CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-148

CORRESPONDENCE

Date: May 9, 2000

To: Crystal King
US Food and Drug Administration

From: Lisa Suttner
Novo Nordisk Pharmaceuticals

Fax #: 301-443-9282

Re: NDA 21-148

Dear Crystal—

These are the configurations for the name designation for Norditropin® cartridges:

This is the proposed heading on the package insert:

Norditropin® cartridges
somatropin (rDNA origin) injection
5mg/1.5mL, 10mg/1.5mL, or 15mg/1.5mL cartridges

Under "How Supplied" the products will be listed as:

Norditropin 5mg/1.5mL cartridge (orange)
NDC 0169-7768-11
Norditropin 10mg/1.5mL cartridge (blue)
NDC 0169-7769-11
Norditropin 15mg/1.5mL cartridge (green)
NDC 0169-7770-11

→

Page 2 of 2

To: Crystal King, FDA

From: Lisa Suttner

The other way the product may be written — is:

Please leave me a voicemail message to let me know if this is ok.

Also, on the cartons, an example might be:

Norditropin 5mg/1.5mL somatropin (rDNA origin) injection cartridge OR Norditropin 5mg/1.5mL somatropin (rDNA origin) injection cartridge

I hope to hear from you soon. Best regards—
Lisa Suttner

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

March 1, 2000

By facsimile

Monique Wakelkamp, PhD, Reviewer
Division of Pharmaceutical Evaluation II (HFD-870)
Floor 13B-17, Room 46
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 21-148, Norditropin® SimpleXx™ Cartridges
[Somatropin (rDNA origin) for subcutaneous injection]
Response to FDA Request for Information

Dear Dr. Wakelkamp:

Please refer to the subject NDA and to your phone call on 2/25/00 regarding the statistical analysis of the bioequivalence study GHPHKIN/BPD/14/UK. You asked for clarification as to whether the efficacy analysis was based on 21 subjects or on 23 subjects. The following is our response to your question, using Cmax as an example:

The safety population comprises 23 subjects who received the study drug. Subjects no. 50 and 63 only received the study drug at the first of the four dosing visits. In the analyses, subjects 50 and 63 will therefore not contribute to the comparisons between doses. The SAS program for the Cmax comparisons:

```
proc mixed;
  class subject_ visit_co tmt;
  model lcmax = subject_ visit_co tmt / noint;
  estimate '5mg/Nor 8mg'  tmt -1 1 0 0 / cl alpha=0.1;
  estimate '10mg/Nor 8mg' tmt -1 0 1 0 / cl alpha=0.1;
  estimate '15mg/Nor 8mg' tmt -1 0 0 1 / cl alpha=0.1;
  estimate '15mg/10mg' tmt 0 0 -1 1 / cl alpha=0.1;
  estimate '15mg/5mg'  tmt 0 -1 0 1 / cl alpha=0.1;
  estimate '10mg/5mg'  tmt 0 -1 1 0 / cl alpha=0.1;
```

will disregard the two above mentioned Cmax observations. The SAS programmer has, however, set these two observations to missing values to be quite sure that they are not included in the analysis. The output shows that 23 subjects are read in, but the SUBJECT_ NDF (numerator degrees of freedom, which is the number of subjects minus 1) of 20 means that there are 21 subjects with non-missing Cmax values.

Monique Wakelkamp, PhD
NDA 21-148, Norditropin® SimpleX
[Somatropin (rDNA origin) for subcutaneous injection]
Response to FDA request for information

Novo Nordisk Pharmaceuticals, Inc.
March 1, 2000

If the two Cmax values for subjects 50 and 63 are not set to missing the parameter estimates and their standard errors will be unchanged, but the SUBJECT_ NDF will now be 22 with a TYPE III F-value of 6.25. All other output will be unchanged.

Please call Lisa Suttner, Assistant Director, Regulatory Affairs at (609) 987-5877 if you have any questions or comments regarding this information.

Sincerely,

NOVO NORDISK PHARMACEUTICALS, INC.

