naïve or insulin-experienced, treatment with once-weekly insulin icodec was non-inferior in the outcome of change in glycated hemoglobin (A1C) from baseline compared to daily basal insulins (insulin glargine or insulin degludec) at week 26 or week 52 of treatment. Secondary analyses of superiority showed that insulin icodec was statistically superior compared with once-daily insulin analogues evaluated for this outcome, but the magnitude of the difference was not likely to be clinically important. Treatment with insulin icodec resulted in similar clinical benefit in the secondary outcomes, such as time spent in glycemic range and change in body weight, compared to daily basal insulins.

Patients indicated that there is a need for new treatments that reduce hyperglycemia events, provide better weight and A1C control, improve blood flow improvement to extremities, have fewer side effects, and improve health-related quality of life (HRQoL). CDEC concluded that insulin icodec may meet these needs in a similar manner to existing insulin analogue therapies for glycemic control in T2D.

Using the sponsor submitted price for insulin icodec and publicly listed price for all other long-acting basal insulin comparators, insulin icodec was more costly than the lowest cost comparator. Insufficient evidence was provided to demonstrate improved treatment efficacy with insulin Icodec versus other long-acting basal insulin analogues. To ensure cost-effectiveness, the total drug cost of insulin icodec should not exceed the total drug cost of the least costly long-acting basal insulin analogue.

Table 1. Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Adult patients with T2D whose A1C is between 7.0% and 11.0% inclusive	All patients in the ONWARDS trials had to have A1C from 7.0 to 11.0% confirmed by central laboratory analysis	Based on clinical expert input, therapy with basal insulin is typically initiated in patients who are not meeting glycemic targets (A1C ≤ 7.0%) despite lifestyle modification and the use of, or contraindication to metformin and/or other non-insulin antihyperglycemic medications (e.g., GLP1 RAs, SGLT2is). Insulin icodec may be used in conjunction with bolus insulin or other non-insulin pharmacotherapeutic interventions.
Pricing		
2. Insulin icodec should be negotiated so that it does not exceed the drug program cost of treatment with the least costly long-acting basal insulin reimbursed for the treatment of patients with T2D who require insulin for glycemic control.	Insufficient evidence was provided to demonstrate improved treatment efficacy with insulin Icodec versus other long-acting basal insulin analogues. As such, there is insufficient evidence to justify a cost premium for insulin icodec over the least costly long-acting basal insulin analogue reimbursed for the treatment of patients with T2D who require insulin for glycemic control.	—
Feasibility of adoption		
3. The feasibility of adoption of insulin icodec must be addressed	At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate and CADTH's estimate.	—

A1C = glycated hemoglobin; GLP1 RAs = glucagon-like peptide 1 receptor agonists; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; SGLT-2is = odium-glucose cotransporter 2 inhibitors; T2D = type 2 diabetes; U = unit.

Discussion Points

- The Health Canada indication supports the use of insulin icodec in the once-weekly treatment of adults with diabetes mellitus to improve glycemic control regardless of diabetes type. This recommendation only applies for the use of insulin icodec for the once weekly treatment of adults with type 2 diabetes to improve glycemic control. The clinical expert noted to CDEC that insulin icodec fits within the existing treatment paradigm currently occupied by daily basal insulins such as insulin degludec and insulin glargine.
- GRADE assessment of the primary outcome of the ONWARDS trials concluded that insulin icodec was non-inferior in change from baseline in glycated hemoglobin at week 26 or week 52, with moderate certainty in the insulin-naïve population and high certainty in the insulin-experienced population. Secondary analyses of superiority suggested that, statistically, there may be a benefit associated with insulin icodec over the once daily comparators for this outcome, but the clinical meaningfulness of this result is uncertain. The clinical expert consulted by CADTH indicated that the magnitude of difference in A1C between the treatment arms was unlikely to be clinically significant, given the reduction of 0.19 to 0.38% in insulin naïve patients and 0.02 to 0.22% in insulin experienced patients when comparing insulin icodec to daily basal insulins. Additionally, GRADE assessment of the secondary outcomes in the ONWARDS studies concluded with moderate to high levels of certainty that insulin icodec results in

little to no difference in the time spent in glycemic range of 3.9 to 10.0 mmol/L, below 3.0 mmol/L, and above 10.0 mmol/L.

- CDEC discussed that the ONWARDS trials did not include any comprehensive measures of HRQoL, hence there is a lack of evidence to support the hypothesis that weekly injections would improve HRQoL compared to daily injections. The outcomes related to HRQoL evaluated in the ONWARDS trials included treatment satisfaction (using the Diabetes Treatment Satisfaction Questionnaire [DTSQ]), for which there was little to no difference between treatment groups, and treatment compliance (using the Treatment Related Impact Measure for Diabetes [TRIM-D] compliance domain), which was increased among patients receiving insulin icodec compared to daily basal insulins, but the clinical importance of the increase was uncertain.
- The clinical expert noted to CDEC that the patients most likely to use insulin icodec in place of daily basal insulins are patients newly beginning basal insulin therapy due to the perceived advantages of a lower administration frequency. Insulin icodec may also be used by patients who are unable or unwilling to take daily injections.
- CDEC noted there is an absence of evidence for insulin icodec compared to daily basal insulins in the outcomes of cardiovascular mortality, other diabetes-related long-term micro- or macro-vascular complications, and long-term all-cause mortality beyond 1 year.
- CDEC discussed that although the proportion of patients with hypoglycemic events was similar across treatment arms in the insulin-naïve populations and results were inconclusive in the insulin-experienced populations, there were more level 2 hypoglycemic events among patients treated with insulin icodec than comparators in 4 of the 5 trials, although a few patients accounted for many events in ONWARDS 1 and 3.
- CDEC discussed that the Sponsor's submitted NMA had various limitations which precluded CADTH from being able to draw conclusions regarding the long-term comparative efficacy and safety of insulin icodec relative to long-acting basal insulin analogues. This uncertainty is propagated into the submitted economic model given that the mean reductions in change from baseline in HbA1c and the annual event rate of severe hypoglycemia were used to generate transition probabilities extrapolating disease progression across the 40-year lifetime horizon.
- The committee discussed the potential impact of insulin icodec weekly dosing compared to daily dosing with regards to cost-effectiveness. Due to inadequate evidence, the magnitude of this impact remains uncertain, resulting in considerable uncertainty regarding the cost-effectiveness of once-weekly injections.
- The committee noted concerns regarding the anticipated budget impact associated with the reimbursement of insulin icodec. This may result in an unknown proportion of patients with T2D who are not currently on insulin for glycemic control to start once weekly insulin injections given the improved dosing convenience. While there is insufficient evidence to suggest that once-weekly dosing may improve patient HRQoL, some patients with T2D may express a preference for once weekly over once daily insulin injections.

Background

T2D is a chronic health condition that develops when the body is no longer able to use insulin efficiently or produce enough insulin to manage blood glucose levels within a normal range. This persistent hyperglycemia results in a constellation of symptoms and downstream impacts on the body. Diabetes Canada estimates that over 4 million Canadians, representing around 10% of the population, live with diabetes mellitus in 2023, and that this will increase to over 5 million (12%) by 2033. Approximately 90% of patients with diabetes specifically have T2D. The prevalence of T2D may be higher in racialized and minority groups such as Indigenous Peoples and South Asian or Black populations, compared to white populations. Indigenous Peoples are also at higher risk for diabetes-related complications.

The main goals of treatment for patients with T2D are to reduce the risk of long term complications through control of glycemia and blood pressure, and cardiovascular (CV) risk reduction through control of lipids and hypertension. Management of T2D is individualized and ideally combines lifestyle modifications (e.g., dietary modification, exercise, quitting smoking) with pharmacological interventions, most commonly beginning with metformin. If a patient is unable to lower or maintain their A1C or blood glucose levels with metformin treatment alone, additional therapies may be combined with continued metformin therapy, such as sulfonylureas, dipeptidyl peptidase 4 inhibitors (DPP4is), sodium-glucose cotransporter 2 inhibitors (SGLT2is), glucagon like peptide-1 receptor agonists (GLP1-RAs), and insulin.

According to Diabetes Canada treatment guidelines, insulin (in combination with metformin) should be initiated in the event of a patient in whom fasting glucose levels and/or A1C are not at target on current antihyperglycemic agents, or with

symptomatic hyperglycemia and/or metabolic decompensation. Basal insulin should be initiated and titrated to achieve fasting glucose targets, and metformin should be continued unless contraindicated. Other antihyperglycemic agents may also be used in combination with these therapies as needed, and therapy should be advanced if the patient's A1C is not at target within 3 to 6 months despite adequate titration of basal insulin and supports for lifestyle and other pharmacotherapeutic interventions. Basal insulins for treatment of T2D can include long-acting or intermediate-acting insulins. Currently available long-acting insulins include insulin degludec (U100 or U200), insulin glargine (U100 or U300), and insulin detemir, while insulin NPH is an intermediate-acting insulin. Insulin and its analogues work to lower blood glucose by stimulating peripheral glucose uptake and by inhibiting hepatic glucose production.

