

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER: 20-986

CORRESPONDENCE

MEMORANDUM

June 6, 2000

TO: John K. Jenkins, M.D.

Leah Ripper

FROM: Kenneth L. Hastings, Dr.P.H.

SUBJECT: NDA 20-986 (NovoLog; insulin aspart [rDNA origin] injection)

I have reviewed the Pharmacology/Toxicology information and concur with the approval of this NDA. The labeling, as amended, is acceptable (I have made some very minor modifications).

KS

Kenneth L. Hastings, Dr.P.H.

Acting Associate Director for Pharmacology/Toxicology

**APPEARS THIS WAY
ON ORIGINAL**

FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS
5600 FISHERS LANE, HFD-510
ROCKVILLE, MARYLAND 20857-1706

DATE: June 7, 2000



TO:

Name: Mr. Robert Fischer

Fax No: (609) 987-3916

Phone No.: (609) 987-5891

Location: Novo Nordisk

Pages (including this cover sheet): 41

FROM:

Name: Julie Rhee

Fax No.: (301) 443-9282

Phone No.: (301) 827-6424

Location: FDA

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COMMENTS:

NDA 20-986 NovoLog (insulin aspart [rDNA orgin] injection)

Congratulations!! Here is a copy of an approval letter. Please send me a fax acknowledging you've received a copy of the letter. Thank you.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 20-986

JUN 7 2000

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 mellitus 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.

NDA 20-986

Page 4

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,~~

/S/

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.

**APPEARS THIS WAY
ON ORIGINAL**

WITHHOLD 35 PAGE (S)

Draft

Labeling

RECORD OF TELEPHONE CONVERSATION/MEETING	Date: May 26, 2000
<p>I called Mr. Fischer concerning the timeline of Phase 4 commitments that were included in our 9/15/99 approvable letter.</p> <p>Mr. Fischer informed me that the protocol has been submitted to the Agency on 12/24/99 and the study has begun last March. He also stated that he expects the final study report to be submitted no later than September of this year.</p> <p>cc:OrigNDA HFD-510/DivFile</p> <p style="text-align: center;">APPEARS THIS WAY ON ORIGINAL</p> <p style="text-align: center;">/S/</p> <p>----- Name: Julie Rhee</p>	<p>NDA#: 20-986</p> <p>Telecon/Meeting initiated by:</p> <p><input type="radio"/> FDA</p> <p>By: Telephone</p> <p>Product Name: NovoLog™</p> <p>Firm Name: Novo Nordisk</p> <p>Name and Title of Person with whom conversation was held: Mr. Robert Fischer Regulatory Affairs</p> <p>Phone: (609) 987-5891</p>

**APPEARS THIS WAY
ON ORIGINAL**

NDA AMENDMENT
Human Pharmacokinetics and Bioavailability-Phase IV Commitment

DUPLICATE

August 5, 1999

NEW CORRESP NC

Solomon Sobel, M.D.
Director, Division of Metabolism
& Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



Novo Nordisk

**Novo Nordisk
Pharmaceuticals Inc.**
Suite 200
100 Overlook Center
Princeton, NJ 08540-781
Tel. 609-987-5800
Fax 609-921-8082

RE: NDA 20-986

**Insulin aspart (Insulin X-14)
(recombinant DNA origin)**

Dear Dr. Sobel:

Reference is made to NDA 20-986 for Insulin aspart (Insulin X-14) which was submitted September 15, 1998. Reference is also made to the July 20, 1999 fax we received from Dr. Hae-Young Ahn, which contained a request that we provide a commitment to perform Phase IV studies to determine the impact on the PK/PD of insulin aspart in certain special populations.

We are providing our commitment to perform the following Phase IV studies:

1. PK/PD in renally and hepatically impaired patients
2. PK/PD in obese vs. thin patients

We expect to submit protocols for these studies by March 31, 2000.

If you have any questions regarding this amendment, please contact Robert Fischer, Assistant Director, Regulatory Affairs, at (609) 987-5891.

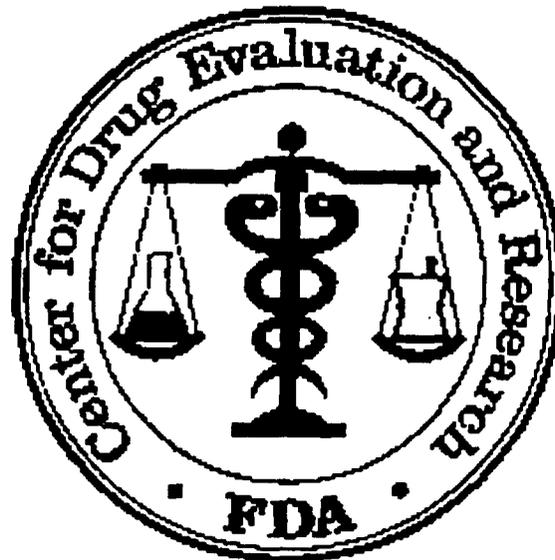
Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.

Barry Reit, Ph.D.
Vice President, Regulatory Affairs

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE

FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS
5600 FISHERS LANE, HFD-510
ROCKVILLE, MARYLAND 20857-1706

DATE: July 20, 1999



TO:

Name: Mr. Robert Fischer

Fax No: (609) 987-3916

Phone No.: (609) 987-5891

Location: Novo Nordisk

FROM:

Name: Julie Rhee

Fax No.: (301) 443-9282

Phone No.: (301) 827-6424

Location: FDA

Pages (including this cover sheet): 2

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COMMENTS:

NDA 20-986 NovoLog (insulin aspart)

Phase 4 commitment request from Biopharm.

500 OAS NDA
HFD-510/DJF/le
HFD-870/Fossier

NDA 20-986 NovoLog (insulin aspart)

Date of original NDA submission: September 15, 1998

Phase 4 request from Biopharm

Please provide your commitment to perform Phase 4 studies in the following special populations in order to determine the impact on the PK/PD of insulin aspart:

1. Renally and hepatically-impaired patients
2. Obese vs. thin patients

APPEARS THIS WAY
ON ORIGINAL

Cleared for faxing by:

/S/

01/20/99

Hae-Young Ahn, Ph.D., Biopharm Team Leader, DPE II

APPEARS THIS WAY
ON ORIGINAL

Labeling Review

NDA 20-986 NovoLog (insulin aspart [rDNA origin] injection)

Date of submission: June 7, 2000

I've compared Novo's revised physician PI dated June 7, 2000, against what we had faxed to them yesterday and found it to be identical to our yesterday's fax with the following minor corrections that need to be made, preferably when they print FPL:

1. Page 5, 2nd line in the 2nd paragraph, add a hyphen between the word "active" and "controlled.", so it would read "active-controlled."
2. Page 8, "Information for patients" subsection, change "dosage" to "dose" in the 2nd sentence.
3. Page 12, HOW SUPPLIED section, change "ml" to "mL" on cartridges.