Barry Reit, PhD
Vice President, Regulatory Affairs

C: Crystal King, CSO

FAX TRANSMISSION

Novo Nordisk Pharmaceuticals Inc.
100 Overlook Center, Suite 200
Princeton, New Jersey 08540

Telephone: (609) 987-5877

Fax: (609) 987-3916

Please contact addressee for delivery as soon as possible.
Thank you.

TO: **Crystal King**

FAX #: **301-443-9282**

FROM: **Lisa Suttner**

DATE: **March 1, 2000**

PAGE 1 OF 3 PAGE(S)

COMMENTS:

RE: Norditropin SimpleXx NDA 21-148

Dear Crystal,

Attached is a response to Monique Wakelkamp's question about the number of patients analyzed for the GHPHKIN/BPD/14/UK study. Please forward this response to Dr. Wakelkamp.

Please call me if you have any questions.

Best regards. Lisa

Printed by Crystal King

Electronic Mail Message

.tivity: COMPANY CONFIDENTIAL

Date: 01-Mar-2000 06:17pm
From: Monique Wakelkamp-Barnes
WAKELKAMPM
Dept: HFD-870 PKLN 10B45
Tel No: 301-827-1093 FAX t-

'O: Suttner, Lisa (LSTT) (LSTT@nnpi.com)

:C: Crystal King (KINGC)
:C: Hae Young Ahn (AHNH)
;ubject: Re: FW: Request - Novo Nordisk

'o: Lisa Suttner, Assistant Director, Regulatory Affairs, Novo Nordisk
'harmaceuticals, Inc.

larch 1, 2000

:ef: NDA 21-148 (Norditropin Simplexx)

)ear Lisa:

received the figures of the GHPHKIN/BPD/14/UK study by email and also
our faxed reply with regard to the statistical analysis of this study,
.hank you.

would also need some additional information with regard to the
nalytical methods of Human Growth Hormone.

nformation I have sofar is contained in volume 1.20, page 239-261
ndix H) and consists of a description of the method by
and a one-page summary by (page 239).

still have the following questions with regard to the methods
'alidation, that I could not answer using the documentation submitted in
:he Human Pharmacokinetics and Bioavailability section.

.) Was the analytical method for Human Growth Hormone as used by
:or the GHPHKIN/BPD/14/UK study modified in any way as compared to the
ıethod described by ? If so, were these
ıodifications validated? In that case I would like to see additional
'alidation data. Note also that the date on the method description by
(volume 1.20, page 240) was later than the
late on the validation summary sheet by

:) Specificity: description of
:ross-reactivity (page 255) does not mention the degradation products of
IGH. Does the method distinguish between HGH and the degradation
)roducts?

;) The summary of the Human Pharmacokinetics and Bioavailability section
)nly briefly mentions these degradation products on page 166 (volume
..1). Could you supply me with a comparative list of the relative
:ontent of degradation products between Norditropin and Norditropin
;implexx and their respective biological activities?

:) What was the Lower Limit of Quantitation (LOQ) of the assay method
:as used by
Were inter-assay and intra-assay accuracy and precision calculated for
LOQ?

.e inter-assay and intra-assay accuracy and precision data on the
summary sheet are not entirely clear to me. E.g. it is not clear
/hy the quoted inter-assay or intra-assay data should have a CV. Also,
lo these summarized data represent the entire analysis of study 14/UK
;amples?

BEST POSSIBLE COPY

) Could you supply me with a some more information with regard to the
nter and intra-assay accuracy and precision data as shown on the
validation summary sheet, e.g. how many quality controls were
at each time? On how many occasions was this determined?

.iat were the acceptance criteria for linearity of the calibration
urve, accuracy, precision, sensitivity and specificity?

