CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

INSULIN DEGLUDEC (TRESIBA — NOVO NORDISK CANADA INC.)
Indication: Diabetes Mellitus, Types I and II

RECOMMENDATION:
The CADTH Canadian Drug Expert Committee (CDEC) recommends that insulin degludec be reimbursed for the once-daily treatment of adults with diabetes mellitus to improve glycemic control, if the following conditions are met:

Conditions:

- Reimburse in a manner similar to other long-acting insulin analogues that are reimbursed for the treatment of diabetes mellitus.
- The overall drug plan costs for insulin degludec should not exceed the cost of treatment with the least costly long-acting insulin analogue reimbursed for the treatment of diabetes mellitus.

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Redactions: Confidential information in this document has been redacted at the request of the manufacturer in accordance with the *CADTH Common Drug Review Confidentiality Guidelines.*

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Reason for the Recommendation:

In one double-blind randomized controlled trial comparing insulin degludec with insulin glargine in patients with type 2 diabetes mellitus (T2DM) and established cardiovascular disease (DEVOTE, N = 7,637), insulin degludec was noninferior to insulin glargine for the composite outcome of major adverse cardiovascular events, including cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. In 19 other studies, including the SWITCH and BEGIN studies, insulin degludec was consistently noninferior to insulin glargine for the change from baseline in glycated hemoglobin (A1C) at 16, 26, and 52 weeks, and results for changes in fasting plasma glucose and variability in blood glucose did not differ significantly between insulin degludec and either insulin glargine or insulin detemir.

Of Note:

The CDR reanalyses of the cost-utility model submitted by the manufacturer suggested that, at the submitted price, insulin degludec is cost-effective for patients with type 1 diabetes mellitus (T1DM) compared with insulin glargine. However, for patients with T2DM, treatment with insulin degludec will likely be associated with incremental costs for several patient populations, because the incremental cost-utility ratio (ICUR) for various populations of patients with T2DM ranged from $73,000 per quality-adjusted life-year (QALY) to > $1 million per QALY.

Discussion Points:

- CDEC noted that the pharmacoeconomic submission (and CDR reanalyses) considered a unit price for insulin glargine (Basaglar) of $78.92 per 1,500 units, which was the reflected price at the time of submission. The publicly available unit price for Basaglar at the time of CDEC deliberation decreased to $69.64 per 1,500 units. The reduction in the unit price for Basaglar is expected to impact the cost-effectiveness results and the subsequent price reductions necessary for insulin degludec to be cost-effective compared with insulin glargine.
- CDEC noted that hypoglycemia was identified by patient groups as a key safety issue, particularly for patients with T1DM. Input from patient groups emphasized the need for therapies that are effective in reducing the frequency of hypoglycemia events, and the perception from the same patient groups suggested that insulin degludec was effective in addressing this need. However, it was noted by CDEC that the results reported in the reviewed trials were mixed. There was a statistically significant reduction in the risk of severe hypoglycemic events in the DEVOTE trial and in the SWITCH studies, although the proportional difference between groups experiencing a hypoglycemic event was relatively small. In the BEGIN trials, there was no consistent evidence of superiority of insulin degludec compared with insulin glargine or insulin detemir for events of confirmed hypoglycemia.

- CDEC recognized that the pharmacodynamics of insulin, and the findings from the Flex T1 and T2 studies, suggest that insulin degludec can be administered at any time of day and that the timing of injection can vary without compromising glycemic control or safety. This may improve basal insulin adherence by allowing injection-time adjustment according to individual needs; however, there is no evidence that this advantage translates into improvements in quality of life.
- Although insulin degludec was compared with neutral protamine Hagedorn (NPH) in the manufacturer-submitted network meta-analysis (NMA) and in the manufacturer-submitted pharmacoeconomic analysis, CDEC recognized that insulin degludec is a long-acting insulin analogue and, therefore, thought it appropriate to limit the reimbursement conditions to comparisons within this class (e.g., insulin glargine and insulin detemir).

Background:

Insulin degludec has a Health Canada–approved indication for the treatment of adults with diabetes mellitus to improve glycemic control. It is an ultra-long-acting (duration of 42 hours) basal insulin analogue. Insulin degludec is administered by subcutaneous injection, and the Health Canada–approved starting dose for patients with T2DM is 10 units. In patients with T1DM, the dose is to be adjusted based on individual needs.

