CEDAC FINAL RECOMMENDATION

INSULIN DETEMIR
(Levemir ® – Novo Nordisk Canada Inc.)
New Indication: Type 1 Diabetes Mellitus in Pediatric Patients

Recommendation:
The Canadian Expert Drug Advisory Committee (CEDAC) recommends that insulin detemir not be listed at the submitted price.

Reasons for the Recommendation:
1. No economic evaluation was provided in a pediatric population; therefore, the cost-effectiveness of insulin detemir at the submitted price is uncertain.

2. There were two randomized controlled trials evaluating the effects of insulin detemir in pediatric patients with type 1 diabetes. In the CDR pooled analysis of the two trials, insulin detemir was non-inferior to NPH insulin in control of hemoglobin A1c.

Of Note:
1. The Committee noted the open-label design of trials and the unblinded classification of hypoglycemic episodes. This makes the outcome of hypoglycemia subject to potential reporting bias. The Committee observed that, although non-inferiority was demonstrated, hemoglobin A1c was numerically higher in the insulin detemir group compared with NPH insulin, which may have contributed to the decreased incidence of hypoglycemic episodes.
2. The Committee noted a statistically significant reduction in the proportion of patients with at least one major hypoglycemic episode for insulin detemir compared with NPH insulin in only one of two trials in the CDR systematic review.
3. Based on a review of the evidence, the Committee felt that a reduced price would improve insulin detemir's cost-effectiveness and increase the likelihood of a recommendation to "List" or "List with Criteria".

Background:
This resubmission was initiated by the Advisory Committee on Pharmaceuticals (members from the CDR-participating drug plans) for the use of insulin detemir in pediatric patients (≥ 6 years of age) with type 1 diabetes mellitus who require long-acting (basal) insulin for the control of hyperglycemia. Insulin detemir is also approved by Health Canada for the treatment of adult patients with type 1 or type 2 diabetes who require a long-acting (basal) insulin for the control of hyperglycemia and for the treatment of type 2 diabetes in combination with oral antidiabetic agents (metformin, sulfonylureas, or a thiazolidinedione) in adult patients who are not in adequate metabolic control on oral antidiabetic drugs alone.

© 2009 CADTH

Insulin detemir is a long-acting (basal) insulin analogue. It is available as a 100 U/mL solution for injection, supplied in 3 mL cartridges. Dosing is individualized and may be administered once daily when used in combination with short- or rapid-acting insulin or oral antidiabetic agents, or twice daily, if needed, when used as part of a basal-bolus insulin regimen.

Submission History:

Insulin detemir has been previously reviewed by CEDAC for the treatment of type 1 and type 2 diabetes in adults. The most recent recommendation for the adult population is Do Not List at the submitted price (see Notice of CEDAC Final Recommendation, August 19, 2009). The Committee's initial recommendation for insulin detemir in the adult population was Do Not List (see Notice of CEDAC Final Recommendation, August 2, 2006).

Summary of CEDAC Considerations:

The Committee considered a systematic review of randomized controlled trials for insulin detemir in children and adolescents with type 1 diabetes. The manufacturer did not provide an economic evaluation in a pediatric population for the Committee's consideration.

Clinical Trials

The CDR systematic review included two open-label randomized controlled trials (N = 695). Insulin detemir was compared with NPH insulin over 26 weeks in Study 1379, and over 52 weeks in Study 1689. Insulin detemir was administered once or twice daily, based on the regimen patients had received prior to the trial. Insulin aspart was used as the bolus insulin. For the determination of the initial dose, one unit of insulin detemir was considered similar to one unit of NPH insulin. Initial doses were subsequently modified using dosing algorithms that were based on premeal glucose targets. Across both studies, the mean age was 9.8 to 11.9 years, with [redacted]% of patients in study 1689 under six years of age. Withdrawals were low in both studies. In Study 1689, patients with [redacted] were not included, which decreased the external validity of the results for those with recurring hypoglycemia.

Outcomes

Outcomes were defined *a priori* in the CDR systematic review protocol. Of these, the Committee discussed the following outcomes: mean difference in hemoglobin A1c, hypoglycemia, quality of life and weight change.

The primary outcome of the studies was the mean difference in hemoglobin A1c (%). Trials used a non-inferiority design with a margin of 0.4% hemoglobin A1c.

The following definitions of hypoglycemia were applied in the trials:

- Major hypoglycemia was defined differently in the two trials. In Study 1379, an episode was classified as major hypoglycemia if the patient was unable to treat himself or herself and another person had to administer food, glucagon or intravenous glucose. However, as patients were children and adolescents, they may often need help from parents when hypoglycemic episodes occur, especially during the night. In Study 1689, hypoglycemia was classified as a major episode if the patient was semi-conscious, unconscious, in coma or in convulsion and may have required glucagon or intravenous glucose. It is not known how semi-consciousness was defined, therefore, it is not clear that the definition of major hypoglycemia in Study 1689 was stricter than the definition used in Study 1379.
- Nocturnal hypoglycemia was defined as an episode occurring between 11:00 p.m. and 6:00 a.m.

