



CDEC FINAL RECOMMENDATION

EXENATIDE

(Byetta — Eli Lilly Canada)

Indication: Diabetes Mellitus, Type 2

Recommendation:

The Canadian Drug Expert Committee (CDEC) recommends that exenatide not be listed at the submitted price.

Reasons for the Recommendation:

1. Based on a systematic review including six active comparator randomized controlled trials (RCTs), exenatide demonstrated similar reductions in hemoglobin A1c compared with sulfonylureas, when used in combination with metformin. When used in combination with metformin plus a sulfonylurea, exenatide demonstrated a similar reduction in hemoglobin A1c compared with insulin glargine; evidence was conflicting versus biphasic insulin aspart, with one trial reporting exenatide to be inferior and one trial reporting exenatide to be non-inferior. Exenatide was associated with statistically significant weight loss compared with glibenclamide and both insulin products. The clinical significance of these results with respect to diabetes-related morbidity and mortality is unknown.
2. At recommended doses, the daily cost of exenatide (\$4.59; 5 mcg or 10 mcg twice daily) is greater than sulfonylureas (< \$1.00), thiazolidinediones (< \$3.00), dipeptidyl peptidase-4 (DPP-4) inhibitors (< \$3.00), biphasic insulin aspart (< \$2.00), 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:

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

- metformin, when diet and exercise plus metformin alone do not provide adequate glycemic control

Common Drug Review

- a sulfonylurea, when diet and exercise plus a sulfonylurea alone do not provide adequate glycemic control
- metformin and a sulfonylurea when diet and exercise plus metformin and a sulfonylurea do not provide adequate glycemic control.

Exenatide is an analogue of human glucagon-like peptide-1. It is available as a 1.2 mL prefilled pen (60 doses of 5 mcg/dose) or 2.4 mL prefilled pen (60 doses of 10 mcg/dose) for subcutaneous injection. The Health Canada-recommended dose is 5 mcg twice daily for a month, followed by 10 mcg twice daily if needed to improve glycemic control.

Summary of CDEC Considerations:

The Committee considered the following information prepared by the Common Drug Review (CDR): a systematic review of RCTs of exenatide and a critique of the manufacturer's pharmacoeconomic evaluation. No patient groups responded to the CDR Call for Patient Input.

Clinical Trials

The systematic review included 11 RCTs of adult patients with type 2 diabetes mellitus. Trials investigated the use of exenatide in dual therapy (studies 112, 113, Derosa 2010, and Derosa 2011), triple therapy (studies 115, GWAA, GWAD, and Bergenstal), and either dual or triple therapy (studies LEAD-6, GWBA, and Apovian).

Dual Therapy Trials

Three trials evaluated exenatide as add-on therapy in patients with inadequate glycemic control on a stabilized dose of metformin.

- Study 112 (N = 336) was a 30-week, triple-blind RCT that randomized patients to one of three treatment groups: exenatide (5 mcg twice a day), exenatide (10 mcg twice a day), or placebo.
- Derosa 2010 (N = 128) was a 52-week, open-label RCT that randomized patients to exenatide (10 mcg twice a day) or glibenclamide (5 mg three times a day).
- Derosa 2011 (N = 111) was a 52-week, open-label RCT that randomized patients to exenatide (10 mcg twice a day) or glimepiride (2 mg three times a day).

One trial evaluated exenatide as an add-on therapy in patients with inadequate glycemic control on a sulfonylurea.

- Study 113 (N = 377) was a 30-week, triple-blind RCT that randomized patients to one of three treatment groups: exenatide (5 mcg twice a day), exenatide (10 mcg twice a day), or placebo.

Triple Therapy Trials

Four trials evaluated exenatide as an add-on therapy in patients with inadequate glycemic control on metformin plus a sulfonylurea.

- Study 115 (N = 734) was a 30-week, triple-blind RCT that randomized patients to one of three treatment groups: exenatide (5 mcg twice a day), exenatide (10 mcg twice a day), or placebo.
- Study GWAA (N = 555) was a 26-week, open-label RCT that randomized patients to one of two treatment groups: exenatide (10 mcg twice a day) or insulin glargine once a day.
- Study GWAD (N = 505) was a 52-week, open-label RCT that randomized patients to one of two treatment groups: exenatide (10 mcg twice a day) or biphasic insulin aspart twice a day.