Summary of CDEC Considerations:

The Committee considered the following information prepared by the CADTH Common Drug Review (CDR): a systematic review of randomized controlled trials of insulin degludec, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group–submitted information about outcomes and issues important to patients.

Patient Input Information:

Three patient groups responded to the CDR call for patient input (Type 1 Together, Patient Commando, and Diabetes Canada). The following is a summary of information provided by patient groups:

- The primary concern of patients is hypoglycemia, and glycemic control is seen as a major predictor of hypoglycemia. The variability in blood glucose is not only seen as a major source of stress related to risk of hypoglycemia but may also require patients to wake during the night to monitor therapy. Patients emphasized the trade-off between the benefits of tight glycemic control on morbidity and the risk of hypoglycemia.
- Although patients recognized the improvements in glycemic control afforded by currently available therapies and delivery systems, they also identified lingering issues with adherence, variability in blood glucose from day to day, side effects and issues with managing the disease symptoms, the serious long-term complications of diabetes mellitus, and the stress and frustration inherent in managing strict treatment regimens.
- Patients are looking for a therapy that can provide more consistent glycemic control over a longer, more predictable time frame. They are also looking for a therapy that can provide this consistency with a reduced risk of weight gain. Patients hope to improve adherence while at the same time reducing the emotional burden of managing their condition. They also hope for improved access and coverage and reduced cost through public drug plans.

Clinical Trials

The systematic review included 15 randomized controlled trials and five extension studies of insulin degludec in patients with diabetes mellitus.

The largest trial, DEVOTE (N = 7,637, randomized 1:1 between insulin degludec and insulin glargine over a mean of 24 months), was a noninferiority cardiovascular outcomes study that focused on a population of patients with T2DM and with cardiovascular disease.

The two SWITCH studies compared insulin degludec to insulin glargine in a crossover design in patients with T1DM (SWITCH-1) and T2DM (SWITCH-2). These studies were much smaller than DEVOTE (SWITCH-1, N = 501; SWITCH-2, N = 721), and had a 32-week treatment period.

The DEVOTE study and the two SWITCH studies were double-blind randomized controlled trials, while all but one of the remaining trials were open label. The open-label studies were part of the BEGIN clinical trial program, which focused on four separate subgroups of patients:

- patients with T1DM: Studies 3770 (N = 493), 3585 (N = 456) and 3583 (N = 629), each with an extension
- T2DM and insulin-naive patients: Studies 3579 (N = 1,030) plus extension, 3580 (N = 458), 3672 (N = 460), 3586 (N = 435), 3587 (N = 833), and 3944 (N = 346)
- T2DM patients on a basal insulin: Studies 3668 (N = 687), 3943 (N = 145)
- T2DM patients with a bolus insulin: Study 3582 (N = 1,006) plus extension.

Of the BEGIN trials, Study 3943 was 16 weeks, Studies 3583, 3579, and 3582 were 52 weeks, and the remaining studies were 26 weeks (without extensions). Across the 12 BEGIN trials, the most common comparator was insulin glargine (nine studies); while insulin detemir, placebo, and sitagliptin were comparators in one study each. None of the included studies had insulin NPH as a comparator.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed the following:

- Cardiovascular morbidity and mortality: time from randomization to first occurrence of a three-component major adverse cardiovascular event (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) confirmed by an event adjudication committee
- Hypoglycemia: confirmed hypoglycemic episodes consisting of episodes of severe hypoglycemia as well as minor hypoglycemic episodes with a confirmed plasma glucose value of < 3.1 mmol/L. Hypoglycemic episodes were defined as nocturnal if the time of onset was between 00:01 and 05:59 (both included). Severe hypoglycemia was defined as an episode requiring assistance of another person to actively administer carbohydrate, glucagons, or other resuscitative actions.
- Health-related quality of life: changes in patients' health-related quality of life and treatment-related impacts of minor hypoglycemic episodes on patients' daily function and well-being, evaluated using the Short Form (36) Health Survey version 2 (SF-36v2) and the Treatment-Related Impact Measure for Hypoglycemic Events (TRIM-HYPO) questionnaires, respectively
- Blood glucose measures: change in A1C, fasting plasma glucose, and glucose variability

The primary outcome in the DEVOTE study was the incidence of major adverse cardiovascular events. The primary outcome in the SWITCH studies was the incidence of severe or blood glucose–confirmed hypoglycemic events, and the primary outcome in all the BEGIN trials was the change in A1C from baseline to end of treatment.

