CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

INSULIN DEGLUDEC AND LIRAGLUTIDE (XULTOPHY — Novo Nordisk Canada Inc.)

Indication: Adjunct to lifestyle modifications, for the once-daily treatment of adults with type 2 diabetes mellitus (T2DM) to improve glycemic control in combination with metformin, with or without sulfonylurea, when these combined with basal insulin (less than 50 units daily) or liraglutide (less than or equal to 1.8 mg daily), do not provide adequate glycemic control.

RECOMMENDATION

The CADTH Canadian Drug Expert Committee (CDEC) recommends that insulin degludec and liraglutide (IDegLira) should be reimbursed as an adjunct to lifestyle modification, for the once-daily treatment of adults with T2DM to improve glycemic control in combination with metformin (MET), with or without sulfonylurea (SU), when these, combined with basal insulin (at doses of 20 to 50 units per day) do not provide adequate glycemic control, only if the following conditions are met:

Conditions for Reimbursement

Discontinuation criteria

- IDegLira should be discontinued if the patient does not achieve a desirable level of glycemic control despite receiving a maximum dose of IDegLira (50 units of insulin degludec [IDeg] and 1.8 mg of liraglutide) after 26 weeks of treatment.

Pricing condition

- Drug plan costs for IDegLira should not exceed the cost of the least costly glucagon-like peptide-1 receptor agonist (GLP-1 RA) plus the least costly basal insulin administered separately or in combination.

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- Drug plan costs for IDegLira should not exceed the cost of the least costly glucagon-like peptide-1 receptor agonist (GLP-1 RA) plus the least costly basal insulin administered separately or in combination.

Reasons for the Recommendation

1. In DUAL VII, an open-label randomized controlled trials (RCT) in patients with inadequate glycemic control on insulin glargine (IGlar) at a daily dose between 20 units and 50 units (inclusive) in combination with MET, IDegLira was noninferior to IGlar plus prandial insulin aspart (IAsp), both groups in combination with MET, for the change from baseline in glycated hemoglobin (A1C) after 26 weeks of treatment based on a 0.3% noninferiority margin (least squares [LS] mean difference was −0.02; 95% confidence interval [CI] −0.16 to 0.12). Of the three phase III RCTs of patients with T2DM who experienced inadequate glycemic control on basal insulin in combination with oral hypoglycemics, DUAL VII was most clinically relevant to the Canadian context, with respect to the comparator; multiple daily insulin injections.
2. In one phase III open-label RCT (DUAL III), conducted in insulin-naive patients with inadequate glycemic control on a combination of the maximum recommended (or tolerated) dose of a GLP-1 RA (Victoza [liraglutide] or Byetta [exenatide]) and MET ± pioglitazone ± SU, IDegLira in combination with MET resulted in statistically significantly reduced A1C levels after 26 weeks of treatment compared with the baseline regimen; LS Mean difference (95% CI) was −0.94 (−1.11 to −0.78).
3. In clinical practice, initiation of IDegLira in patients previously stabilized on liraglutide could result in a lower maintenance liraglutide dose, which may compromise the ability of IDegLira to achieve effectiveness outcomes other than glycemic control. Therefore, CDEC does not recommend reimbursement of IDegLira in patients with T2DM who have inadequate glycemic control on a combination of MET (with or without SU) and liraglutide.
4. The extent to which IDegLira represents a cost-effective treatment option in the patient population for whom reimbursement is recommended is uncertain, given several limitations of the clinical and economic evidence with respect to relevant comparators and clinical outcomes.

Discussion Points

- The place for IDegLira in the management of T2DM remains uncertain. The reviewed trials required patients enrolled to have poor glycemic control, which is defined but does not specify why insulin doses between 20 and 40 units (DUAL II) or 20 and 50 units (DUAL V and DUAL VII) (which are relatively modest) could not be increased. This, together with the exclusion of patients with high body mass index, may limit the generalizability of trial evidence to the T2DM population in Canada.
- IDegLira is proposed as a convenience therapy, likely to be preferred by patients facing multiple insulin injections. There is, however, little evidence from the included trials that the perceived convenience is associated with meaningful improvements in

patient satisfaction or health-related quality of life, or that patients prefer the relatively inflexible fixed-ratio product to a single daily administration of the constituent products or to the use of multiple insulin preparations.