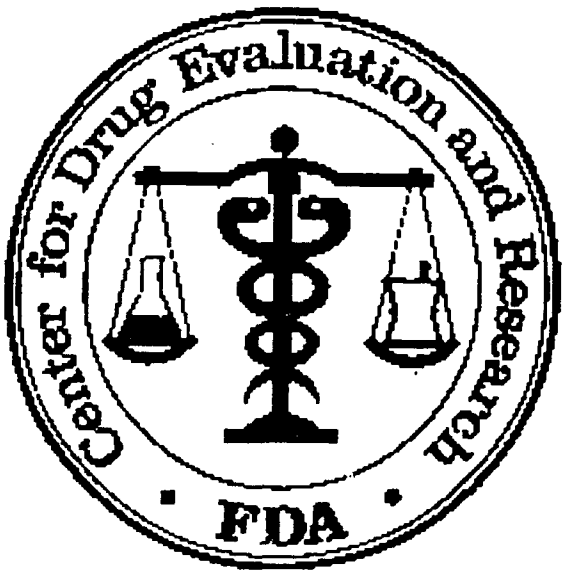
would appreciate if you could provide me with this information at your
arliest convenience. Maybe you could fax your reply to Crystal King?
lternatively by email to me at wakelkampm@cder.fda.gov

ith kind regards,

onique Wakelkamp, M.D., Ph.D.,Reviewer,
ivision of Pharmaceutical Evaluation II
DER/FDA.

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

DATE: April 13, 2000



Lisa:
Following are the points we relayed to you at yesterday's telecon.

Thanks,

-Crystal

TO:

Name Lisa Suttner

Fax No. 609-987-3916

Phone No. 609-987-5877

Location Novo Nordisk

FROM:

Name Crystal King, P.D., M.G.A.

Fax No. 301-443-9282

Phone No. 301-827-6423

Pages (including this cover sheet): Three (3)

FAX Clearance: 151

Saul Malozowski, M.D., Ph.D.
Medical Team Leader

NDA 21-148 SUBMISSION DATE: 04/06/00
BRAND NAME: Norditropin SimpleXx
GENERIC NAME: somatropin
REVIEWERS: X. Ysern, Ph.D.
SPONSOR: Novo Nordisk

Our chemistry reviewer, Dr. Xavier Ysern has completed his review of your April 6, 2000, submission. Following are his comments:

> If the proposed — is capable of discriminating somatropin from somatropin-related compounds that have similar molecular weight to somatropin (i.e., —, the — method is an adequate identification test. In this case, the use of the — method would not be required, unless the applicant desires to retain it as an additional identification test. On the contrary, if the — method lacks this discrimination power, the — method is not an acceptable test for identification, and consequently, the — method will be the [only] acceptable method for identification.

Should you have any questions, please do not hesitate to contact me at 301-827-6423.

/S/

Crystal Anne King, P.D., M.G.A.
Regulatory Project Manager

Fax Clearance:

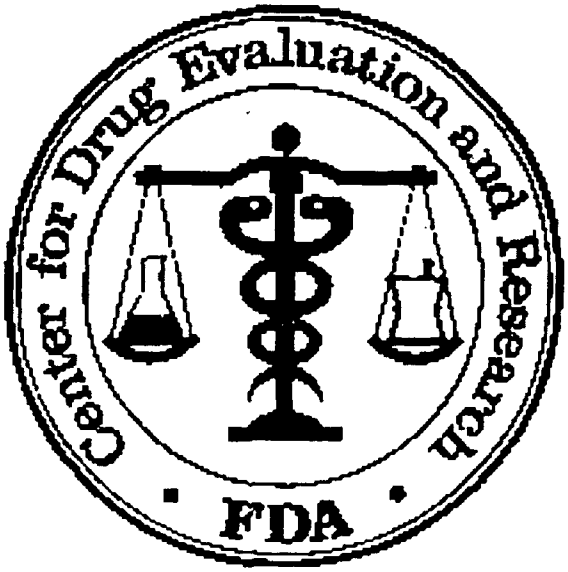
/S/

Stephen Moore, Ph.D.
Chemistry Team Leader

NDA 21-148
Division File

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

DATE: April 11, 2000



Comments:
Following are chemistry comments.

-Crystal

TO:

Name Lisa Suttner

Fax No. 609-987-3916

Phone No. 609-987-5877

Location Novo Nordisk

FROM:

Name Crystal King, P.D., M.G.A.

