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
100 College Road West
Princeton, NJ 08540

Written Request
Amendment #1

Dear Dr. Reit:

Reference is made to your correspondence dated March 15, 2001, requesting changes to FDA's December 14, 1999, Written Request 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. All other terms stated in our Written Request issued on December 14, 1999, remain the same.

1. ***Study design:***

   Six-month minimum on NovoLog®, active-controlled (NovoLog® vs human regular insulin), randomized, open-label clinical trial in children with Type 1 diabetes. The study design may be either cross-over or parallel. While not required under this Written Request, you are encouraged to add a third arm treated with Humalog®.

2. ***Number of patients to be studied:***

   A minimum of 150 patients completing the six-month study on NovoLog® and a minimum of 75 patients completing the six-month study in the control group(s).

3. ***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 HbA1c as the dependent variable and treatment and center as the independent variables. Non-inferiority of the test drug compared to control will be assessed by constructing a 97.5% one-sided confidence interval for the between-group difference in change from baseline HbA1c using the least square means. The test drug will be considered non-inferior to the control if the confidence bound falls within a non-inferiority margin of 0.4%.

4. ***Timeframe for submitting reports of the study:***

   Reports of the studies that meet the terms of the Written Request dated December 14, 1999, as amended by this letter, must be submitted to the Agency on or before August 31, 2003, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

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. 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.

Reports of the studies should be submitted as a supplement to your 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, please submit 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 to the pediatric population.

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

Sincerely,

{See appended electronic signature page}

John K. Jenkins, 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/

John Jenkins
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