- There are no data to inform the effectiveness or safety of IDegLira greater than 50 units of IDeg and 1.8 mg of liraglutide, though they could be administered using the pen device. The maximum recommended dose of liraglutide for glycemic management is 1.8 mg per day. CDEC discussed that if glycemic control is not achieved on the maximum dose of IDegLira then it should be discontinued to allow for higher dose more flexible regimens of insulin administration.
- The Health Canada indication for the use of IDegLira, to replace liraglutide in patients with T2DM on combination therapy and inadequate glycemic control may lead to implementation difficulties. There is no evidence that it is possible to predict which patients will require less than 50 units a day of basal insulin to achieve adequate glycemic control. It is difficult to recommend primary use of IDegLira during the period of insulin initiation and the sole benefit is likely to be only a small reduction in the number of daily subcutaneous injections, particularly in view of the recent introduction of a once weekly GLP-1 RA preparation.
- CDEC discussed that the reduction in mean body weight observed in IDegLira groups, compared with those treated with basal insulin in combination with other oral hypoglycemics (a difference of 2.5 kg to 3.5 kg over 26 weeks) was of uncertain long-term clinical benefit. CDEC further noted that between-treatment differences in blood glucose confirmed hypoglycemia events are of uncertain clinical relevance, and that severe hypoglycemic events were too infrequent to identify important differences.
- The duration of the DUAL clinical trials at 26 weeks is relatively short and in the context of diabetes management (as a chronic disease with progressively increasing therapeutic requirements), the durability of clinical effectiveness of IDegLira is not established.

Background

IDegLira is a titratable fixed-ratio combination of IDeg and the GLP-1 RA liraglutide, which is delivered subcutaneously once-daily. The Health Canada approved indication for IDegLira is as an adjunct to lifestyle modifications, for the treatment of adults with T2DM to improve glycemic control in combination with MET, with or without SU, when these combined with basal insulin (less than 50 units daily) or liraglutide (less than or equal to 1.8 mg daily), do not provide adequate glycemic control. IDegLira is available in a pre-filled pen format that contains 3 mL, which is equivalent to 300 units of IDeg and 10.8 mg of liraglutide. One unit contains one unit of IDeg and 0.036 mg of liraglutide. The IDegLira pen delivers doses from one to 50 units with each injection.

The recommended starting dosage of IDegLira is 16 units (16 units of IDeg and 0.58 mg of liraglutide) given subcutaneously once daily. The dosage is then titrated upward or downward by two units every three to four days based on the patient's metabolic needs, blood glucose monitoring results, and glycemic control goal until the desired fasting plasma glucose is achieved. The maximum daily dosage of IDegLira is 50 units (50 units of insulin degludec and 1.8 mg of liraglutide). If patients require IDegLira daily dosage persistently below 16 units, or over 50 units, then alternative antihyperglycemic agents should be used.

Summary of Evidence Considered by CDEC Considerations

CDEC considered the following information prepared by the CADTH Common Drug Review: a systematic review of RCTs of IDegLira, an indirect treatment comparison submitted by the manufacturer for each of the relevant patient populations, and a critique of the manufacturer's pharmacoeconomic evaluation. CDEC also considered input from a clinical expert with experience in treating patients with T2DM, and patient group–submitted information about outcomes and issues important to patients.

Summary of Patient Input

Two patient groups, Diabetes Canada and Type 2 Diabetes Experience Exchange, provided patient input for this submission. Patient perspectives were obtained from online surveys, personal interviews, facilitated group discussions, and social media conversation threads. The following is a summary of key input from the perspective of the patient groups:

- T2DM requires considerable self-management, including eating well, regular physical activity, maintaining a healthy body weight, taking medications (oral and/or injectable) as prescribed, monitoring blood glucose, and managing stress.
- Diabetes affects all aspects of patients' lives from eating and exercising to working and socialization. Patients are anxious and fearful of complications of the disease, and face stigma due to diabetes. A wide range of comorbidities are associated with the disease, and patients indicated that even with diligence they often still pay a price with multiple complications.