Fax No. 301-443-9282

Phone No. 301-827-6423

Pages (including this cover sheet): Two (2)

NDA 21-148 SUBMISSION DATE: 06/30/99
BRAND NAME: Norditropin SimpleXx
GENERIC NAME: somatropin
REVIEWERS: X. Ysern, Ph.D. and N. Sweeney, Ph.D.
SPONSOR: Novo Nordisk

Our chemistry reviewer, Dr. Xavier Ysern, and our microbiology review, Dr. Neal Sweeney, have completed their reviews of your June 30, 1999, submission. Following are their comments:

Chemistry:

1. Regulatory Specifications
   a) [redacted] is not an adequate technique for identification purposes because it does not discriminate between somatropin and somatropin-related compounds that have similar molecular weight (i.e [redacted]). Please provide an alternate "Identity" specification test. Identity Determination using [redacted] methodology is suggested.
   b) Although [redacted] products retain the biological activity, as they are main degradation products, limits for [redacted] should be provided as part of the Drug Product Specifications. Please provide specifications for the determination of both [redacted] content.

2. The labeling should contain a warning statement that cartridges with one color code must not be inserted into pens with a different color code.

Microbiology:

1. Regarding [redacted] of containers, closures, equipment, and components:
   a) The [redacted] were not specified in the "Norditropin SimpleXx Validation Data Summary, [redacted] Sterilization" report.
   b) No [redacted] validation information was included in the submission.

2. Regarding the post approval stability commitment and protocol:
   a) The post approval stability protocol should include endotoxin testing at initial and expiry.

Should you have any questions, please do not hesitate to contact me at 301-827-6423.

151

Crystal Anne King, P.D., M.G.A.
Regulatory Project Manager

Fax Clearance:

151

Stephen Moore, Ph.D.
Chemistry Team Leader

NDA 21-148
Division File

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

DATE: March 24, 2000

Comments:
Following are chemistry and microbiology deficiencies.

-Crystal

TO:

Name Lisa Suttner

Fax No. 609-987-3916

Phone No. 609-987-5877

Location Novo Nordisk

FROM:

Name Crystal King, P.D., M.G.A.

Fax No. 301-443-9282

Phone No. 301-827-6423

Pages (including this cover sheet): Three (3)

Labeling for 21-148, Norditropin SimpleXx

Please send a copy of new, marked up labeling incorporating the following:

1. Language based upon medical review comments faxed 3/22/00 regarding the 2/25/00 submission.

2. Immediately prior to the INDICATIONS AND USAGE section, add the following, "Norditropin is bioequivalent to Norditropin."

3. Changes to the Pharmacology section:

   Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenicity, mutagenicity, and fertility studies have not been conducted with Norditropin

   Pregnancy Category C: Animal reproduction studies have not been conducted with Norditropin It is also not know whether Norditropin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Norditropin should be given to a pregnant woman only if clearly needed.

   Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Norditropin administered to a nursing woman.

4. Addition to the WARNINGS section: A statement that cartridges with one color code must not be inserted into pens with a different color code.

5. Language similar to item #4 (in bold and capital letters) should be inserted in the device labeling. This could be done: (1) on the initial page (below "Welcome to your Nordipen); (2) on page two (listed in the document as page 15) and should be highlighted in order to further clarify the need not to mix; (3) on page 33, incorporated into Important Things You Should Know.

   (Note that the language additions addressed in items #4 and #5 could be removed if you address our request of making each cartridge dose (5, 10, and 15 mg) only able to fit its respective pen.)

Should you have any questions, please do not hesitate to contact me at 301-827-6423.

