CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

INSULIN GLARGINE AND LIXISENATIDE (SOLIQUA — SANOFI-AVENTIS CANADA INC.)
Indication: Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus inadequately controlled on basal insulin (less than 60 units daily) alone or in combination with metformin.

RECOMMENDATION
The CADTH Canadian Drug Expert Committee recommends that insulin glargine and lixisenatide (iGlarLixi) be reimbursed as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus, if the following condition is met:

Condition
Drug plan costs for iGlarLixi should not exceed the combined drug plan costs of lixisenatide and insulin glargine provided separately in jurisdictions that reimburse both drugs for the treatment of type 2 diabetes mellitus.

Service Line: CADTH Drug Reimbursement Recommendation
Version: Final
Publication Date: January 3, 2019
Report Length: 7 Pages

CADTH

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

CADTH

Insulin Glargine and Lixisenatide (Soliqua — Sanofi-Aventis Canada Inc.)

Indication: Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM) inadequately controlled on basal insulin (less than 60 units daily) alone or in combination with metformin.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that insulin glargine and lixisenatide (iGlarLixi) be reimbursed as an adjunct to diet and exercise, with or without metformin, to improve glycemic control in adults with T2DM, if the following condition is met:

Condition

- Drug plan costs for iGlarLixi should not exceed the combined drug plan costs of lixisenatide and the least costly insulin glargine reimbursed separately in jurisdictions that reimburse both drugs for the treatment of T2DM.

Reasons for the Recommendation

1. One open-label, multi-centre, parallel-group randomized controlled trial (RCT) (Lixilan-L) in adults with T2DM (N=736) who were inadequately controlled on basal insulin compared the use of iGlarLixi to insulin glargine for up to 30 weeks. The RCT demonstrated a statistically significant improvement in glycated hemoglobin (hemoglobin A1C) in favour of iGlarLixi compared with insulin glargine from baseline to week 30 (–0.52%; 95% CI, –0.633 to –0.397; $P < 0.0001$). Although there were limitations associated with this study, CDEC noted that the individual components of iGlarLixi have been reviewed previously through the CADTH Common Drug Review (CDR) — specifically, lixisenatide (Adlyxine, 0.05 mg/mL or 0.1 mg/mL pre-filled pen) and insulin glargine (Basaglar, solution for injection 100 U/mL) — and that the clinical evidence reviewed at that time was sufficient for CDEC to recommend that these products be reimbursed.
2. A manufacturer-provided indirect comparison of iGlarLixi versus currently available regimens for T2DM suggested that iGlarLixi has a favourable hypoglycemic profile against basal insulin regimens alone and against glucagon-like peptide-1 (GLP-1) receptor agonists in combination with basal insulin, although comparisons between iGlarLixi and insulin degludec in combination with liraglutide, liraglutide alone, dulaglutide, or any dipeptidyl peptidase-4 (DPP-4) inhibitor, were not available.

Implementation Considerations

- The cost of iGlarLixi will depend on the dose; at lower doses, iGlarLixi will be less costly than the publicly available prices of the individual components; at higher doses, iGlarLixi will be more costly than the individual components.

Discussion Points

- The committee noted that there were several limitations of the Lixilan-L trial, including the open-label design, outcomes of greatest interest such as two-hour post-prandial glucose, health-related quality of life (HRQoL), risk of hypoglycemic events, and the proportion of patients achieving a hemoglobin A1C < 7% or ≤ 6.5% were not adjusted for multiplicity. The duration of the trial (30 weeks) was thought to limit the ability to detect changes in clinically important outcomes, such as cardiovascular-related harms and mortality.
- A fixed-ratio combination of lixisenatide and insulin glargine may be convenient to patients on stable doses of lixisenatide and insulin glargine and might improve adherence to therapy. However, no evidence to support this possibility was provided by the manufacturer. Administering the drugs separately likely allows for better dose titration to meet therapeutic objectives.
- The committee noted that in a trial designed to demonstrate superiority of Insulin glargine and lixisenatide versus insulin glargine, the generalizability of the results was impacted by the capped insulin dose (60 units) and that no other drugs that might improve post-prandial hyperglycemia were used in the glargine only group.