- About two-thirds of patients indicated that they were either “satisfied” or “very satisfied” with the medication or combination of medications they were currently taking for their diabetes management.
- Keeping blood glucose at a satisfactory level, avoiding low blood sugar, avoiding weight gain or facilitating weight loss, reducing the risk of heart problems, and avoiding gastrointestinal issues (nausea, vomiting, diarrhea, pain) and urinary tract and/or yeast infections were considered “quite important” or “very important” factors in choosing diabetes medications among respondents.
- Patients want new treatments that enhance weight loss and improve health outcomes at an affordable cost. They want treatments that are easily administered, cause the least amount of disruption to lifestyle, and allow for flexibility with food intake and choices. They also want medications that will help avoid polypharmacy and eliminate the need for injections while minimizing the risk of any short-term medication-related side effects or long-term disease-related side effects.

Clinical Trials

The systematic review included four phase III RCTs (DUAL II, DUAL V, DUAL VII, and DUAL III). The DUAL II trial (N = 413) was a randomized, double-blind, superiority trial in patients with T2DM inadequately controlled with basal insulin (between 20 and 40 units per day) and MET with or without SU or glinides comparing the efficacy and safety of IDegLira once daily with insulin degludec (IDeg) once daily, both added on to MET. The DUAL V trial (N = 557) was a randomized, open-label, noninferiority (NI) trial that compared the efficacy and safety of IDegLira once daily with insulin glargine (IGlar) once daily, both in combination with MET in patients with T2DM inadequately controlled on IGlar at a daily dose between 20 and 50 units (both inclusive) in combination with MET. The DUAL VII trial (N = 506) was a randomized, open-label, NI trial that compared the efficacy and safety of IDegLira once daily with basal-bolus therapy (once daily IGlar plus prandial insulin aspart [IAsp]), both arms in combination with MET in patients with T2DM inadequately controlled on IGlar at a daily dose between 20 units and 50 units (both inclusive) in combination with MET. The DUAL III trial (N = 438) was a randomized, open-label, superiority trial that compared IDegLira versus unchanged GLP-1 RA therapy in controlling glycaemia in insulin-naive patients with T2DM inadequately controlled on a maximum tolerated dose or maximum dose according to local label of GLP-1 RA (Victoza [liraglutide] or Byetta [exenatide injection]) and MET ± pioglitazone ± SU. These trials examined short-term (26 weeks) surrogate outcomes including A1C, body weight, and blood pressure.

There were a number of limitations noted for these trials. Firstly, DUAL V, DUAL VII, and DUAL III trials were open-label in their design, which increases potential for bias in reporting of subjective outcomes, such as the reporting of adverse events (AEs) and health-related quality of life (HRQoL). Secondly, in the DUAL V, and DUAL VII trials, although secondary outcomes for the change from baseline in body weight, and number of treatment-emergent confirmed hypoglycemic episodes were adjusted for multiple testing, there was no control of multiplicity for the other secondary outcomes analyzed. None of the secondary outcomes in DUAL II, and DUAL III trials were adjusted for multiple testing. Hence, results of the outcomes measures that were not adjusted for multiple testing, such as body weight (in DUAL II, and DUAL III), fasting plasma glucose (FPG), systolic blood pressure (SBP), diastolic blood pressure in all of the included trials, and patient-reported outcomes (in DUAL V, DUAL VII, and DUAL III) should be interpreted with consideration of the potential for inflated type I error. Thirdly, in the DUAL II trial, titration in the IDeg comparator arm was limited by a maximum dose of 50 units in order to match the maximum allowable IDeg dose in IDegLira. In a trial which is designed to demonstrate superiority of IDegLira versus IDeg, there is a concern for the impact of the use of a capped insulin dose in this trial on the clinical generalizability of the results. In the DUAL III trial, IDegLira dosing was continuously titrated to achieve a FPG target of 4 mmol/L to 5 mmol/L; whereas the GLP-1 RA dose was unchanged from the baseline level for which patients had inadequate glycemic control and had no glycemic drugs added even though insulin-naive patients inadequately controlled on liraglutide and in need of treatment intensification would not remain on unchanged liraglutide in clinical practice. Finally, all included trials were limited by the duration of 26 weeks (a maximum of 32 weeks including the screening period and follow-up period).