/S/

Crystal Anne King, P.D., M.G.A.
Regulatory Project Manager

/S/

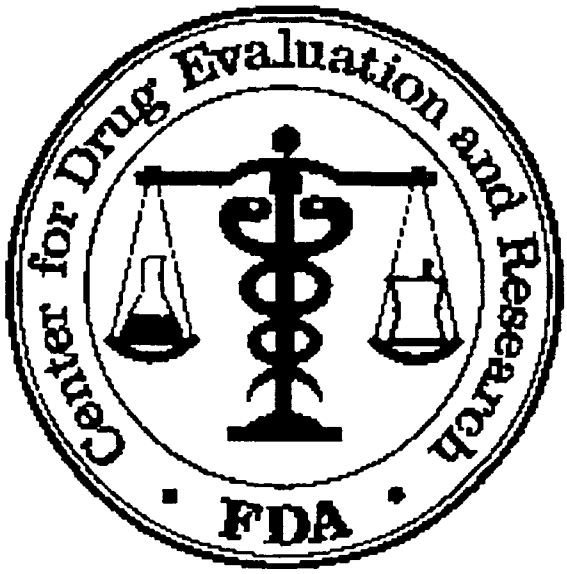
Fax Clearance:

Saul Malozowski, M.D., Ph.D.
Medical Team Leader

NDA 21-148
Division File

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

DATE: March 22, 2000



Comments:
Following are labeling review comments.

-Crystal

TO:

Name Lisa Suttner

Fax No. 609-987-3916

Phone No. 609-987-5877

Location Novo Nordisk

FROM:

Name Crystal King, P.D., M.G.A.

Fax No. 301-443-9282

Phone No. 301-827-6423

Pages (including this cover sheet):

NDA 21-148 SUBMISSION DATE: 2/25/00
BRAND NAME: Norditropin SimpleXx
GENERIC NAME: somatropin
REVIEWER: S. Malozowski, M.D., Ph.D.
SPONSOR: Novo Nordisk

Our medical reviewer, Dr. Saul Malozowski, has completed his review of your February 25, 2000, submission. Following are his comments:

Contraindications:
The sponsor proposes to insert language to discontinue GH if evidence of active malignancy is present. There is not information that suggests that this is indeed true. Clinical practice is such that patients with malignancies are not prescribed GH. In addition, it has been customary to have a diagnosis of tumor free before GH is indicated. However, this wording is present in other GH labels and the proposal could be accepted.

Precautions:
a) The sponsor proposes [redacted] This is well known by physicians using this product. The sponsor does not provide information to assist the physician and it may implicate an endorsement of combined treatment for diabetic subjects with GH. Studies in diabetic patients using GH have not been conducted and I do not support this wording in this section. More elaborate wording on this issue is present in products approved for adults with GHD.

Current wording in this section is adequate for this GH only approved for children.

b) The fact that [redacted] may occur more frequently in short patients does not necessary patients to GH treatment. The current label is adequate as is.

c) The statement regarding [redacted] is not adequate because implicitly adds a claim ([redacted] for this product, although no information has been sent for review. This wording shouldn't be incorporated into the label.

d) The statement regarding scoliosis does two different things, one disassociates the cause and effect relationship and second recommends monitoring of scoliosis. The following language is suggested: Progression of scoliosis can occur in patients who experience rapid growth. Because GH increases growth

rate, patients with a history of scoliosis who are treated with GH should be monitored for progression of scoliosis.

e) The fluid retention statement is adequate.

Please note that these are preliminary comments only; we fully expect to have additional labeling comments on the original June 30, 1999, submission shortly.

Should you have any questions, please do not hesitate to contact me at 301-827-6423.

/S/

Crystal Anne King, P.D., M.G.A.
Regulatory Project Manager

Fax Clearance:

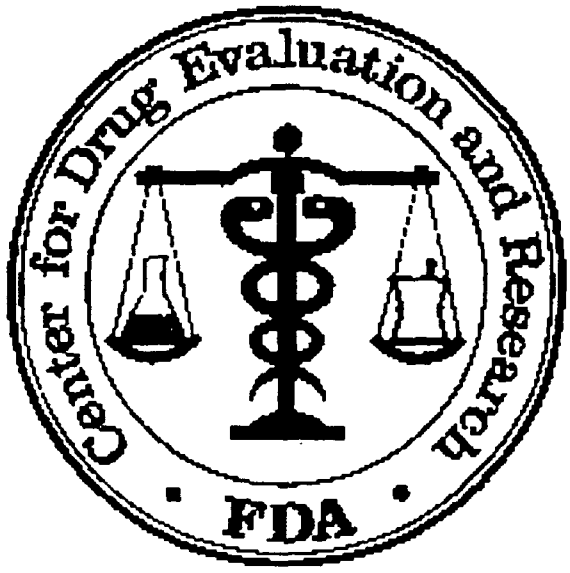
/S/

Saul Malozowski, M.D., Ph.D.
Medical Team Leader

NDA 21-148
Division File

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

DATE: March 20, 2000



Comments:
Following are medical review comments.