- Lixisenatide (Adlyxine, 0.05 mg/mL or 0.1 mg/mL pre-filled pen) was reviewed by CDEC in October 2017; CDEC recommended reimbursement with the condition that lixisenatide cost does not exceed the cost of the least costly pharmacotherapy reimbursed for T2DM in combination with basal insulin (with or without metformin).
- Insulin glargine and lixisenatide has a dose limitation of 60 units of insulin glargine, which makes it unsuitable for patients who require more than 60 units of insulin glargine daily. It is unknown whether insulin glargine and lixisenatide would be a better treatment option than insulin glargine alone in a setting where basal insulin therapy was optimized.

Background

iGlarLixi has a Health Canada indication for use as an adjunct to diet and exercise to improve glycemic control in adults with T2DM inadequately controlled on basal insulin (less than 60 units daily) alone or in combination with metformin. Insulin glargine is a long-acting insulin analogue and lixisenatide is a GLP-1 receptor agonist. It is available as a fixed-ratio combination pen for subcutaneous injection, containing 100 units/mL insulin glargine and 33 mcg/mL lixisenatide, and the Health Canada–approved dose is between 15 units insulin glargine/5 mcg lixisenatide and 60 units insulin glargine/20 mcg lixisenatide.

Summary of Evidence Considered by CDEC

The committee considered the following information prepared by CDR: a systematic review of RCTs of iGlarLixi, an indirect comparison and network meta-analysis submitted by the manufacturer, and a critique of the manufacturer's pharmacoeconomic evaluation. The committee 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 and caregivers.

Summary of Patient Input

One patient group, Diabetes Canada, provided input for this submission. Patient perspectives were obtained from two separate online surveys, conducted in October 2016 and April 2018. The following is a summary of key input from the perspective of the patient group(s):

- T2DM requires considerable self-management, including eating well, regular physical activity, maintaining a healthy body weight, taking medications as prescribed, and monitoring blood glucose and stress management. The majority of patients indicate that this self-management is very challenging and overwhelming.
- Many patients with T2DM fail to achieve optimal glycemic control and are therefore at risk for acute and chronic diabetes complications.
- Patients indicated that current therapies have resulted in better blood glucose and hemoglobin A1C levels, but often experience adverse effects, such as low blood glucose, weight gain, gastrointestinal adverse effects, or urinary tract and/or yeast infections.
- Responders in both surveys indicated a desire for new treatments to enhance weight loss and improve health outcomes at an affordable cost, which can be easily administered and cause the least disruption to lifestyle, while allowing for flexibility.
- Several patients indicated that it would make a difference to their quality of life to reduce the number of drugs they administer.

Clinical Trials

The systematic review included one phase III RCT (Lixilan-L, N = 736) of patients with T2DM with inadequate glycemic control, despite the use of basal insulin with or without metformin. Lixilan-L was an open-label, active-controlled, treat-to-target, parallel-group superiority trial. Patients were randomly assigned to either iGlarLixi or insulin glargine, with or without the use of metformin, for at least 30 weeks, after a six-week run-in period.

This trial included adult patients with a T2DM diagnosis for at least one year, who were receiving treatment with basal insulin for at least six months prior to screening at a stable dose of 15 units to 40 units per day, with or without oral antidiabetic medication, and with a hemoglobin A1C between 7.5% and 10% at the time of screening.

Limitations of the RCT included its open-label design; the lack of adjustment for multiplicity regarding end points of interest, such as HRQoL, risk of hypoglycemic events, and the proportion of patients achieving a hemoglobin A1C < 7% or ≤ 6.5%; and the capped

dose of insulin glargine at 60 units in this trial in both groups, in order to match the maximum allowable insulin glargine dose in iGlarLixi. This study was also limited by its duration of 30 weeks (a maximum of 39 weeks including the run-in period), which would limit its ability to detect changes in more clinically important outcomes, such as cardiovascular outcomes and mortality. Finally, the external validity of the study may be compromised as the majority of the included patient population was older white males, which may not accurately represent the Canadian diabetic population.

Outcomes

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

- glycemic control — change from baseline in hemoglobin A1C, fasting plasma glucose, post-prandial plasma glucose or glucose excursion, proportion of patients with A1C less than 7% at end point
- body weight — change from baseline in body weight
- hypoglycemia — events of hypoglycemia, including severe hypoglycemia
- HRQoL
- serious adverse events (AEs), total AEs, and withdrawals due to AEs.

The primary outcome in the Lixilan-L trial was change in hemoglobin A1C from baseline to week 30.