/S/

6-7-00

Julie Rhee
Project Manager

cc:OrigNDA
HFD-510/DivFile
HFD-510/Koller/Antonipillai/Moore
HFD-715/Pian
HFD-870/Ahn

**APPEARS THIS WAY
ON ORIGINAL**

Labeling review

Note to the file

NDA 20-986 NovoLog™ (insulin aspart [rDNA origin] injection)

Date of submission: May 24, 2000

Date of review: May 26, 2000

The May 24 submission is a revised draft physician PI in response to our tele-con that was held on May 15, 2000, between DMEDP and the sponsor, Novo Nordisk.

I have compared the May 24 submission against the recommendations that were made during the 5/15/00 t-con and note that the sponsor has incorporated all of our recommendations.

However, there are alternative languages for the following three subsections for the Agency's consideration per our request:

- 1) Pharmacodynamics,
- 2) Antibody production, and
- 3) Pregnancy.

I recommend the following minor changes are made in the next revision:

- a. Page 2, Figure 2, delete extra spaces following "dose of".
- b. Page 3, Pharmacodynamics subsection, change "The" to "the" in the 1st sentence of the 2nd parag.
- c. Page 5, add colon after "Clinical Studies".
- d. Page 8, "Renal Impairment" and "Hepatic Impairment" subsection, change "dosage" to "dose" and delete "s" from "requirements".

JS/
Julie Rhee
Project Manager

5-26-00

cc:OrigNDA
HFD-510/DivFile
HFD-510/Koller/Antonipillai/Moore
HFD-715/Pian
HFD-870/Ahn

**APPEARS THIS WAY
ON ORIGINAL**

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Novo Nordisk Pharmaceuticals, Inc.	DATE OF SUBMISSION May 24, 2000
TELEPHONE NO. (Include Area Code) (609) 987-5800	FACSIMILE (FAX) Number (Include Area Code) (609) 987-3916
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 100 Overlook Center, Suite 200 Princeton, New Jersey 08540-7810	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 20-986		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Insulin Aspart	PROPRIETARY NAME (trade name) IF ANY	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) 28-L-Aspartic Acid-Insulin (human)	CODE NAME (If any) Insulin X-14	
DOSAGE FORM: Parenteral	STRENGTHS: 100 Units/ml	ROUTE OF ADMINISTRATION: Subcutaneous
(PROPOSED) INDICATION(S) FOR USE: Treatment of Diabetes Mellitus		

APPLICATION INFORMATION

APPLICATION TYPE (check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50) <input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR part 601)
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input checked="" type="checkbox"/> 505 (b)(1) <input type="checkbox"/> 505 (b)(2)
IF AN ANDA, or 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug Holder of Approved Application
TYPE OF SUBMISSION (check one) <input type="checkbox"/> ORIGINAL APPLICATION <input checked="" type="checkbox"/> AMENDMENT TO A PENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input type="checkbox"/> OTHER
IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____
IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY <input type="checkbox"/> CBE <input type="checkbox"/> CBE-30 <input type="checkbox"/> Prior Approval (PA)
REASON FOR SUBMISSION
PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)
NUMBER OF VOLUMES SUBMITTED <u> 1 </u> THIS APPLICATION IS <input type="checkbox"/> PAPER <input checked="" type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g., Final dosage form, Stability/testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

WITHHOLD 12 PAGE (S)

Draft

Labeling

Additional Labeling Considerations

As agreed in our May 22, 2000 teleconference to discuss NovoLog™ labeling, we are submitting the following suggested wording changes for FDA review. These suggested changes have not been incorporated into the revised label we are submitting, however, should FDA find them acceptable, we request that they be included in the labeling text.

“Pharmacodynamics

Studies in normal volunteers and patients with diabetes demonstrated that NovoLog™ has a more rapid onset of action than regular human insulin.



We request that the second paragraph, in blue above, be included in the text.

“Antibody production- Insulin antibodies may develop during treatment with insulin.

In large clinical trials, levels of antibodies that cross react with human insulin and insulin aspart were higher in patients treated with NovoLog™ compared to regular human insulin.

_____ The clinical significance of these antibodies is uncertain.”

We request the inclusion of the statement _____

in blue above. In addition to patient specific antibody results from the 036 extension study, which were submitted per Dr. Koller's request, antibody results through twelve months are included in the ANA/036 extension study report, which was submitted on March 31, 1999.

“Pregnancy Teratogenic effects: Pregnancy Category C.

Subcutaneous reproduction and teratology studies have been performed with NovoLog™ 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 generally differ from those observed with subcutaneous regular human insulin. NovoLog™, like human insulin, caused pre- and post-implantation losses and visceral/skeletal abnormalities in rats at a dose of 200 U/kg/day (approximately 32 times the human subcutaneous dose, based on U/body surface area) and in rabbits at a dose of 10 U/kg/day (approximately three times the human subcutaneous dose, 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 for rats and equal to the human subcutaneous dose for rabbits, based on U/body surface area.

There are no well-controlled clinical studies of the use of NovoLog™ in pregnant women. It is essential for patients with diabetes or a history of gestational diabetes to maintain good metabolic control before conception and throughout pregnancy. Insulin requirements may decrease during the first trimester, generally increase during the second and third trimesters, and rapidly decline after delivery. Careful monitoring of glucose control is essential in such patients. Because animal reproduction studies are not always predictive of human response, ~~it~~ should be used during pregnancy only if ~~it~~

We request that the Agency include the above proposed wording, in blue, for the Pregnancy section of the label. This paragraph has been transcribed exactly from the recently approved Lantus label.

**APPEARS THIS WAY
ON ORIGINAL**

Memo to the file

NDA 20-986 NovoLog

The attached draft physician package insert (FDA revision dated 5_15_00) has been forwarded to Mr. Robert Fischer, Regulatory Affairs, at Novo Nordisk as an attachment to the today's e-mail.

