CDEC FINAL RECOMMENDATION

LINAGLIPTIN
(Trajenta – Boehringer Ingelheim Canada)
Indication: Type 2 Diabetes Mellitus

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that linagliptin be listed as a third drug added on to metformin and a sulfonylurea for patients with inadequate glycemic control on metformin and a sulfonylurea and for whom insulin is not an option.

Reasons for the Recommendation:
1. In one double-blind randomized controlled trial (RCT) of patients with inadequate glycemic control on a combination of metformin and a sulfonylurea, the addition of linagliptin resulted in a statistically significantly greater reduction in hemoglobin A1c compared with the addition of placebo.
2. At the submitted price, the daily cost of linagliptin is more than the daily cost of sulfonylureas, but less than the cost of sitagliptin.

Of Note:
The Committee noted that in patients with an inadequate response on metformin and a sulfonylurea, a CADTH Therapeutic Review Panel recommended in 2010 that insulin NPH is the preferred therapy. However, both the Panel and CDEC also recognized that insulin may not be an option for all patients.

Background:
Linagliptin has a Health Canada indication for the treatment of adult patients with type 2 diabetes mellitus to improve glycemic control as:

Monotherapy
- In conjunction with diet and exercise in patients for whom metformin is inappropriate due to contraindications or intolerance.

Combination Therapy
- In combination with metformin when diet and exercise plus metformin alone do not provide adequate glycemic control.
- In combination with a sulfonylurea when diet and exercise plus a sulfonylurea alone do not provide adequate glycemic control.
• In combination with metformin and a sulfonylurea when diet and exercise plus metformin and a sulfonylurea do not provide adequate glycemic control.

Linagliptin is a selective dipeptidyl peptidase-4 (DPP-4) inhibitor. It is available as 5 mg oral tablets, and the Health Canada–recommended dose is 5 mg once daily.

Summary of CDEC Considerations:
The Committee considered the following information prepared by the Common Drug Review (CDR): a systematic review of RCTs of linagliptin 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 five double-blind RCTs of adult patients with type 2 diabetes mellitus. Four trials investigated the use of linagliptin in dual therapy (studies 1218.6, 1218.17, 1218.20, and study 1218.35) and one trial investigated the use of linagliptin in triple therapy (study 1218.18).

Dual Therapy Trials
Three trials evaluated linagliptin as add-on therapy in patients with inadequate glycemic control on a stabilized dose of metformin (≥ 1,500 mg or the maximum tolerated dose):
• Study 1218.6 (N = 333) was a 12-week RCT that randomized patients to one of five treatment groups: linagliptin (1 mg, 5 mg, or 10 mg daily), glimepiride (1 mg to 3 mg daily), or placebo.
• Study 1218.17 (N = 701) was a 24-week RCT that randomized patients to linagliptin 5 mg daily or placebo.
• Study 1218.20 (N = 1,552) was a 104-week, non-inferiority RCT that randomized patients to linagliptin 5 mg daily or glimepiride (1 mg to 4 mg daily).

One trial evaluated linagliptin as an add-on therapy in patients with inadequate glycemic control on a sulfonylurea (at least half the maximum daily dose or the maximum tolerated dose).
• Study 1218.35 (N = 245) was an 18-week RCT that randomized patients to linagliptin 5 mg daily or placebo.

Triple Therapy Trial
One trial evaluated linagliptin as an add-on therapy in patients with inadequate glycemic control on metformin (≥ 1,500 mg or the maximum tolerated dose) plus a sulfonylurea (maximum tolerated dose).
• Study 1218.18 (N = 1,058) was a 24-week RCT that randomized patients to linagliptin 5 mg daily or placebo.

Mean baseline hemoglobin A1c in the five trials ranged from 7.7% to 8.6%. The percentage of patients who prematurely discontinued study medication varied from 6.9% in study 1218.35, to [unpublished study results were removed at the manufacturer’s request] in study 1218.20. However, the frequency of premature study drug discontinuation was roughly similar between linagliptin 5 mg treatment groups and comparator treatment groups (placebo or glimepiride) in all studies.

The Committee noted there are no RCTs comparing linagliptin with sitagliptin, or with a basal insulin, when added as a third agent to metformin plus a sulfonylurea. The included trials were
not powered to detect differences between treatments in the microvascular or macrovascular complications of diabetes

**Outcomes**

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

The primary outcome in the included trials was the change from baseline in hemoglobin A1c. In study 1218.20, linagliptin would be considered non-inferior to glimepiride (based on the change from baseline in hemoglobin A1c at 104 weeks) if the upper limit of the 97.5% confidence interval (CI) for the between-treatment difference was below 0.35%.

Quality of life data were reported for three trials in the CDR systematic review (1218.20, 1218.35, and 1218.18), measured using the European Quality of Life – 5 Dimension questionnaire (EQ-5D).

**Results**

Linagliptin results described below are for the Health Canada–recommended dose only (5 mg daily). Results for the glimepiride treatment group in study 1218.6 are not reported, as the manufacturer did not report inferential statistics directly comparing linagliptin with glimepiride in this trial.

