CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

INSULIN GLARGINE
(Basaglar — Eli Lilly Canada)
Indications: Type 1 and Type 2 Diabetes Mellitus

Recommendation:
The CADTH Canadian Drug Expert Committee (CDEC) recommends that Basaglar (insulin glargine subsequent entry biologic [SEB]) be listed in accordance with the Health Canada–approved indications, if the following conditions are met:

Conditions:
- List in a similar manner to the public plan listing criteria for Lantus.
- The cost of treatment with Basaglar should provide significant cost savings for jurisdictions compared with the cost of treatment with Lantus.

Reasons for the Recommendation:
1. One phase 1 clinical trial and two phase 3clinical trials demonstrated that Basaglar has similar pharmacokinetics, pharmacodynamics, efficacy, and safety compared with Lantus.
2. At the submitted price ($0.0526 per unit), Basaglar is less costly than Lantus ($0.0619 per unit).

Of Note:
CDEC noted that a patient being treated with Lantus should be considered for switching to Basaglar, following a discussion between the patient and his or her physician.

Background:
Basaglar is an insulin glargine SEB based on Lantus as a reference product. It has been approved in Canada for the following indications:
- Treatment of patients over 17 years of age with type 1 or type 2 diabetes mellitus who require basal (long-acting) insulin for the control of hyperglycemia.
- Treatment of pediatric patients (over six years of age) with type 1 diabetes mellitus who require basal (long-acting) insulin for the control of hyperglycemia.

Summary of CDEC Considerations:
CDEC considered the following information prepared by the CADTH Common Drug Review (CDR): a review of manufacturer-provided information on the clinical efficacy, biosimilarity, and

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extrapolation of data for Basaglar; a critique of the manufacturer's pharmacoeconomic evaluation; and patient group–submitted information about outcomes and issues important to patients.

Patient Input Information

The following is a summary of key information provided by two patient groups that responded to the CDR call for patient input:

- Patients indicated that uncontrolled diabetes mellitus and the stigma associated with the disease can result in reduced quality of life and feeling frustrated that they cannot lead a "normal life" due to diabetes. Patients emphasized the psychological and emotional impacts on their lives and on loved ones.
- Therapeutic options that help better control blood glucose fluctuations and eliminate or minimize adverse effects are a top priority for patients.
- Some patients expect that Basaglar will be less costly than the reference product, Lantus, and will therefore lower health care costs and potentially increase access to treatment.
- Patients expressed concern about the following:
  - Whether the SEB will work as well and be at least as safe as the reference product.
  - Being "switched" to the SEB from Lantus, and how this may impact their condition, particularly for those who have established a stable treatment regimen.

Clinical Trials

The manufacturer provided efficacy and safety data from two pivotal clinical trials, and biosimilarity data from one pharmacokinetic (PK) and pharmacodynamic (PD) study:

- ELEMENT 1 (N = 536) was a phase 3, randomized, open-label, multi-centre, multinational, parallel-group, clinical non-inferiority study designed to compare the efficacy and safety of Basaglar with Lantus, in adult patients with type 1 diabetes mellitus. The primary end point was the change in glycated hemoglobin (A1C) from baseline to end point at week 24. If the upper limit of the 95% confidence interval (CI) for the primary analysis was < 0.4%, then non-inferiority was concluded.
- ELEMENT 2 (N = 759) was a phase 3, randomized, double-blind, multi-centre, multinational, parallel-group, clinical non-inferiority study designed to compare the efficacy and safety of Basaglar with Lantus, in adult patients with type 2 diabetes mellitus. The primary end point was the change in A1C from baseline to end point at week 24. If the upper limit of the 95% CI for the primary analysis was < 0.4%, then non-inferiority was concluded.
- ABEO (N = 91) was a phase 1, randomized, double-blind, single-site, two-treatment, four-period, crossover, replicate treatment, euglycemic clamp study in healthy patients designed to compare the PK and PD of Basaglar and Lantus. The primary end point was to demonstrate PK equivalence at a steady state of area under the concentration-time curve and observed maximum steady state serum concentration between Basaglar and Lantus. Equivalence was demonstrated if the 90% CIs lay within the equivalence margin of 80% to 125%.

Outcomes

CDEC discussed the following outcomes:

- Glycemic control — change from baseline in A1C, proportion of patients with A1C less than 7% and less than or equal to 6.5% at end point, and change from baseline in fasting plasma glucose.
- Body weight — change from baseline in body weight.
- Hypoglycemia — events of hypoglycemia, including severe hypoglycemia.

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- Adult Low Blood Sugar Survey (ALBSS) — a 33-item patient-experience questionnaire with items categorized in two domains: behaviour (or avoidance) and worry (or affect). Behaviour total score (TS) range is 0 to 60 and worry TS range is 0 to 72. Higher scores on behaviour items (related to avoidance of hypoglycemia) reflect greater awareness and/or effort of the participant to prevent low blood sugar. Higher scores on worry items (related to worries about low blood sugar and its consequences) reflect greater participant concern about having low blood sugar.
- Insulin Treatment Satisfaction Questionnaire (ITSQ) — a 22-item questionnaire that assesses treatment satisfaction for participants with diabetes and on insulin. The items are categorized among five content clusters, forming a total ITSQ score transformed as 0 to 100%, where 100% indicates complete satisfaction with insulin treatment.
- Serious adverse events (SAEs), total adverse events (AEs), and withdrawals due to adverse events.