Outcomes

Outcomes were defined a priori in the CADTH Common Drug Review systematic review protocol. Of these, the committee discussed the following:

- Glycemic control — change from baseline in A1C, FPG, proportion of patients with A1C less than 7% or ≤ 6.5% after 26 weeks of treatment.
- Body weight — change from baseline in body weight.
- Hypoglycemia — events of hypoglycemia, including severe hypoglycemia. Hypoglycemic episodes were classified according to the Novo Nordisk classification of confirmed hypoglycemia and the American Diabetes Association (ADA) classification of hypoglycemia. According to the ADA classification, severe hypoglycemia was defined as an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other resuscitative actions. Asymptomatic hypoglycemia was defined as an episode not accompanied by typical symptoms of hypoglycemia, but with a measured plasma glucose concentration of ≤ 3.9 mmol/L or 70 mg/dL.
- HRQoL was assessed by generic (the Short Form-36 [SF-36]) and diabetes-specific questionnaires (the Treatment-Related Impact Measure for Diabetes [TRIM-D], or the Diabetes Treatment Satisfaction Questionnaire [DTSQ] status. The SF-36 is a generic health assessment questionnaire. The SF-36 consists of 36 items representing eight dimensions: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. Item response options are presented on a three to six-point, Likert-like scale. All items are scored so that a high score defines a more favourable health state. In addition, each item is scored on a zero to 100 range so that the lowest and highest possible scores are zero and 100, respectively. Scores represent the percentage of total possible score achieved. Item scores are averaged together to create the eight domain scores. The SF-36 also provides two component summaries, the physical component summaries (PCS) and the mental component summary (MCS), which are created by aggregating the eight domains according to a scoring algorithm, with scores ranging from zero to 100 with higher scores indicating better health status. The domain and summary scores (PCS and MCS) are standardized T scores to the US population with a mean equal to 50 and standard deviation equal to 10. In general, with the use of the SF-36 version 2, the User's Manual proposed the following minimal clinically important differences (MCID): a change of two points on the PCS, and three points on the MCS. Comprehensive validation of the SF-36 in T1DM and T2DM is incomplete and no MCID specifically in diabetes has been established.
    - The TRIM-D is a diabetes-specific instrument designed to measure the treatment-related impact of diabetes medications on patients. TRIM-D is a 28-item, self-reported questionnaire encompassing five domains: treatment burden (six items), daily life (five items), diabetes management (five items), psychological health (eight items), and compliance (four items). Response options are presented on a five-point, Likert-like scale. An increase in score indicates an improvement in the health state. Domains can be scored individually, or the measure can be scored as a total of these domains. The highest possible summed score within a subdomain ranges from 20 (compliance subdomain) to 40 (psychological health subdomain) points and the highest possible total score is 140 points. All domain scores and the total score are transformed to a 0 to 100 scale. No MCID has been determined for the TRIM-D.
    - The DTSQ was used to assess patient satisfaction with treatment (six items) and perception of change in hyperglycemia and hypoglycemia (two items). Six of the eight items measure treatment satisfaction (satisfaction with current treatment, convenience, flexibility, satisfaction with own understanding of diabetes, and likelihood of continuing on or recommending current treatment). The item scores range from "very satisfied" (= a score of six) to "very unsatisfied" (= a score of zero), and the sum of these items is used to generate a DTSQ score, ranging from 0 to 36. Higher DTSQ scores indicate greater satisfaction with treatment. For the two items measuring perceived frequency of hyperglycemia and frequency of hypoglycemia, the items are scored on seven-point response scales ranging from "most of the time" (= a score of six) to "none of the time" (= a score of zero). Lower DTSQ scores indicate more ideal blood glucose levels in this case. A MCID for the DTSQ in patients with T2DM was not identified.
- AEs, serious adverse events (SAEs), AEs leading to premature treatment discontinuation, and notable harms.

