DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-986

Novo Nordisk Pharmaceuticals, Inc.
Attention: Barry Reit, Ph.D.
Vice President
Regulatory Affairs and Quality Assurance
100 College Road West
Princeton, NJ 08540

Written Request
Amendment #3

Dear Dr. Reit:

Please refer to your correspondence dated October 3, 2003, requesting changes to FDA's December 14, 1999, Written Request, revised July 20, 2001, and April 15, 2003, for pediatric studies for NovoLog® (insulin aspart [rDNA origin] injection).

We have reviewed your proposed changes and are amending the below-listed sections of the Written Request.

- ***Number of patients to be studied***
- ***Timeframe for submitting reports of the study***

For convenience, the full text of the Written Request, as amended, follows. This Written Request supercedes the Written Requests dated December 14, 1999, July 20, 2001, and April 15, 2003.

1. *Type of study*:

Six-month minimum, active-controlled, randomized, open-label clinical trial in children with Type 1 diabetes.

2. Objectives/Indication to be studied:

Safety and effectiveness of NovoLog® treatment in pediatric patients with Type 1 diabetes.

The objectives of the study are to determine (a) HgbA1c levels, hypoglycemia rates, and diabetic ketoacidosis rates in children with Type 1 diabetes treated with NovoLog® insulin analogue before meals, and (b) whether children can be dosed with NovoLog® insulin before all meals. If alternative dosing regimens are used, these data should be captured. Alternate dosing regimens could include twice daily dosing, additional injections of basal or rapid-acting insulin, or different injection times, e.g. after meals.

3. ***Age group in which study will be performed*:**

Children ages 6 through 18 years old, stratified by age.

4. Study design:

Six-month minimum on NovoLog®, 3-arm, active-controlled (NovoLog® versus human regular insulin versus Humalog®), randomized, open-label clinical trial in children with Type 1 diabetes. The comparisons in the analysis of the data should be between NovoLog® and human regular insulin and Humalog®, dividing the alpha for each comparison.

5. Number of patients to be studied:

Approximately 150 patients should be randomized to NovoLog and approximately 75 patients should be randomized to each of the control groups. All patients who have at least one post-randomization HbA1c measurement should be included in the statistical analysis.

6. Entry criteria:

i. Male and female patients with Type 1 diabetes treated with insulin for at least one year.
ii. HgbA1c <12% at entry.
iii. Patients (parents, guardian) with the ability and willingness to perform glucose monitoring with a glucometer.

7. ***Study endpoints:***

i. The primary endpoint will be change in HgbA1c from study baseline.
ii. Secondary endpoints will include the incidence and frequency of clinically significant hypoglycemia, the incidence and frequency of hyperglycemia-diabetic ketoacidosis, and fasting serum glucose values.
iii. Safety evaluation will include reporting of adverse events and evaluation for the development of anti-insulin (cross-reacting) antibodies.

8. Drug information:

- ***dosage form:*** Injection
- ***route of administration:*** Subcutaneous
- ***regimen:*** Immediately before meals for NovoLog® and Humalog®; 20 to 30 minutes before meals for human regular insulin
- ***formulation:*** Same as proposed for marketing in NDA 20-986

9. ***Drug-specific safety concerns*:**

i. The incidence, frequency, and severity of clinically significant hypoglycemia.
ii. The incidence, frequency, and severity of hyperglycemia-diabetic ketoacidosis.

10. Statistical information, including power of study and statistical assessments:

The analysis of the primary efficacy variable will use a statistical model with the change from baseline HgbA1c as the dependent variable, and treatment and randomization stratification factors as independent variables. Non-inferiority of the test drug compared to control will be assessed by constructing a 97.5% two-sided confidence interval for the between-group difference in change from baseline HgbA1c using the least square means. The test drug will be considered non-inferior to each control if the appropriate confidence bound falls within a non-inferiority margin of 0.4%.

11. ***Labeling that may result from the study*****:**

There may be changes to the following sections of the labeling: DOSAGE AND ADMINISTRATION, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, INDICATIONS AND USAGE, and CLINICAL PHARMACOLOGY.

12. ***Format of reports to be submitted*****:**

Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation, with accompanying computer-based clinical and safety data listings.

13. Timeframe for submitting reports of the study:

Reports of the studies that meet the terms of this Written Request must be submitted to the Agency on or before March 31, 2005, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission, **"PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY"** in large font, bolded type at the beginning of the cover letter of the submission. Notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Please clearly mark your submission, **"PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission.

Submit reports of the studies as a **supplement to NDA 20-986** with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. In addition, send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger, to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits to the pediatric population.

If you have any questions, call Julie Rhee, Regulatory Project Manager, at (301) 827-6424.

Sincerely,

{See appended electronic signature page}

Robert J. Meyer, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Meyer

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