Quality of life was typically assessed only as an exploratory outcome in the included studies, with no adjustments made for multiple comparisons, and was not assessed at all in DEVOTE, the largest study.

The fear of hypoglycemia was a key concern noted by patients in their input to CDR. Hypoglycemia was assessed as a primary end point in the two SWITCH studies and as a key secondary outcome in DEVOTE. Patients also identified blood glucose variability as an outcome related to hypoglycemia that was of concern, and although this was often among the key secondary outcomes in the included trials, it was often lower in the statistical hierarchy and was therefore often not tested.

Efficacy

Insulin degludec was noninferior to insulin glargine for the primary outcome, a composite of major adverse cardiovascular events, in the DEVOTE study after a mean of 24 months' treatment. Several secondary outcomes related to cardiovascular events, such as

myocardial infarction or stroke, as well as overall and cardiovascular mortality, were not statistically significantly different between insulin degludec and insulin glargine. Severe hypoglycemic events were also assessed as a secondary outcome, and the risk of severe hypoglycemic events was lower with insulin degludec than with insulin glargine; this difference was statistically significant.

In the SWITCH studies, the primary outcome was severe or blood glucose–confirmed hypoglycemic events, and in both studies insulin degludec was superior to insulin glargine for the primary outcome. SWITCH employed a crossover design, with each treatment period extending over 32 weeks. There was no difference in the proportion of participants experiencing a major adverse cardiovascular event in the SWITCH studies, although there were few of these events in both studies.

The remaining included trials were the BEGIN trials, which all had a primary outcome of change from baseline in A1C. All studies that compared insulin degludec to another basal insulin (insulin glargine, nine studies; insulin detemir, one study) demonstrated noninferiority for insulin degludec for this primary outcome, while two double-blind studies found superiority of insulin degludec, one versus sitagliptin and the other placebo-controlled. Both of these double-blind studies were in a population with T2DM that was insulin-naive. Confirmatory secondary outcomes in the BEGIN studies included change from baseline in fasting plasma glucose, glucose variability, confirmed hypoglycemic events, and confirmed nocturnal hypoglycemic events; superiority was rarely demonstrated for insulin degludec versus insulin glargine or insulin detemir for any of these outcomes. There were no consistent differences between insulin degludec and comparators in any health-related quality of life measures on either the SF-36v2 or the Treatment-Related Impact Measure for Diabetes (TRIM-D) and TRIM-HYPO scales.

Harms (Safety and Tolerability)

Across all studies, there were no consistent differences between insulin degludec and comparators in the proportion of patients experiencing an adverse event, serious adverse event, or withdrawal due to adverse event.

Hypoglycemia, of key concern to patients based on their input to CDR, was often assessed as a confirmatory secondary outcome, and in DEVOTE and in the SWITCH studies the risk of severe or blood glucose–confirmed hypoglycemic events was lower with insulin degludec than with insulin glargine. However, in the BEGIN trials, there was no evidence of superiority for insulin degludec over insulin glargine or insulin detemir for confirmed hypoglycemic events for any of the included studies, with the exception of study 3582, in T2DM with a basal-bolus regimen.

Network Meta-Analysis

Three NMAs were reviewed: one submitted by the manufacturer and two identified in the systematic literature search conducted by CADTH. The manufacturer-submitted NMA was limited to three treatments (insulin degludec, glargine, and NPH) and focused on hypoglycemic events as the primary outcome. The other two NMAs included all the basal insulins of interest to this CDR review and examined efficacy outcomes (e.g., A1C, body weight) as well as hypoglycemia. In patients with T1DM, the direct evidence for insulin degludec versus insulin glargine showed no statistically significant differences in the rate of severe hypoglycemia or change from baseline in A1C. The indirect evidence also suggested no statistically or clinically important differences between insulin degludec and insulin glargine, insulin detemir, or NPH on the rate of hypoglycemia or change in A1C. In T2DM, results differed between the NMAs, as a published report found a reduced risk of nocturnal hypoglycemia but an increased risk of symptomatic hypoglycemia with insulin degludec versus insulin glargine, both statistically significant. Conversely, in the manufacturer-submitted analysis, there was a reduction in nocturnal hypoglycemia with insulin degludec versus both insulin glargine and NPH which was statistically significant; however, the analysis of overall hypoglycemia could not be interpreted because the authors stated that both the fixed-effects and random-effects models showed poor fit with high residual deviance values. All analyses were limited by the quality of the included studies.