Insulin icodec has been approved by Health Canada for the once-weekly treatment of adults with diabetes mellitus to improve glycemic control. Insulin icodec is a long-acting insulin which is administered subcutaneously (SC) on a once-weekly basis, in contrast to the currently available once-daily long-acting basal insulins. Like other insulins, the dose of insulin icodec is individualized and titrated based on the patient's needs to achieve their glycemic control goal. The pre-filled FlexTouch pen delivers doses in 10 unit increments up to 700 units in a single injection. 1 mL of solution contains 700 units of insulin icodec (700 U/mL; equivalent to 26.8 mg insulin icodec). Insulin icodec should not be taken in combination with other long-acting insulins, but may be used in combination with rapid-acting insulins, short-acting insulins, and/or non-insulin antidiabetic therapies.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 3 RCTs in patients with T2D who are insulin-naïve, 2 RCTs in patients with T2D who are insulin-experienced, 1 long term extension (LTE) study, and 1 indirect treatment comparison (ITC)
- patients perspectives gathered by 1 patient group, Diabetes Canada
- input from public drug plans that participate in the CADTH review process
- 1 clinical specialist with expertise diagnosing and treating patients with T2D
- a review of the pharmacoeconomic model and report submitted by the sponsor

Stakeholder Perspectives

Patient Input

Patient input was submitted for this CADTH review by Diabetes Canada, which fielded a self-directed questionnaire to people living with T2D and their caregivers across Canada between October 3rd and 23rd, 2023, inquiring about respondents' lived experiences with diabetes and with several questions pertaining to insulin icodec. Of the 21 respondents, 13 identified as living with T2D and 1 identified as a caregiver, 93% (of 14 respondents for the question) were over 55 years old, 35% were 75-84 years of age and 71% reported living with T2D for over 10 years (of which 29% reported living with T2D for over 20 years).

Most respondents indicated that living with T2D was preoccupying, inconvenient, and burdensome, with constant management requiring foresight and planning. A total of 24% (out of 20 respondents) reported experiencing hyperglycemia more than once per day and 10% reported experiencing it more than once per week. A total of 43% (out of 20 respondents) indicated they did not experience hypoglycemia or experienced it in the past but not currently, while 14% experienced it more than once per week - none reported experiencing hypoglycemia daily.

All respondents (n = 19, 100% of whom answered this question) reported taking antihyperglycemic medication including long-, short-, and rapid-acting insulin, insulin icodec, and other non-insulin antihyperglycemic agents, either as single agent products or combined with metformin. A total of 5 of 18 (28%) respondents reported current insulin icodec use. A total of 61% (out of 18) respondents said they were very satisfied or satisfied with their medication; no respondents indicated dissatisfaction. Respondents indicated that ease of use, lack of side effects, and helping to lower A1C were aspects they liked about their medications.

When choosing a medication for diabetes management, several considerations were important to respondents including avoiding hypoglycemia and hyperglycemia, reducing the risk of heart problems, reducing high blood pressure, maintaining satisfactory blood sugar levels throughout the day, and avoiding yeast infections, urinary tract infections, fluid retention or weight gain. Affordability was also highlighted as an important consideration. Improvements that respondents wished to see in a new treatment that is not currently being achieved with available therapies included fewer side effects, blood flow improvement to extremities, weight control and better A1C results.

Clinician Input

Input From Clinical Expert Consulted by CADTH

The clinical expert consulted by CADTH indicated that treatment of T2D must be individualized, provided in a culturally appropriate manner, and equitably and affordably accessible across Canada. Treatment goals for patients with T2D include reducing symptoms of hyperglycemia, reducing risk of long-term complications through control of glycemia and blood pressure, and reducing CV risk through control of lipids and hypertension, through a combination of lifestyle modifications and pharmacotherapeutic approaches. The key unmet need highlighted by the clinical expert was a lack of widespread access to primary care and therefore lack of access to diabetes prevention, detection, and treatment. In particular, access to diabetes education and specialist care varies greatly across the country.

The clinical expert highlighted that insulin icodec would fit into the current paradigm for introduction of basal insulin in the management of T2D. This includes patients who are not meeting glycemic targets despite lifestyle modification, and use of or intolerance or contraindication to metformin, GLP-1 receptor agonists, and/or SGLT2 inhibitors. It may also be used as a first-line therapy in patients with T2D who present with symptomatic hyperglycemia and/or metabolic decompensation with or without metformin. The clinical expert noted that insulin icodec may be preferred over daily basal insulins by some patients who are unable or unwilling to take daily basal insulin, or who would prefer a lower burden related to administration frequency.

The clinical expert consulted by CADTH noted that the timing of assessments varies substantially between physicians and between patients, but ideally a patient would be supported through phone and e-mail to adjust dosing over the first 2 to 3 months, followed by an assessment of treatment suitability after 3 to 6 months of therapy. Diabetes management is complex and individualized. As such, there are several factors a monitoring physician or nurse practitioner will assess with regards to insulin icodec, including: treatment acceptance; treatment adherence; A1C target achievement; time in range with continuous glucose monitoring (CGM) of over 70%; time below range less than 4%; and no severe hypoglycemic episodes. A sign of positive response to insulin icodec would also be improved HRQoL, including but not limited to less diabetes distress and more treatment satisfaction. Factors influencing a decision to discontinue insulin icodec would include allergy, nonadherence, or diabetes remission or glycemic control improvement through weight loss or use of other antihyperglycemic agents or bariatric surgery. The clinical expert stated that diagnosis, prescribing of therapies, and management of treatment for patients with T2D may occur in primary care. The diagnosis of T2D and the use of insulin icodec were described by the clinical expert to be uncomplicated and do not necessarily require specialist care. Additionally, there are limitations to access of specialist care due to the low number of endocrinologists in Canada and the high number of patients with T2D.

Clinician Group Input

No clinician group feedback was received by the deadline of the call for input.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a CADTH recommendation for insulin icodec:

- considerations for initiation of therapy
- considerations for prescribing of therapy
- care provision issues
- system and economic issues

The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Table 2. Responses to Questions from the Drug Programs

Implementation Issues	Advice from CADTH
Considerations for initiation of therapy	
Is insulin icodec appropriate for all T2D patients regardless of any previous medications tried or currently on? Studies included both insulin naïve and previous insulin users as well as concurrent non-insulin antihyperglycemic agents.	The clinical expert noted to CDEC that insulin icodec would fall within the existing treatment paradigm for the introduction of basal insulins, which includes patients who are both insulin-naïve or insulin-experienced, and patients who may or may not be on non-insulin antihyperglycemic agents such as metformin or others.
Considerations for prescribing of therapy	
For patients with well-controlled blood glucose levels who need to switch back to one-or twice-daily basal insulin from insulin icodec, could the weekly dose be divided by 7 to determine the daily basal insulin dose?	The clinical expert confirmed to CDEC that this is an appropriate way to estimate the dose.
For patients who require multiple daily injections of rapid-acting insulin or regular insulin, will changing basal insulin from one-daily to once-weekly result in significant improvements in adherence or quality of life for most patients?	The clinical expert indicated to CDEC that the response to this is only speculative due to a lack of robust evidence, but hypothetically a change from once-daily to once-weekly injections would not be likely to cause a substantial improvement in adherence or quality of life for most patients.
Any issues with combining this with short-acting insulins or non-insulin antihyperglycemic agents for diabetes? Various medications were used in the study populations.	There were no issues flagged by the clinical expert with regards to combining insulin icodec with short-acting insulins or non-insulin antihyperglycemic agents for diabetes.
Care provision issues	
How difficult will it be to treat a patient who intentionally or accidentally overdoses on insulin icodec? What might this management look like?	The clinical expert referred to an article by Pieber et al., (2023)[a] which tested intentional overdoses of insulin icodec and stated: "*double or triple doses of once-weekly icodec lead to a similar risk of hypoglycaemia compared with double or triple doses of once-daily glargine U100. During hypoglycaemia, comparable symptomatic and moderately greater endocrine responses are elicited by icodec vs glargine U100*." The clinical expert also noted to CDEC that management of overdose on insulin icodec is done in the same was as overdose on once-daily long-acting insulin.
System and economic issues	
Do you think there will there be a large number of patients who want to switch from a daily insulin to icodec for the dosing convenience?	The clinical expert discussed with CDEC that most of the market would likely be patients who are newly starting basal insulin and who are potentially reluctant to begin daily injections. Patients already stable on a daily regimen would be less likely to switch in the opinion of the expert.

T2D = type 2 diabetes.

[a] Pieber TR, Arfelt KN, Cailleteau R, et al. Hypoglycaemia frequency and physiological response after double or triple doses of once-weekly insulin icodec vs once-daily insulin glargine U100 in type 2 diabetes: a randomised crossover trial. Diabetologia. 2023;66(8):1413-1430.

