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APPLICATION NUMBER:
21-878

MEDICAL REVIEW

MEDICAL OFFICER REVIEW

Division of Metabolic and Endocrine Drug Products (HFD-510)

APPLICATION #: NDA 21878 APPLICATION TYPE: NDA.....
SPONSOR: Novo Nordisk PROPRIETARY NAME: LEVEMIR.....
CATEGORY OF DRUG: Antidiabetic USAN / Established Name: Insulin Detemir.....
MEDICAL REVIEWER: Robert I Misbin.. REVIEW DATE: September 26, 2005.....

SUBMISSIONS REVIEWED IN THIS DOCUMENT

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The efficacy and safety of Insulin Detemir has been established for pediatric patients with type 1 diabetes. Pending small changes in the label, Insulin Detemir can be approved.

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Executive Summary:

Recommendations:

The efficacy and safety of Insulin Detemir has been established for pediatric patients with type 1 diabetes. Pending small changes to the label, Insulin Detemir can be approved.

Summary of Clinical Findings

Glycemic control with Detemir in children/adolescents with type 1 diabetes is similar to glycemic control with NPH insulin. Patients on Detemir tend to require slightly more basal insulin than patients on NPH and may be more likely to have findings at the injection site. The smaller increase in BMI with Detemir would be a distinct advantage if it is maintained long-term. Insulin Detemir appears to be more antigenic than NPH insulin. But the difference appears to have little, if any, clinical significance.

The efficacy and safety of Insulin Detemir has been established for pediatric patients with type 1 diabetes. Pending small revisions to the label, Insulin Detemir can be approved.

4 Description of Data Sources and Integrity

The application contains data from one phase 3 controlled clinical trials.

The review was conducted of the hard copy of the NDA. Routine inspections of sites involved in the pivotal trials were not performed. Although the consent document was not reviewed, the trials appear to have been conducted in accordance with acceptable ethical standards. The financial disclosure documentation appears adequate.

The Sponsor, Novo Nordisk submitted debarment and financial disclosure documents December 5, 2002 and updated the submission in December 2004. I have examined these documents and found them to be acceptable. The debarment statement indicated that Novo Nordisk had not and will not use the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act.

The following financial disclosure information has been submitted:

- 1 Form OMB No. 0910-0396. The applicant certifies that Novo Nordisk has not entered into any financial arrangement with the clinical investigators named in the lists included in the NDA whereby the value of compensation to the investigator could be affected by the outcome of the study. It was signed 6/12/04.
- 2 The applicant further certifies that none of the listed clinical investigators disclosed a proprietary interest in the product or an equity interest in Novo Nordisk.
- 3 The applicant certifies that no listed investigator was the recipient of other payments such as honoraria, consultation fees, research grants, or compensation in the form of equipment from Novo Nordisk .
- 4 Analyses of efficacy data in this NDA did not reveal any significant effect of center on outcomes. Furthermore, the data on both safety and effectiveness were consistent across the multiple trials submitted to the NDA. Thus a potential conflict of interest from any investigator does not call into question the overall integrity of the data submitted.

5 Clinical Pharmacology – N/A

6 Review of Efficacy:

Trial 1379

This was a 26 week open label trial comparing NPH insulin (600 nmol/mL) to insulin Detemir (2400 nmol/mL) in children and adolescent patients with type 1 diabetes. Most patients had been on basal-bolus insulin regimens. Approximately 20% had been on premix insulin.

Patients were between 6 and 17 years of age and had had type 1 diabetes for at least 12 months. Major exclusion criteria were HbA1c > 12%, insulin dose > 2 U/kg and hypoglycemia unawareness.

Patients with treated with either Detemir or NPH insulin, once daily or twice daily depending on their previous regimens and patients/investigator preference. The starting dose of basal insulin for both Detemir and NPH arms was 70% of the previous dose of NPH insulin. All patients received boluses of insulin aspart before meals. The primary endpoint variable was HbA1c at 26 weeks,

The goal of treatment was pre breakfast glucose of 4.5-7.8 mmol/L (81-140 mg/dl) and postprandial glucose of 6.7-10.1 mmol/L. For patients on twice daily basal insulin, there was an additional pre-dinner goal of 4.5 –7.8 mmol/L.

Subject depositions: 226/232 (97%) of subjects randomized to Detemir completed the trial. 109/115 (95%) of subjects randomized to NPH completed the trial.

Baseline characteristics: Subjects were 50% male, and 99.7% white. The mean age was 11.9 years with five year mean duration of diabetes. The two arms were well matched. Mean weight was 46.3 kg for patients randomized to Detemir and 46.2 kg for patients randomized to NPH. Mean height was 1.5 m in both groups. Mean BMI was 19.2 kg/m² for patients randomized to Detemir and 19.1 for patients randomized to NPH. Mean HbA1c at baselines 8.75% for patients randomized to Detemir and 8.77 for patients randomized to NPH.

