CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 019938/S019

Trade Name: NOVOLIN R

Generic Name: HUMAN INSULIN (rdna ORIGIN) INJECTION

Sponsor: NOVO NORDISK PHARMACEUTICALS, INC.

Approval Date: 04/10/97

Indication(s): TREATMENT OF DIABETES

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 019938/S019

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tenative Approval Letter				X
Approvable Letter				X
Final Printed Labeling				X
Medical Review(s)	X			
Chemistry Review(s)				X
EA/FONSI				X
Pharmacology Review(s)				X
Statistical Review(s)				X
Microbiology Review(s)				X
Clinical Pharmacology Biopharmaceutics Review(s)				X
Bioequivalence Review(s)				X
Administrative Document(s)/ Correspondence	X			

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number:019938/S019

APPROVAL LETTER

NDA 19-938/S-019

APR 10 1997

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

APPEARS THIS WAY
ON ORIGINAL

Dear Dr. Reit:

Please refer to your supplemental new drug application dated May 13, 1996, received May 20, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Novolin® R [human insulin (rDNA origin) injection].

The supplemental application provides for the following changes (use of oral antidiabetic therapy in combination with insulin treatment) in the package insert:

1. "INSULIN USE IN DIABETES" section:

APPEARS THIS WAY
ON ORIGINAL

Addition of "Your physician . . . or insulin therapy combined with an oral antidiabetic medicine" at the end of the first sentence, first paragraph.

2. "INSULIN REACTION AND SHOCK" section:

APPEARS THIS WAY
ON ORIGINAL

Addition of "Hypoglycemia can also happen if you combine insulin therapy and other medications that lower blood glucose, such as oral antidiabetic agents or other prescription and over-the-counter drugs" as a second sentence, first paragraph.

3. "IMPORTANT NOTES" section:

APPEARS THIS WAY
ON ORIGINAL

Addition of item #6 "Always ask your physician or pharmacist before taking any drug."

We have completed the review of this supplemental application including the submitted draft labeling 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 draft labeling in the submission dated May 13, 1996. Accordingly, the supplemental application is approved effective on the date of this letter.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

The following recommendations are not a requirement for the approval of this supplemental application. However, we recommend that you include them when you print the Final Printed Labeling (FPL).

1. Add "R" in the "INSULIN DELIVERY SYSTEMS" section of the Novolin® R PenFill package insert. So it would read "These **Novolin® R PenFill®** cartridges are for use with **NovoPen®** and . . . ."

2. Add "Even" at the beginning of the statement under item #4, "IMPORTANT NOTES" section. So it would read "Even if you have an acute illness, especially with vomiting or fever, continue taking your insulin."

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 "FINAL PRINTED LABELING" for approved supplemental NDA 19-938/S-019. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

In addition, please submit three copies of the introductory promotional material 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 material and the package insert directly to:

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

APPEARS THIS WAY
ON ORIGINAL

Should a letter communicating important information about this drug product (i.e., a "Dear Doctor" letter) be issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20852-9787

APPEARS THIS WAY
ON ORIGINAL

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, please contact Julie Rhee, Consumer Safety Officer, at (301) 443-3490.

Sincerely yours,

/S/ 14-10-97

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

cc:
Original NDA 19-938
HFD-510/Div. files
HFD-510/CSO/J.Rhee
HFD-510/Misbin/Berlin/HRhee
DISTRICT OFFICE
HF-2/Medwatch (with labeling)
HFD-92/DDM-DIAB (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFI-20/Press Office (with labeling)

Drafted by: JRhee/March 29, 1997/ c:wpfiles/supplement/19938s19.ap
Initialed by:Galliers 4-1-97/Misbin 4-2-97/Fleming 4-2-97/Berlin 4-8-97/Moore 4-8-97
final: JRhee 4-9-97

/S/ 4-9-97

SUPPLEMENT APPROVAL (AP S-019)

FINAL PRINTED LABELING HAS NOT BEEN SUBMITTED TO THE FDA.

DRAFT LABELING IS NO LONGER BEING SUPPLIED SO AS TO ENSURE ONLY CORRECT AND CURRENT INFORMATION IS DISSEMINATED TO THE PUBLIC.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:019938/S019

MEDICAL REVIEW(S)

ORIGINAL

MAY 1996

MEDICAL OFFICER'S REVIEW

NDA 19-938 NOVOLIN R
NDA 19-959 NOVOLIN N
NDA 19-965 NOVOLIN L
NDA 19-991 NOVOLIN 70/30
NDA 19-450 VELOSULIN
NDA 18-381 REGULAR PURIFIED PORK INSULIN
NDA 18-383 LENTE PURIFIED PORK INSULIN
NDA 18-623 NPH PURIFIED PORK INSULIN

APPEARS THIS WAY
ON ORIGINAL

LABEL CHANGE submitted May 13, 1996

Novo Nordisk wishes to change their package inserts to reflect the fact that patients are being treated with a combination insulin plus a sulfonylurea, as outlined by Johnson et al in the February 12, 1996 edition of Archives of Internal Medicine. The change adds the words" or insulin combined with an oral antidiabetic medication" where "insulin therapy" had previously appeared alone, and adds to the section entitled INSULIN REACTION AND SHOCK "hypoglycemia can also happen if you combine insulin therapy and other medications that lower blood glucose, such as oral antidiabetic agents or other prescription and over-the-counter drugs."