Clinical Evidence

Systematic Review

Description of Studies

Five active-controlled, multi-centre RCTs were included in this review, all of which compared insulin icodec once weekly to once-daily basal insulins (insulin degludec and/or insulin glargine). Three of the included studies enrolled adult patients with T2D who were insulin-naïve (ONWARDS 1, 3, and 5); of these, ONWARDS 1 was 52 weeks in duration, while 3 and 5 were 26 weeks in duration. ONWARDS 5 additionally included the DoseGuide App to inform dosing choices in the insulin icodec arm. The remaining two included studies enrolled adult patients with T2D who were insulin-experienced. In ONWARDS 2, patients were experienced with basal insulin, and in ONWARDS 4, patients were experienced with basal + bolus insulin. Both of these studies were 26 weeks in duration. ONWARDS 4 additionally included insulin aspart (bolus) administered 2 to 4 times per day before mealtimes. In all 5 studies, the primary outcome was an assessment of non-inferiority of insulin icodec once-weekly compared to the once-daily comparator for the outcome of change in A1C from baseline. In all but ONWARDS 4, a secondary confirmatory analysis of superiority was also conducted for this outcome. Secondary outcomes varied between the studies and included percent time in range (3.9 to 10.0 mmol/L blood glucose [BG] using CGM), time below range (<3 mmol/L BG using CGM), and time above range (>10.0 mmol/L BG using CGM) in ONWARDS 1, 2, and 4, change in body weight in all included studies, the number of clinically significant (level 2; < 3.0 mmol/L confirmed by BG meter) or severe hypoglycemic episodes (level 3; any hypoglycemic event requiring active assistance of another person, for instance to administer corrective actions or receive medical care) in all studies, change in treatment satisfaction (measured via Diabetes Treatment Satisfaction Questionnaire [DTSQ] in which higher scores [ranging from 0 to 36] represent higher satisfaction with diabetes treatment) in ONWARDS 5 and ONWARDS 2 (exploratory), and treatment compliance (measured via the Treatment Related Impact Measure for Diabetes (TRIM-D) compliance domain, in which higher scores [ranging from 4 to 20] represent higher compliance with treatment) in ONWARDS 5. All-cause mortality was a safety outcome in all trials. Additional outcomes of interest that were not reported include the long-term efficacy regarding cardiovascular death, non-fatal myocardial infarction (MI), non-fatal stroke, and other micro- or macro-vascular complications of T2D.

At baseline, patients in the ONWARDS study treatment arm had mean ages ranging from 58 to 62 years, and 53% to 63% were male. Across all studies, the majority of patients were white (60% to 90%) followed by Asian (4% to 42%), Black or African American (2% to 5%), Other (<1% to 4%), American Indian or Alaska Native (0 to <1%), and Native Hawaiian or Other Pacific Islander (0 to <1%). In the insulin-naive populations of ONWARDS 1, 3, and 5, the mean duration of diabetes was 11 to 12 years and the mean A1C was 8.44% to 8.88% at baseline. In the insulin-experienced populations of ONWARDS 2 and 4, the mean duration of diabetes was [redacted] years, and the mean A1C was 8.17% to 8.31% at baseline. Approximately 90% of patients were receiving metformin at baseline, and other common (>15%) antidiabetic background medications included sulfonylureas, SGLT2is, DPP-4i, and GLP-1 RA. Uncommon antidiabetic background medications included thiazolidinediones, alpha-glucosidase inhibitor, and glinides. In ONWARDS 2 and 4, insulin glargine U100 (approximately 41% to 50%) followed by insulin degludec (approximately 23% to 29%) were the most common basal insulins in use at screening; most patients in ONWARDS 4 were receiving basal insulin once daily (OD) and bolus insulin three times daily (TID) (approximately 75%).

Efficacy Results

Change in A1C from Baseline

In the primary analyses for non-inferiority among insulin-naïve patients (ONWARDS 1 , ONWARDS 3, and ONWARDS 5), the between-group differences in mean change from baseline in A1C were –0.19%-points (95% confidence interval [CI], –0.36 to –0.03; P <0.0001) in ONWARDS 1 at 52 weeks, –0.21%-points (95% CI, –0.34 to –0.08; P <0.0001) in ONWARDS 3 at 26 weeks, and –0.38 (95% CI, –0.66 to –0.09; P < 0.0001) in ONWARDS 5 at 52 weeks, indicating that insulin icodec once-weekly is non-inferior to the once-daily comparator for the outcome of change in A1C from baseline in insulin-naïve patients. In the secondary analyses for superiority, the P values were 0.0210, 0.0016, and 0.0092, respectively, indicating that insulin icodec once-weekly is superior to the once-daily comparator for the outcome of change in A1C from baseline in insulin-naïve patients.

In the primary analyses for non-inferiority among insulin-experienced patients (ONWARDS 2 and ONWARDS 4, the between-group differences in mean change from baseline in A1C was –0.22%-points (95% CI, –0.37 to –0.08; P <0.0001) in ONWARDS 2 and 0.02%-points (95% CI, –0.11 to 0.15; P <0.0001) for ONWARDS 4 , indicating that insulin icodec once-weekly is non-inferior to the once-daily comparator for the outcome of change in A1C from baseline in insulin-experienced patients. In ONWARDS 2, a secondary analysis for superiority was also conducted (P = 0.0028), indicating that insulin icodec once-weekly is non-inferior to the once-daily Insulin glargine for the outcome of change in A1C from baseline in insulin-experienced patients. No superiority analysis was conducted in ONWARDS 4.

For each of ONWARDS 1, 3, 5, 2, and 4, a two-dimensional tipping point sensitivity analysis was performed to evaluate the robustness of the assumptions regarding missing data; the results were consistent with the primary analysis for non-inferiority of A1C.

Time in Range (3.9 to 10.0 mmol/L)

In ONWARDS 1 from Week 48 to Week 52, the least squares (LS) mean time in glycemic range was 71.27% (standard error [redacted]) for insulin icodec and 67.00% ([redacted] for insulin glargine, representing an estimated treatment difference of 4.27%-points (95% CI, 1.92 to 6.62; P = 0.0004). A two-dimensional tipping point sensitivity analysis was conducted, which aligned with the primary analysis for time in range. This outcome was not assessed in ONWARDS 3 or 5.

In ONWARDS 2 from Week 22 to Week 26, the LS mean time in glycemic range between 3.9 and 10.0 mmol/L was 62.34% [redacted] for the insulin icodec group and 59.93% ([redacted] for the insulin degludec group. The estimated treatment difference between insulin icodec and insulin degludec was 2.41% (95% CI, –0.84 to 5.56; P = 0.1461). In ONWARDS 4 from Week 22 to Week 26, the LS mean time in glycemic range between 3.9 and 10.0 mmol/L was 66.75% ([redacted]) for the insulin icodec group and 66.46% ([redacted] for the insulin glargine group. The estimated treatment difference between insulin icodec and insulin glargine was 0.29% (95% CI, –2.52 to 3.09; P = 0.8406).

Time Spent <3.0 mmol/L

In ONWARDS 1 from Week 48 to Week 52, the LS mean time in glycemic range below 3 mmol/L was [redacted] ([redacted]) for insulin icodec and [redacted] for insulin glargine ([redacted]), representing an estimated treatment ratio (insulin icodec / insulin glargine) of [redacted] (95% CI, [redacted]; P = [redacted]). This outcome was not assessed in ONWARDS 3 or 5.

In ONWARDS 2 from Week 22 to Week 26, the LS mean time in glycemic range below 3.0 mmol/L was 0.33% in the insulin icodec group and 0.24% in the insulin degludec group. The estimated treatment ratio of insulin icodec and insulin degludec was 1.37 (95% CI, 0.92 to 2.04; P = 0.1180). In ONWARDS 4 from Week 22 to Week 26, the LS mean time in glycemic range below 3.0 mmol/L was 0.69% in the insulin icodec group and 0.58% in the insulin glargine group. The estimated treatment ratio of insulin icodec and insulin glargine was 1.20 (95% CI, 0.91 to 1.58; P = 0.2050).

Time Spent >10.0 mmol/L

In ONWARDS 1 from Week 48 to Week 52, the LS mean time in glycemic range above 10 mmol/L was [redacted] for insulin icodec and [redacted] for insulin glargine, representing an estimated treatment difference of [redacted] (95% CI, [redacted]; P = [redacted]). This outcome was not assessed in ONWARDS 3 or 5.

In ONWARDS 2 from Week 22 to Week 26, the LS mean time in glycemic range above 10 mmol/L was 36.34.52% ([redacted]) for insulin icodec and 39.28% ([redacted]) for insulin degludec, representing an estimated treatment difference of –2.93% (95% CI, –6.25 to 0.39; P = 0.0833). In ONWARDS 4 from Week 22 to Week 26, the LS mean time in glycemic range above 10 mmol/L was 30.64% for insulin icodec ([redacted] and 31.24% ([redacted]) for insulin glargine, representing an estimated treatment difference of –0.60% (95% CI, –3.47 to 2.28; P = 0.6826).

Change in Body Weight

In ONWARDS 1 (at 52 weeks), 3 (at 26 weeks), and 5 (at 52 weeks), the between group differences in change in body weight from baseline were 0.46 kg (95% CI, –0.12 to 1.04[redacted] 0.46 kg (95% CI, –0.19 to 1.10; P [redacted] and 0.83 kg (95% CI, –0.37 to 2.02; P = 0.1747), respectively.

In ONWARDS 2 (at 26 weeks) and 4 (at 26 weeks), the between group differences in change in body weight from baseline were 1.70 kg (95% CI, 0.76 to 2.63; [redacted] and 0.57 kg (95% CI, –0.39 to 1.54[redacted] respectively.