-Crystal

TO:

Name Lisa Suttner

Fax No. 609-987-3916

Phone No. 609-987-5877

Location Novo Nordisk

FROM:

Name Crystal King, P.D., M.G.A.

Fax No. 301-443-9282

Phone No. 301-827-6423

Pages (including this cover sheet): 3 (three)

Memo

Date: August 18, 1999

To: Lisa Suttner, NovoNordisk

From: Crystal King, P.D., M.G.A., Project Manager

RE: **Norditropin SimpleXx, NDA 21-148**

Based upon our filing meeting for this application, we have the following requests and comments.

1. If you have long-term toxicity data or, alternatively, carcinogenicity data, on the poloxamer, please supply it.
2. The device as presented cannot be evaluated—it appears that a part may be missing (a cap on the cartridge). Please send one working unit as soon as possible.
3. How does the lot/batch size and production site/method of Norditropin SimpleXx used in study GHPHKIN/BPD/14/UK compare with the proposed commercial lot/batch size and production method/site?
4. Please submit labeling on disk (preferably in WORD format) that clearly distringuishes portions of approved product labeling from portions that are proposed for Norditropin SimpleXx (e.g., different colored text or underlining/strikeouts). Eight disks are requested.
5. Please provide seven copies of annotated labeling.
6. Please provide one packet of all labeling referred to in the Table of Contents (clean, annotated, other).
7. The cover letter stated that financial disclosure information was not submitted. Please note that foreign studies not conducted under an IND may still be considered as covered studies. The fact that the rule is silent does not exclude such studies. If the approval relies on a bioequivalence or bioavailability study, it is a covered study.

Please call me at 301-827-6423 if you have further questions.

cc: NDA 21-148

HFD-510/CKing

NDA 21-148
Div File

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

DATE: August 18, 1999

Lisa:
Following are comments/requests arising from our filing meeting.

Thanks,

-Crystal

TO:

Name Lisa Suttner

Fax No. 609-987-3916

Phone No. 609-987-5877

Location Novo Nordisk

FROM:

Name Crystal King, P.D., M.G.A.

Fax No. 301-443-9282

Phone No. 301-827-6423

Pages (including this cover sheet): Two (2)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-148

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

Dear Dr. Reit:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Norditropin SimpleXx (somatropin [rDNA origin] injection) Cartridges

Therapeutic Classification: Standard (S)

Date of Application: June 30, 1999

Date of Receipt: July 1, 1999

Our Reference Number: 21-148

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on August 31, 1999, in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be May 1, 2000, and the secondary user fee goal date will be July 1, 2000.

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). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within 120 days of receipt of your pediatric drug development plan, we will notify you of the pediatric studies that are required under section 21 CFR 314.55.

If you believe that this drug qualifies for a waiver of the study 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. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" in addition to your plans for pediatric drug development described above. If you do not submit a Proposed Pediatric Study Request within 120 days from the date of this letter, we will presume that you are not interested in obtaining pediatric exclusivity and will notify you of the pediatric studies that are required under section 21 CFR 314.55. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Division Document Room 14B-19
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, contact Crystal King, P.D., M.G.A., Regulatory Project Manager, at (301) 827-6423.

