



CEDAC FINAL RECOMMENDATION

LIRAGLUTIDE

(Victoza – Novo Nordisk Canada Inc.)

Indication: Diabetes, Type 2

Recommendation:

The Canadian Expert Drug Advisory Committee (CEDAC) recommends that liraglutide not be listed at the submitted price.

Reasons for the Recommendation:

1. Based on a systematic review including six randomized controlled trials (RCTs), liraglutide demonstrated similar or greater reductions in hemoglobin A1c in combination with metformin, or with metformin and a sulfonylurea, compared with antihyperglycemic agents from other drug classes. Liraglutide was also associated with statistically significant weight loss compared with other drug classes. The clinical significance of these results with respect to diabetes-related morbidity and mortality is unknown for this new class of drug therapy.
2. The daily cost of liraglutide (\$4.89 to \$7.34) is greater than sulfonylureas (< \$1.00), thiazolidinediones (< \$3.00), dipeptidyl peptidase-4 (DPP-4) inhibitors (< \$3.00), insulin NPH (< \$2.00), and insulin analogues (< \$3.00).

Of Note:

Based on a review of the clinical evidence, the Committee noted that a reduced price would increase the likelihood of a recommendation to “list with criteria” for patients with inadequate glycemic control on metformin and a sulfonylurea. The Committee noted insulin NPH was the most appropriate comparator for this patient population.

Background:

Liraglutide has a Health Canada indication for the treatment of adults with type 2 diabetes mellitus to improve glycemic control in combination with:

- metformin, when diet and exercise plus maximal tolerated dose of metformin do not achieve adequate glycemic control, or
- metformin and a sulfonylurea, when diet and exercise plus dual therapy with metformin and a sulfonylurea do not achieve adequate glycemic control.

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Liraglutide is an analog of human glucagon-like peptide-1, the first of a new class of hypoglycemic agents. It is available as a 6 mg/mL solution for subcutaneous (SC) injection in a pre-filled pen. The recommended starting dose is 0.6 mg SC once daily. After one week, the dose should be increased to 1.2 mg SC once daily. Based on clinical response after at least one week, the dose can be increased to 1.8 mg SC once daily.

Summary of CEDAC Considerations:

The Committee considered the following information prepared by the Common Drug Review (CDR): a systematic review of RCTs of liraglutide, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to patients.

Clinical Trials

The systematic review included six RCTs of patients with type 2 diabetes mellitus. Trials investigated the use of liraglutide in dual therapy (LEAD-1, LEAD-2, Study 1860, and Study 1796), triple therapy (LEAD-5), and either dual or triple therapy (LEAD-6).

Dual Therapy Trials

- LEAD-1 (N = 1,041) was a 26-week double-blind RCT that randomized patients with inadequate glycemic control (based on a run-in period of up to four weeks with glimepiride titrated to 4 mg daily) to one of the following five treatment groups: liraglutide (1.8 mg, 1.2 mg, or 0.6 mg daily), rosiglitazone 4 mg daily, or placebo. All patients continued glimepiride as established during the run-in period.
- LEAD-2 (N = 1,091) was a 26-week double-blind RCT that randomized patients with inadequate glycemic control (based on a run-in period of up to six weeks with metformin 1,500 mg to 2,000 mg daily) to one of the following five treatment groups: liraglutide (1.8 mg, 1.2 mg, or 0.6 mg daily), glimepiride 4 mg daily, or placebo. All patients continued metformin as established during the run-in period.
- Study 1860 (N = 665) was a 26-week open-label RCT that randomized patients with inadequate glycemic control (based on pre-study metformin of $\geq 1,500$ mg daily for at least three months) to one of the following three treatment groups: liraglutide (1.8 mg or 1.2 mg daily), or sitagliptin 100 mg daily. All patients continued metformin at stable pre-study doses.
- Study 1796 (N = 929) was a 16-week double-blind RCT that randomized patients with inadequate glycemic control (based on a run-in period of up to six weeks with metformin 1,500 to 2,000 mg daily) to one of the following four treatment groups: liraglutide (1.8 mg, 1.2 mg, or 0.6 mg daily) or glimepiride 4 mg daily. All patients continued metformin as established during the run-in period.

Triple Therapy Trial

- LEAD-5 (N = 581) was a 26-week double-blind (liraglutide and placebo) and open-label (insulin glargine) RCT that randomized patients with inadequate glycemic control (based on a run-in period of up to six weeks with metformin 2,000 mg daily plus glimepiride 4 mg daily) to one of the following three treatment groups: liraglutide 1.8 mg daily, placebo, or insulin glargine titrated as per algorithm. All patients continued metformin and glimepiride as established during the run-in period.

Dual or Triple Therapy Trial

- LEAD-6 (N = 464) was a 26-week open-label RCT that randomized patients with inadequate glycemic control (based on stable pre-study doses of maximally tolerated metformin and/or a sulfonylurea for at least three months) to either liraglutide 1.8 mg daily or exenatide 10 mcg twice daily. All patients continued pre-study doses of metformin and/or sulfonylureas.

