CEDAC FINAL RECOMMENDATION

INSULIN DETEMIR RESUBMISSION #2
(Levemir ® – Novo Nordisk Canada Inc.)
Indication: Type 1 or Type 2 Diabetes Mellitus in Adults

Recommendation:

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

Reasons for the Recommendation:

1. At the submitted price, insulin detemir costs more ($7.32) per mL than NPH insulin ($1.94 to $2.53). The results of the manufacturer's economic evaluation were sensitive to the choice of clinical inputs and estimates for the loss in utility associated with hypoglycemia. As a result, the Committee felt that the cost-effectiveness of insulin detemir was not demonstrated when compared with NPH.
2. In adults with type 1 diabetes mellitus, the results of a CDR pooled analysis of six open-label randomized controlled trials showed that hemoglobin A1c was statistically significantly lower in the insulin detemir group compared with the NPH insulin group [weighted mean difference - 0.08% (95%CI: -0.16 to -0.01)] but the clinical relevance of the observed difference was uncertain. The proportion of patients experiencing at least one major hypoglycemic event, at least one nocturnal hypoglycemic event or at least one major nocturnal hypoglycemic event was statistically significantly lower with insulin detemir compared with NPH insulin.
3. In adults with type 2 diabetes mellitus, the results of a CDR pooled analysis of seven open-label randomized controlled trials showed that insulin detemir was non-inferior to NPH insulin in control of hemoglobin A1c. There was no statistically significant difference between insulin detemir and NPH insulin for the proportion of subjects experiencing at least one major hypoglycemic episode or major nocturnal hypoglycemic episode. The proportion of patients with at least one nocturnal hypoglycemic episode was statistically significantly lower with insulin detemir compared with the NPH insulin.

Of Note:

1. Despite the statistically significant differences in major hypoglycemia favouring insulin detemir that were observed, the Committee had concerns about the open-label design of trials and the unblinded classification of hypoglycemic episodes. This makes the outcome of hypoglycemia subject to potential reporting bias.
2. 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 indication of treatment of adult patients with type 1 or type 2 diabetes mellitus who require a long-acting (basal) insulin for the control of hyperglycemia. Insulin detemir is also approved by Health Canada for the treatment of pediatric patients (≥ six years of age) with type 1 diabetes mellitus who require long-acting (basal) insulin for the control of hyperglycemia and for the treatment of type 2 diabetes mellitus 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.

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 was previously reviewed by CEDAC for the treatment of type 1 and type 2 diabetes in adults and received a recommendation of "Do Not List" (see Notice of CEDAC Final Recommendation, August 2, 2006).

The original CDR systematic review of insulin detemir for adults included six trials in type 1 diabetes, five trials in type 2 diabetes and one trial in a mixed type 1 and 2 diabetes population. With the exception of two randomized controlled trials (RCTs) using insulin glargine as a comparator (one in type 1 and one in 2 diabetes), all RCTs compared insulin detemir with NPH insulin. In considering the results of these RCTs, the Committee found no convincing evidence that insulin detemir consistently led to a reduced hemoglobin A1c with an accompanying equal or lower incidence of major hypoglycemia compared with other insulins. The original economic model submitted by the manufacturer was in type 1 diabetes only and assumed that insulin detemir was associated with a reduction in hemoglobin A1c and hypoglycemia compared with NPH insulin. The Committee felt that these assumptions were not supported by the results from the RCTs and that the three-fold increase in the cost of insulin detemir relative to NPH insulin was excessive.

The manufacturer had previously filed a resubmission for insulin detemir but subsequently withdrew it. The basis of the current ACP resubmission is new clinical trials in adults with type 1 and type 2 diabetes. In addition, the manufacturer provided a new economic evaluation which used new clinical trial information in both type 1 and type 2 diabetes.

Summary of CEDAC Considerations:

The Committee considered a systematic review of RCTs of insulin detemir in adults with type 1 and type 2 diabetes mellitus as well as a critique of the manufacturer's economic evaluation.