- Bergenstal (N = 372) was a 26-week, open-label RCT that randomized patients to one of three treatment groups: exenatide (10 mcg twice a day), biphasic insulin aspart once a day, or biphasic insulin aspart twice a day.

Dual or Triple Therapy Trials

Three trials evaluated exenatide as an add-on therapy in patients with inadequate glycemic control on metformin and/or a sulfonylurea.

- LEAD-6 (N = 464) was a 26-week, open-label RCT that randomized patients to one of two treatment groups: exenatide (10 mcg twice a day) or liraglutide (1.8 mg once a day).
- Study GWBA (N = 472) was a 16-week, double-blind RCT that randomized patients to one of two treatment groups: exenatide (10 mcg twice a day) or placebo.
- Apovian (N = 196) was a 24-week, double-blind RCT that randomized patients to one of two treatment groups: exenatide (10 mcg twice a day) or placebo.

Mean baseline hemoglobin A1c in the 11 trials ranged from 7.6% to 10.2%. The percentage of patients who prematurely discontinued study medication ranged from 9% to 31% across the trials. The percentage of patients who discontinued was relatively balanced across treatment groups in most trials, with the exception of studies GWAA, GWAD, and Bergenstal, which reported a higher frequency of discontinuation in exenatide groups compared with insulin.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, the Committee discussed the following: change in hemoglobin A1c, body weight change, quality of life, serious adverse events, withdrawal due to adverse events, and hypoglycemia.

In all included studies, except the Apovian study, the primary outcome was the change from baseline in hemoglobin A1c. The primary outcome in the Apovian study was change from baseline in body weight.

Two studies (GWAA and GWAD) tested the non-inferiority of exenatide compared with insulin glargine and biphasic insulin aspart respectively, while Bergenstal and LEAD-6 tested the superiority and non-inferiority of biphasic insulin aspart and liraglutide respectively, compared with exenatide. Non-inferiority was concluded if the upper limit of the 95% confidence interval (CI) for the between-treatment difference (based on the change from baseline in hemoglobin A1c) was below 0.4%.

Quality of life data in two trials (GWAA and GWAD) were measured using the vitality scale of the 36-item Short-Form Health Survey (SF-36) and the European Quality of Life-5 Dimension Questionnaire (EQ-5D).

None of the included trials reported the effect of exenatide on diabetes-related macrovascular or microvascular complications, or mortality.

Results

Efficacy or Effectiveness

The Committee focused its discussion of efficacy on the active-comparator trials, the results of which are described below.

Dual therapy, in combination with metformin (Derosa 2010 and Derosa 2011)

- When added-on to metformin, the mean change from baseline in hemoglobin A1c was not statistically significantly different between exenatide and glibenclamide in Derosa 2010 or between exenatide and glimepiride in Derosa 2011.
- In Derosa 2010 and Derosa 2011, exenatide demonstrated a statistically significantly greater reduction in body weight compared with glibenclamide (mean difference [MD], -12.3 kg) and a numerically greater reduction in body weight compared with glimepiride (MD, -4.20 kg).
- Quality of life outcomes were not reported in these trials.

Triple therapy, in combination with metformin and a sulfonylurea (studies GWAA, GWAD, and Bergenstal)

- Based on the mean change from baseline in hemoglobin A1c, exenatide was reported to be non-inferior to once daily insulin glargine in study GWAA; MD (95% CI), 0.05% (-0.12 to 0.22), and non-inferior to twice daily biphasic insulin aspart in study GWAD; MD (95% CI), -0.10% (-0.29 to 0.09). In the Bergenstal study, both once and twice daily biphasic insulin aspart were superior to exenatide; MD (95% CI), 0.59% (0.21 to 0.97) and 1.01% (0.59 to 1.43) respectively.
- In all three studies, reductions in body weight were statistically significantly greater for exenatide versus comparators; MD: -4.07 kg compared with insulin glargine in study GWAA; -5.46 kg compared with twice daily biphasic insulin aspart in GWAD; and -4.70 kg and -6.00 kg compared with once daily and twice daily biphasic insulin aspart respectively in Bergenstal.
- No notable between-treatment differences in quality of life were reported in studies GWAA or GWAD. Quality of life measures were not reported in the Bergenstal study.