Mean baseline hemoglobin A1c was similar between all trials and ranged from 8.2% to 8.6%. There were a large and disproportionate number of withdrawals (for any reason) in the placebo groups of LEAD-1, LEAD-2, and LEAD-5, primarily due to ineffective therapy. In studies 1796 and 1860, study withdrawal occurred more frequently in liraglutide treatment groups compared with glimepiride and sitagliptin, respectively.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, the Committee discussed the following: hemoglobin A1c, body weight change, hypoglycemia, blood pressure, lipid profile changes, and quality of life. Input from patient groups noted that increases in weight and hypoglycemic episodes negatively affect quality of life, which is an important outcome for patients.

The primary outcome was the same in all trials: change in hemoglobin A1c from baseline to end of study. All trials were designed to test the non-inferiority of liraglutide with the comparators based on the primary outcome. Non-inferiority was concluded if the upper limit of the 95% confidence interval (CI) for the treatment difference between liraglutide and the active comparator was below 0.4%.

None of the included trials evaluated clinical end points in general, or those related to known macrovascular or microvascular complications of type 2 diabetes mellitus.

Results

The Committee focused its discussion on comparisons of liraglutide (in doses of 1.2 mg or 1.8 mg daily) in combination with metformin or metformin plus a sulfonylurea with other antihyperglycemic agents available in Canada; specifically, data from LEAD-2, LEAD-5, study 1860, and study 1796.

Efficacy or Effectiveness

Dual Therapy in Combination with Metformin (LEAD-2, study 1796, and study 1860)

- Neither LEAD-2 nor study 1796 reported statistically significant differences in hemoglobin A1c reduction between glimepiride and liraglutide (1.2 mg or 1.8 mg). In the open-label study 1860, hemoglobin A1c reduction was statistically significantly greater for patients treated with either dose of liraglutide compared with sitagliptin; mean difference (MD): -0.4% and -0.6% for liraglutide 1.2 mg and 1.8 mg, respectively.
- In LEAD-2, reductions in body weight were statistically significantly greater for patients treated with liraglutide compared with glimepiride; MD: -3.5 kg and -3.8 kg for liraglutide 1.2 mg and 1.8 mg, respectively. In study 1860, reductions in body weight were statistically significantly greater for patients treated with liraglutide compared with sitagliptin;

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MD: -1.9 kg and -2.4 kg for liraglutide 1.2 mg and 1.8 mg, respectively.

- The one trial that assessed the impact of weight on quality of life (LEAD-2) reported no notable between-treatment differences, however only a subgroup of patients enrolled in the trial provided data for this outcome.
- Few statistically significant differences in lipid profiles were observed between liraglutide and glimepiride or between liraglutide and sitagliptin, and these few were of questionable clinical importance.
- One trial (LEAD-2) reported small but statistically significant differences in systolic blood pressure lowering, favouring liraglutide 1.2 mg and 1.8 mg compared with glimepiride; however, differences were of questionable clinical importance.

Triple Therapy in Combination with Metformin and Glimepiride (LEAD-5)

- Hemoglobin A1c and body weight reductions were statistically significantly greater for patients treated with liraglutide 1.8 mg compared with insulin glargine; MD: -0.3% and MD: -3.4 kg for hemoglobin A1c and body weight respectively.
- LEAD-5 did not examine quality of life.
- Few statistically significant differences were observed between liraglutide and insulin glargine in lipid profiles, and these few were of questionable clinical importance.
- A small but statistically significant difference in systolic blood pressure lowering, favouring liraglutide 1.8 mg compared with insulin glargine (open-label), was reported; however, the clinical importance of the difference was questionable.

Harms (Safety and Tolerability)

- Withdrawal due to adverse events occurred more frequently with liraglutide compared with glimepiride in LEAD-2 and study 1796, and compared with sitagliptin in study 1860, and compared with insulin glargine in LEAD-5.
- Liraglutide was consistently associated with a higher incidence of treatment-emergent gastrointestinal adverse events than all comparators.
- Major hypoglycemic episodes were infrequent with all treatments. In combination with metformin, liraglutide resulted in a statistically significantly lower percentage of patients experiencing minor hypoglycemia compared with glimepiride, but a similar percentage of patients experiencing minor hypoglycemia compared with sitagliptin. In combination with metformin and glimepiride, there was no statistically significant difference in the number of patients with minor hypoglycemia between insulin glargine and liraglutide. There were no statistically significant differences between 1.8 mg and 1.2 mg doses of liraglutide in terms of hypoglycemia.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-utility analysis comparing liraglutide with sulfonylureas, thiazolidinediones, or sitagliptin, when taken in combination with metformin; and liraglutide compared with insulin glargine in combination with metformin and a sulfonylurea. The economic model was based on data from the United Kingdom Prospective Diabetes Study 68, liraglutide RCTs (LEAD 1, LEAD 2, LEAD 5, and Study 1860), and published studies (for cost and utility information). The manufacturer reported that treatment with liraglutide in combination with metformin is associated with an incremental cost per quality-adjusted life-year (QALY) of \$23,777 (versus rosiglitazone), \$27,556 (versus glimepiride), and \$25,425 (versus sitagliptin).