Number of Clinically Significant Hypoglycemic Episodes (Level 2) (<3.0 mmol/L [54 mg/dL] Confirmed by BG Meter) or Severe Hypoglycemic Episodes (Level 3)

In ONWARDS 1, a similar number of patients experienced level 2 hypoglycemic events in the two groups, but there were numerically more level 2 events in the insulin icodec group. There were 143 events in 48 patients (9.8%) in the insulin icodec group and 75 events occurring in 49 patients (10.0%) in the insulin glargine group. In the insulin icodec group, 3 of the 492 patients (0.6%) experienced 61 of the 143 clinically significant hypoglycemic events. The remaining patients in the insulin icodec group and all of the patients in the insulin glargine groups experienced between 1 and 5 episodes of level 2 hypoglycemic events. The estimated treatment ratio for level 2 events (insulin icodec/insulin glargine) was 1.67 (95% CI, 0.99 to 2.84; = 0.0561). Severe (level 3) hypoglycemic events occurred in one patient (0.2%) in the insulin icodec group, and 3 patients (0.6%) in the insulin glargine group.

In ONWARDS 3, there were 53 clinically significant events of hypoglycemia (level 2) reported in 26 patients (8.9%) in the insulin icodec group, and 23 events occurring in 17 patients (22.1%) in the insulin degludec group. In the insulin icodec group, 2 patients (0.7%) experienced 15 of the 53 clinically significant hypoglycemic events. The remaining patients in the insulin icodec group experienced between 1 and 4 episodes of level 2 hypoglycemic events. Patients in the insulin degludec group experienced between 1 and 3 episodes of level 2 hypoglycemic events. The estimated treatment ratio for level 2 events (insulin icodec/insulin degludec) was 2.09 (95% CI, 0.99 to 4.41; *P* = 0.0536). Severe hypoglycemic events occurred in zero patients in the insulin icodec group, and 2 patients (0.7%) in the insulin degludec group.

In ONWARDS 5, there were 104 clinically significant (level 2) hypoglycemic events that were reported in 64 patients (11.8%) in the insulin icodec group, and 81 events occurring in 45 patients (8.4%) in the OD analogues group[redacted]In ONWARDS 2, there were 113 clinically significant events of hypoglycemia (level 2) reported in 37 patients (14.1%) in the insulin icodec group, and 41 events occurring in 19 patients (7.2%) in the insulin degludec group. The estimated treatment ratio for level 2 events (insulin icodec/insulin degludec) was 1.98 (95% CI, 0.95 to 4.12; *P* = 0.067). Severe hypoglycemic events occurred in zero patients in the insulin icodec group, and 1 patient (0.4%) in the insulin degludec group.

In ONWARDS 4, clinically significant events of hypoglycemia (level 2) were reported in 148 patients (50.9%) in the insulin icodec group, and 160 patients (55.0%) in the insulin glargine group. The estimated treatment ratio for level 2 events (insulin icodec/insulin glargine) was 0.99 (95% CI, 0.73 to 1.34; *P* = 0.93). Severe (level 3) hypoglycemic events occurred in 4 patients (1.4%) in the insulin icodec group, and 2 patients (0.7%) in the insulin glargine group.

Diabetes Treatment Satisfaction Questionnaire (DTSQ)

This outcome was assessed only in ONWARDS 5 and ONWARDS 2.

In ONWARDS 5, the observed mean DTSQ total score at baseline was [redacted] in the insulin icodec plus DoseGuide group and [redacted] in the OD analogues group. The estimated LS mean DTSQ total score at Week 52 was [redacted] in the insulin icodec group and [redacted] in the OD analogues group, representing a LS mean change from baseline in DTSQ total satisfaction score of 4.68 [redacted] and 3.90 ([redacted]), respectively. The LS mean difference between groups was 0.78 (95% CI 0.10, 1.47; [redacted].

In ONWARDS 2, the observed mean DTSQ total score at baseline was [redacted] in the insulin icodec group and [redacted] in the insulin degludec group. The estimated LS mean DTSQ total score at Week 26 was [redacted] in the insulin icodec group and [redacted] in the insulin degludec group, representing a LS mean change from baseline in DTSQ total satisfaction score of [redacted] and [redacted], respectively. The estimated LS mean treatment difference between insulin icodec and insulin degludec was 1.25 (95% CI, 0.41 to 2.10, P = 0.0036).

Treatment Related Impact Measure for Diabetes (TRIM-D) Compliance Domain

This outcome was assessed only in ONWARDS 5. The estimated treatment difference was 3.04 (95% CI 1.28 to 4.81[redacted]) at 52 weeks.

CV Death

CV death was not measured as an outcome in the included trials.

Non-fatal MI

Non-fatal MI was not measured as an outcome in the included trials.

Non-fatal Stroke

Non-fatal stroke was not measured as an outcome in the included trials.

Other Micro and Macro Vascular Complications of T2D

Other micro and macro vascular complications of T2D were not measured as outcomes in the included trials.

Harms Results

Adverse Events

The proportion patients who had adverse events (AEs) was similar between the insulin icodec and OD insulin analogue comparator groups in all ONWARDS studies. The most common AEs were COVID-19, nasopharyngitis, diarrhea, and back pain. The majority of AEs were determined by the study investigators to be non-serious, mild to moderate in severity, unlikely related to trial products, and recovered or recovering by the end of the trial duration in each trial.

In the insulin-naïve populations (ONWARDS 1, 3, and 5), 50% to 71% of patients across each treatment arm experienced at least 1 AE.

In the insulin-experienced populations (ONWARDS 2 and 4), 51% to 62% of patients across each treatment arm experienced at least 1 AE.

Serious Adverse Events

Serious adverse events (SAEs) occurred in similar proportions across both the insulin icodec groups and the OD analogues groups in each trial.

In the insulin-naïve populations (ONWARDS 1, 3, and 5), amongst patients treated with insulin icodec, 5.1% to 10.4% of patients had at least 1 SAE. In these same trials, amongst patients treated with the comparator OD analogues, 5.1% to 10.6% of patients had at least 1 SAE.

In the insulin-experienced populations (ONWARDS 2 and 4), amongst patients treated with insulin icodec or OD analogues, 7.6% to 8.4% and 6.1% to 8.6% had at least 1 SAE, respectively.

Reported SAEs included: [redacted]. Each of these SAE categories occurred in 0 to <5% of patients. The most frequent category of SAE observed was [redacted]

Withdrawals Due to Adverse Events

In the insulin-naïve populations (ONWARDS 1, 3, and 5), permanent discontinuation of the study drug due to AE occurred in 0.7% to 1.2% of patients treated with insulin icodec, and 0.8% to 1.3% of patients treated with comparators (insulin glargine or insulin degludec). In the insulin-experienced populations (ONWARDS 2 and 4), permanent discontinuation of the study

drug due to AE occurred in 1.0% to 1.9% of patients treated with insulin icodec, and 1.0 to 1.1% of patients treated with insulin degludec or insulin glargine. Temporary discontinuation was similarly uncommon, as were AEs leading to dose increases or dose decreases.

Mortality

In ONWARDS 1, there were 6 (0.6%) patients with fatal outcomes, of which 4 (0.8%) patients died in the insulin icodec treatment group and 2 (0.4%) patients in the insulin glargine treatment group died. The events (of which some patients may have had multiple) included infections and infestations (n = 2) and 1 each of COVID-19, cardiac disorders (angina pectoris), postoperative infection, pancreatic neoplasm, glioblastoma, unknown cause, and acute coronary syndrome. The death due to unknown cause in the insulin glargine treatment group was judged by investigators as 'possibly' related to the trial product.

In ONWARDS 3, there were 2 patients (0.7%) in the insulin icodec group, and 1 patient (0.3%) in the insulin degludec group with fatal outcomes. In the insulin icodec group, deaths were due to malignancy and an undetermined cause (n = 1 for each). In the insulin degludec group, death was due to acute MI (n = 1).

In ONWARDS 5, there were 3 patients (0.6%) who died in the insulin icodec plus DoseGuide group, and 7 patients (1.3%) in the OD analogues group. [redacted]

In ONWARDS 2, there were 2 patients (0.8%) who died in the insulin icodec group and 2 patients (0.8%) in the insulin degludec group who died. [redacted]

In ONWARDS 4, there were 2 patients (0.7%) in the insulin icodec group and 1 patient (0.3%) in the insulin glargine group who died. In the insulin icodec group, deaths were due to other CV causes and infection (including sepsis) (n = 1 for each). In the insulin glargine group, there was one instance of gastrointestinal bleeding which resulted in death.

Notable Harms

Pre-specified notable harms included hypersensitivity, injection site reactions, hypoglycemia, and nocturnal hypoglycemia.

Events of hypersensitivity were reported among <7% patients during all ONWARDS studies and were similar between treatment groups in each trial. Serious events were rare.

Injection site reactions occurred among <9% of patients across all ONWARDS studies. In ONWARDS 1, 6 patients (1.2%) experienced 6 events in the insulin icodec group compared to 12 patients (2.4%) experiencing 12 events in the insulin glargine group. All events were considered mild or moderate in severity. In ONWARDS 3, 25 patients (8.5%) experienced 62 events in the insulin icodec group compared to 13 patients (4.4%) who experienced 22 events in the insulin degludec group. Of the 62 injection site reactions reported in the insulin icodec group, 24 events were reported by only two patients. No events were considered serious. In ONWARDS 5, 5 patients (0.9%) experienced 6 events in the insulin icodec plus DoseGuide group compared to 7 patients (1.3%) who experienced 28 events in the OD insulin analogue group. No events of injection site reactions were considered serious. In ONWARDS 2, 3 patients (1.1%) experienced 3 events in the insulin icodec group compared to 1 patient (0.4%) who experienced 1 event in the insulin degludec group. All events of injection site reactions were considered mild or moderate in severity. In ONWARDS 4, 2 patients (0.7%) experienced 2 events in both the insulin icodec and insulin glargine groups. No events of injection site reactions were considered serious, and all were mild in severity.