These changes seem quite appropriate. They foster patient education and safety. I propose that we accept these changes

/S/

APPEARS THIS WAY
ON ORIGINAL

Robert I Misbin MD
Medical officer

5/31/96

/S/

5/31/96

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 019938/S019

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date MAY 30 1996

NDA No. 19-938

NOVO NORDISK PHARMACEUTICALS INC.
100 Overlook Center, Suite 200
Princeton, New Jersey 08540-7810

APPEARS THIS WAY
ON ORIGINAL

Attention: Barry Reit, PH.D., Vice President

Dear Sir/Madam:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: NOVLIN R Regular, Human Insulin Injection

NDA Number: 19-938

Supplement Number: S-019

APPEARS THIS WAY
ON ORIGINAL

Date of Supplement: MAY 13, 1996

Date of Receipt: MAY 20, 1996

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on JUL 19 1996 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products
Attention: Document Control Room
5600 Fishers Lane, HFD-510
Rockville, MD 20857

Sincerely yours.

APPEARS THIS WAY
ON ORIGINAL

/S/

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

FORM FDA 3217g (11/95)

PREVIOUS EDITION IS OBSOLETE

NO 19938 SER NO 049
NDA SUPPL FOR SLR

ORIGINAL
NDA SUPPLEMENT

Special Supplement: Labeling - Change

Novo Nordisk

May 13, 1996

CENTER FOR DRUG
REC'D
MAY 2 0 1996
HFD-510
EVALUATION AND RESEARCH

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 19-938**	**Novolin® R**	**Regular, Human Insulin Injection (recombinant DNA origin) USP**
	NDA 19-959	**Novolin® N**	**NPH, Human Insulin Isophane Suspension (recombinant DNA origin)**
	NDA 19-965	**Novolin® L**	**Lente®, Human Insulin Zinc Suspension (recombinant DNA origin)**
	NDA 19-991	**Novolin® 70/30**	**70% NPH, Human Insulin Isophane Suspension and 30% Regular Human Insulin Injection (recombinant DNA origin)**
	NDA 19-450	**Velosulin® BR**	**Buffered Regular Human Insulin Injection (semi-synthetic)**
	NDA 18-381	**Regular Purified Pork Insulin Injection USP**	
	NDA 18-383	**Lente® Purified Pork Insulin Zinc Suspension USP**	
	NDA 18-623	**NPH Purified Pork Isophane Insulin Suspension USP**	

5/17/96
/S/

APPEARS THIS WAY
ON ORIGINAL

Dear Dr. Sobel:

Reference is made to the above-listed NDAs for Novo Nordisk Pharmaceuticals, Inc.'s marketed insulin products. With the recent approvals of several new antidiabetic agents and the trend to reevaluate current treatment strategies to obtain better outcomes, we anticipate increasing use of treatment combinations, whether of several oral agents or oral agents with insulin. Pursuant to 21 CFR § 314.70 (c)(2)(iii), we are submitting supplements for revisions to the patient package insert for the subject products to include statements that mention the use of oral antidiabetic therapy in combination with insulin treatment as a treatment option being used today in medical

practice. Novo Nordisk believes that this may place the patient receiving such combination therapy at increased risk of hypoglycemia and thinks that this information should be provided in the patient package insert. Thus, we propose the following additional label text to aid in the safe use of our product:

- Insulin Use in Diabetes: Your physician has explained that you have diabetes and that your treatment involves injections of insulin or insulin therapy combined with an oral antidiabetic medicine.

- Hypoglycemia can also happen if you combine insulin therapy and other medications that lower blood glucose, such as oral antidiabetic agents or other prescription and over-the-counter drugs.

- Always ask your physician or pharmacist before taking any drug.

Please refer to the Table of Contents for a listing of the documentation provided in this supplement to support our request for labeling revisions.

The request for labeling revisions for the eight referenced NDAs is submitted as a single supplement. The full submission is made to NDA 19-938 and by cross-reference to the other NDAs listed. A separate 356h form and product specific draft labeling is attached to the cover letter for each remaining highlighted NDA.

If you have any questions concerning this submission, please contact Lynn Joesten, Manager, Regulatory Affairs at the above telephone number.

Sincerely,
NOVO NORDISK PHARMACEUTICALS INC.

APPEARS THIS WAY
ON ORIGINAL

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

BR/pk
Enclosure

REVIEWS COMPLETED

CSO ACTION:
☑ LETTER ☐ N.A.I. ☐ MEMO

4-10-97
CSO INITIALS DATE

/S/

APPEARS THIS WAY
ON ORIGINAL

F:\...\labeling\Maysupp.ltr