**Efficacy or Effectiveness**

**Dual Therapy Trials**

- Compared with placebo, linagliptin produced statistically significantly greater reductions in hemoglobin A1c when added on to metformin (mean differences [MD] –0.74% and –0.64% in studies 1218.6 and 1218.17, respectively) and when added on to a sulfonylurea (MD –0.47% in study 1218.35).
- Non-inferiority of linagliptin to glimepiride, when added on to metformin, was demonstrated, based on the reduction in hemoglobin A1c for the full analysis set (the primary analysis) in study 1218.20: MD (97.5% CI) 0.20% (0.09 to 0.30). However, for the per-protocol population [unpublished study results were removed at the manufacturer’s request].
- In 1218.20, the reported frequency of cardiovascular events (a composite of cardiovascular death, myocardial infarction, stroke, or unstable angina) was statistically significantly lower for linagliptin than for glimepiride. However, the number of events was small (n = 12 and N = 26 for linagliptin and glimepiride, respectively) and the trial was of too short a duration to adequately assess the effect of linagliptin on macrovascular complications of diabetes.
- Compared with placebo, linagliptin did not produce statistically significant changes in body weight in any of the reviewed trials. In study 1218.20, patients in the glimepiride group had a mean weight gain of 1.29 kg, which was statistically significantly greater than with linagliptin [unpublished study results were removed at the manufacturer’s request].
- Between-treatment differences in quality of life, in study 1218.20 (linagliptin versus glimepiride) and in study 1218.35 (linagliptin versus placebo) were [unpublished study results were removed at the manufacturer’s request].
Triple Therapy Trials

- Compared with placebo, linagliptin produced a statistically significantly greater reduction in hemoglobin A1c when used as add-on to metformin plus a sulfonylurea (MD –0.62%).
- There were no statistically significant differences in body weight changes or quality of life between linagliptin and placebo when used as add-on to metformin plus a sulfonylurea.

Harms (Safety and Tolerability)

- The percentage of patients with a serious adverse event was not statistically significantly different between linagliptin and comparators in any of the reviewed trials.
- The percentage of patients with an adverse event or withdrawal due to an adverse event was not statistically significantly different between linagliptin and placebo in any of the reviewed trials. In study 1218.20, the percentage of patients with an adverse event or who withdrew due to an adverse event was statistically significantly less for linagliptin than for glimepiride: 85.4% versus 91.1%, and 7.9% versus 11.6%, respectively.
- Episodes of severe hypoglycemia (requiring medical or non-medical assistance) were reported in two studies. In study 1218.20, a statistically significantly smaller percentage of linagliptin-treated patients experienced severe hypoglycemia, compared with glimepiride: [unpublished study results were removed at the manufacturer’s request]. In study 1218.18, the percentage of patients experiencing severe hypoglycemia was not statistically significantly different between linagliptin and placebo: 2.7% versus 4.8%, respectively.
- The percentage of patients reporting any hypoglycemia was not statistically significantly different between linagliptin and placebo in studies 1218.6 and 1218.35, but was statistically significantly less for linagliptin compared with placebo in study 1218.17 (0.6% versus 2.8%) and compared with glimepiride in Study 1218.20 (7.5% versus 36.1%). The percentage of patients reporting any hypoglycemia was statistically significantly higher for linagliptin than for placebo, when added on to metformin plus a sulfonylurea in study 1218.18 (23.7% versus 16.0%).

Cost and Cost-Effectiveness

The manufacturer submitted a cost-minimization analysis comparing linagliptin with sitagliptin for patients with type 2 diabetes requiring second- and third-line therapy. Efficacy data to support the use of a cost-minimization analysis were obtained from an indirect comparison of linagliptin with sitagliptin in terms of hemoglobin A1c control. Because linagliptin and sitagliptin are from the same drug class, the manufacturer assumed other aspects of patient management were equivalent (compliance, adverse events, and discontinuation) between the two drugs and considered drug treatment costs.

The manufacturer’s cost-minimization analysis was limited by the lack of head-to-head RCT evidence versus sitagliptin. In addition, less expensive oral therapies in other drug classes, available for treatment of patients who are not adequately controlled with metformin monotherapy, were not considered.

The daily drug cost of linagliptin ([confidential price removed at manufacturer’s request]; 5 mg) is less than sitagliptin ($2.55; 100 mg) but is higher than glyburide ($0.03 to $0.23; 2.5 mg to 20 mg), generic gliclazide ($0.09 to $0.37; 40 mg to 320 mg), long-acting gliclazide ($0.14 to $0.56; 30 mg to 120 mg), generic pioglitazone ($0.93 to $1.96; 15 to 45 mg), and acarbose ($0.78 to $1.08; 150 to 300 mg).
Patient Input Information:
No patient groups responded to the CDR Call for Patient Input.

Other Discussion Points:
- The Committee noted that the manufacturer requested linagliptin be reimbursed in a manner similar to sitagliptin.
- 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 discussed the point that DPP-4 inhibitors are a relatively new class of antihyperglycemic agents for which potentially rare and long-term harms have not been fully elucidated. The Committee noted regulatory concerns regarding the potential risk of pancreatitis with linagliptin and that the US Food and Drug Administration has recommended further post-market evaluation to assess the risk.
- The Committee noted that none of the reviewed trials were designed to examine the effects of linagliptin on microvascular or macrovascular outcomes, and that the relationship between hemoglobin A1c and vascular outcomes may differ for new drug classes with novel mechanisms of action, and between drugs within a class.
- The Committee noted that there is an ongoing trial (CAROLINA) to evaluate the cardiovascular safety of linagliptin compared with glimepiride in patients with type 2 diabetes and high cardiovascular risk.

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.

January 18, 2012 Meeting

Regrets:
None

Conflicts of Interest:
One member did not participate in the 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 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.

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