# CENTER FOR DRUG EVALUATION AND RESEARCH

# APPROVAL PACKAGE FOR:

# APPLICATION NUMBER
# 21-172

# Approval Letter

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-172

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

Dear Dr. Reit:

Please refer to your new drug application (NDA) dated December 17, 1999, received December 22, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for NovoLog Mix 70/30 (70% insulin aspart [rDNA origin] protamine suspension and 30% insulin aspart [rDNA origin] injection).

We acknowledge receipt of your submissions dated December 1, 2000; February 9, March 15 and 22, April 10 and 30, July 11, 19, 23, 25, and 26, August 6, 14, 16, and 30, September 20, October 3, 4, 12, 16, 25, 30, and 31, and November 1, 2001. Your submission of April 30, 2001, constituted a complete response to our November 15, 2000, action letter.

This new drug application provides for the use of NovoLog Mix 70/30 (70% insulin aspart [rDNA origin] protamine suspension and 30% insulin aspart [rDNA origin] injection) for the treatment of 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 for the following presentations:

1. 10 mL vials,
2. 3 mL PenFill® cartridges for use with NovoPen® 3, Innovo®, and InDuo® insulin delivery devices and NovoFine® disposable needles, and
3. 3 mL Prefilled® syringe.

Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted November 1, 2001, patient package insert submitted November 1, 2001, immediate container and carton labels submitted February 9, 2001). 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 the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no 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 21-172." Approval of this submission by FDA is not required before the labeling is used.

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 are waiving the pediatric study requirement for this action on this application.

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 submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the 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, at (301) 827-6424.

Sincerely,

/S/

*{See appended electronic signature page}*

David G. Orloff, M.D.
Director
Division of Metabolic
and Endocrine Drug Products, HFD-510
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/
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David Orloff
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**APPEARS THIS WAY ON ORIGINAL**

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We acknowledge receipt of your submissions dated January 4 and 24, March 28, April 7 and 13, May 12, June 21, July 6 and 19, August 4, 23, and 29, September 7, 11, 12, and 14, and October 19, 20, and 25, 2000.

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 address the following:

**I. Clinical and Clinical Pharmacology and Biopharmaceutics:**

a. The complete data from study 1086 should be submitted for review.

b. Whether from study 1086 or from additional studies, data generated using euglycemic clamp methodology are needed to show, by weight of evidence, the distinctiveness of NovoLog Mix 70/30 compared to other insulin mixes in the insulin aspart family. For fixed dose combination insulin products, we require pharmacokinetic (PK) and pharmacodynamic (PD) data to show that the proposed combination product is different from its components individually and is also different from other combinations. For reasons that are self-evident, the comparisons to other insulin combinations should, at a minimum, include those insulin mixes expected to be closest in PK/PD characteristics to the new product. It therefore follows that, where possible, the new product should be studied so as to provide "bracketing" data with these closest comparators. Thus, in the present case, the proposed NovoLog Mix 70/30 should be compared both to a 50/50 mix of protamine insulin aspart and insulin aspart ——————————. You have already demonstrated that NovoLog Mix 70/30 is pharmacokinetically distinct from Novolin 70/30, specifically with a more rapid early absorption, time to peak concentration, and with a markedly higher Cmax. We do not feel, therefore, that a comparison to ———— is warranted.

For any data from studies submitted, the following parameters should be calculated for the purpose of comparing the *in vivo* performance of the two insulin products:

1. The ratio (product 1: product 2) of the geometric means (with 90% CI) of PK and PD parameters,
2. The time to reach 25, 50, 75, and 100% AUC for each product and the ratios (product 1: product 2) of the geometric means for each value, and
3. The time to reach a predetermined reference AUC value for each product and the ratio (product 1: product 2) of the geometric means for this value.

c. Submit a table comparing the PK/PD profiles of the insulin and insulin analog products that you market. Such a table will obviously not rely solely on head-to-head comparison studies. The product reference guide prepared by your company in 1998 may be used as a template.

d. The methodology for determining the concentrations of cross-reacting antibodies used in the studies submitted to this NDA should be submitted. Methodology should be described in order to indicate how non-specific antibody binding is distinguished from specific antibody binding and how concentrations of total antibody are delineated from concentrations of free antibody.