/S/

5-15-00

Julie Rhee
Project Manager

cc:OrigNDA
HFD-510/DivFile

**APPEARS THIS WAY
ON ORIGINAL**

WITHHOLD 30 PAGE (S)

Draft

Labeling

RHEEJ
APPOINTMENT DETAILED
22-May-2000 to 22-May-2000

Date: Monday, 22-May-2000	Time: 10:00am	Length: 02:00 Hrs:Min
Subject: TCON/Novo/Labeling/NovoLog		Loc: 7-63
Attendees		
RHEEJ, #510CAL, MALOZOWSKIS, KOLLERE, STEIGERWALTR, ANTONIPILLAI, AHNH, !INDUSTRY, !NOVO, PIAN,		
Agenda		
T-con with the sponsor.		
To discuss NovoLog labeling dated 4/28/00.		
Meeting scheduled: 5/2/00		
Call (800) 457-0184		
Participant code: _____		
APPEARS THIS WAY ON ORIGINAL		

Key to Attendee Status

Bold = Confirmed Underline = Rejected All Others = Pending

March 27, 2000

Memo to the file

NDA 20-986 NovoLog™ (insulin aspart [rDNA origin] injection)

Sponsor: Novo Nordisk Pharmaceuticals, Inc.

The attached draft physician package insert (FDA revision #3) was forwarded to Mr. Robert Fischer and Mary Ann McElligott, Ph.D., Regulatory Affairs at Novo today by e-mail. The document was saved with the password _____

/S/

Julie Rhee
Regulatory Project Manager

cc:OrigNDA
HFD-510/DivFile

**APPEARS THIS WAY
ON ORIGINAL**

WITHHOLD 64 PAGE (S)

Draft

Labeling

DUPLICATE

NDA SUPP AMEND
N.B.C.

Novo Nordisk



This is the most recent PPI.

I'll compare it against what we had sent to Novo.

/S/ 6/1/00



**NDA AMENDMENT
Labeling**

May 31, 2000

John K. Jenkins, M.D., F.C.C.P.
Acting Director, Division of Metabolic
& Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Novo Nordisk
Pharmaceuticals, Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-921-8082

**RE: NDA 20-986 NovoLog™
Insulin aspart (rDNA origin) injection**

Dear Dr. Jenkins:

Reference is made to NDA 20-986 for NovoLog™ (insulin aspart [rDNA origin] injection), which was submitted September 15, 1998. Reference is also made to the FDA revised patient inserts for NovoLog™, which we received by e-mail on May 24 and 25, 2000

At this time, we are submitting, in duplicate, new revised patient inserts for vials, PenFill®, and Prefilled™ syringe, which incorporate the changes suggested by DDMAC in their review of the labeling. The labeling is also being submitted electronically on diskette.

In addition, we have proposed some minor additional wording changes for FDA consideration. Of these, the only substantive change is to the Storage section, where we have reiterated some wording already in the label as an added safety measure for the patient.

If you have any questions regarding this amendment, please contact Robert Fischer, Assistant Director, Regulatory Affairs, at (609) 987-5891 or via e-mail at rofi@nnp.com.

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.

Barry Reit, Ph.D.
Vice President, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Novo Nordisk Pharmaceuticals, Inc.	DATE OF SUBMISSION 5/31/00
TELEPHONE NO. (Include Area Code) (609) 987-5822	FACSIMILE (FAX) Number (Include Area Code) (609) 987-3916
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 100 Overlook Center Suite 200 Princeton, New Jersey 08540	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued) 20-986		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Insulin Aspart	PROPRIETARY NAME (trade name) IF ANY NovoLog™	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any) 28 -L-Aspartic Acid-Insulin (human)	CODE NAME (if any) Insulin X-14	
DOSAGE FORM: Parenteral	STRENGTHS: 100 Units/ml	ROUTE OF ADMINISTRATION: Subcutaneous
(PROPOSED) INDICATION(S) FOR USE: Treatment of Diabetes Mellitus		

APPLICATION INFORMATION

APPLICATION TYPE (check one)	<input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50)	<input type="checkbox"/> ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
	<input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR part 601)	
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE	<input checked="" type="checkbox"/> 505 (b) (1)	<input type="checkbox"/> 505 (b) (2) <input type="checkbox"/> 507
IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION	Name of Drug _____ Holder of Approved Application _____	

TYPE OF SUBMISSION (check one)	<input type="checkbox"/> ORIGINAL APPLICATION	<input checked="" type="checkbox"/> AMENDMENT TO A PENDING APPLICATION	<input type="checkbox"/> RESUBMISSION
	<input type="checkbox"/> PRESUBMISSION	<input type="checkbox"/> ANNUAL REPORT	<input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> SUPAC SUPPLEMENT
	<input type="checkbox"/> EFFICACY SUPPLEMENT	<input checked="" type="checkbox"/> LABELING SUPPLEMENT	<input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input type="checkbox"/> OTHER

REASON FOR SUBMISSION Updated Manufacturing Process for Drug Substance

PROPOSED MARKETING STATUS (check one)	<input type="checkbox"/> PRESCRIPTION PRODUCT (Rx)	<input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)
---------------------------------------	--	---

NUMBER OF VOLUMES SUBMITTED <u>1</u>	THIS APPLICATION IS <input type="checkbox"/> PAPER <input checked="" type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC
--------------------------------------	---

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

WITHHOLD 37 PAGE (S)

Draft

Labeling

Note to the file

This is the most recent
patient PI.

waiting the company's
response 5/31/00

NDA 20-986 NovoLog (insulin aspart [rDNA origin] for injection)

/S/

The attached patient PI has been forwarded to the sponsor on the following dates as an e-mail attachment:

1. Information For The Patient for Vial: May 24, 2000
2. Information For The Patient for PenFill: May 25, 2000
3. Information For The Patient for Prefilled: May 25, 2000

Received Novos
revision dated 5/31/00
on 6/1/00.

/S/

/S/

5-25-00

Julie Rhee
Project Manager

cc:OrigNDA
HFD-510/DivFile

APPEARS THIS WAY
ON ORIGINAL

WITHHOLD 71 PAGE (S)

Draft

Labeling

**RECORD OF TELEPHONE
CONVERSATION/MEETING**

Date:
August 24, 1999

Re: 8/20/99 submission

I called Mr. Fischer and asked him to move "Rx only" statement to between the trade name and the established name on the front panel of a 10 ml vial carton label. He agreed to submit a corrected label.

cc: OrigNDA
HFD-510/DivFile
HFD-510/Berlin

**APPEARS THIS WAY
ON ORIGINAL**

/S/

Name: Julie Rhee

NDA#: 20-986

**Telecon/Meeting
initiated by:**

FDA

By: Telephone

Product Name:
NovoLog

Firm Name:
Novo Nordisk

**Name and Title of Person
with whom conversation
was held:**

Mr. Robert Fischer
Regulatory Affairs

Phone:
(609) 987-5891

**NDA AMENDMENT
Labeling**

August 20, 1999

Solomon Sobel, M.D.
Director, Division of Metabolism
& Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



