CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-986

APPROVAL LETTER

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

Dear Dr. Reit:

Please refer to your new drug application (NDA) dated September 15, 1998, received September 16, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for NovoLog (insulin aspart [rDNA origin] injection), 10 mL vials, NovoLog PenFill, 3 mL cartridges, and NovoLog Prefilled, 3 mL syringes.

We acknowledge receipt of your submissions dated December 6, 8, and 14, 1999, and April 24 and 28, May 18, 24, and 31, and June 7 (2), 2000. Your submission of December 6, 1999, constituted a complete response to our September 15, 1999, letter.

This new drug application provides for the use of NovoLog, NovoLog PenFill, and NovoLog Prefilled for the treatment of adult patients with diabetes mellitus, for the control of hyperglycemia.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed-upon labeling text with the minor editorial revisions listed below. Accordingly, the application is approved effective on the date of this letter.

1. The established name should be made more prominent in relation to the tradename. Per 21 CFR 201.10(g)(2), the prominence of the generic name should be similar to the prominence of the tradename, taking into account such factors as type font and contrast.

2. During today's telephone conversations with Ms. Julie Rhee of the Division of Metabolic and Endocrine Drug Products, Mr. Robert Fischer of your office agreed to include the generic name whenever the tradename is mentioned on carton labels of the vial, PenFill 3 mL cartridge, and Prefilled 3 mL syringe and to make the revisions indicated on the enclosed patient package inserts.

The final printed labeling (FPL) must include the minor editorial revisions indicated above and on the enclosed patient package inserts but otherwise be identical to the submitted draft labeling (package insert submitted June 7, 2000, patient package inserts submitted June 7, 2000, immediate container and carton labels for PenFill 3mL cartridges and Prefilled 3 mL syringes submitted August 20, 1999, and immediate container and carton labels for 10 mL vials submitted August 26, 1999). These revisions are terms of the NDA approval. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 20-986." Approval of this submission by FDA is not required before the labeling is used.

As specified in our September 15, 1999, letter, we remind you of your Phase 4 commitments to perform studies on the pharmacokinetics/pharmacodynamics of insulin aspart in the following special populations. These commitments, along with the completion dates agreed upon during the May 26, 2000, telephone conversation between Mr. Robert Fischer of your office and Ms. Julie Rhee of the Division of Metabolic and Endocrine Drug Products, are listed below.

1. Renally-impaired patients:

Protocol Submission:	December 24, 1999
Study Start:	March 2000
Final Report Submission:	No later than September 2000

2. Hepatically-impaired patients:

Protocol Submission:	December 24, 1999
Study Start:	March 2000
Final Report Submission:	No later than September 2000

3. Obese versus non-obese patients:

Protocol Submission:	December 24, 1999
Study Start:	March 2000
Final Report Submission:	No later than September 2000

Final reports should be submitted to this NDA and a copy of the cover letter sent to the appropriate IND. In addition, under 21 CFR 314.81(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments should be prominently labeled **"Phase 4 Commitments."**

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We note that you have not fulfilled the requirements of 21 CFR 314.55. We are deferring submission of your pediatric studies until December 31, 2002. However, in the interim, please submit your pediatric drug development plans within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. We note that a Written Request for studies of insulin aspart in pediatric patients with diabetes mellites was issued on December 14, 1999. Satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Metabolic and Endocrine Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of each drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

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

Sincerely,

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

Enclosures: Patient package inserts for vial, PenFill, and Prefilled.

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APPLICATION NUMBER: 20-986

APPROVABLE LETTER

NDA 20-986

SEP 1 5 1999

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

Dear Dr. Reit:

Please refer to your new drug application (NDA) dated September 15, 1998, received September 16, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for NovoLog™ (insulin aspart [rDNA origin] injection) 100 units/mL (U-100).

We acknowledge receipt of your submissions dated October 1, 8, and 20, November 16, and December 14, 1998; and January 14, 21, and 29, February 19 and 26, March 8, 15, and 31, April 12, 19, and 20, May 7, 13, 25, 26, 27, and 28, June 3, 8(2), 10, 15, 16, 21, and 29, July 13 and 21(2), and August 5 (2), 9, 10 (2), 16, 17 (3), 20, 25, and 26, 1999.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit draft labeling revised as in the enclosure.

Please revise the patient package inserts to a Question and Answer format to improve their readability and clarity for patients. Please consult the Division of Metabolic and Endocrine Drug Products for further guidance regarding this request.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

During recent inspections of the manufacturing facilities for your NDA, a number of deficiencies were noted and conveyed to you or your suppliers by the inspector. Satisfactory inspections will be required before this application may be approved.

Under 21 CFR 314.50(d)(5)(vi)(*b*), any resubmission should update all the safety information in this application. Please provide updated information as listed below. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

1. Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now will facilitate review.

2. Retabulation of drop-outs with new drop-outs identified. Discuss, if appropriate.

3. Details of any significant changes or findings.

4. Summary of worldwide experience on the safety of this drug.

5. Case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

6. English translations of any approved foreign labeling not previously submitted.

7. Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action, FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

We remind you of your Phase 4 commitments specified in your submission dated August 5, 1999. These commitments, along with any completion dates agreed upon and their associated timelines, are listed below.

1. To perform studies in the following special populations in order to determine the impact, if any, on the pharmacokinetics/pharmacodynamics of insulin aspart:

a) Renally-impaired patients
b) Hepatically-impaired patients
c) Obese versus non-obese patients

During the August 27, 1999, telephone conversation between Mr. Robert Fischer of your office and Ms. Julie Rhee of the Division of Metabolic and Endocrine Drug Products, Mr. Fischer committed the following time lines to complete these Phase 4 commitments:

Protocol Submission:	No later than December 1999
Study Start:	No later than March 2000
Final Report Submission:	No later than September 2000

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

Sincerely,

/S/

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

Enclosure: Marked-up Physician Package Insert

APPEARS THIS WAY
ON ORIGINAL

WITHHOLD 48 PAGE (S)

Draft

Labeling