Efficacy

- iGlarLixi as add-on therapy in patients with inadequate glycemic control on basal insulin with or without the use of metformin was associated with statistically significant ($P < 0.0001$) reductions in hemoglobin A1C% after 30 weeks compared with insulin glargine (least squares mean [LSM] difference: –0.52%; 95% confidence interval [CI], –0.633% to –0.397%). Additional glycemic outcomes are reported below:
  - A numerically higher proportion of patients in the iGlarLixi group achieved a hemoglobin A1C < 7.0% at week 30 (54.9% in the iGlarLixi group compared with 29.6% in the insulin glargine group), and a hemoglobin A1C ≤ 6.5% at week 30 (22.9% in the iGlarLixi group versus 14.2% in the insulin glargine group); however, these results were not adjusted for multiplicity and should be considered exploratory.
  - Patients treated with iGlarLixi experienced a statistically significantly greater reduction two-hour plasma excursion from baseline to week 30 compared with insulin glargine (LSM difference: –3.43 mmol/L; 95% CI, –3.925 to –2.939; $P < 0.0001$).
  - There was no significant difference observed in change from baseline to week 30 in fasting plasma glucose (LSM difference: 0.11 mmol/L; 95% CI, –0.207 to 0.428); however, these results were not adjusted for multiplicity and should therefore be considered exploratory.
- Input from patient groups reported weight loss as an important outcome; however, it is unclear what degree of change would be considered significant. Mean body weight from baseline to week 30 decreased in the iGlarLixi group (–0.67 kg, standard error [SE]: 0.181) and increased in the insulin glargine group (+0.70 kg, SE: 0.178). There was a statistically significant difference observed between groups (adjusted LSM difference: –1.37 kg; 95% CI, –1.808 to –0.930; $P < 0.0001$).
- Input from patient groups reported HRQoL as an important outcome. [redacted]; however, these results should be considered exploratory as they were not adjusted for multiplicity.

Harms (Safety)

- In the Lixilan-L trial, there were similar proportions of patients with serious AEs while taking iGlarLixi (5.5%) compared with insulin glargine (4.9%).
- The proportion of patients experiencing AEs overall were similar in those taking iGlarLixi group (53.4%) compared with insulin glargine (52.3%) in Lixilan-L.
- The proportion of patients who withdrew due to AEs was higher in the iGlarLixi group (2.7%) than in the insulin glargine group (0.8%). The most commonly cited reason for withdrawal in the iGlarLixi group was nausea (1.1%).
- The proportion of patients who experienced severe hypoglycemia (an event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions) was 1.1% in the iGlarLixi group and 0.3% in the insulin glargine group.
- The proportion of patients who experienced documented symptomatic hypoglycemia (an event with typical hypoglycemic symptoms and a plasma glucose concentration ≤ 3.9 mmol/L) was 40.0% for the iGlarLixi group and 42.5% for the insulin glargine group.
- The most frequently reported AEs occurring in the iGlarLixi group was nausea (10.4% compared with 0.5%), headache (5.8% compared with 2.7%), diarrhea (4.4% compared with 2.7%), and vomiting (3.6% compared with 0.5%).

Indirect Treatment Comparisons

Two indirect treatment comparisons (IDC) were reviewed (one submitted by the manufacturer, and one was found in a CDR literature search). The manufacturer-submitted IDC compared the efficacy of iGlarLixi against currently available regimens for T2DM. The primary outcomes for this study included glycemic control end points, weight changes, and risk of hypoglycemic events.

Regarding glycemic control, the only comparison consistently showing a favourable result to iGlarLixi was basal insulin (once daily) + one oral antidiabetic. iGlarlixi was potentially better at reducing weight gain when compared against insulin regimens, and DPP-4 inhibitors in combination with basal insulin, but not compared against GLP-1 receptor agonists in combination with basal insulin (with the exception of albiglutide). Finally, iGlarLixi showed a favourable hypoglycemic profile against basal insulin regimens alone and against GLP-1 receptor agonists in combination with basal insulin, but results were not available for comparisons with insulin degludec/liraglutide (iDegLira), liraglutide, dulaglutide, or any DPP-4 inhibitor.

The indirect comparison found in the literature (Evans et al. 2018) examined phase III trials comparing iGlarLixi and iDegLira in insulin-experienced patients. iDegLira was found to be better than iGlarLixi at reducing hemoglobin A1C from baseline and at reducing weight.