NOVO NORDISK

DUPLICATE

~~ORIG. AMENDMENT~~

**Novo Nordisk
Pharmaceuticals Inc.**

Suite 200
100 Overlook Center
Princeton, NJ 08540-7810

Tel. 609-987-5800
Fax 609-921-8082

RE: NDA 20-986

**Insulin aspart (Insulin X-14)
(recombinant DNA origin)**

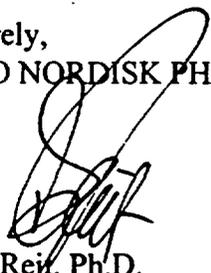
Dear Dr. Sobel:

Reference is made to NDA 20-986 for Insulin aspart (Insulin X-14) which was submitted September 15, 1998. Reference is also made to a fax from Dr. Stephen Moore, dated August 12, 1999 containing marked-up labeling for carton (for 10 mL vial), vial, carton (for 3 mL Prefilled syringe), Prefilled syringe, package (for 3 mL PenFill), and 3 mL PenFill cartridge.

Please find attached, in duplicate, revised draft labeling for the above mentioned presentations reflecting the changes requested by Dr. Moore. Please note also that additional minor revisions have been made such as including actual NDC number and product list number for the 10mL vial and the 3mL Penfill. The files are submitted as paper copy as well as on diskette. The file names are; CARTON1_Version3.doc, CARTON2_Version3.doc and CARTON3_Version3.doc.

If you have any questions regarding this amendment, please contact Robert Fischer, Assistant Director, Regulatory Affairs, at (609) 987-5891.

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.


Barry Reix, Ph.D.
Vice President, Regulatory Affairs

**APPEARS THIS WAY
ON ORIGINAL**

Enclosure

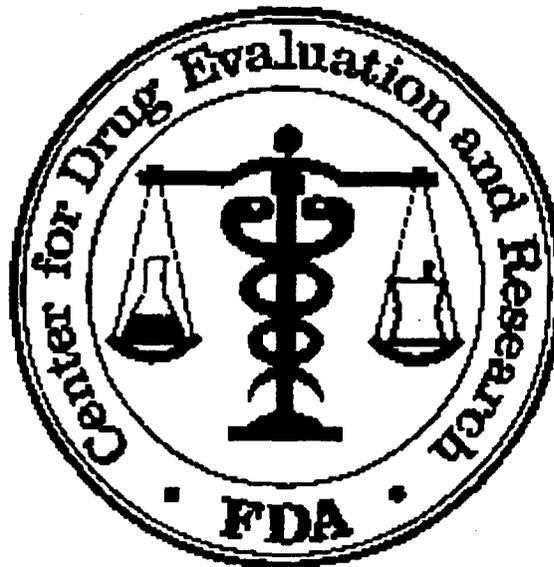
WITHHOLD 10 PAGE (S)

Draft

Labeling

FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS
5600 FISHERS LANE, HFD-510
ROCKVILLE, MARYLAND 20857-1706

DATE: August 12, 1999



TO:

Name: Mr. Robert Fischer

Fax No: (609) 987-3916

Phone No.: (609) 987-5891

Location: Novo Nordisk

Pages (including this cover sheet): 11

FROM:

Name: Julie Rhee

Fax No.: (301) 443-9282

Phone No.: (301) 827-6424

Location: FDA

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COMMENTS:

NDA 20-986 NovoLog™

Marked-up labeling for carton (for 10 mL vial), vial, carton (for 3 mL Prefilled syringe), Prefilled syringe, package (for 3 mL PenFill), and 3 mL PenFill cartridge.

WITHHOLD 10 PAGE (S)

Draft

Labeling

Free

OCT 30 1998

**NDA #20986 X-14 Insulin Analogue
BB**

Letter date: 10/8/98 Received: 10/9/98
Letter date: 10/20/98 Received: 10/21/98
Received and reviewed by physician: 10/28/98
Amended: 10/30/98
Sponsor: NovoNordisk

The sponsor has supplied data files for euglycemic clamp studies. What is needed by the medical reviewer are data files for the clinical results. The statisticians had not yet received the clinical efficacy and safety data as of 10/23/98. It will be important to merge the line listings for the outcome variables eg. HgbA1c vs hypoglycemia rate. Preferably the information will be in an Excel file.

The sponsor will be notified after we have had the opportunity to inspect the electronic data package or if the data package is delayed much longer.

/S/

Elizabeth Koller, M.D.
CC: HFD 510 Sahlroot/Pian/RheeJ/Koller/Ahn/Fossler

W. J. Koller
/S/
10/30/98

**APPEARS THIS WAY
ON ORIGINAL**

ORIGINAL

ORIG AMENDMENT

SU

*Review
Pending*

6/1/00

/S/

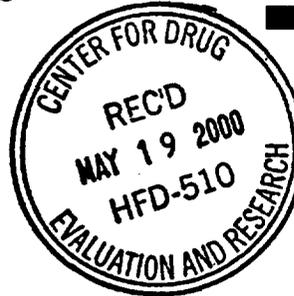
Novo Nordisk



**NDA AMENDMENT
Safety Update**

May 18, 2000

John K. Jenkins, M.D., F.C.C.P.
Acting Director, Division of Metabolic
& Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



**Novo Nordisk
Pharmaceuticals, Inc.**

Suite 200
100 Overlook Center
Princeton, NJ 08540-7810

Tel. 609-987-5800
Fax 609-921-8082

**RE: NDA 20-986 NovoLog™
Insulin aspart (rDNA origin) injection**

Dear Dr. Jenkins:

Reference is made to NDA 20-986 for NovoLog™ (insulin aspart [rDNA origin] injection) which was submitted September 15, 1998. Further reference is made to the telephone conversation between Ms. Julie Rhee and Dr. Mary Ann McElligott on May 9, 2000 in which Ms. Rhee requested a new Safety Update.

Enclosed, in duplicate, is the updated safety information.

If you have any questions regarding this amendment, please contact Robert Fischer, Assistant Director, Regulatory Affairs, at (609) 987-5891.

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.