Mean daily insulin dose (U/kg) is given in the following table. Insulin dose increased in both arms. There was little difference between Detemir and NPH, except that the increase in basal insulin was about 10% more with Detemir than with NPH. This is consistent with the findings from the trials in adults with type 1 diabetes:

Mean daily basal and bolus insulin dose

	Basal insulin (U, IU)*				Bolus insulin (IU)			
	Detemir (N=228)		NPH (N=112)		Detemir (N=228)		NPH (N=112)	
	Mean	SD	Mea n	SD	Mean	SD	Mea n	SD
Baseline	19	(11)	19	(11)	22	(13)	22	(14)
Week 26	32	(18)	31	(15)	26	(14)	26	(15)
Change	14	(12)	12	(9)	4	(8)	5	(8)

Insulin Detemir U = 24 nmol
 NPH insulin IU= 6 nmol
 Bolus insulin (aspart) IU = 6 nmol

	Detemir (N=231)		NPH (N=112)	
	Mean	SD	mean	SD
Baseline	8.8	(1.3)	8.7	(1.1)
Endpoint	8.0	(1.3)	8.0	(1.1)
Change	-0.7	(1.1)	-0.8	(1.0)

Change in HbA_{1c} for the entire population is shown in the preceding table. The result is broken down based on previous insulin regimen in the following table. There was little difference between the two treatments.

HbA_{1c}, descriptive statistics by basal insulin regimen (once daily or twice daily)

	Basal insulin once daily				Basal insulin twice daily			
	Detemir (n=93)		NPH (n=42)		Detemir (n=138)		NPH (n=70)	
	Mean	SD	Mea n	SD	Mean	SD	Mea n	SD
Baseline	8.8	(1.3)	8.9	(1.0)	8.7	(1.1)	8.6	(1.2)
Endpoint	7.9	(1.2)	8.1	(1.1)	8.1	(1.3)	7.9	(1.1)
Change	-0.9	(1.1)	-0.9	(1.1)	-0.6	(1.0)	-0.8	(1.0)

There were no deaths. Serious adverse events were reported in 24/232 (10%) of patients on Detemir and 10/115 (9%) of patients on NPH. These included one case of ketoacidosis in each group. Hypoglycemia as an SAE was reported in 5/232 patients on Detemir and 3/115 patients on NPH.

Major hypoglycemia was reported by 15.9% of patients on Detemir and 20% of patients on NPH. Minor hypoglycemia was reported by 93% of patients on Detemir and 96% of patients on NPH.

Major hypoglycemia = severe CNS symptoms consistent with hypoglycemia in which patients require assistance, with Glucose < 3.1 mM (50 mg/dl) or reversal by food or glucagon.

Minor hypoglycemia = episode with < 3.1 mM handled by patients or asymptomatic.

“Injection site disorder” was reported by 3% of patients on Detemir and 1.7% of patients on NPH. One patient on Detemir withdrew because of local swelling and edema at the injection site.

Antibody formation, Bound/Total

Detemir specific antibody		
Screening	1.9	1.7
Follow-up	13.1	1.8
Insulin antibody		
Screening	1.4	1.3
Follow-up	1.2	1.3
Cross-reacting antibody		
Screening	28.5	32.8
Follow-up	43.9	33.1

There was a correlation between change in Detemir specific antibodies and change in dose of basal insulin. The Spearman coefficient was 0.34 ($p < 0.001$). There was a negative correlation in patients on Detemir between change in cross-reacting antibody and change in HbA1c (-0.13 , $p = 0.05$).

No clinically relevant findings were observed for any clinical laboratory or vital signs assessments.

8 Dosing and Administrative Issues

Labeling:

The proposed labeling contains a brief description of the pediatrics study. Safety data from the pediatrics study have been added to table 4 in the current label. These revisions are appropriate, except that the footnote regarding “nocturnal hypoglycemia” should be removed. Other minor revisions are clerical in nature and are acceptable.

There are no specific recommendations about the dosing regimen for children/adolescents with type 1 diabetes. This is appropriate. Considerations about dosing of Detemir in children/adolescents with type 1 diabetes are the same as for adults with type 1 diabetes.

9 Overall Assessment: Conclusion and recommendations:

Glycemic control with Detemir in children/adolescents with type 1 diabetes is similar to glycemic control with NPH insulin. Patients on Detemir tend to require slightly more basal insulin than patients on NPH and may be more likely to have findings at the injection site. The smaller increase in BMI with Detemir would be a distinct advantage if it persists after long-term use. Insulin Detemir appears to be more antigenic than NPH insulin. But the difference appears to have little, if any, clinical significance.

The findings of the study in type 1 diabetes in children/adolescents reviewed in this application are similar to the findings reported in type 1 diabetes in adults in the original NDA. Labeling for children with type 1 diabetes should be the same as labeling for adults.

The efficacy and safety of Insulin Detemir has been established for pediatric patients with type 1 diabetes. Pending small revisions to the label, Insulin Detemir can be approved.

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/s/

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9/26/2005 04:54:58 PM
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recommendation ofr papproval of Detemir in pediatric patients

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