



Canadian Expert Drug Advisory Committee Final Recommendation – Plain Language Version

LIRAGLUTIDE (Victoza – Novo Nordisk Canada Inc.) Indication: Diabetes, Type 2

Recommendation:

The Canadian Expert Drug Advisory Committee (CEDAC) recommends that Victoza, which is also called liraglutide, not be listed by Canada's publicly funded drug plans at the submitted price for the treatment of type 2 diabetes mellitus.

Reasons for the Recommendation:

1. A review of six studies showed that Victoza resulted in similar or greater lowering of hemoglobin A1c (a test for blood sugar control) when used with just metformin, or when used with metformin and a sulfonylurea, compared with medications belonging to different classes of blood sugar-lowering drugs. Victoza also resulted in more weight loss than did medications in the other drug classes. The importance of these results for patients, specifically in relation to diabetes-related complications or death, is not known for this new class of drug therapy.
2. The daily cost of Victoza (\$4.89 to \$7.34) is greater than sulfonylureas (less than \$1.00), thiazolidinediones (less than \$3.00), dipeptidyl peptidase-4 (DPP-4) inhibitors (less than \$3.00), insulin NPH (less than \$2.00), and insulin analogues (less than \$3.00).

Of Note:

After reviewing the results of the studies, the Committee felt that a reduced price would increase the likelihood of a recommendation to "list with criteria" for patients with poor control of their blood sugar on metformin and a sulfonylurea. The Committee noted that insulin NPH was the most appropriate comparison treatment for this group of patients.

Background:

Victoza belongs to a class of drugs called glucagon-like peptide-1 (GLP-1) analogs. Victoza helps the body make more insulin when the blood sugar is high. Victoza is approved by Health Canada for treatment of adults with type 2 diabetes mellitus to improve glycemic (blood sugar) control in combination with:

- metformin, when diet and exercise plus maximal tolerated dose of metformin do not achieve adequate glycemic control, or

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

Type 2 diabetes is a condition in which the body does not make enough insulin, and/or does not use as well as it should the insulin that the body does produce. When this happens, sugar (glucose) builds up in the blood. This can lead to serious problems.

Victoza is available as a 6 mg/mL solution for subcutaneous (SC; under the skin) 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 the blood sugar levels after at least one week, the dose can be increased to 1.8 mg SC once daily.

Summary of CEDAC Considerations:

To make their decision, the Committee considered the following information prepared by the Common Drug Review (CDR): a review of the medical studies of Victoza and a review of economic information prepared by the manufacturer of Victoza. Also, CEDAC considered information that patient groups submitted about outcomes and issues important to patients who have the condition for which the drug is indicated, or who might use the drug.

Clinical Trials

The review included six studies of patients with type 2 diabetes mellitus. Studies investigated the use of Victoza 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 (Two Medications) Therapy Trials

- LEAD-1 (with 1,041 patients) was a 26-week-long study of patients whose blood sugar was not well controlled while taking glimepiride (also called Amaryl), in doses up to 4 mg daily, for up to four weeks prior to the study. Patients were then given one of the following five treatments: Victoza 1.8 mg, 1.2 mg, or 0.6 mg daily; rosiglitazone (also called Avandia) 4 mg daily; or placebo (a tablet or injection with no active medication). All patients continued taking glimepiride, in the same dosage as before the start of the study.
- LEAD-2 (with 1,091 patients) was a 26-week-long study of patients whose blood sugar was not well controlled while taking metformin in doses of 1,500 mg to 2,000 mg daily for up to six weeks prior to the study. Patients were then given one of the following five treatments: Victoza 1.8 mg, 1.2 mg, or 0.6 mg daily; glimepiride 4 mg daily; or placebo. All patients continued taking metformin, in the same dosage as before the start of the study.
- Study 1860 (with 665 patients) was a 26-week-long study of patients whose blood sugar was not well controlled while taking metformin in doses of at least 1,500 mg daily for three months or more. Patients were then given one of the following three treatments: Victoza 1.8 mg or 1.2 mg daily, or sitagliptin (also called Januvia) 100 mg daily. All patients continued taking metformin, in the same dosage as before the start of the study.
- Study 1796 (with 929 patients) was a 16-week-long study of patients whose blood sugar was not well controlled while taking metformin in doses of 1,500 to 2,000 mg daily for up to six weeks. Patients were then given one of the following four treatments: Victoza 1.8 mg, 1.2 mg, or 0.6 mg daily, or glimepiride 4 mg daily. All patients continued metformin, in the same dosage as before the start of the study.

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Triple (Three Medications) Therapy Trial

- LEAD-5 (with 581 patients) was a 26-week-long study of patients whose blood sugar was not well controlled while taking metformin 2,000 mg daily plus glimepiride 4 mg daily for up to six weeks. Patients were then given one of the following three treatments: Victoza 1.8 mg daily, placebo, or insulin glargine (also called Lantus) adjusted as per study guidelines. All patients continued metformin and glimepiride, in the same dosages as before the start of the study.