Barry Reit, Ph.D.
Vice President, Regulatory Affairs

Enclosure

REVIEWS COMPLETED
CSO ACTION:
<input type="checkbox"/> LETTER <input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS _____
TE

^{SU}
ORIG AMENDMENT

Novo Nordisk



**NDA AMENDMENT
Safety Update**

August 5, 1999

Solomon Sobel, M.D.
Director, Division of Metabolism
& Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



**Novo Nordisk
Pharmaceuticals Inc.**

Suite 200
100 Overlook Center
Princeton, NJ 08540-7810

Tel. 609-987-5800
Fax 609-921-8082

RE: NDA 20-986

**Insulin aspart (Insulin X-14)
(recombinant DNA origin)**

Dear Dr. Sobel:

Reference is made to NDA 20-986 for Insulin aspart (Insulin X-14) which was submitted September 15, 1998. Further reference is made to a telephone conversation between Julie Rhee and Robert Fischer on August 3, 1999. In that conversation, Ms. Rhee requested that Novo Nordisk submit a Pre-Approval Safety Update for Insulin aspart.

At this time, we are submitting the requested Pre-Approval Safety Update. If you have any questions regarding this amendment, please contact Robert Fischer, Assistant Director, Regulatory Affairs, at (609) 987-5891.

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.

M. A. McEllyott for Barry Reit

Barry Reit, Ph.D.
Vice President, Regulatory Affairs

Enclosure

*MSI
8/13/99
Included
in NDA review
Not much new in b
NAI for CSO*

*NAI
8-18-99*

MEMORANDUM

June 6, 2000

TO: John K. Jenkins, M.D.

Leah Ripper

FROM: Kenneth L. Hastings, Dr.P.H.

SUBJECT: NDA 20-986 (NovoLog; insulin aspart [rDNA origin] injection)

I have reviewed the Pharmacology/Toxicology information and concur with the approval of this NDA. The labeling, as amended, is acceptable (I have made some very minor modifications).

/S/

/ Kenneth L. Hastings, Dr.P.H.

Acting Associate Director for Pharmacology/Toxicology

**APPEARS THIS WAY
ON ORIGINAL**

WITHHOLD 2 PAGE (S)

Draft

Labeling

**RECORD OF TELEPHONE
CONVERSATION/MEETING**

Date:
June 7, 2000

I called Mr. Fischer and requested the following:

1. Please include the established name whenever the tradename is mentioned on cartons, vial, PenFill 3 mL cartridge, and Prefilled 3 mL syringes.
2. Please change "ml" to "mL" on cartons, vial, PenFill cartridge, and Prefilled syringe.

Mr. Fischer agreed to make the above changes when they print FPL.

cc:OrigNDA
HFD-510/DivFile
HFD-510/Moore/Wu

**APPEARS THIS WAY
ON ORIGINAL**

/S/

Name: Julie Rhee

NDA#: 20-986

**Telecon/Meeting
initiated by:**

FDA

By: Telephone

Product Name:
NovoLog

Firm Name:
Novo Nordisk

**Name and Title of Person
with whom conversation
was held:**

Mr. Robert Fischer
Regulatory Affairs

Phone:
(609) 987-5891

RECORD OF TELEPHONE CONVERSATION/MEETING	Date: June 5, 2000
<p>Background: The UF goal date fir this NDA is 6/7/00. This NDA includes 3 presentations—10 ml vial, 3 ml PenFill, and 3 ml Prefilled syringes. However, the sponsor informed the Agency that Prefilled syringes are going to be launched later and, therefore, it was not included under HOW SUPPLIED section of PI although Novo did submit patient PI for Prefilled syringes. The reviewing chemist approved Prefilled syringe presentation in his review.</p> <p>*****</p> <p>I called Mr. Fischer concerning what Novo needs to do when they get ready to launch Prefilled syringes. I informed him of the following options:</p> <ol style="list-style-type: none"> 1. When they launch Prefilled syringes, report the launch in the annual report. 2. If there're any pending labeling/efficacy supplement at the time they launch Prefilled syringes, they could include the change in the labeling when the supplement is approved. 3. If Prefilled syringes are launched before they print FPL, they could include the syringes under HOW SUPPLIED section when they print FPL. <p style="text-align: center;">/S/</p> <p>----- Name: Julie Rhee</p>	<p>NDA#: 20-986</p> <p>Telecon/Meeting initiated by:</p> <p><input type="radio"/> FDA</p> <p>By: Telephone</p> <p>Product Name: NovoLog</p> <p>Firm Name: Novo Nordisk</p> <p>Name and Title of Person with whom conversation was held: Mr. Robert Fischer Regulatory Affairs</p> <p>Phone: (609) 987-5891</p>

APPEARS THIS WAY
ON ORIGINAL

**RECORD OF TELEPHONE
CONVERSATION/MEETING**

Date:
September 1, 1999

Re: Biopharm phase 4 commitment

NDA#: 20-986

I asked Mr. Fischer about their planned timelines for the biopharm phase 4 commitment and he told me the following timelines:

**Telecon/Meeting
initiated by:**

Protocol Submission: December 1999
Study Start: March 2000
Final Report Submission: Sept. 2000

FDA
By: Telephone

Product Name:
NovoLog™

cc:OrigNDA
HFD-510/DivFile
HFD-870/Fossler

Firm Name:
Novo Nordisk

**Name and Title of Person
with whom conversation
was held:**

Mr. Robert Fischer
Regulatory Affairs

Phone:
(609) 987-5891

/S/

Name: Julie Rhee

**RECORD OF TELEPHONE
CONVERSATION/MEETING**

Date:
August 24, 1999

Re: 8/17/99 submission (PPSR)

I called Mr. Fischer and asked him not to submit a pediatric study report until after they receive WR from us.

cc:OrigNDA
HFD-510/DivFile

**APPEARS THIS WAY
ON ORIGINAL**

/S/

Name: Julie Rhee

NDA#: 20-986

**Telecon/Meeting
initiated by:**

FDA

By: Telephone

Product Name:
NovoLog

Firm Name:
Novo Nordisk

**Name and Title of Person
with whom conversation
was held:**

Mr. Robert Fischer
Regulatory Affairs

Phone:
(609) 987-5891

**RECORD OF TELEPHONE
CONVERSATION/MEETING**

Date:
August 16, 1999

Re: 6/2/99 submission

NDA#: 20-986

I called Mr. Fischer and informed him that Dr. Koller is interested finding out the definition of "demographic" that was in their 6/2/99 submission.

**Telecon/Meeting
initiated by:**

Mr. Fischer called me back later and stated that "demographic" included such information as age, gender, race, weight, height, BMI, duration of diabetes, baseline HbA1c, and concomitant illness.

FDA

By: Telephone

He also stated that the 6/2 submission was made to correct their error with patient treatment.