The primary end point in all trials was change from baseline in A1C after 26 weeks of treatment.

Efficacy

- IDegLira in combination with MET statistically significantly reduced A1C levels after 26 weeks of treatment compared with IDeg (DUAL II trial) or IGlar (DUAL V trial) in combination with MET. The estimated LS mean difference (95% CI) was −1.05% (−1.25 to −0.84) in DUAL II, and −0.59% (−0.74 to −0.45) in DUAL V.

- In the DUAL VII trial, IDegLira, in combination with MET, was noninferior to IGlar + IAsp plus MET for the change from baseline in A1C after 26 weeks of treatment based on a 0.3% noninferiority margin (LS mean difference was −0.02; 95% CI −0.16 to 0.12). No statistically significant difference was detected between treatments in the test for superiority.
- The DUAL III trial reported that IDegLira in combination with MET ± pioglitazone ± SU statistically significantly reduced A1C levels after 26 weeks of treatment compared with GLP-1 RA in combination with MET ± pioglitazone ± SU. The estimated LS mean difference (95% CI) was −0.94 (−1.11 to −0.78), which was statistically significant, favouring IDegLira versus GLP-1 RA (*P* < 0.001).
- In the DUAL II, DUAL V, and DUAL III trials, more patients in the IDegLira treatment groups achieved target A1C levels (< 7.0% or ≤ 6.5%) than in the IDeg, IGlar, or GLP-1 RA treatment groups. In the DUAL II, DUAL V, and DUAL III trials, the proportion of patients achieving A1C < 7% in the IDegLira treatment group was 60.3%, 71.6%, and 75.3 and was 23.1%, 47.0%, and 35.6% in the IDeg, IGlar, and GLP-1 RA treatment groups, respectively. In these same trials, the proportion of patients achieving A1C ≤ 6.5% in the IDegLira treatment group was 45.2%, 55.4%, and 63.0 and was 13.1%, 30.8%, and 22.6% in the IDeg, IGlar, and GLP-1 RA treatment groups, respectively. In addition, in the DUAL II, and DUAL V trials, the proportion of patients reaching the pre-defined A1C targets (A1C < 7.0% or ≤ 6.5%) after 26 weeks of treatment without either weight gain or hypoglycemic episodes or both was also higher in the IDegLira treatment groups than in the IDeg or IGlar, treatment groups.
- No differences were detected in the proportion of patients achieving glycemic targets for IDegLira group versus IGlar plus IAsp group in the DUAL VII trial. However, in the DUAL VII trial, treatment with IDegLira, compared with IGlar plus IAsp, resulted in higher proportions of patients achieving glycemic targets (A1C < 7.0% or ≤ 6.5%) after 26 weeks of treatment without either weight gain or treatment-emergent severe or blood glucose confirmed symptomatic hypoglycemic episodes, or both.
- Input from patient groups reported weight loss as an important outcome. In DUAL V, and DUAL VII, IDegLira showed statistically significant reductions in body weight after 26 weeks compared with IGlar, and IGlar + IAsp (LS mean difference −3.20 kg, and −3.57 kg, respectively). In the DUAL II trial, IDegLira also showed reductions in body weight after 26 weeks compared with IDeg (LS mean difference −2.51). In contrast, in the DUAL III trial, patients treated with IDegLira gained significantly more weight than patients that continued GLP-1 RA therapy. This is to be expected when an insulin-naive population previously treated with GLP-1 RA transfers to an insulin containing antidiabetic product. This outcome was not adjusted for multiplicity in DUAL II and DUAL III trials, hence any result reported should be interpreted with consideration of the potential for inflated type I error.
- Input from patient groups reported HRQoL as an important outcome. The HRQoL outcomes measured in the trials were the TRIM-D in DUAL V, DUAL VII, and DUAL III, the SF-36 in DUAL V and DUAL VII, and the DTSQ in DUAL III. Analyses of these outcomes were not adjusted for multiplicity, and any result reported should be interpreted with consideration of the potential for inflated type I error. While results from patient-reported outcome questionnaires seemed to favour IDegLira treatment groups, no MCIDs were established specific to patients with T2DM, and the clinical significance of the benefit of IDegLira compared with IGlar, IGlar + IAsp, or GLP-1 RA for these assessed outcomes was unclear from the literature. In addition, the difference seen between IDegLira treatment groups and IGlar, and IGlar + IAsp treatment groups in SF-36 did not exceed the proposed MCID in the SF-36 User's Manual for PCS, MCS, and all of SF-36 domains.