© 2009 CADTH

- Overall hypoglycemia was defined as any type of hypoglycemia (symptomatic or plasma glucose).

In both trials, hypoglycemic episodes were reported in a diary. It was not clear if this was done by the parent or the child. Episodes in the diary were then transcribed to the case report form by an unblinded investigator and then entered in the study database by unblinded manufacturer staff. Methods involving self-report and unblinded individuals risk reporting and misclassification bias of hypoglycemic episodes, given the subjective nature of the reporting, the variable confirmation by plasma glucose levels and the large number of episodes that required classification. Hypoglycemia was reported in Study 1389 from week six to week 26 after an initial dose titration and lead-in period. In Study 1689, hypoglycemia was reported for the entire 52-week study period because there was no initial titration period.

Diabetes-related mortality, long-term complications, and quality of life were not reported in any of the included trials. Weight change was reported in only one of the two trials.

Efficacy or Effectiveness

- Based on CDR pooled results of two trials, insulin detemir was non-inferior to NPH insulin in terms of mean difference in percent hemoglobin A1c (weighted mean difference 0.10%, 95% confidence interval [CI]: -0.05 to 0.26%). It was noted that, although non-inferiority was demonstrated, hemoglobin A1c was numerically higher in the insulin detemir group compared with NPH insulin.
- The proportion of patients with at least one major hypoglycemic episode was statistically significantly lower by CDR analysis for insulin detemir compared with NPH insulin ([redacted]% versus [redacted]%, respectively), in Study 1689, the trial with the stricter definition of major hypoglycemia, but not in Study 1379. The absolute risk difference in Study 1689 was approximately [redacted]%. Major nocturnal hypoglycemia was similar between insulin detemir and NPH insulin in both trials. CDR pooled analyses of the two trials showed statistically significant improvements in nocturnal hypoglycemia but not overall hypoglycemia.
- Insulin detemir was associated with statistically significantly lower weight gain than NPH insulin in Study 1689 (mean difference [redacted] kg, 95%CI: [redacted] to [redacted]); however the clinical significance of this difference is not clear.

Other Harms (Safety and Tolerability)

- There were no deaths in either of the two trials. Serious adverse events were similar between insulin detemir and NPH insulin.

Cost and Cost-Effectiveness

The manufacturer did not provide an economic evaluation for the pediatric population; therefore, the cost-effectiveness of insulin detemir in the treatment of children and adolescents is uncertain. Insulin detemir costs more ($7.32) per mL than NPH insulin ($1.94 to $2.53) and insulin glargine ($5.68).

Other Discussion Points

- Some Committee members felt that an absolute risk difference of 5% for the proportion of patients with at least one major hypoglycemic episode was an important difference in children.
- Hypoglycemia can be reported as either the rate of hypoglycemic episodes or the proportion of patients experiencing at least one hypoglycemic episode. Both measures were reported in the CDR review and were found to be consistent with each other with the exception of overall hypoglycemia; the rate ratio was significantly lower for insulin detemir compared with NPH insulin but the proportion of patients with at least one hypoglycemic episode was similar between the two treatment groups.

© 2009 CADTH

- Insulin detemir should not be mixed with other insulins. Therefore, patients using insulin detemir vials potentially require more injections compared with those using NPH insulin vials.
- Findings of the 2008 Canadian Optimal Medication Prescribing and Utilization Service (COMPUS) meta-analysis on long-acting insulin analogues were generally consistent with those of the CDR systematic review. In children with type 1 diabetes, the COMPUS meta-analysis only included one published trial which reported no difference between insulin detemir and NPH insulin in the proportion of patients experiencing at least one episode of major hypoglycemia whereas CDR found an additional unpublished trial with a statistically significantly lower proportion of patients with at least one major hypoglycemic episode with insulin detemir compared with NPH insulin.

CEDAC Members Participating
Dr. Robert Peterson (Chair), Dr. Anne Holbrook (Vice-Chair), Dr. Michael Allan, Dr. Ken Bassett, Dr. Bruce Carleton, Mr. John Deven, Dr. Alan Forster, Dr. Laurie Mallery, Mr. Brad Neubauer, Dr. Lindsay Nicolle, Dr. Yvonne Shevchuk, and Dr. Kelly Zarnke.

Regrets
Dr. Michael Evans.

Conflicts of Interest
CEDAC members reported no conflicts of interest related to this submission.

About This Document:
CEDAC provides formulary listing recommendations to publicly funded drug plans.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CEDAC made its recommendation. An overview of these reviews as well as a plain language version of this document are posted on the CADTH website when available.

The manufacturer has reviewed this document and has requested the removal of confidential information in conformity with the CDR Confidentiality Guidelines.

The CEDAC Final 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.

© 2009 CADTH