Product Name:
NovoLog

Firm Name:
Novo Nordisk

cc:OrigNDA
HFD-510/DivFile
HFD-510/Koller
HFD-715/Pian

**Name and Title of Person
with whom conversation
was held:**
Mr. Robert Fischer
Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

Phone:
(609) 987-5891

/S/

Name: Julie Rhee

**RECORD OF TELEPHONE
CONVERSATION/MEETING**

Date:
August 13, 1999

Re: 7/21/99 submission (physician PI)

I called Mr. Fischer to convey the request from Dr. Berlin that _____ do not need to be included on the structural formula. However, if Novo wants to include them on the formula, they (_____) should be included in both A-chain and B-chain.

cc: Orig NDA
HFD-510/DivFile
HFD-510/Berlin

**APPEARS THIS WAY
ON ORIGINAL**

/S/

Name: Julie Rhee

NDA#: 20-986

**Telecon/Meeting
initiated by:**

FDA

By: Telephone

Product Name:
NovoLog™

Firm Name:
Novo Nordisk

**Name and Title of Person
with whom conversation
was held:**

Mr. Robert Fischer
Regulatory Affairs

Phone:
(609) 987-5891

**RECORD OF TELEPHONE
CONVERSATION/MEETING**

Date:
August 11, 1999

I called Mr. Bob Fischer but because he was not available, I spoke with Ms. Carol Foster to ask the following questions from Dr. Koller concerning the start date of run-in and the start date of treatment with randomized drug on the following three patients:

1. Patient 148/631-6459
2. Patient 35/012-0291
3. Patient 37/14-0177

Ms. Foster agreed to get back to me with the information.

cc: OrigNDA
HFD-510/DivFile
HFD-510/Koller

APPEARS THIS WAY
ON ORIGINAL

/S/

Name: Julie Rhee

NDA#: 20-986

**Telecon/Meeting
initiated by:**

FDA

By: Telephone

Product Name:

NovoLog™

Firm Name:
Novo Nordisk

**Name and Title of Person
with whom conversation
was held:**

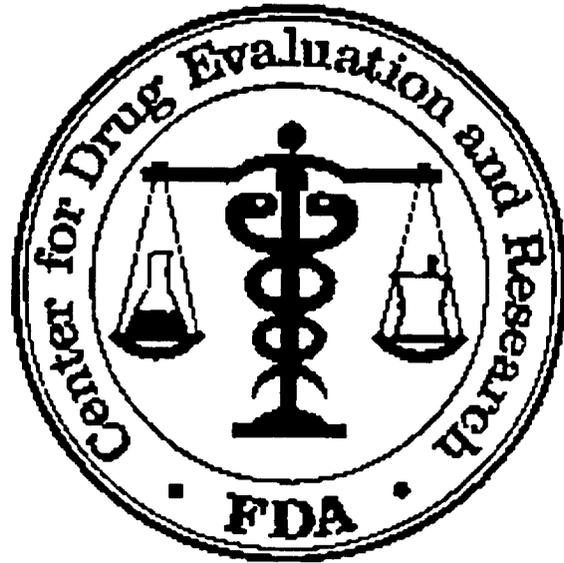
Ms. Carol Foster
Regulatory Affairs

Phone:
(609) 987-5891

thee

FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS
5600 FISHERS LANE, HFD-510
ROCKVILLE, MARYLAND 20857-1706

DATE: February 3, 1999



TO:

Name: Mr. Robert Fischer

Fax No: (609) 987-3916

Phone No.: (609) 987-5891

Location: Novo Nordisk

FROM:

Name: Julie Rhee

Fax No.: (301) 443-9282

Phone No.: (301) 827-6424

Location: FDA

Pages (including this cover sheet): 2

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COMMENTS:

NDA 20-986 Insulin Aspart

Request from Biopharm. Please submit your response to the NDA file. Thank you.

*cc: Orig NDA
HFD-510/Div File
HFD-870/Foster*

NDA 20-986 Insulin Aspart
Date of Submission: July 15, 1998

OCPB Comment re: Study ANA/DCD/022/UK
Statistical Report, vol. 1.34, app.K, Section 6

The equation derived to correct the insulin aspart levels derived on page 5 of the above report (the alternative method) was derived assuming "there is a subject specific ratio between [the production of c-peptide and insulin]". This relationship was expressed as

$$P_i(t) = k_2 * P_c(t)$$

Where $P_i(t)$ is the production rate of insulin, $P_c(t)$ is the production rate of c-peptide, and k_2 is a proportionality constant relating the two. In fact, insulin and c-peptide are released in equimolar quantities and at the same time¹, so a proportionality constant is not needed. One may write instead

$$P_i(t) = P_c(t)$$

and the final expression simplifies to

$$I(t) = k_1 * I(t-1) + C(t) - k_3 * C(t-1)$$

Where $I(t)$ is measured insulin at time t , $C(t)$ is the measured c-peptide at time t , and k_1 and k_3 are the elimination constants for insulin and c-peptide, respectively.

Was this investigated as another method for correcting of endogenous insulin levels? The firm is asked to compute the results of Study ANA/DCD/022/UK assuming $P_i(t) = P_c(t)$ and to construct a table showing the results from all three methods side-by-side.

Cleared for faxing by Hae-Young Ahn, Ph.D., Team Leader



2/3/99

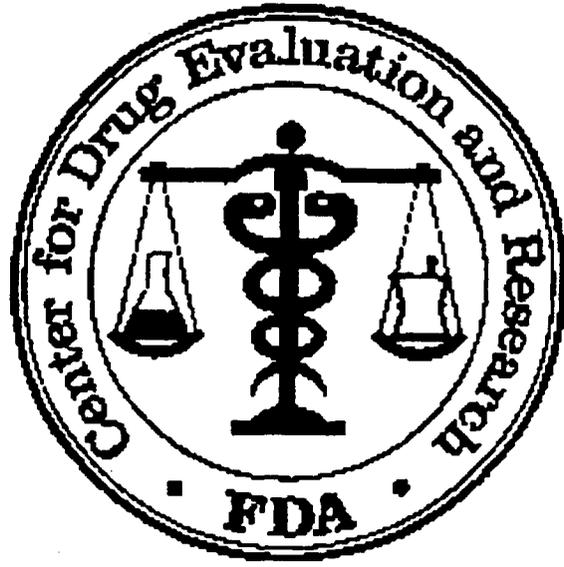
**APPEARS THIS WAY
ON ORIGINAL**

¹ Goodman and Gilman's The Pharmacologic Basis of Therapeutics, 9th ed, pg. 1489

ORIGINAL

FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS
5600 FISHERS LANE, HFD-510
ROCKVILLE, MARYLAND 20857-1706

DATE: January 14, 1999



TO:

FROM:

Name: Mr. Robert Fischer

Name: Julie Rhee

Fax No.: (609) 987-3916

Fax No.: (301) 443-9282

Phone No.: (609) 987-5891

Phone No.: (301) 827-6424

Location: Novo Nordisk

Location: FDA

Pages (including this cover sheet): 2

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Thank you

COMMENTS:

NDA 20-986 Insulin Aspart

Microbiology review comments on the September 15, 1998, submission. Please let me know when we could expect your response. Thank you.

cc: Orig NDA
HFD 510/DIV File
HFD 160/Stimovage

Novo Nordisk, NDA 20-986, Insulin Aspart X-14, Microbiologist's Review #1

List of Microbiology Deficiencies and Comments

Reference is made to your New Drug Application dated 16 September 1998 for Insulin Aspart (Insulin X-14)(NDA 20-986). The submission was reviewed for microbiological issues concerning sterility assurance and the following issues were not completely addressed. Please provide an amendment to address the following concerns.