Nocturnal Hypoglycemia

[redacted]

[redacted]

In ONWARDS 5, level 1 nocturnal hypoglycemic events occurred in 48 patients (8.9%) in the insulin icodec group and 46 patients (8.6%) in the OD analogues group. Clinically significant (level 2) nocturnal hypoglycemic events occurred in 11 patients (2,0%) in both treatment groups, and severe (level 3) nocturnal hypoglycemic events occurred in zero patients in the insulin icodec group and 1 patient (0.2%) in the OD analogues groups. The estimated treatment ratio between insulin icodec and OD analogues for clinically significant (level 2) or severe (level 3) nocturnal hypoglycemic events was [redacted].

In ONWARDS 2, level 1 nocturnal hypoglycemic events occurred in 60 patients (22.9%) in the insulin icodec group and 35 patients (13.3%) in the insulin degludec group. Clinically significant (level 2) nocturnal hypoglycemic events occurred in 16 patients (6.1%) in the insulin icodec group and 9 patients (3.4%) in the insulin degludec group. Severe (level 3) nocturnal hypoglycemic events occurred in zero patients in both treatment groups. The estimated treatment ratio between insulin icodec and insulin degludec for clinically significant (level 2) nocturnal hypoglycemic events was [redacted]. The estimated treatment ratio between insulin icodec and insulin degludec for clinically significant (level 2) or severe (level 3) nocturnal hypoglycemic events was [redacted].

In ONWARDS 4, level 1 nocturnal hypoglycemic events occurred in 108 patients (37.1%) in the insulin icodec group and 132 patients (45.4%) in the insulin glargine group. Clinically significant (level 2) nocturnal hypoglycemic events occurred in 54 patients (18.6%) in the insulin icodec group and 71 patients (24.4%) in the insulin glargine group, and severe (level 3) nocturnal hypoglycemic events occurred in zero patients and 1 patient (0.3%) in the insulin icodec and insulin glargine groups, respectively. The estimated treatment ratio between insulin icodec and insulin glargine for clinically significant (level 2) nocturnal hypoglycemic events was 0.74 (95% CI, 0.47 to 1.15; P = 0.1818). The estimated treatment ratio between insulin icodec and insulin glargine for clinically significant (level 2) or severe (level 3) nocturnal hypoglycemic events was 0.73 (95% CI, 0.47 to 1.14; P = 0.1694).

Critical Appraisal

All of the ONWARDS trials were randomized, active-controlled trials with adequate methodology related to randomization and allocation concealment, and there were no concerning between-arm imbalances in patient characteristics at baseline, nor in diabetes-related background medications. As such, the risk of bias arising from the randomization process is low in all trials. Each trial was adequately powered for the purpose of their primary hypotheses. ONWARDS 1, 2, 4 and 5 were open-label trials, which is associated with a risk of bias in subjective and self-report outcomes, while ONWARDS 3 was double-blinded with adequate blinding and concealment procedures including placebos matched in visual quality and administration methods to the active trial products.

The primary outcome in each trial was the change in A1C from baseline, and the non-inferiority margin of 0.3%-points was chosen based on established Food and Drug Administration (FDA) guidance and previous trials of insulin products in the treatment of type 2 diabetes. Change in A1C from baseline was considered a clinically relevant outcome by the clinical expert consulted by CADTH. This outcome is considered acceptable by the FDA for trials of new antihyperglycemic therapies seeking a glycemic control indication, the rationale being that it is a validated surrogate of microvascular disease risk reduction, and further it is currently recognized as the key surrogate marker for the development of long-term diabetes complications in people with type 1 or 2 diabetes. The selection of this non-inferiority margin was determined based on FDA guidance as previously described, and was considered clinically relevant as a threshold of minimally important difference according to the clinical expert consulted by CADTH. However, A1C is ultimately a surrogate biomarker, and there is evidence to suggest that A1C may not be appropriate as a surrogate outcome for downstream complications in diabetes trials due to poor associations with mortality, CV mortality, MI, heart failure, kidney injury, and stroke. Other limitations of A1C include a lack of information about acute glycemic events (i.e., hypo- or hyperglycemia) and insensitivity regarding day-to-day variations of glucose, and measurement of A1C can be confounded by other conditions such as anemia, hemoglobinopathies, iron deficiency, and pregnancy.

Use of CGM allows for observation of time in and outside of range and daily glycemic variability, and the clinical expert consulted by CADTH indicated that this is of growing importance in clinical trials of glycemic control in patients with T2D in addition to A1C. Time in range as measured by CGM is a useful as a measure of short-term glycemic control, and there is good correlation between time in range and A1C. Time in range has been demonstrated to be associated with diabetic retinopathy and microalbuminuria but publications assessing this outcome as a surrogate for other diabetes-related complications (e.g., mortality, MI, and other major cardiovascular or renal events) were not identified.

The primary outcome in all trials was adjusted for multiple comparisons. Additionally, in ONWARDS 1, the outcome of time in range (3.9 to 10 mmol/L) was also adjusted for multiple comparisons. As the remaining outcomes were not adjusted for multiplicity, there is an increased risk of type 1 error (i.e., false positive results) for statistically significant results for those outcomes.

Multiple imputation was used for all outcomes to account for missing data. Multiple imputation methods will not remove or reduce bias that occurs when missingness is not random, but the proportion of missing data in each case was low, so this was not considered cause for concern. Additionally, sensitivity analyses were conducted for the primary outcome which bolstered confidence in the primary analyses.

The study designs with respect to patient eligibility criteria and characteristics at baseline were appropriately reflective of the target population in Canada, with the exception that there is a notable lack of inclusion of Indigenous Peoples, who are at higher risk of T2D and its complications. The selected comparators, medications at baseline among included patients, and concomitant mediations during the trials were considered by the consulted clinical expert to be appropriate and to reflect Canadian clinical practice.

The impact of insulin icodec on patients' HRQoL was not measured in the ONWARDS trials. Although the DTSQ and TRIM-D compliance domain provide information about treatment satisfaction and compliance, they are not comprehensive measures of HRQoL. As such, the influence of insulin icodec on HRQoL as compared with insulin degludec or insulin glargine is not known. Additionally, there were no compliance data reported for the insulin experienced populations.

There is a data gap regarding the long-term effect of insulin icodec versus daily insulins on outcomes such as CV death, non-fatal MI, non-fatal stroke, and long-term all-cause mortality beyond the duration of the included clinical trials. Additionally, the clinical trials did not evaluate any global HRQoL measures.

GRADE Summary of Findings and Certainty of the Evidence

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members:

- Outcomes related to blood glucose (Percent change in A1C from baseline, percent time in range [3.9 to 10.0 mmol/L], percent time spent below range, percent time spent above range)
- Mortality and morbidity (all-cause mortality, cardiovascular death, non-fatal MI, non-fatal stroke, micro and macrovascular complications of T2D)
- Change in body weight from baseline
- Treatment satisfaction (DTSQ) and compliance (TRIM-D compliance domain)
- Proportion of patients with clinically significant or severe hypoglycemic events

Table 2: Summary of Findings for Insulin Icodec versus Daily Basal Insulins[a] for Patients with Type 2 Diabetes Mellitus – Insulin-naïve Patients

Outcome and follow–up	Patients (studies), N	Effect[b]	Certainty	What happens
Blood glucose outcomes				
LS mean change in A1C from baseline (95% CI), %–point Follow–up: 26 weeks (ONWARDS 3) 52 weeks (ONWARDS 1 & 5)	2657 (3 RCTs)	ONWARDS 1 • Insulin icodec: –1.55 [redacted] • Insulin glargine: –1.35 [redacted] • Difference: –0.19 (–0.36 to –0.03) ONWARDS 3 • Insulin icodec: –1.6 [redacted] • Insulin degludec: –1.4 [redacted] • Difference: –0.2 (–0.3 to –0.1) ONWARDS 5 • Insulin icodec: –1.68 (–1.85 to –1.52) • Insulin degludec or glargine: –1.31 (–1.55 to –1.07) • Difference: –0.38 (–0.66 to –0.09)	Moderate[c]	Insulin icodec likely results in little to no difference in change from baseline in A1C when compared with insulin glargine or insulin degludec.
LS mean time in range (3.9 to 10.0 mmol/L) (95% CI), % Follow-up: 52 weeks	984 (1 RCT)	ONWARDS 1 • Insulin icodec: [redacted] • Insulin glargine: [redacted] • Difference: 4.27 (1.92 to 6.62)	Moderate[d]	Insulin icodec likely results in little to no difference in the percent time in range (3.9 to 10.0 mmol/L) compared with insulin glargine.
LS mean time spent < 3.0 mmol/L (95% CI), % Follow-up: 52 weeks	984 (1 RCT)	[redacted]	High	Insulin icodec results in little to no difference in the percent time spent < 3.0 mmol/L compared with insulin glargine.
LS mean time spent > 10.0 mmol/L (95% CI), % Follow–up: 52 weeks	984 (1 RCT)	[redacted]	Moderate[f]	Insulin icodec likely results in little to no difference in percent time spent > 10.0 mmol/L compared with insulin glargine.
Mortality and morbidity				
Patients who died (95% CI), % Follow-up: 26 weeks (ONWARDS 3) 52 weeks (ONWARDS 1 & 5)	2657 (3 RCTs)	ONWARDS 1 • Insulin icodec: 0.8 (NR) • Insulin glargine: 0.4 (NR) • Difference: NR ONWARDS 3 • Insulin icodec: 0.7 (NR) • Insulin degludec: 0.3 (NR) • Difference: NR	Very Low[g]	The evidence is very uncertain about the effect of insulin icodec on mortality when compared with insulin glargine or insulin degludec.