Clinical Trials

The CDR systematic review of insulin detemir that was considered by CEDAC in August 2006 was updated. Seven new trials were included in the updated CDR systematic review: two in adults with type 1 diabetes and five in adults with type 2 diabetes. Therefore, the total number of trials considered was 19 with eight trials in type 1 diabetes, 10 trials in type 2 diabetes and one trial in a mixed population with type 1 or type 2 diabetes. All trials were open-label. In both type 1 and type 2 diabetes trials, for the determination of the initial dose, one unit of insulin detemir was considered similar to one unit of insulin glargine and one unit of NPH insulin. Initial doses were subsequently modified using dosing algorithms

that were based on premeal glucose targets. Withdrawal rates were low across all studies ranging from 5% to 15%.

Patients with a history of recurrent major hypoglycemia and pregnant women were not included in any of the trials, decreasing the external validity of the results for those with recurring hypoglycemia.

Type 1 Diabetes Mellitus
Of the nine trials in type 1 diabetes, insulin detemir was compared with NPH in seven trials and with insulin glargine in two trials. In the two new trials (N = 944), insulin detemir was compared with NPH insulin over 24 months (trial 1595) and with insulin glargine over 52 weeks (trial 1430). In the two new studies and one original study, insulin detemir was administered once daily at study entry, but patients were allowed to switch to a twice-daily regimen during the trial. In the remaining studies, insulin detemir was initiated twice-daily. Insulin aspart was used as the bolus insulin.

Type 2 Diabetes Mellitus
Of the 11 trials in type 2 diabetes, insulin detemir was compared with NPH in eight trials and with insulin glargine in three trials. Of the five new trials (N = 1,754) insulin detemir was compared with NPH insulin in three trials (Study 1632, Study 1659, Study 1684) and with insulin glargine in two trials (Study 1431, Study 2175), over a range of 20 to 52 weeks. In the new type 2 diabetes trials, insulin detemir was initiated as a once-daily regimen in all the trials, and two trials allowed patients to switch to a twice-daily regimen during the trial. Concomitant medications in the new trials included insulin aspart and/or oral antidiabetic agents.

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 in all but one of the seven new trials was the mean difference in hemoglobin A1c (%). These trials used a non-inferiority design with a margin of 0.4% hemoglobin A1c. Mean weight at endpoint was the primary outcome for the remaining trial that was in type 2 DM adults, and used a superiority design.

The following definitions of hypoglycemia were applied in the trials:
- Major hypoglycemia was defined as an episode where the patient is unable to treat himself or herself, requiring food, glucagon or intravenous glucose
- Nocturnal hypoglycemia was defined as an episode occurring between 11:00 p.m. and 6:00 a.m.
- Overall hypoglycemia was defined as any type of hypoglycemia (symptomatic or plasma glucose).

In all trials, hypoglycemic episodes were self-reported in a diary, then transcribed to the case report form by an unblinded investigator and then recorded 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 by the patient, the variable confirmation by plasma glucose levels and the large numbers of episodes that required classification.

Diabetes-related mortality and long-term complications were not reported in any of the included trials.