┌

└

Cleared for faxing by:

PS

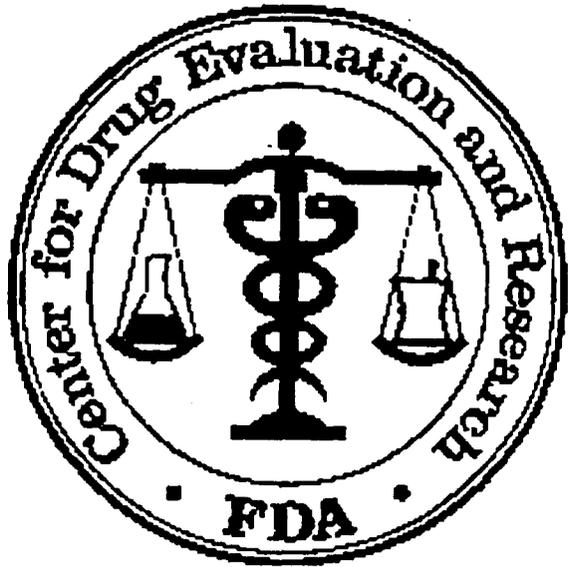
1/15/99

Peter Cooney, Ph.D., Microbiology Team Leader

Free

FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS, HFD-510
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20857

DATE : October 7, 1998



TO:

Name: Mr. Bob Fischer

Fax No.: (609) 987-3916

Phone No.: (609) 987-5891

Location: Novo Nordisk

Pages: 2 (including cover)

FROM:

Name: Julie Rhee

Fax No.: (301) 443-9282

Phone No.: (301) 827-6424

Location: FDA

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Comments:

NDA 20-986 Insulin Aspart (insulin X-14)

Requests from Biopharm on your 9/16/98 submission.

*CC: Orig NDA
HFD-510/DIU File
HFD-870/Fossler*

NDA 20-986 Insulin Aspart (Insulin X-14)

Date of Submission: September 16, 1998

Biopharm Requests

Comments to be sent to firm:

- 1) When submitting the raw insulin concentration vs. time data for all studies, the data uncorrected for c-peptide levels should be submitted in addition to the corrected data.
- 2) Please provide any data on the effect of mixing insulin aspart with other long-acting insulins such as NPH and ultralente.

APPEARS THIS WAY
ON ORIGINAL

11/15/98
10/17/98

Cleared for faxing by: _____

Hae-Young Ahn, Ph.D., Biopharm Team Leader

MEMORANDUM OF TELECON

DATE: April 29, 1999

APPLICATION NUMBER: NDA 20-986; Insulin X-14

BETWEEN:

Names: Mr. Robert Fischer
Poul Strange, M.D.
Anita Osborne
Ole Noudfang
Lennart Andersen
Phone: (609) 987-5891
Representing: Novo Nordisk Pharmaceuticals, Inc.

AND

Names: Michael Fossler, Ph.D.
Julie Rhee
Division of Metabolic and Endocrine Drug Products, HFD-510

SUBJECT: Biopharm t-con

1. The Agency requested and Novo agreed to provide the actual numbers for Table 2B of Report 950106 in NDA page 196 of the 9/15/98 submission using the proposed correction and to provide precision and accuracy data.
2. The Agency asked for the following data for the _____ assay:
[]
3. []
4. Novo stated that Insulin X-14 is stable at _____ days when tested by _____ The Agency agreed to use _____ data that was included in the 9/15/98 submission.

/S/
5-11-99
Julie Rhee
Project manager

Page 2
NDA 20-986

cc:
Original NDA 20-986
HFD-510/Div. File
HFD-870/Fossler
R/D by: Jrhee 5-10-99
edits by: Fossler 5-11-99
F/T by: JRhee 5-11-99

TELECON

**APPEARS THIS WAY
ON ORIGINAL**

Filing Meeting Minutes

NDA 20-986 Insulin Aspart X-14

Date: October 14, 1998

Time: 3:00 - 4:00 pm

Location: Parklawn Bldg. Room 14-56

Attendees:

Solomon Sobel, M.D., Director, DMEDP
Elizabeth Koller, M.D., Medical Officer, DMEDP
Stephen Moore, Ph.D., Chemistry Team Leader, DMEDP
William Berlin, Ph.D., Chemist, DMEDP
Ronald Steigerwalt, Ph.D., Pharmacology Team Leader, DMEDP
Lee Pian, Ph.D., Statistician, Division of Biometrics II
Hae-Young Ahn, Ph.D., Biopharm Team Leader, Div. of Pharmaceutical Evaluation II
Mike Fossler, Ph.D., Biopharm Reviewer, Div. of Pharmaceutical Evaluation II
Julie Rhee, Project Manager, DMEDP

Discussion:

Clinical:

- The NDA is filable with the following deficiencies:
- i. Data to support indication is missing.
 - ii. Studies include not many NIDDM patients (n= 180 patients) although there are enough IDDM patients in the studies.
 - iii. Photo copies of graphs are not legible.
 - iv. The sponsor did not address a major biopharm issues concerning mixing with other insulins.
 - v. Expect a copy of the filing check list from Dr. Koller in order to convey the deficiencies to the sponsor.

Biopharm:

The NDA is filable since mixing with other insulins is not a safety issue.

Chemistry:

- i. The NDA is filable.
- ii. Waiting for the sponsor to submit a new proposed trade name. Their previously proposed trade name _____ was turned down by the Nomenclature Committee.

Biometrics:

- i. The NDA is filable.
- ii. Sponsor is claiming superiority though original hypothesis involved testing for non-inferiority. Superiority claim is not acceptable because it involves a small clinically insignificant, treatment difference.

Pharmacology:

The NDA is filable.