Outcome and follow–up	Patients (studies), N	Effect[b]	Certainty	What happens
		ONWARDS 5 • Insulin icodec: 0.6 (NR) • Insulin degludec or glargine: 1.3 (NR) • Difference: NR		
Cardiovascular death	-	No data available.	NA	There is no evidence for the effect of insulin icodec on cardiovascular death compared to insulin degludec or insulin glargine.
Non-fatal MI	-	No data available.	NA	There is no evidence for the effect of insulin icodec on non-fatal MI compared to insulin degludec or insulin glargine.
Non-fatal stroke	-	No data available.	NA	There is no evidence for the effect of insulin icodec on non-fatal stroke compared to insulin degludec or insulin glargine.
Micro and macrovascular complications of T2D	-	No data available.	NA	There is no evidence for the effect of insulin icodec on the micro and macrovascular complication of T2D when compared with insulin degludec or insulin glargine.
Body weight				
LS mean change in body weight from baseline (95% CI), kilograms Follow-up: 26 weeks (ONWARDS 3) 52 weeks (ONWARDS 1 & 5)	2657 (3 RCTs)	ONWARDS 1 • Insulin icodec: 2.29 [redacted] • Insulin glargine: 1.83 [redacted] • Difference: 0.46 (–0.12 to 1.04) ONWARDS 3 • Insulin icodec: 2.8 [redacted] • Insulin degludec: 2.3 [redacted] • Difference: 0.46 (–0.19 to 1.10) ONWARDS 5 • Insulin icodec: 2.28 (1.55 to 3.00) • Insulin degludec or glargine: 1.45 (0.47 to 2.42) • Difference: 0.83 (–0.37 to 2.02)	High	Insulin icodec results in little to no difference in change from baseline in body weight when compared with insulin glargine or insulin degludec.
Treatment Satisfaction and Compliance				

Outcome and follow–up	Patients (studies), N	Effect[b]	Certainty	What happens
LS mean change in DTSQ score (0 [worst] to 36 [best]) from baseline (95% CI), points Follow-up: 52 weeks	1085 (1 RCT)	ONWARDS 5[e] • Insulin icodec: 4.68 (4.20 to 5.16) • Insulin degludec or glargine: 3.90 (3.41 to 4.38) • Difference: 0.78 (0.10 to 1.47)	Moderate[h]	Insulin icodec likely results in little to no difference in DTSQ score when compared with insulin glargine or insulin degludec. The clinical importance of the observed effect is uncertain.
LS mean TRIM-D (0 [worst] to 100 best]) compliance domain score (95% CI), points Follow-up: 52 weeks	1085 (1 RCT)	ONWARDS 5[e] • Insulin icodec: 90.42 (89.17 to 91.67) • Insulin degludec or glargine: 87.37 (86.12 to 88.62) • Difference: 3.04 (1.28 to 4.81)	Moderate[i]	Insulin icodec likely results in an increase in the TRIM-D compliance domain score when compared with insulin glargine or insulin degludec. The clinical importance of the increase is unclear.
Hypoglycemia				
Proportion of patients experiencing ≥1 clinically significant (level 2) or severe (level 3) hypoglycemia events (95% CI), % Follow-up: 26 weeks (ONWARDS 3) 52 weeks (ONWARDS 1 & 5)	2657 (3 RCTs)	ONWARDS 1 • Insulin icodec: [redacted] • Insulin glargine: [redacted]) • Difference: [redacted] ONWARDS 3 • Insulin icodec: [redacted] • Insulin degludec: [redacted]) • Difference [redacted] ONWARDS 5 • Insulin icodec: [redacted] • Insulin degludec or glargine: [redacted] • Difference [redacted]	Moderate[j]	Insulin icodec likely results in little to no difference in the proportion of patients experiencing ≥1 level 2 or 3 hypoglycemia events when compared to insulin glargine or insulin degludec.

DTSQ = Diabetes Satisfaction treatment Questionnaire; LS = least square; MI = myocardial infarction; MID = minimally important difference; NR = not reported; OD = once daily; RCT = randomized controlled trial; TD = treatment difference; TR = treatment ratio; TRIM-D = Treatment-Related Impact Measure for Diabetes.

[a] The comparator for ONWARDS 1 was insulin glargine, the comparator for ONWARDS 3 was insulin degludec, and the comparators for ONWARDS 5 were insulin glargine and insulin degludec.

[b] Additional information was requested from the sponsor to obtain 95% CIs for the LS mean estimates in each treatment group within the trials, and to obtain between-group differences with 95% CI for hypoglycemia outcomes. This information was not necessarily part of the sponsor's statistical analysis plan and is considered as exploratory evidence.

[c] –1 level for serious imprecision. The target of the certainty appraisal is little to no difference based on a threshold of 0.3%-point for a clinically important between-group difference (the non-inferiority margin). The 95% CI for all trials includes the potential for important benefit. There is high certainty that insulin icodec is non-inferior to insulin glargine or insulin degludec with respect to change from baseline in A1C.

[d] – 1 level for serious imprecision. The CI for the percent time in range (3.9 – 10.0 mmol/L) included a potential benefit (based on a threshold of importance of 5% provided by the clinical expert).

[e] In the trial, statistical testing for this outcome was not adjusted for multiplicity. The results are considered as supportive evidence.

[f] – 1 level for serious imprecision. The CI for the percent time above 10.0 mmol/L included a potential benefit (based on a threshold of importance of 5% provided by the clinical expert).

[g] – 1 level for serious indirectness due to the short follow-up length in the trials, and – 2 levels for very serious imprecision due to the small number of events.

[h] – 1 level for serious study limitations. The open-label design may bias reporting of subjective measures because patients were aware of the treatment they were receiving.

[i] – 1 level for serious imprecision. The CI for difference between groups in all trials included a potentially important increase (based on a threshold of importance of 3% provided by the clinical expert).

[j] – 1 level for serious imprecision. The CI for the proportion of patients experiencing level 2 or 3 hypoglycemia included potential harm (based on a threshold of importance of 3% provided by the clinical expert).

Note: Study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

Source: ONWARDS 1 Clinical Study Report, ONWARDS 3 Clinical Study Report, ONWARDS 5 Clinical Study Report, ONWARDS 2 Clinical Study Report, ONWARDS 4 Clinical Study Report, and additional information provided by the sponsor at CADTH request.

Table 3: Summary of Findings for Insulin Icodec versus Daily Basal Insulins for Patients with Type 2 Diabetes Mellitus – Insulin-experienced Patients[a]

Outcome and follow–up	Patients (studies), N	Effect[b]	Certainty	What happens
Blood glucose outcomes				
LS mean change in A1C from baseline (95% CI), %-point Follow-up: 26 weeks	1108 (2 RCTs)	ONWARDS 2 • Insulin icodec: –0.93 [redacted] • Insulin degludec: –0.71 [redacted] • Difference: –0.22 (–0.37 to –0.08) ONWARDS 4 • Insulin icodec: –1.16 [redacted] • Insulin glargine: –1.18 [redacted] • Difference: 0.02 (–0.11 to 0.15)	Moderate[c]	Insulin icodec likely results in little to no difference in change from baseline in A1C when compared with insulin glargine or insulin degludec.
LS mean time in range (3.9 to 10.0 mmol/L) (95% CI), % Follow-up: 26 weeks	1108 (2 RCTs)	ONWARDS 2 • Insulin icodec: [redacted] • Insulin degludec: [redacted] • Difference: 2.41 (–0.84 to 5.65) ONWARDS 4 • Insulin icodec: [redacted] • Insulin glargine: [redacted] • Difference: 0.29 (–2.52 to 3.09)	High	Insulin icodec results in little to no difference in the percent time in range (3.9 to 10.0 mmol/L) when compared with insulin glargine or insulin degludec.
LS mean time spent < 3.0 mmol/L (95% CI), % Follow-up: 26 weeks	1108 (2 RCTs)	ONWARDS 2 • Insulin icodec: 0.3 [redacted] • Insulin degludec: 0.2 [redacted] • Treatment ratio: 1.37 (0.92 to 2.04) ONWARDS 4 • Insulin icodec: [redacted] • Insulin glargine: [redacted] • Treatment ratio: 1.20 (0.91 to 1.58)	High	Insulin icodec results in little to no difference in time spent < 3.0 mmol/L when compared with insulin glargine.