Harms (Safety)

- The overall frequency of AEs was similar between-treatment groups within trials. In DUAL II, DUAL V, and DUAL VII trials AEs were reported by 57.6% to 59.1% of patients who received IDegLira, and by 61.3%, 50.5%, and 56.9% of patients who received IDeg, IGlar, and IGlar + IAsp, respectively. In DUAL III trial, AEs were reported by 65.6% of patients treated with IDegLira and by 63.4% of patients treated with GLP-1 RA.
- SAEs were reported by 1.8% to 4.8% of patients who received IDegLira, and by 5.5%, 3.2%, 4.0%, and 2.1% of patients who received IDeg, IGlar, IGlar + IAsp, and GLP-1 RA respectively. In all of the included trials, no SAEs occurred in ≥ 1% of the patients.
- The rates of AEs leading to withdrawal from the trials were reported by 0.3% to 2.5% of patients who received IDegLira, and by 1.5%, 0.4%, 0%, and 1.4% of patients who received IDeg, IGlar, IGlar + IAsp, and GLP-1 RA respectively.
- No deaths were reported during the DUAL II, DUAL VII, and DUAL III trials. In DUAL V trial, one patient died during the trial; that patient was treated with IGlar, and died due to hemorrhagic stroke. The event was considered unlikely to be related to the trial product.

- The proportion of patients who experienced a severe hypoglycemia event as defined by the ADA in each individual study was too low (ranged from 0% to 1.6% across the included trial) to make a judgment on the comparative incidence of severe hypoglycemia.
- Gastrointestinal AEs were reported more frequently in the IDegLira group compared with the IDeg, IGlar, and IGlar + IAsp treatment groups, which was expected from the safety profile of liraglutide. The most frequent gastrointestinal AEs in the IDegLira treated groups were nausea, diarrhea, and vomiting.

Indirect Treatment Comparisons

The indirect treatment comparison (ITC) submitted by the manufacturer for the patients with T2DM inadequately controlled with basal insulin (in combination with MET ± SU), reported a greater [redacted] in patients treated with IDegLira compared with [redacted] or [redacted]. A greater reduction was reported in [redacted] in IDegLira compared with [redacted]. A greater reduction in [redacted] in IDegLira compared with [redacted] regimen was also observed. However, due to the considerable high level of heterogeneity across the included studies, the reported ITC estimates are highly uncertain, especially for the comparison of IDegLira with [redacted], where there was no supportive evidence from head-to-head trials. No ITC comparing IDegLira with [redacted] or [redacted] was conducted in this patient population, and the ITC did not assess clinically important outcomes (e.g., [redacted]).

For the patients with T2DM inadequately controlled with liraglutide (in combination with MET ± SU), the [redacted] ITC submitted by the manufacturer showed that IDegLira was associated with [redacted], but also associated with [redacted], which was in line with findings from the [redacted]. In the comparison of IDegLira versus [redacted], there was [redacted] observed in [redacted]. However, the [redacted] ITC provided only limited evidence for the comparative efficacy and safety of IDegLira due to the small number of included studies, in addition there was a lack of evidence for the comparative efficacy and safety results versus a number of relevant comparators (e.g., [redacted]).