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Treatment with liraglutide in combination with metformin and a sulfonylurea is associated with an incremental cost per QALY of \$28,815 when compared with insulin glargine.

A number of limitations with the manufacturer's economic analysis were noted. The manufacturer assumed that benefits of liraglutide treatment (e.g., weight gain, glycemic control) would be sustained over 40 years, although patients discontinue (and no longer incur the costs of) liraglutide after five years in the model. The manufacturer considered higher-cost comparators (e.g., glimepiride versus glicazide; glargine versus insulin NPH) in its analysis. The utility decrements for gain in body mass index and mild hypoglycemic episodes potentially overestimated the impact on patients, while a number of aspects associated with treatment with liraglutide (gastrointestinal adverse events and disutility associated with injections) were not considered. When aligning clinical benefits with treatment duration, considering lower-cost comparators, and using alternate disutilities, the incremental cost per QALY estimate for liraglutide versus sulfonylurea or insulin increases to more than \$70,000.

The daily cost of liraglutide (\$4.89 to \$7.34) is greater than sulfonylureas (< \$1.00), thiazolidinediones (< \$3.00), DPP-4 inhibitors (< \$3.00), insulin NPH (< \$2.00), and insulin analogues (< \$3.00).

Patient Input Information:

The following is a summary of information provided by one patient group that responded to the CDR Call for Patient Input:

- It was noted that the complications of diabetes mellitus (such as cardiovascular disease, stroke, peripheral vascular disease, associated depression), as well as weight gain and hypoglycemia associated with many available therapies, negatively affect quality of life.
- The route of administration (subcutaneous injection) may be a deterrent to some patients. The high frequency of gastrointestinal adverse events was identified as a drawback to liraglutide therapy; however, patients consider mild nausea to be an acceptable adverse event.

Other Discussion Points:

- Therapeutic reviews and subsequent recommendations issued by CADTH indicate that in patients inadequately controlled on metformin, sulfonylurea agents are the most cost-effective therapies, and that in patients inadequately controlled on metformin plus a sulfonylurea, insulin NPH is the most cost-effective option.
- The Committee noted that there is an absence of direct evidence on whether liraglutide reduces microvascular or macrovascular outcomes and that the relationship between hemoglobin A1c and cardiovascular outcomes may differ for new drug classes with novel mechanisms of action. The long-term safety profile of liraglutide, particularly regarding cardiovascular outcomes, is not established. The Committee noted that a large randomized, placebo-controlled clinical trial to evaluate cardiovascular outcomes after treatment with liraglutide was ongoing.
- The Committee questioned the clinical relevance of the reported weight changes with liraglutide.
- The Committee noted that the US Food and Drug Administration has issued warnings regarding the possible risk of pancreatitis and thyroid C-cell tumours in patients who use liraglutide.

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- Liraglutide is administered by subcutaneous injection; thus, there may be no convenience advantage in terms of patient acceptability compared with insulin.
- The Committee noted that patient treatment satisfaction was assessed using the Diabetes Treatment Satisfaction Questionnaire in three trials (LEAD-2, study 1860, and LEAD-6), but for only a subgroup of patients enrolled in each trial. Overall treatment satisfaction did not differ statistically between liraglutide and glimepiride in LEAD-2, the only double-blind trial that examined this subjective outcome.
- The Committee noted there appeared to be little difference in therapeutic benefit between liraglutide 1.2 mg and 1.8 mg in the reviewed trials.

CEDAC Members:

Dr. Robert Peterson (Chair), Dr. Anne Holbrook (Vice-Chair), Dr. Michael Allan, Dr. Ken Bassett, Dr. Bruce Carleton, Dr. Doug Coyle, Mr. John Deven, Dr. Alan Forster, Dr. Laurie Mallery, Mr. Brad Neubauer, Dr. Lindsay Nicolle, Dr. Yvonne Shevchuk, and Dr. James Silvius.

June 15, 2011 Meeting

Regrets:

Two CEDAC members did not attend

Conflicts of Interest:

One CEDAC member did not participate due to considerations of conflict of interest.

September 21, 2011 Meeting

Regrets:

Two CEDAC members did not attend

Conflicts of Interest:

One CEDAC member did not participate due to considerations of conflict of interest.

About this Document:

CEDAC provides formulary listing recommendations to publicly funded drug plans. Both a technical recommendation and plain language version of the recommendation are posted on the CADTH website when available.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CEDAC made its recommendation. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CEDAC deliberations.

The manufacturer has reviewed this document and has not requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*. The Final CEDAC Recommendation neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

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