Outcome and follow–up	Patients (studies), N	Effect[b]	Certainty	What happens
LS mean time spent > 10.0 mmol/L (95% CI), % Follow-up: 26 weeks	1108 (2 RCTs)	ONWARDS 2 • Insulin icodec: [redacted] • Insulin degludec: [redacted] • Difference: –2.93 (–6.25 to 0.39) ONWARDS 4 • Insulin icodec: 30.5 [redacted] • Insulin glargine: 31.3 [redacted] • Difference: –0.60 (–3.47 to 2.28)	High	Insulin icodec results in little to no difference in the percent time spent > 10.0 mmol/L compared with insulin glargine or insulin degludec
Mortality and morbidity				
Patients who died, % Follow-up: 26 weeks	1108 (2 RCTs)	ONWARDS 2 • Insulin icodec: 0.8 (NR) • Insulin degludec: 0.8 (NR) • Difference: NR ONWARDS 4 • Insulin icodec: 0.7 (NR) • Insulin glargine: 0.3 (NR) • Difference: NR	Very Low[d]	The evidence is very uncertain about the effect of insulin icodec on mortality when compared with insulin glargine or insulin degludec.
Cardiovascular death	-	No data available.	NA	There is no evidence for the effect of insulin icodec on cardiovascular death compared to insulin degludec or insulin glargine.
Non-fatal MI	-	No data available.	NA	There is no evidence for the effect of insulin icodec on non-fatal MI compared to insulin degludec or insulin glargine.
Non-fatal stroke	-	No data available.	NA	There is no evidence for the effect of insulin icodec on non-fatal stroke compared to insulin degludec or insulin glargine.
Micro and macrovascular complications of T2D	—	No data available.	NA	There is no evidence for the effect of insulin icodec on micro and macrovascular complications of T2D compared to insulin degludec or insulin glargine.
Body weight				

Outcome and follow–up	Patients (studies), N	Effect[b]	Certainty	What happens
LS mean change in body weight from baseline (95% CI), kilograms Follow-up: 26 weeks	1108 (2 RCTs)	ONWARDS 2[e] • Insulin icodec: 1.40 [redacted] • Insulin degludec: –0.30 [redacted] • Difference: 1.70 (0.76 to 2.63) ONWARDS 4[e] • Insulin icodec: 2.7 [redacted] • Insulin glargine: 2.2 [redacted] • Difference: 0.57 (–0.39 to 1.54)	High	Insulin icodec results in little to no difference in change from baseline in body weight when compared with insulin glargine or insulin degludec.
Treatment Satisfaction and Compliance				
LS mean change in DTSQ score (0 [worst] to 36 [best]) from baseline (95% CI), points Follow-up 26 weeks	526 (1 RCT)	ONWARDS 2[e] • Insulin icodec: 4.22 [redacted] • Insulin degludec: 2.96 [redacted] • Difference: 1.25 (0.41 to 2.10)	Moderate[f]	Insulin icodec likely results in little to no difference in DTSQ score when compared with insulin degludec. The clinical importance of the observed effect is uncertain.
Treatment compliance	—	No data available.	NA	There is no evidence for the effect of insulin icodec on treatment compliance compared to insulin degludec or insulin glargine.
Hypoglycemia				
Proportion of patients experiencing ≥1 clinically significant (level 2) or severe (level 3) hypoglycemia event, % Follow-up: 26 weeks	526 (1 RCT)	ONWARDS 2[e] • Insulin icodec: 14.27 (NR) • Insulin degludec: 8.38 (NR) • [redacted]	Moderate[g]	Among those previously treated with basal insulin only, insulin icodec likely results in an increase in the proportion of patients experiencing ≥1 level 2 or 3 hypoglycemic events when compared with insulin degludec.
Proportion of patients experiencing ≥1 clinically significant (level 2) or severe (level 3) hypoglycemia event, % Follow-up: 26 weeks	582 (1 RCT)	ONWARDS 4 • Insulin icodec: 52.63 (NR) • Insulin glargine: 57.12 (NR) • [redacted]	Low[h]	Among those previously treated with basal and bolus insulin, insulin icodec may result in a decrease in the proportion of patients experiencing level 2 or 3 hypoglycemic events when compared with insulin glargine.

DTSQ = Diabetes Satisfaction treatment Questionnaire; HRQoL = health-related quality of life; LS = least square; MI = myocardial infarction; MID = minimally important difference; NR = not reported; OD = once daily; RCT = randomized controlled trial; TD = treatment difference; TR = treatment ratio; TRIM-D = Treatment-Related Impact Measure for Diabetes.

[a] The patient population for ONWARDS 2 was patients experienced with basal insulin, and the patient population for ONWARDS 4 was patients experienced with basal + bolus insulin.

[b] Additional information was requested from the sponsor to obtain 95% CIs for the LS mean estimates in each treatment group within the trials, and to obtain between-group differences with 95% CI for hypoglycemia outcomes. This information was not necessarily part of the sponsor's statistical analysis plan and is considered as exploratory evidence.

[c] –1 level for serious imprecision. The target of the certainty appraisal is little to no difference based on a threshold of 0.3%-point for a clinically important between-group difference (the non-inferiority margin). The 95% CI for all trials includes the potential for important benefit. There is high certainty that insulin icodec is non-inferior to insulin glargine or insulin degludec with respect to change from baseline in A1C.

[d] – 1 level for serious indirectness; the short follow-up length in the trials is insufficient to fully capture this outcome. – 2 levels for very serious imprecision; there is a very small number of events captured.

[e] In the trial, statistical testing for this outcome was not adjusted for multiplicity. The results are considered as supportive evidence.

[f] – 1 level for serious study limitations. The open-label design may bias reporting of subjective measures because patients were aware of the treatment they were receiving.

[g] – 1 level for serious imprecision. The target of the certainty appraisal is an increase based on a threshold for a clinically important between-group difference of 3% as informed by the clinical expert. The 95% CI includes the possibility of little to no difference.

[h] – 2 levels for very serious imprecision. The target of the certainty appraisal is a decrease based on a threshold for a clinically important between-group difference of 3% as informed by the clinical expert. The 95% CI includes the possibility of little to no difference and an increase.

Note: Study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

Source: Details included in the table are from the sponsor's Summary of Clinical Evidence, ONWARDS 2 CSR, ONWARDS 4 CSR, and additional information provided by the sponsor.

Long-Term Extension Studies

Description of Studies

The sponsor submitted the long term extension (LTE) phase of the ONWARDS 1 trial, which extended the original open-label trial design an additional 26 weeks to provide 78 weeks of data. Patients originally randomized to either insulin icodec or insulin glargine continued their treatment as per the protocol of ONWARDS 1 until the end of the LTE phase. Patient population, interventions, comparators and trial design elements remained the same. The same efficacy and safety outcomes were also assessed using the same statistical methods with some exceptions; the efficacy outcomes were not controlled for multiplicity and there was no hierarchical testing procedure for the primary outcome.

Efficacy outcomes summarized by CADTH included change in A1C from baseline, change in body weight from baseline, proportion of patients with level 2 or 3 hypoglycemic events, as well as time spent in range (3.9 to 10.0 mmol/L), time spent < 3.0 mmol/L and time spent > 10.0 mmol/L, all between weeks 74 and 78.

Efficacy Results

Briefly, similar to the 52-week mark of ONWARDS 1 there was little to no difference between insulin icodec and insulin glargine in terms of change in A1C from baseline to week 78, change in body weight from baseline to week 78, or time spent < 3.0 mmol/L. Similar to the 52-week mark of ONWARDS 1, insulin icodec was statistically favoured for time spent in range 3.9 to 10.0 mmol/L (TD [95[redacted]) and time spent > 10.0mmol/L (TD [95[redacted]) between weeks 74 and 78. The treatment ratio for level 2 or 3 hypoglycemic in the LTE phase was [redacted]

Harms Results

Harms in the two study arms were broadly similar during the LTE phase of the study, with some exceptions. Patients in the insulin glargine arm had a numerically higher incidence of AEs requiring temporary discontinuation, although the proportion was low in each group (<5%). There were a numerically higher proportion of patients in the insulin icodec arm who experienced level 1 hypoglycemic events (55.9% versus 48.2%). Level 2 events occurred in the same proportion of patients (12.4% in both arms) and level 3 hypoglycemic events were rare in both arms (1 patient [0.2%] in the insulin Icodec arm and 5 patients [1.0%] in the insulin glargine arm). All-cause mortality was similar between treatment arms with 5 patients (1.0%) in the insulin icodec arm and 3 patients (0.6%) in the insulin glargine arm (1 additional death per group relative to the 52-week mark of ONWARDS 1).

Critical Appraisal

All appraisal points pertaining to the main phase of ONWARDS 1 also pertain here as this LTE was a continuation of the same study design, patients, and outcomes. In addition to those, the fact that all efficacy outcomes here are exploratory and not adjusted for multiplicity, resulting in an increased risk of type I error (false positive conclusions) for statistically significant results, is an additional internal validity limitation. Regarding external validity, the LTE results are only applicable to insulin naïve patients as this was the only patient population included in ONWARDS 1, leaving a knowledge gap for these outcomes in insulin experienced patients. Data on all-cause mortality are only provided during the LTE phase and thus information on mortality beyond 78 weeks is lacking. The comparison was also based on a small number of events, limiting a conclusion as to which treatment may be favoured. Lastly, results on long-term treatment adherence or satisfaction and clinical outcomes such as micro- and macrovascular complications (e.g., non-fatal MI, stroke) were not assessed.

Indirect Comparisons

A network meta-analysis (NMA) was submitted with the objectives of assessing the relative efficacy and safety of insulin icodec compared to other basal insulin analogues used by Canadian patients. Analyses were conducted for insulin-naïve patients, basal insulin-experienced patients, and basal + bolus-insulin experienced patients. Outcomes of interest appraised by CADTH were change in A1C, overall hypoglycemia, level 2 and 3 hypoglycemia, and nocturnal hypoglycemia. Relevant comparators were insulin glargine U100/U300, insulin degludec U100/U200, and insulin detemir.