General:

- i. 10-month User Fee due date is 7/16/99 and 12-month due date is 9/16/99. Since we try to aim for the 10-mon goal date, I asked the final review to be ready by the end of 5/99.
- ii. Advisory Committee meeting is not necessary since this NDA is not the first fast acting analog insulin.
- iii. An action letter will be signed by the Office level.

Conclusion:

1. The NDA is filable.
2. Get a list of deficiencies from Dr. Koller to be sent to the sponsor.
3. Final review due by the end of 5/99.
4. No Advisory Committee meeting is needed.

/S/

Julie Rhee

cc:OrigNDA

HFD-510/DivFile

HFD-510/Koller/Berlin/HRhee

HFD-715/Pian

HFD-870/Fossler

R/D by: JRhee

Concurrence: Koller 10-22-98/Berlin 10-21-98/Moore 10-21-98/Steigerwalt 10-21-98/Pian 10-20-98/Fossler 10-21-98/Ahn 10-21-98

F/T by:JRhee 11-3-98

Meeting Minutes

**APPEARS THIS WAY
ON ORIGINAL**

Clinical Requests

Please provide the following information requested by Dr. Koller :

1. The major A & B data on the diskettes (6/16/99 submission) do not match the original data. Please explain the discrepancy.
2. The case narratives for the U.S. and NIDDM studies were requested. A fax for the location of the European case narratives was received, but we already had these at the time of the request. Please provide case narratives for the U.S. and NIDDM studies.
3. Also the following information was requested but was not included on the diskettes (6/16/99 submission): Those patients who were treated for periods of time that were longer or shorter than protocol and for visits that were not correctly timed.
4. Please provide number and timing of injections. Also please include information on whether or not any of the patients mixed their insulin.
5. Case reports/narratives of those patients with pruritis, urticaria, or other allergic symptoms, should also be provided.
6. Please provide case reports/narratives of patients with increased or increases in alkaline phosphatase.

8/9
BCH
I spoke to Bob Fischer re: this fax. He said he'll send the submission in response to items # 1 - 4 tomorrow (to be received Wed 8/11).
He said he is still waiting response from _____ re: items 5 + 6.

/S/

Cleared for faxing by: _____
Saul Malozowski, M.D., Acting Medical Team Leader, DMEDP

Clinical Requests

Please provide the following information:

1. Please provide the actual results of blood glucose (not the differences) at baseline, 6-months, and endpoint. Also, please specify whether the results were FBS or not.
2. Please explain the problems, i.e., high PVC, with the delivery of baby for 050 — 0186.
3. Please provide information on the following:
 - i. how many patients were 1, 2, 3, 4, or more than 4 shots of rapid acting insulin?
 - ii. how many patients were 1, 2, 3, 4, or more than 4 shots of basal insulin?
 - iii. how many patients were 3, 4, 5, 6, 7, 8, or more than 8 shots total of rapid and basal insulin?
4. How many patients received:
 - i. rapid acting insulin at all 3 meals only?
 - ii. rapid acting insulin at all 3 meals and one other time during the day?
 - iii. rapid acting insulin at all 3 meals and 2 other times during the day?
 - iv. basal insulin at bed time only?
 - v. basal insulin at dinner only?
 - vi. basal insulin at breakfast and supper only?
 - vii. basal insulin at breakfast and bed time only?
 - viii. basal insulin with each meal and at bed time?
 - ix. other?
5. Number of patients who were older than 65 years and enrolled in the pivotal trials.

Cleared for faxing by:

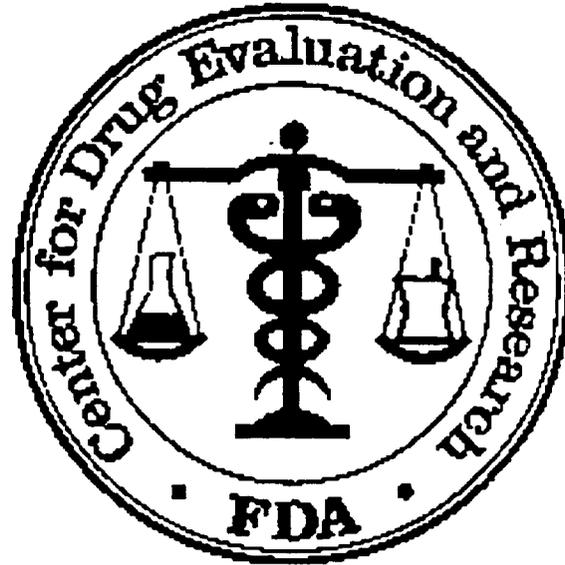
**APPEARS THIS WAY
ON ORIGINAL**

Elizabeth Koller, M.D.
Medical Officer, DMEDP

Saul Malozowski, M.D.
Acting Medical Team leader, DMEDP

FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS, HFD-510
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20857

DATE : October 7, 1998



TO:

Name: Mr. Bob Fischer

Fax No.: (609) 987-3916

Phone No.: (609) 987-5891

Location: Novo Nordisk

Pages: 2 (including cover)

FROM:

Name: Julie Rhee

Fax No.: (301) 443-9282

Phone No.: (301) 827-6424

Location: FDA

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Comments:

NDA 20-986 Insulin Aspart (insulin X-14)

Requests from Biopharm on your 9/16/98 submission.

CC: Orig NDA
HFD-510/DIV File
HFD-870/Fosler

NDA 20-986 Insulin Aspart (Insulin X-14)

Date of Submission: September 16, 1998

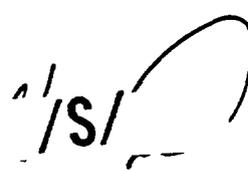
Biopharm Requests

Comments to be sent to firm:

- 1) When submitting the raw insulin concentration vs. time data for all studies, the data uncorrected for c-peptide levels should be submitted in addition to the corrected data.
- 2) Please provide any data on the effect of mixing insulin aspart with other long-acting insulins such as NPH and ultralente.

APPEARS THIS WAY
ON ORIGINAL

Cleared for faxing by:

 10/10/98

Hae-Young Ahn, Ph.D., Biopharm Team Leader



Food and Drug Administration
Rockville MD 20857

NDA 20-986

SEP 28 1998

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

Dear Dr. Reit:

Please refer to your new drug application (NDA) for TRADEMARK (insulin aspart) Injection and to our acknowledgement letter dated September 22, 1998. This communication corrects the receipt date, filing date, and user fee goal date that were incorrectly stated in the referenced letter.

Date of Receipt: September 16, 1998
Filing Date: November 15, 1998
User Fee Goal Date: September 16, 1999.

We apologize for any inconvenience this may have caused.

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

Sincerely yours,

/S/ 9.28.98

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

**APPEARS THIS WAY
ON ORIGINAL**