Dual or triple therapy, in combination with metformin and/or a sulfonylurea (LEAD-6)

- Mean change from baseline in hemoglobin A1c was statistically significantly less for exenatide-treated patients compared with liraglutide; MD (95% CI), 0.33% (0.11 to 0.55).
- Change in body weight was not statistically significantly different between exenatide and liraglutide.
- Quality of life measures were not reported in the LEAD-6 study.

Harms (Safety and Tolerability)

- There were no treatment-related deaths and few serious adverse events in the reviewed trials.
- Exenatide-treated patients experienced a higher incidence of withdrawal due to adverse events compared with placebo (range 4% to 23% versus 1% to 10%), insulin glargine (9.6% versus 0.7%), and biphasic insulin aspart (range 4.8% to 7.8% versus 0% to 0.8%). Common adverse events leading to withdrawal were gastrointestinal disorders, including abdominal pain, diarrhea, nausea, and vomiting.

- Severe hypoglycemia was rare in all included trials. The incidence of overall hypoglycemia was similar between exenatide and placebo when added on to metformin, but higher for exenatide compared with placebo when added on to a sulfonylurea (either in dual or triple therapy).
- The incidence of overall hypoglycemia in exenatide groups was similar to that of insulin glargine and biphasic insulin aspart in studies GWAA and GWAD respectively, but lower than that of biphasic insulin aspart in the Bergenstal study. Compared with liraglutide in LEAD-6, exenatide-treated patients experienced a higher incidence of overall hypoglycemia.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-utility analysis comparing exenatide in combination with metformin plus a sulfonylurea with insulin glargine in combination with metformin plus a sulfonylurea in adult patients diagnosed with type 2 diabetes mellitus with insufficient glycemic control after an adequate trial of diet and exercise, and metformin or metformin plus sulfonylurea, over a 50-year time horizon. The manufacturer used the IMS CORE Diabetes Model to forecast long-term diabetes-related complications and cost consequences. Patient characteristics were based on study GWAA to forecast the incidence of diabetes-related complications using equations from the United Kingdom Prospective Diabetes Study 68. The manufacturer reported that treatment with exenatide in combination with metformin plus a sulfonylurea is associated with a cost per quality-adjusted life-year of \$53,904 when compared with insulin glargine in combination with metformin plus a sulfonylurea.

CDR was unable to reproduce the results reported in the manufacturer's base-case analysis, which limited the confidence in the estimates and use of the model for further re-analyses. Other limitations noted by CDR included: the choice of a higher cost comparator (glargine compared with NPH or biphasic insulin aspart), and use of different doses of insulin glargine for treatment effects (25 units daily) and calculation of cost (48 units daily).

At recommended doses, the daily cost of exenatide (\$4.59; 5 mcg or 10 mcg twice daily) is greater than sulfonylureas (< \$1.00), thiazolidinediones (< \$3.00), dipeptidyl peptidase-4 (DPP-4) inhibitors (< \$3.00), biphasic insulin aspart (< \$2.00), insulin NPH (< \$2.00) and insulin analogues (< \$3.00).

Patient Input Information:

No patient groups responded to the CDR Call for Patient Input.

Other Discussion Points:

- Therapeutic reviews and subsequent recommendations issued by CADTH in 2010 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 preferred option.
- The Committee noted that there is an absence of direct evidence on whether exenatide reduces microvascular or macrovascular outcomes and that the relationship between hemoglobin A1c and cardiovascular outcomes may differ by drug class.
- The Committee noted that warnings regarding the potential risk for thyroid C-cell tumours and pancreatitis with exenatide are consistent with those for the other glucagon-like peptide-1 analogues approved in Canada.

- Exenatide is administered twice daily by subcutaneous injection; thus, there may be no advantage in terms of patient acceptability compared with insulin.

CDEC Members:

Dr. Robert Peterson (Chair), Dr. Lindsay Nicolle (Vice-Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Ms. Cate Dobhran, Mr. Frank Gavin, Dr. John Hawboldt, Dr. Peter Jamieson, Dr. Julia Lowe, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. James Silvius, and Dr. Adil Virani.

June 20, 2012 Meeting**Regrets:**

None

Conflicts of Interest:

One CDEC member did not vote due to considerations of conflict of interest.

About this Document:

CDEC 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 CDEC made its recommendation. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC 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 CDEC Recommendation neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

CADTH is not legally responsible for any damages arising from the use or misuse of any information contained in or implied by the contents of this document.

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