Description of Studies

The literature search yielded a total of 8,760 citations which were screened at the title and abstract phase. Of these, 22 studies were considered for data extraction for the feasibility assessment of the NMA. For insulin-naïve patients the NMAs contained 14 studies (11 phase III/IV studies, one phase II trial and two studies with unreported trial phases). Trials were either open label (n = 13), or double-blinded (n = 1). For the basal insulin-experienced patients, there were a total of 5 unique trials contributing to the NMA. All trials were multi-centre, open-label phase III trials. For the basal + bolus-experienced patients, a total of 3 unique trials contributed to the NMA. Two studies were multi-centre, multinational, open-label trials. One trial was a phase III study, and the phase was not reported for the other.

Efficacy Results

[redacted]

Harms Results

No safety analysis was run beyond the NMAs for hypoglycemia outcomes.

Critical Appraisal

The systematic literature review (SLR) which informed the NMA did not specify which comorbidities were used for the exclusion criteria of “patients with comorbidities”. This could impact the generalizability of the NMA results and affect confidence in the transitivity assumption if patient populations with different comorbidities are included.

With regards to the feasibility assessment in the NMA, the risk of bias appraisals were undertaken at the level of the trial, rather than at the level of the reported result (within each trial), ignoring that risk of bias can differ across outcomes within the same trial. Furthermore, the methods for appraising risk of bias were not reported. In addition, there was no discussion of how the treatment effect modifiers were chosen for the feasibility assessment, or how the assessment ensured that the list of treatment effect modifiers was comprehensive. There are also concerns with unmeasured treatment effect modifiers and heterogeneity across trials in treatment effect modifiers (e.g., a paucity of studies reported ethnicity and the ranges reported were wide). Overall, there remains uncertainty in the plausibility of the transitivity assumption underpinning the NMA.

Small treatment networks, particularly for the hypoglycemia outcomes and insulin-experienced patients, necessitated the selection of fixed-effect models for most comparison-outcomes as the standard error was unstable to estimate with such a small network; however, these models do not account for between-study variance and this adds some uncertainty to the results. Furthermore, the submission did not contain any consistency assessments for the instances where there were closed loops in the network, which limits assessing the consistency of the results in the NMA with results from the individual trials.

In addition, in several analyses the proportion of patients experiencing hypoglycemic events was much lower in the insulin icodec studies (ONWARDS trials) than the comparator studies. The submission raised the question whether the comparison was appropriate but did not adjust for these differences in any way or explore them in sensitivity analyses. For nearly all hypoglycemia outcome comparisons the effect estimates were also affected by imprecision due to wide credible intervals, precluding any conclusions regarding which treatment in the comparison may be favoured.

Furthermore, the NMA is subject to some limitations in clinical meaningfulness. The clinical expert consulted by CADTH noted that while the results for A1C change from baseline across study populations may attain statistical significance, they overall do not provide an important clinical benefit. In addition, while the rationale for the NMA was to include insulin detemir and provide data for

insulin icodec compared to insulin detemir, a lack of available results limited the outcomes for which insulin icodec could be compared to insulin detemir. Lastly the NMA is limited in its generalizability; non-white participants and/or those over age 70 with poorly-controlled diabetes would not be represented in this analysis and the impact of insulin icodec on the long-term control of blood glucose and the long-term safety relative to daily insulin comparators remains unknown.

Studies Addressing Gaps in the Evidence From the Systematic Review

No studies were submitted addressing gaps in the evidence.

Economic Evidence

Cost and Cost-Effectiveness

Table 4: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Markov cohort model
Target population	Adult patients aged 18 years and older with type 2 diabetes (T2D) who require insulin for glycemic control. Three populations are evaluated in separate analyses: • Insulin-naïve patients with T2D on non-insulin antihyperglycemic agents (NIAHAs) (henceforth, T2D insulin-naive). • Basal insulin-experienced patients with T2D with or without NIAHAs (henceforth, T2D basal switch). • Basal-bolus insulin-experienced patients with T2D with or without NIAHAs (henceforth, T2D basal + bolus switch).
Treatment	Insulin icodec
Dose regimen	The recommended starting dose of insulin icodec in insulin-naïve patients with T2D is 70 units administered once weekly. For basal insulin-experienced patients with T2D switching to insulin icodec, the corresponding weekly dose of insulin icodec is the previous basal insulin dose multiplied by 7. A one-time additional 50% insulin icodec dose is recommended for the week 1 dose.
Submitted price	Insulin icodec, 700 units/mL, pre-filled pen: $78.05 for 1,050 units (1.5 mL) and $156.10 for 2,100 units (3 mL).
Treatment cost	The annual per-patient drug acquisition cost of insulin icodec is $1,148 for insulin-naïve patients, $1,230 for basal insulin-experienced patients, and $1,956 for basal-bolus insulin-experienced patients.
Comparators	• Insulin glargine (U100 and U300) • Insulin degludec (U100 and U200) • Insulin detemir
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (40 years)

Key data sources	• T2D insulin-naïve population:
	  • ONWARDS 1: insulin icodec vs. insulin glargine (week 26)
	  • ONWARDS 3: insulin icodec vs. insulin degludec (week 26)
	• T2D basal switch population:
	  • ONWARDS 2: insulin icodec vs. insulin degludec (week 26)
	• T2D basal + bolus switch population:
	  • ONWARDS 4: insulin icodec vs. insulin glargine (week 26)
	• Results from network meta-analyses (NMAs) regarding change from baseline (CFB) in glycated hemoglobin (HbA1C), and proportion of patients with severe hypoglycemia were used to estimate comparative efficacy and safety. NMA results regarding mean insulin dose were used to model treatment costs.

Component	Description
Key limitations	• The utility decrements associated with administration of insulin therapies are highly uncertain and may not accurately capture the impact on health-related quality of life for patients with T2D in Canada. For example, the values used in the sponsor's submission assume that daily treatment administration has a larger impact on patient utility (-0.107) than severe vision loss (-0.05). The disutility estimates used by the sponsor, therefore, likely overestimate the benefit associated with once weekly injections versus daily injections. • The long-term relative effectiveness of insulin icodec compared to long-acting basal insulin analogues is highly uncertain due to limitations in the submitted NMA. However, due to small differences in clinical outcomes from the NMA this limitation has a small impact on cost effectiveness conclusions. • The estimated weekly basal insulin dose for insulin icodec and long-acting basal insulin analogues is uncertain due to lack of significant differences and limitations in the submitted NMA. It is uncertain whether numerically different doses received by patients with T2D in real-world clinical practice will reflect the doses estimated from the NMA.
CADTH reanalysis results	• The CADTH base case was derived by excluding the utility decrements associated with once weekly, once daily, and multiple daily insulin injections, due to the high degree of uncertainty regarding what these utility decrements may be. • In the CADTH base case, insulin icodec was associated with an ICER of $435,800 per QALY gained compared to insulin glargine U100 (incremental costs: $7,559; incremental QALYs: 0.02) among insulin-naïve patients. For basal insulin-experienced patients, insulin icodec was associated with an ICER of $937,280 per QALY gained compared to insulin glargine U100 (incremental costs: $7,473; incremental QALYs: 0.01). Conversely, as treatment for basal-bolus insulin-experienced patients, insulin icodec was strictly dominated (fewer QALYs at a greater cost) by insulin glargine U100. • To ensure cost-effectiveness, insulin icodec should be priced no more than the lowest cost long-acting basal insulin analogue used to treat T2D. A price premium may be warranted due to the lower administration burden associated with insulin icodec (once weekly), although evidence to inform the degree of this premium is highly uncertain.

CFB = change from baseline; HbA1c = glycated hemoglobin; ICER = incremental cost-effectiveness ratio; LY = life-year; NIAHA = non-insulin antihyperglycemic agent; NMA = network meta-analysis; QALY= quality-adjusted life-year; T2D = type 2 diabetes; U = unit; WTP = willingness-to-pay.

Budget Impact

CADTH identified the following limitations in the sponsor's base case: the estimated basal insulin dose for insulin icodec and long-acting basal insulin analogues is uncertain; the proportion of claims assumed to originate from patients with type 1 diabetes (T1D) is overestimated; the projected market uptake of insulin icodec is uncertain. CADTH conducted reanalyses of the budget impact analysis (BIA) by adopting average daily doses calculated from RWE and using published estimates to inform the proportion of claims that are likely to be generated by patients with T1D. Based on the CADTH base case, the estimated budget impact associated with the reimbursement of insulin icodec as treatment for adult patients with T2D requiring glycemic control is expected to be $650,056 in Year 1, $4,288,283 in Year 2, and $10,317,977 in Year 3, for a 3-year budgetary impact of $15,256,316. CADTH conducted a scenario analysis to address remaining uncertainty. If the projected market share of insulin icodec is assumed to be 10%, 20%, and 30% in Years 1, 2, and 3, respectively, the 3-year budget impact associated with reimbursing insulin icodec is expected to be $41,043,671.

CDEC Information

Members of the Committee:

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Edward Xie, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Peter Jamieson, Mr. Morris Joseph, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Trudy Huyghebaert, Dr. Danyaal Raza, and Dr. Peter Zed.

Meeting date: March 28, 2024

Regrets:

Three expert committee members did not attend.

Conflicts of interest:

None