The two identified IDCs have several limitations that reduce the overall certainty in the results; the manufacturer IDC is not up to date and is missing evidence published within the past two years, while the literature-identified IDC did not follow a systematic review approach and only included pivotal trials of various diabetes interventions.

Cost and Cost-Effectiveness

iGlarLixi is administered as a once-daily subcutaneous injection via a pre-filled pen injector. The dose is individualized per clinical response based on the basal insulin dose in the previous regimen, but should not exceed the recommend starting dose of lixisenatide (i.e., 10 mcg [30 units insulin glargine]). At the manufacturer's submitted price of $37.96 for a 3 mL pre-filled pen (equivalent to 300 units insulin glargine and 100 mcg lixisenatide), the annual treatment cost of iGlarLixi is estimated to vary between $693 (15 units insulin glargine) and $2,770 (60 units insulin glargine) depending on the dose administered.

The manufacturer submitted a cost-utility analysis comparing iGlarLixi (average dose: 47 units, 15.7 mcg) with a regimen of basal insulin once a day (average dose: 47 units) together with rapid-acting insulin three times a day (88 units daily) (basal-prandial three times daily) from the perspective of the Canadian health care payer over a 25-year time horizon. Both treatment groups may also receive metformin. The manufacturer's model was based on the United Kingdom Prospective Diabetes Study – Outcomes Model version two to predict the incidence of micro- and macro-vascular diabetic complications and death. Patient characteristics and iGlarLixi efficacy on hemoglobin A1C and body weight were taken from the Lixilan-L study, while efficacy of the comparator regimen

came from a manufacturer-sponsored IDC that was supplemented with results from the GETGOAL DUO-2 study. In the manufacturer's base case, iGlarLixi was estimated to be dominant (i.e., more effective, less expensive) over basal-prandial three times daily with lifetime savings of $17,898 and incremental quality-adjusted life-years (QALYs) of 0.10.

CADTH identified several key limitations to the manufacturer's analysis:

- Although a basal-prandial three times daily regimen was the traditional approach, the manufacturer's analysis did not include relevant comparators in line with the 2018 Canadian Clinical Practice Guidelines, such as sodium-glucose cotransporter-2 (SGLT2), DPP-4 inhibitors, and other GLP-1 receptor agonists.
- The size of the comparative treatment effect is uncertain due to limitations with the evidence sources. This impacts the reliability of the cost-effectiveness analyses undertaken.
- There is uncertainty regarding the duration of iGlarLixi benefit, as short-term surrogate outcomes such as A1C and body weight were used to estimate 25-year impact on micro- and macro-vascular diabetic complications and survival.
- The manufacturer incorporated a disutility when the body mass index is above 25 kg/m^2, which was considered inappropriate.
- The dose and costs for the basal-prandial three times daily regimen were overestimated.

CADTH reviewers could not address limitations pertaining to the quality of the clinical data inputs, and were limited in their ability to alter the duration of iGlarLixi benefit (and resulting survival benefit) due to the model structure. CADTH reanalysis addressed the other limitations by revising costing assumptions associated with the basal-prandial three times daily insulin regimen, and removing disutility associated with body mass index. Several alternate scenarios were tested, and exploratory analyses were performed for three additional comparators (i.e., SGLT2, DPP-4, other GLP-1 receptor agonists).

Based on CADTH reanalysis, the incremental cost-utility ratio (ICUR) of iGlarLixi compared with a basal-prandial three times daily regimen was $170,875 per QALY. Scenario analyses highlight the extent in which uncertainty impacted the model: when the costs of diabetic disposables were included, the ICUR reduced to $72,255 per QALY; however, when alternative disutility values for hypoglycemic events were used, the ICUR increased to $19,420,053 per QALY. The ICUR was above $100,000 per QALY in the exploratory pairwise analyses comparing iGlarLixi with other GLP-1 receptor agonists, DPP-4, or SGLT2 inhibitors. Although a 20% to 25% price reduction was suggested to achieve an ICUR in the $25,000 to $50,000 per QALY range based on the CADTH base case, uncertainty exists with the clinical inputs and model structure that could not be adequately addressed in the present reanalysis.

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.

October 17, 2018 Meeting

Regrets

One CDEC member did not attend.

Conflicts of Interest

None

November 21, 2018 Meeting

Regrets

Three CDEC members did not attend.

Conflicts of Interest

None