Results

Type 1 Diabetes Mellitus in Adults

- In adults with type 1 diabetes, the results of a CDR pooled analysis of six open-label randomized controlled trials showed that hemoglobin A1c was statistically significantly lower in the insulin detemir group compared with the NPH insulin group [weighted mean difference (WMD) -0.08% (95%CI: -0.16 to -0.01)] but the clinical relevance of the observed difference was uncertain.
- In the CDR pooled analysis of six trials, the proportion of subjects experiencing at least one major hypoglycemic event [relative risk (RR) 0.73, 95% CI: 0.57 to 0.93], the proportion of patients with at least one nocturnal hypoglycemic event (RR 0.90, 95% CI: 0.83 to 0.99), and one major nocturnal hypoglycemic event (RR 0.52, 95% CI: 0.35 to 0.77) was statistically significantly lower in the insulin detemir group compared with NPH insulin. There was no significant difference between insulin detemir and NPH insulin in the proportion of patients with at least one hypoglycemic event of any type.
- Addition of the one new NPH insulin trial, Study 1595, to the five original trials led to a change in the pooled results compared with the original CDR review. The updated review found a lower hemoglobin A1c, a lower risk of major hypoglycemia and a lower risk of major nocturnal hypoglycemia for insulin detemir compared with NPH insulin. Study 1595 had a large sample size (n = 495) and had the longest duration of all trials conducted in adults with type 1 diabetes (24 months).
- Quality of life was measured in only one original trial and there were no statistically significant differences between insulin detemir and NPH.
- The Committee considered the results of the CDR pooled results of two trials (one new and one from the original submission) comparing insulin detemir with insulin glargine; however, the primary focus of the discussion was on the comparison with NPH insulin. The CDR pooled analysis showed that insulin detemir was non-inferior to insulin glargine in terms of mean difference in percent hemoglobin A1c. In addition, there was no statistically significant difference between insulin detemir and insulin glargine for the proportion of patients experiencing at least one nocturnal hypoglycemic episode, one major nocturnal hypoglycemic episode or one hypoglycemic episode of any type. In one of two trials, the proportion of patients experiencing at least one major hypoglycemic episode was statistically significantly lower in the insulin detemir group compared with the insulin glargine group. Because results of the new insulin glargine trial differed from the original insulin glargine trial, it is not clear if risk of major hypoglycemia differs between insulin detemir and insulin glargine. In the one trial that measured quality of life, differences between insulin detemir and insulin glargine were not statistically significant.
- In all trials, there was statistically significantly lower weight gain for insulin detemir compared with NPH insulin (differences ranging from -0.61 kg to -0.99 kg) but the clinical significance of small differences in weight change is uncertain. Weight change was similar between insulin detemir and insulin glargine.
- In adults with type 1 diabetes, serious adverse events were similar between insulin detemir and NPH insulin; however, when insulin detemir was compared with insulin glargine, in one out of two trials the proportion of patients reporting at least one serious adverse event was statistically significantly [redacted] in the insulin detemir group.

Type 2 Diabetes Mellitus in Adults

- In the CDR pooled analysis of seven trials, although non-inferiority was demonstrated, insulin detemir was statistically significantly worse than NPH insulin in controlling hemoglobin A1c (WMD [redacted], 95% CI: [redacted] to [redacted]).

- CDR pooled estimates showed no statistically significant difference between insulin detemir and NPH insulin for the proportion of patients experiencing at least one major hypoglycemic episode or one major nocturnal hypoglycemic episode. The proportion of patients with at least one nocturnal episode (pooled RR 0.58, 95% CI: 0.48 to 0.71) and at least one episode of any type (pooled RR 0.71, 95% CI: 0.61 to 0.83) was statistically significantly lower in the insulin detemir group compared with the NPH group.
- The Committee considered the results of the CDR pooled results of three trials (two new and one from the original submission) comparing insulin detemir with insulin glargine; however, the primary focus of the discussion was on the comparison with NPH insulin. The CDR pooled analysis showed that insulin detemir was non-inferior to insulin glargine in terms of mean difference in percent A1c. In addition, there was no statistically significant difference between insulin detemir and insulin glargine for proportion of patients experiencing at least one major hypoglycemic event, one major nocturnal hypoglycaemic event, one nocturnal hypoglycemic episode or one hypoglycemic event of any type.
- Quality of life was measured by the Short-Form 36 Health Survey (SF-36) in only two of the type 2 diabetes adult studies and no statistically significant differences were observed.
- In all but one study, there was statistically significantly lower weight gain for insulin detemir compared with either NPH insulin (differences ranging from 0.38 kg to 1.58 kg) or insulin glargine (difference ranging from 0.9 kg to 1.37 kg), but the clinical significance of small differences in weight change is uncertain.
- In adults with type 2 diabetes, serious adverse events were similar when comparing insulin detemir to NPH insulin or insulin glargine.