Dual or Triple Therapy Trial

- LEAD-6 (with 464 patients) was a 26-week-long study of patients whose blood sugar was not well controlled while on maximum tolerated doses of metformin and/or a sulfonylurea for at least three months in the period prior to the study. Patients were then given either Victoza 1.8 mg daily or exenatide (also called Byetta) 10 mcg twice daily. All patients continued metformin and/or sulfonylureas, in the same dosages as before the start of the study.

At the beginning of the studies, patients' average level of hemoglobin A1c was similar between the studies and ranged from 8.2% to 8.6%. A larger proportion of patients stopped taking part in the study (for any reason) in the placebo groups of LEAD-1, LEAD-2, and LEAD-5, mostly because the treatment was not working. In studies 1796 and 1860, a larger proportion of patients given Victoza stopped taking part in the study compared with those given glimepiride and sitagliptin, respectively.

Outcomes

Outcomes were defined in advance in the CDR systematic review protocol. Of these, the Committee discussed the following: hemoglobin A1c, body weight change, hypoglycemia (low blood sugar), blood pressure, lipid level (blood levels of fats and cholesterol) changes, and quality of life. Patient groups noted that increases in weight and episodes of low blood sugar result in lower quality of life, and that quality of life is an important concern for patients.

The main purpose of all studies was the same: to examine the change in hemoglobin A1c from the beginning to end of the study. All trials were planned to test if Victoza was not worse than the other medications at lowering hemoglobin A1c, allowing for a difference of not more than 0.4%.

None of the studies looked at the effects of the medications on diabetes complications, including those related to the heart, eyes, and kidneys.

Results

The Committee focused its discussion on comparisons of Victoza (in doses of 1.2 mg or 1.8 mg daily) in combination with metformin or metformin plus a sulfonylurea, with other anti-hyperglycemic (blood sugar-lowering) agents available in Canada; specifically, results 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)

- Glimepiride and Victoza (1.2 mg or 1.8 mg) resulted in about the same amount of lowering of hemoglobin A1c in both LEAD-2 and study 1796. In study 1860, in which patients and

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doctors knew which medication was being given, Victoza (regardless of dose) lowered the hemoglobin A1c more than sitagliptin (on average, -0.4% and -0.6% more for Victoza 1.2 mg and 1.8 mg, respectively).

- In LEAD-2, patients taking Victoza had more weight loss than those taking glimepiride (on average, -3.5 kg and -3.8 kg more for Victoza 1.2 mg and 1.8 mg, respectively). In study 1860, patients taking Victoza had more weight loss than those taking sitagliptin (on average -1.9 kg and -2.4 kg more for Victoza 1.2 mg and 1.8 mg, respectively).
- The one study that looked at the effect of weight on quality of life (LEAD-2) reported no important differences between the treatments; however, not all patients in the trial provided information about this.
- Few differences in lipid levels were seen between Victoza and glimepiride or between Victoza and sitagliptin, and these few differences were of questionable importance.
- One study (LEAD-2) reported slightly more lowering of the systolic blood pressure (upper blood pressure number) with Victoza 1.2 mg and 1.8 mg compared with glimepiride, but these differences were of questionable importance.

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

- Victoza 1.8 mg lowered hemoglobin A1c and body weight more than insulin glargine (an average of -0.3% and -3.4 kg more for hemoglobin A1c and body weight, respectively).
- The LEAD-5 study did not look at quality of life.
- There were not many differences between Victoza and insulin glargine in terms of lipid levels, and these few differences were of questionable importance.
- Victoza 1.8 mg lowered the systolic blood pressure more than insulin glargine, in this study in which patients and doctors knew which medication was being given, but this difference was of questionable importance.

Harms (Safety and Tolerability)

- A greater proportion of patients on Victoza stopped taking part in the study because of side effects, compared with those on glimepiride in LEAD-2 and study 1796, and compared with those on sitagliptin in study 1860, and compared with those on insulin glargine in LEAD-5.
- Victoza resulted in a higher percentage of patients with stomach and bowel side effects than did any of the comparison treatments.
- Major hypoglycemia did not happen frequently with any of the treatments. When used together with metformin, Victoza resulted in a smaller percentage of patients having minor hypoglycemia compared with glimepiride, but a similar percentage of patients having minor hypoglycemia compared with sitagliptin. Regardless of whether it was insulin glargine or Victoza that was used together with metformin and glimepiride, the number of patients with minor hypoglycemia was about the same. Whether patients were treated with 1.2 mg or 1.8 mg of Victoza did not seem to increase the risk of hypoglycemia.

