Emerging Drug List

Insulin Detemir for Diabetes Mellitus

Canadian Coordinating Office for Health Technology Assessment

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Generic (Trade Name): Insulin detemir (Levemir™)

Manufacturer: Novo Nordisk

Indication: For the management of type 1 (insulin dependent) diabetes mellitus (DM) and type 2 (non-insulin dependent) DM.

Current Regulatory Status: Health Canada is reviewing a New Drug Application for insulin detemir submitted by Novo Nordisk.[1]

Novo Nordisk received an "approvable" letter for insulin detemir from the US Food and Drug Administration (FDA) in October 2003.[2] Also, the European Commission granted marketing authorization for insulin detemir in June 2004.[3]

Description: Insulin detemir is a long-acting basal insulin analogue. It has a fatty acid side chain that binds to tissue albumin at the subcutaneous injection site, resulting in prolonged activity.

Current Treatment: The current treatment of type 1 DM involves insulin products that are classified by duration of effect. They include rapid-acting insulin lispro and insulin aspart; short-acting regular insulin; intermediate-acting NPH and Lente insulin; and long-acting Ultralente insulin and insulin glargine.

The treatment of patients with type 2 DM may include a combination of lifestyle management and oral hypoglycemic agents. Multiple oral hypoglycemic agents or insulin in combination with oral hypoglycemic agents may be used if treatment goals are not reached. Insulin monotherapy is generally used when diet, exercise, lifestyle and oral hypoglycemic agents are ineffective or contraindicated. It may be used as initial therapy in the presence of marked hyperglycemia [(hemoglobin A_{1c} (HbA_{1c})>9.0%].[4]

Cost: There is no cost for insulin detemir at this time, since it is not marketed in any country.

Evidence: Three published studies on insulin detemir were identified. Other studies are available only in abstract form.

Vague *et al. e*nrolled 448 patients with type 1 DM in a multinational, open parallel-group, comparative, six-month trial.[5] Patients were randomized in a 2:1 ratio to receive insulin detemir or NPH insulin before breakfast and bedtime; and insulin aspart before each meal. Doses were adjusted over a two-week period. The last five months of the trial were considered the maintenance phase. After six months, there were no significant differences in HbA_{1c} levels at end point, between the insulin detemir and NPH insulin groups (7.60% and 7.64%, respectively) [difference=0.04 (95% CI -0.218 to 0.128, p=0.61)]. Fasting plasma glucose (FPG) levels were also similar in both groups at six

months [difference=-0.76 (95% CI -1.65 to 0.14, p=0.09)] using the evaluative patient population. Fluctuations in plasma glucose (measured by patients with a home glucometer) were significantly lower in the insulin detemir group compared with the NPH insulin group (p<0.001). Patients receiving insulin detemir had a mean weight loss of 0.6 kg, while patients receiving NPH insulin had a mean weight increase of 0.6 kg at six months (p<0.001). Insulin detemir use was associated with a 22% relative risk reduction of all hypoglycemic events per subject month compared with NPH insulin, including major, minor, symptomatic and nocturnal hypoglycemia. There were no significant differences in major events.

Hermanssen *et al.* conducted a multicentre, open, randomized crossover trial enrolling 59 patients with type 1 DM.[6] Patients received a two-week run-in period on a basal-bolus insulin regimen with NPH insulin once daily, followed by two six-week periods of an optimized basal-bolus insulin regimen with either once daily insulin detemir or NPH insulin. The area under the curve (AUC) derived from serum glucose measurements over a 24-hour period on the last day of the treatment period revealed no significant differences between the two groups (95% CI 0.9 to 1.21, p=0.59). The FPG levels during the last four days of the treatment regimen were also similar between the two groups. Patients receiving insulin detemir experienced fewer fluctuations in FPG levels compared with NPH. There were no significant differences between the two groups in the proportion of patients experiencing a hypoglycemic episode during the six-week treatment phases.

Home *et al.* conducted an open-label 16-week trial involving 408 patients with type 1 DM.[7] Patients were randomized into three groups; insulin detemir before breakfast and at bedtime; insulin detemir every 12 hours; or NPH before breakfast and at bedtime. Mean HbA_{1c} decreased by 0.82% in the insulin detemir before breakfast and at bedtime group, 0.85% in the insulin detemir every 12 hours group and 0.65% in the NPH group. There were no significant differences among all three groups. There was a significant decrease in HbA_{1c} when the two insulin detemir groups were combined and then compared with the NPH group (p=0.027). There was a significant difference among all three groups in FPG taken at a clinic and self-monitored fasting blood glucose (p<0.001 and p=0.005).

The remainder of the studies are available only in abstract form from conference proceedings. Most are randomized, open-label parallel trials comparing insulin detemir to NPH insulin in patients with type 1 DM.[8-12] Most trials reported no significant differences in HbA_{1c}[8-12] or FPG[8,9,11] and there were no significant differences in overall hypoglycemic events in most trials.[8,10-12] Two of these trials, however, reported significant differences in nocturnal hypoglycemia.[10,11] Many trials reported lower mean body weight or less weight gain in patients receiving insulin detemir.[9-12] Two trials reported a weight loss with insulin detemir treatment compared with weight gain after NPH treatment.[9,10] Lower fluctuations in self-measured FBG levels were reported.[10,11] Another four-day trial reported significantly less variability (assessed by glucose infusion rates) compared with NPH or insulin glargine.[13]

In another trial, it was reported that patients with type 2 DM had significantly lower HbA_{1c} levels, within patient variation and weight, but similar FPG and all hypoglycemic events compared with NPH insulin.[14]

Adverse Effects:

Adverse event profiles were similar for insulin detemir and NPH. Most comparative trials have demonstrated a similar overall risk of hypoglycemic events with insulin detemir and NPH insulin.[6,8,10-12] One study, however, reported a significantly lower rate of overall hypoglycemic events.[5] Another study reported a significant difference in minor hypoglycemic events (anytime and nocturnal) between insulin detemir before breakfast and at bedtime, insulin detemir every 12 hours and NPH, but there were no significant differences in major hypoglycemic events.[7] The only comparative study with insulin glargine did not report on the risk of hypoglycemia.[13]

Commentary:

Insulin detemir is a new long-acting insulin analogue for the treatment of type 1 and type 2 DM. It does not improve HbA_{1c} control or reduce overall hypoglycemic events in most trials that compare it to NPH insulin. It may be advantageous for those who experience nocturnal hypoglycemia or weight gain with NPH insulin.

The one trial that compared it to insulin glargine (a new long-acting insulin that has been approved by Health Canada but is not yet marketed) did not measure or report on clinical outcomes. It is impossible to make a clinical comparison between these two long-acting insulin products.[15] More published research is needed to clarify insulin detemir's place in therapy.

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