Data addressing the long-term clinical significant (e.g., effect on insulin requirements and glycemic control) of cross-reacting antibodies in patients treated with insulin aspart should be provided.

**II. Chemistry, Manufacturing, and Controls :**

a. [redacted]

b. [redacted]

c. At this time, a shelf-life of only 18-months is granted for the drug product, based on the stability data provided, rather than — months as proposed.

d. The package insert provides a temperature range (2-8°C) for storage of the product; however, other labeling indicates that the product should be stored in ——— This temperature range should be provided on all labeling.

e. Instructions for proper storage of the drug product should be included in the patient package insert.

**III. Labeling:**

We include the following recommended revisions to the pharmacology/toxicology sections (in PRECAUTIONS) of the draft package insert that were faxed to you on October 3, 2000. (Additions appear in **bold** and deletions are noted by strikethrough).

**Carcinogenicity, Mutagenicity, Impairment of Fertility**

**Standard 2-year carcinogenicity** studies in animals have not been performed to evaluate the carcinogenic potential of NovoLog Mix 70/30. In 52 week studies, **SpragueDawley** rats **were** dosed subcutaneously with **NovoLog, the rapid-acting component of NovoLog Mix 70/30, at 10, 50, and** 200 U/kg/day (approximately **2, 8, and** 32 times the human subcutaneous dose of 1.0 U/kg/day, based on U/body surface area, **respectively**). **At a dose of 200 U/kg/day, NovoLog increased the incidence of mammary gland tumors in females when compared to untreated controls. The incidence of mammary tumors for NovoLog was not significantly different than for regular human insulin. The relevance of these findings to humans is not known.**

**NovoLog** was not genotoxic in the following tests: Ames test, mouse lymphoma cell forward gene mutation test, human peripheral blood lymphocyte chromosome aberration test, in vivo micronucleus test in mice, and in ex vivo UDS test in rat liver hepatocytes. In fertility studies in male and female rats, **NovoLog** at subcutaneous doses up to 200 U/kg/day (approximately 32 times the human subcutaneous dose, based on U/body surface area), **had** no direct adverse effects on male and female fertility, or **on** general reproductive performance **of animals** ~~observed~~.

**Pregnancy: Teratogenic Effects: Pregnancy Category – C:**

**NovoLog (the rapid-acting component of NovoLog Mix 70/30) and regular human insulin in rats and rabbits. In these studies, NovoLog was given to female rats before mating, during mating, and throughout pregnancy, and to rabbits during organogenesis.**

The effects of **NovoLog** did not differ from those **observed** with subcutaneous regular human insulin. **NovoLog, like human insulin, caused pre- and post- implantation losses and visceral/skeletal abnomalities in rats at a dose of 200 U/kg/day (approximately 32-times the human subcutaneous dose of 1.0 U/kg/day, based on U/body surface area), and in rabbits at a dose of 10 U/kg/day (approximately three times the human subcutaneous dose of 1.0 U/kg/day, based on U/body surface area). The effects are probably secondary to maternal hypoglycemia at high doses. No significant effects were observed in rats at a dose of 50 U/kg/day and rabbits at a dose of 3 U/kg/day. These doses are approximately 8 times the human subcutaneous dose of 1.0 U/kg/day for rats and equal to the human subcutaneous dose of 1.0 U/kg/day for rabbits, based U/body surface area.**
There are no adequate and well-controlled studies **NovoLog Mix 70/30** in pregnant women.

*Nursing mothers-*

[ ]

We reserve additional labeling comments until the application is otherwise approvable.

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

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. 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 certainly 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.

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

Sincerely,

/S/

David G. Orloff, M.D.
Director
Division of Metabolic
and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

/s/
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David Orloff
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