Cost and Cost-Effectiveness

The manufacturer submitted an economic analysis that compared Victoza with sulfonylureas, thiazolidinediones (e.g., Avandia), or sitagliptin, when taken in combination with metformin, and Victoza compared with insulin glargine in combination with metformin and a sulfonylurea, to evaluate the health benefit. To carry out the analysis, the manufacturer used data from the United Kingdom Prospective Diabetes Study 68, and a number of Victoza studies (LEAD-1, LEAD-2, LEAD-5, and study 1860) as well as other published studies (for information related to cost and quality of life).

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A number of concerns with the manufacturer's economic analysis were noted. The manufacturer assumed that benefits of Victoza treatment (e.g., weight loss, control of blood sugar) would last over a time period of 40 years, although the manufacturer's analysis assumed that patients stopped taking and would no longer be paying for Victoza after five years. The manufacturer considered more expensive medications in its analysis, such as glimepiride instead of gliclazide, and insulin glargine instead of insulin NPH. The effects of weight gain and hypoglycemia on quality of life may have been overestimated, while some aspects of Victoza treatment (such as stomach and bowel side effects and the need for injections) were not considered.

The daily cost of Victoza (\$4.89 to \$7.34) is greater than sulfonylureas (less than \$1.00), thiazolidinediones (less than \$3.00), DPP-4 inhibitors (less than \$3.00), insulin NPH (less than \$2.00), and insulin analogues (less than \$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 heart disease, stroke, blood vessel disease, depression) as well as weight gain and low blood sugar episodes, which are linked with many of the available therapies, lower the quality of life of patients.
- The way in which Victoza is taken (SC injection) may stop some patients from wanting to use Victoza. Patients identified the high frequency of stomach and bowel side effects as a drawback to Victoza therapy; however, patients consider mild nausea to be an acceptable side effect.

Other Discussion Points:

- Previous reviews and recommendations by CADTH state that for patients whose blood sugar is not well controlled on metformin, sulfonylurea agents are the most cost-effective therapies and that in patients who are not well controlled on metformin plus a sulfonylurea, insulin NPH is the most cost-effective option.
- The Committee noted that there is a lack of data showing whether Victoza decreases microvascular (small blood vessel – e.g., eye problems) or macrovascular (large blood vessel – e.g., heart attack) outcomes and also that the impact of hemoglobin A1c levels on cardiovascular (heart disease and stroke) outcomes may be different for new drug classes, which work in new ways. The long-term safety profile of Victoza, particularly regarding cardiovascular outcomes, is not established. It was noted that a large study looking at the cardiovascular outcomes after treatment with Victoza was ongoing.
- The Committee questioned whether the amount of weight change that was reported with Victoza would be important to patients.
- The Committee noted that the US Food and Drug Administration has issued warnings regarding the possible risk of pancreatitis (inflammation of the pancreas) and thyroid cancer in patients who use Victoza.
- Victoza is administered by SC injection; thus, there may be no convenience advantage in terms of patient acceptability compared with insulin.
- The Committee noted that three trials (LEAD-2, study 1860, and LEAD-6) used the Diabetes Treatment Satisfaction Questionnaire to look at patient satisfaction with treatment, but that only some of the patients in the trials filled out the questionnaires. In LEAD-2, the only one of the three trials in which patients did not know what medication they were receiving, satisfaction with treatment was about the same, regardless of whether patients were receiving Victoza or glimepiride.

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- The Committee noted there appeared to be little difference in therapeutic benefit between Victoza 1.2 mg and 1.8 mg in the reviewed studies.

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

The information contained within this plain language version of the Canadian Expert Drug Advisory Committee (CEDAC) Recommendation about this drug is based on the information found within the corresponding technical version of the CEDAC Recommendation.

In making its recommendation, CEDAC considered the best clinical and pharmacoeconomic evidence available, up to that time. Health care professionals and those requiring more detailed information are advised to refer to the technical version available in the [CDR Drug Database](#) on the CADTH website (www.cadth.ca).

Background on CEDAC

CEDAC is a committee of the Canadian Agency for Drugs and Technologies in Health (CADTH). The committee is made up of drug evaluation experts and public members. CEDAC provides recommendations about whether or not drugs should be listed for coverage through the participating publicly funded drug plans; however, the individual drug plans make their own decision about whether or not to cover a drug.

In making its recommendations, CEDAC decides if the drug under review ought to be covered by the participating public drug plans based on an evidence-informed review of the medication's effectiveness and safety, and based on an assessment of its cost-effectiveness in comparison with other available treatments. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CEDAC deliberations.

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The statements, conclusions, and views expressed herein do not necessarily represent the views of Health Canada, the federal government, any provincial or territorial government, or any pharmaceutical manufacturer.

The manufacturer has reviewed this document and has not requested the deletion of any confidential information.

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