Efficacy

- Basaglar was found to be non-inferior to Lantus at both the FDA suggested non-inferiority margin of 0.4% and a more stringent 0.3% non-inferiority margin requested by some other regulatory bodies for mean change in A1C from baseline to week 24 in both ELEMENT 1 and ELEMENT 2. The least squares mean difference between Basaglar and Lantus in A1C between treatments in the full analysis sets was:
    - ELEMENT 1: 0.11% (95% CI, −0.005% to 0.217%)
    - ELEMENT 2: 0.052% (95% CI, −0.070% to 0.175%).
- Similar results were found for the per-protocol analysis set as in the full analysis set.
- Non-inferiority between Basaglar and Lantus was also found for mean change in A1C from baseline to the end of the 28-week extension period (week 52), as a secondary end point in ELEMENT 1.
- The proportion of patients who achieved A1C targets of < 7.0% and ≤ 6.5% at week 24 was similar between treatment groups, and the between-group differences were not statistically significant in both ELEMENT 1 and ELEMENT 2.
- Between baseline and week 24 both treatment groups demonstrated similar increases in mean daily basal insulin dose, but there were no significant between-group differences in actual daily basal insulin dose or change in basal insulin dose from baseline to week 24 in both studies.
- Results for the ALBSS total score and ITSQ total score showed similar improved scores from baseline to week 24 and were not statistically significantly different between groups in both ELEMENT 1 AND ELEMENT 2.
- In the subgroup of patients who were switched from Lantus to Basaglar, in both studies, no statistically significant treatment differences were observed for mean change in A1C from baseline to week 24 or at week 52. Likewise, there were no statistically significant between-treatment group differences with respect to secondary outcomes (e.g., changes in basal and prandial insulin doses, proportion of patients achieving glycemic targets, daily mean blood glucose), except a statistically significant weight gain among Basaglar-treated patients (Basaglar: 1.81% ± 0.42; Lantus: 0.41% ± 0.39, P = 0.035).

Harms (Safety and Tolerability)

- There was one death in the Lantus group in ELEMENT 1 and one death in each treatment group in ELEMENT 2; all deaths were not considered to be related to study drugs.
- The proportion of patients who reported at least one SAE was:

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  - ELEMENT 1: 7.5% with Basaglar and 9.0% with Lantus over 52 weeks
  - ELEMENT 2: 4.0% with Basaglar and 4.7% with Lantus over 24 weeks.
- The proportion of patients who reported at least one AE was:
  - ELEMENT 1: 62.3% with Basaglar and 62.2% with Lantus over 52 weeks
  - ELEMENT 2: 52.1% with Basaglar and 62.2% with Lantus over 24 weeks.
- The proportion of patients who reported at least one severe hypoglycemic event was:
  - ELEMENT 1: 3.7% with Basaglar and 4.1% with Lantus over 52 weeks
  - ELEMENT 2: 0.5% with Basaglar and 0.5% with Lantus over 24 weeks.
- The proportion of patients who withdrew as a result of AEs was:
  - ELEMENT 1: 0.7% with Basaglar and 2.2% with Lantus over 52 weeks
  - ELEMENT 2: 1.6% with Basaglar and 2.9% with Lantus over 24 weeks.

Extrapolation

Health Canada granted the extrapolation of data from the manufacturer's studies of Basaglar versus Lantus in adults with type 1 diabetes mellitus to treatment of pediatric patients (over six years of age) with type 1 diabetes mellitus who require basal (long-acting) insulin for the control of hyperglycemia. Health Canada stated that the indication for pediatric patients with type 1 diabetes mellitus was granted on the basis of similarity and the absence of meaningful differences between Basaglar and Lantus with respect to quality, mechanism of action, disease pathophysiology, safety, dosage regimen, and on clinical experience with the reference product (i.e., Lantus).

Cost and Cost-Effectiveness

The manufacturer submitted a cost comparison between Basaglar and reference insulin glargine (Lantus) for the two indications reviewed. The manufacturer-submitted price of Basaglar ($0.0526 per unit of insulin) is 15% less than that of Lantus when using the Ontario Drug Benefit formulary price of Lantus ($0.0619 per unit of insulin).

CDR identified the following issues for consideration:

- Dosage of insulin glargine is based on patient response. As Basaglar and Lantus were demonstrated to have similar pharmacokinetics, pharmacodynamics, clinical efficacy and harms, and share the same dosing strategies, the relative cost difference between the drugs is likely to be maintained regardless of patient characteristics or required daily dose.
- The listing criteria for Lantus differ across publicly funded drug plans in Canada, with Lantus available as a full benefit in some jurisdictions and as a restricted benefit in others. The expected savings from Basaglar compared with Lantus are based on the assumption that the listing criteria for Lantus would be applied to Basaglar.
- Should the actual cost of Lantus to drug plans differ from the list price used in the analysis, this could impact the cost differential and potential savings to the drug plans.

Other Discussion Points:

- CDEC acknowledged that the manufacturer of Basaglar conducted six phase 1 trials in total, which were reviewed by Health Canada. The CDR review, which the CDEC discussion was in part informed by, focused on the manufacturer-provided pivotal phase 1 study, ABEO.

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CDEC Members:

Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. Adil Virani, and Dr. Harindra Wijeysundera.

March 16, 2016 Meeting

Regrets:

Two CDEC members were unable to attend the meeting.

Conflicts of Interest:

None

About This Document:

CDEC provides formulary listing recommendations or advice to CDR-participating drug plans. CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. 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.

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