Cost and Cost-Effectiveness

IDegLira is available as a pre-filled pen containing 3 mL of solution equivalent to 300 units of IDeg and 10.8 mg of liraglutide (each unit dispensed from the pen contains 1 unit of IDeg and 0.036 mg of liraglutide). The manufacturer submitted the drug at a price of $60.80 per pen. At the recommended dose of 16 units/0.58 mg to 50 units/1.8 mg for IDegLira, the average daily cost is $3.42 to $10.13 per patient.

The manufacturer submitted a cost-utility analysis over a 40-year time horizon (referred to as a lifetime horizon). The analysis was conducted from the perspective of a Canadian public health-care payer. Analyses were conducted for three populations: patients who have not achieved adequate glycemic control on basal insulin (basal insulin stratum); patients who have not achieved adequate glycemic control on liraglutide (liraglutide stratum); and patients who have not achieved adequate glycemic control with oral glucose-lowering medications combined with basal insulin, or basal insulin alone (reimbursement request). All comparators were assumed to be in combination with MET with or without SU. The submission is based on the Institute for Health Economics Cohort Model for T2DM. The model incorporated a variety of health states relating to the important micro and macrovascular complications associated with diabetes, the incidence of hypoglycemic events, and the associated impact of complications and events on mortality. Within the model, the annual probability of major diabetes-related macrovascular complications was derived from risk equations based on the United Kingdom Prospective Diabetes Study (UKPDS) 82. Microvascular complications were modelled based on previously published studies. Macrovascular complications were modelled based on the UKPDS 82 risk models. Thus, the risk of each complication was a function of a range of predictors including biomarkers such as A1C, SBP and low-density lipoprotein.

For all treatment populations considered, the impact of treatment on preventing complications was based on indirect evidence in that the model simulates the progression of biomarkers over time, incorporating the impact of treatment, which then has an impact on the probability of events occurring. This was necessary given that data from the clinical trials only cover a 26-week period, and therefore

assumptions relating to extrapolation of data beyond this period up to 40 years were necessary. Clinical data for the basal insulin stratum and the liraglutide stratum were derived from a manufacturer–submitted network meta-analysis given the limited number of comparators to which IDegLira has been compared. For the reimbursement scenario, data from the DUAL VII clinical trial were used.

For the basal insulin stratum, the manufacturer reported that the incremental cost per quality-adjusted life-year (QALY) gained (incremental cost-effectiveness ratio [ICER]) for iGlarLixi versus premix insulin was $8,310, while the ICER for IDegLira versus iGlarLixi was $17,984. For the liraglutide stratum, liraglutide was associated with the highest estimated QALY; and, the ICER for liraglutide versus IDegLira was $55,223. For the reimbursement scenario, IDegLira dominated basal-bolus (i.e., IDegLira was associated with lower costs and greater QALYs).

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

- Issues were identified with the manufacturer's ITCs, as highlighted by the CADTH clinical review.
- The clinical trial data were limited to 26-weeks duration, as such more than 90% of the incremental benefit suggested with IDegLira occurs after the clinical trial period. No assumption of differential waning of relative treatment effect was made.
- There were concerns with the manufacturer's assumptions relating to the disutility associated with BMI and hypoglycemic events.
- Given issues with the transparency of the manufacturer's model, verification of it was not possible and there were concerns over the inconsistency of results provided by the manufacturer.

Given the above limitations, it was not possible for CADTH to provide any meaningful reanalyses.

Since there were no ITCs provided considering clinically important outcomes, such as [redacted], and the ITC does not include a comparison of IDegLira with [redacted], it is unclear if IDegLira represents a clinical benefit over all treatment alternatives.

Based on the manufacturer's economic submission, the estimated treatment costs by the manufacturer are generally higher for IDegLira relative to included comparators in all analyses. Given the lack of comparative clinical information for IDegLira, and concerns with the submitted economic evaluation, it is uncertain if IDegLira represents a cost-effective treatment option.

CDEC Members

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Peter Jamieson, Mr. Allen Lefebvre, Ms. Heather Neville, Dr. Rakesh Patel, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

September 18, 2019 Meeting

Regrets

None

Conflicts of Interest

None