Cost and Cost-Effectiveness

The economic evaluation provided by the manufacturer for the Advisory Committee on Pharmaceuticals resubmission was a cost utility analysis comparing insulin detemir and NPH insulin based on the CORE model structure. Separate analyses were conducted for patients with type 1 and type 2 diabetes, with analysis time horizons of 60 years for type 1 diabetes and 35 years for type 2 diabetes. Information on clinical effects were based on one trial for type 1 diabetes (Bartley 2008) and one trial for type 2 diabetes (Meneghini 2007), and the loss of utilities (disutilities) for hypoglycemic events and the fear associated with these events were based on self reported surveys conducted in the UK (Currie 2006). The manufacturer reported that when comparing insulin detemir to NPH insulin, it was associated with an incremental cost per QALY of $24,389 in type 1 diabetes and $18,677 in type 2 diabetes.

The economic model was driven by changes in hemoglobin A1c and hypoglycemic events, and the loss of utility associated with hypoglycemic events (which includes the fear of hypoglycemia). When comparing the results of the clinical trials used by the manufacturer with those from CDR Clinical Review, the single trials do not appear to provide a good reflection of the full body of clinical evidence for these patients. Consequently, the clinical benefits for insulin detemir predicted by the model may be overestimated. Further, the estimates of the disutility associated with hypoglycemic events and the fear of hypoglycemia were obtained from a publication by Currie (2006), which appears to represent a poorly controlled patient population, experiencing a greater number of severe hypoglycemic events compared to the population being considered by the manufacturer. Consequently, the fear of hypoglycemia may be much greater for the patients in the study by Currie. In sensitivity analyses, when using disutilities for hypoglycemic events from a recently published report on insulin analogues (COMPUS 2008), which do not include the fear of events, the manufacturer reported that the incremental cost per QALY estimates increase to $201,905 for type 1 diabetes, and $178, 947 per QALY for type 2 diabetes. Insulin detemir costs more ($7.32) per mL than NPH insulin ($1.94 to $2.53) and insulin glargine ($5.68).

Other Discussion Points

- Hemoglobin A1c and hypoglycemic episodes should be considered together when evaluating insulin therapy as higher hemoglobin A1c levels can lead to a lower incidence of major hypoglycemia.
- Recent results from trials in type 2 diabetes, ACCORD and ADVANCE, suggest that higher target values for hemoglobin A1c may be appropriate for some patients.
- Hypoglycemia can be reported as either the rate of hypoglycemic episodes or the proportion of patients experiencing a hypoglycemic episode. Both measures were reported in the CDR review and were found generally to be consistent with each other.
- The Committee felt that because most trials excluded patients with a history of recurrent major hypoglycemia and because this is an important population that would be treated with insulin detemir, it was difficult to determine the usefulness of insulin detemir in this population.
- 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.
- Insulin detemir is not always dosed once-daily. In most of the clinical trials that allowed patients in the insulin detemir group to switch from once to twice-daily dosing, about 50 to 66% of patients were on a twice-daily insulin detemir regimen at the end of the trial.
- The Committee observed that at the end of some type 1 and most type 2 diabetes trials, insulin detemir doses were higher than the NPH insulin doses, although comparisons were not always statistically significant.
- 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. The two reports differed with respect to the availability of published and unpublished studies.
- The clinical inputs used by the manufacturer in their pharmacoeconomic analysis differed from both the results of the CDR systematic review and the COMPUS meta-analysis.
- The economic model provided by the manufacturer for the Advisory Committee on Pharmaceuticals resubmission did not permit reanalysis.

CEDAC Members Participating
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Regrets
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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.

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