Cost and Cost-Effectiveness

At the submitted price of $125.28 per 1,500 units, insulin degludec ($7.19 daily) is similar in price to insulin detemir ($7.12 daily) but more expensive than insulin glargine ($6.19 daily) or Basaglar ($5.26 daily).

The manufacturer submitted a cost-utility analysis comparing insulin degludec with insulin glargine (Lantus) in adult patients with T1DM or T2DM when used as part of a basal-bolus or basal–oral therapy regimen. Four patient populations were considered: T1DM

patients on a basal-bolus insulin regimen (T1DM basal + bolus; population 1), T2DM patients who are insulin starters on basal insulin and oral antidiabetes drug therapies (T2DM basal + oral antidiabetes drugs [OAD]; population 2), T2DM patients who are insulin experienced (EX) on basal insulin and OAD therapies (T2DM basal + OAD EX; population 3), and T2DM patients requiring insulin intensification on a basal-bolus insulin regimen (T2DM basal + bolus; population 4). Insulin degludec was compared with NPH insulin in a secondary analysis. The analysis was conducted over a one-year time horizon from the Canadian public payer perspective. The economic model focused only on the risk, costs, and quality-of-life impacts associated with hypoglycemia, as the results for A1C did not differ between treatment regimens. The relative efficacy related to hypoglycemic events and the relative dose ratios were obtained from the SWITCH 1 and SWITCH 2 trials and two manufacturer's meta-analyses. For the comparison of insulin degludec with NPH insulin, relative efficacy related to hypoglycemic events was obtained from the manufacturer's NMA.

In their base case, the manufacturer reported that insulin degludec dominated (i.e., less costly and associated with more QALYs) insulin glargine in the T1DM population (population 1), and for T2DM resulted in an ICUR of $5,564 (population 2), $20,887 (population 3), and $95,155 (population 4) per QALY. For insulin degludec compared with NPH insulin, insulin degludec dominated NPH insulin in populations 1 and 2 and resulted in an ICUR of $9,256 to $164,361 per QALY in populations 3 and 4.

CDR identified the following key limitations with the manufacturer's economic submission:

- The one-year economic model considers only hypoglycemia. The long-term relative risk of hypoglycemia and other clinical outcomes over a longer time horizon are unknown. The ICUR may be higher in subsequent years if the effects of insulin degludec on hypoglycemia change with time.
- Relative efficacy related to hypoglycemic events in the model was derived from a manufacturer-sponsored meta-analysis and NMA. Limitations were noted for both analyses.
- The relative doses of insulin degludec and insulin glargine, as well as NPH insulin, are highly uncertain where direct comparisons are generally unavailable.
- Trial-observed rates of hypoglycemia derived from study populations may be at greater risk of hypoglycemia than the population indicated by the reimbursement request.

In a plausible CDR base case (insulin degludec versus insulin glargine) that considers relative risk of hypoglycemic events from clinical trials of direct comparisons and meta-analyses and that uses a dose ratio of 1 between insulin degludec and insulin glargine and the lowest cost long-acting insulin analogue (Basaglar $94.06 per 1,500 IU),

- for population 1 (T1DM), insulin degludec is dominant (less costly and more effective) over insulin glargine.
- for population 2 (T2DM basal + OAD), the ICUR is more than $1 million per QALY
- for population 3 (T2DM basal + OAD EX), the ICUR is $73,000 per QALY
- for population 4, T2DM basal + bolus, the ICUR is $150,000 per QALY

The incremental differences in QALYs in the cost-effectiveness analysis are very small and are particularly sensitive to baseline hypoglycemia rates. Consequently, the estimates of comparative cost-effectiveness between insulin degludec and insulin glargine are relatively unstable.

Price reductions of 10% to more than 25% would be required for insulin degludec to fall to $50,000 per QALY when compared with insulin glargine.

CDEC Members:

Dr. James Silvius (Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Peter Jamieson, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

October 18, 2017

Regrets:

None

Conflicts of Interest:

None