WR 510

NDA 20-986

Novo Nordisk Pharmaceuticals, Inc.
Attention: Barry Reit, Ph.D.
Vice President, Regulatory Affairs
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810

DEC 14 1999

Dear Dr. Reit:

Reference is made to your Proposed Pediatric Study Request submitted on August 17, 1999, for NovoLog™ (insulin aspart [rDNA origin] injection).

To obtain needed pediatric information on insulin aspart, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from the following studies:

Type of study:

Six-month minimum, active-controlled, randomized, open-label clinical trial in children with Type 1 diabetes. The study design may be either cross-over or parallel.

Objectives/Indication to be studied:

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

The objectives of the study are (1) to determine HgbA1c levels, hypoglycemia rates, and diabetic ketoacidosis rates in children with Type 1 diabetes treated with NovoLog™ insulin analogue before meals, and (2) to determine whether children can be dosed with NovoLog™ insulin before all meals. If alternative dosing regimens are used, these data should be captured to perform subgroup analysis. Alternate dosing regimens could include BID dosing, additional injections of basal or rapid acting insulin, or different injection times, e.g. after meals.

Age group in which study will be performed:

Children ages 6 through 16 years with balanced distribution among the age groups.

Study design:

Open-label, active-controlled (NovoLog™ vs human regular insulin), randomized study, either cross-over or parallel design. The treatment duration for the NovoLog™ group is to be at least six months.

Number of patients to be studied:

A minimum of 200 patients will receive NovoLog™.

Entry criteria:

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

Study endpoints:

1. The primary endpoint will be HgbA1c and change in HgbA1c from study baseline.
2. 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.
3. Safety evaluation will include reporting of adverse events and evaluation for the development of anti-insulin (cross reacting) antibodies.

Drug information:

- ***dosage form:*** Injection
- ***route of administration:*** Subcutaneous
- ***regimen:*** Immediately before meals
- ***formulation:*** Same as proposed for marketing in NDA 20-986

Drug specific safety concerns:

1. The incidence and frequency and severity of clinically significant hypoglycemia.
2. The incidence and frequency and severity of hyperglycemia-diabetic ketoacidosis.

Statistical information, including power of study and statistical assessments:

1. The sample size calculation is to be based on a noninferiority margin of 0.4% for the difference between groups in HgbA1c using a 97.5% upper confidence level.
2. The analysis of the primary efficacy variable will use a statistical model with the change from baseline HgbA1c as the dependent variable and treatment, age group, and center as the independent variables.

***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.

***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.

Timeframe for submitting reports of the study:

Reports of the above studies must be submitted to the Agency on or before December 31, 2002. Please remember that pediatric exclusivity extends only existing patent protection or exclusivity that has not expired or been previously extended at the time you submit your reports of studies in response to this Written Request.

Please 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. Please notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. 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.

Reports of the studies should be submitted as a new **drug application or as a supplement to your approved NDA** with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please 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. Please also 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 the proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

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 in the pediatric population.

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

Sincerely yours,

John K. Jenkins, M.D., F.C.C.P.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Archival NDA 20-986
HFD-510/division file
HFD-510/Malozowski/Koller
HFD-715/Sahlroot
HFD-870/Ahn/Wei
HFD-102/Office Director
HFD-600/Office of Generic Drugs
HFD-2/M.Lumpkin
HFD-104/D.Murphy
HFD-002/T.Crescenzi

Drafted by: JRhee 11-17-99
Initialed by: Koller 11-17-99/Malozowski 11-17-99/Pian 11-18-99/Sahlroot 11-18-99/Wei 11-19-99/Ahn 11-19-99/Galliers 11-29-99/Ripper 12-3-99/Jenkins 12-3-99/Koller 12-6-99/Malozowski 12-7-99/Sahlroot 12-7-99/Pian 12-7-99
Final: JRhee 12-7-99
filename: c:/NDA 20986/Pediatric WR
PdIT meeting date: 12-1-99

12-7-99

PEDIATRIC WRITTEN REQUEST LETTER
INFORMATION REQUEST (IR)

12-7-99

LRipper 12/10/99