Sincerely yours,

EG

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

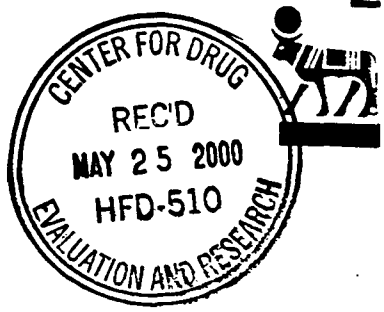
DUPLICATE

[redacted]

BL

May 25, 2000

John Jenkins, M.D., Acting Director
Division of Metabolic and Endocrine
Drug Products (HFD-510)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



Novo Nordisk

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

Re: NDA 21-148
Norditropin® Cartridges [somatropin (rDNA origin) injection] and NordiPen Injection Pen
Amendment – Revised Proposed Labeling

Dear Dr. Jenkins:

Please refer to the subject NDA. We are hereby providing the following revised labeling that incorporates the latest changes as agreed with FDA.

- Norditropin® cartridges – Package Insert
- Norditropin® cartridge vial labels – 5, 10 and 15 mg cartridges
- Norditropin® cartridge box labels – 5, 10 and 15 mg cartridges
- NordiPen™ device cartons – 5, 10, and 15 mg devices
- NordiPen™ instructional brochures – 5, 10 and 15 mg devices

We understand that this submission completes the information required by FDA to approve this application, and we look forward to a timely response.

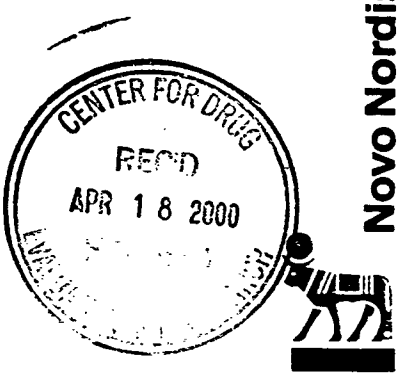
Please call Lisa Suttner, Assistant Director, Regulatory Affairs at (609) 987-5877 if you have any questions or comments.

Sincerely,

NOVO NORDISK PHARMACEUTICALS, INC.

Barry Reit, PhD
Vice President, Regulatory Affairs

April 17, 2000



Novo Nordisk

John Jenkins, M.D., Acting Director
Division of Metabolic and Endocrine
Drug Products (HFD-510)
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 21-148, Norditropin® —
[Somatropin (rDNA origin) for injection] cartridges
Amendment – Response to FDA request for information

Dear Dr. Jenkins:

Please refer to the subject NDA, and a conference call held on 4/12/00 between FDA representatives Dr. Saul Malozowski, Dr. Xavier Ysern, Crystal King, and Lisa Suttner of Novo Nordisk. A record of the comments communicated in that conference call was faxed to Novo Nordisk on 4/13/00.

We are hereby responding to the comments from that conference call and fax.

Tradename

FDA commented that the term SimpleXx is not acceptable as part of the proprietary name for the drug portion of the product.

In response, we propose the alternate name of —. The - in — is —. Upon approval, the final package insert will be modified to reflect this change.

Device/Cartridge Labeling

Novo Nordisk has made the following additional changes as requested by FDA. The modified versions of the Norditropin® cartridge vial and carton labels and the NordiPen device carton and instruction manuals are attached.

A) Cartridge Carton (5, 10, and 15 mg):

1) Language has been added that the cartridge must only be used with the proper color-coded pen.
2) The strength is shown with increased prominence.
3) The statement "Each 1.5 mL contains: Somatropin X mg" (where X is the strength).

B) Cartridge Vial (5, 10, and 15 mg):

1) "For use only with NordiPen X injection pen" (where X is the strength).
2) The strength of the product is expressed in mg/mL (e.g., 5 mg/1.5 mL)
3) The strength is shown with increased prominence.

C) NordiPen Instruction Booklet (5, 10, and 15):

1) Under "Important Things to Know," we have deleted the end of the sentence of the sixth bullet point, "

Although not a barrier to approval, FDA requested that Novo Nordisk increase the prominence of the strength on each of the three NordiPen devices. At this time it is not possible to change the text on the device, but we will consider this for future production.

FDA commented that the three colors used in the graphic on the pen cap could be confusing based on the color-coding system. Novo Nordisk agrees not to include all three colors on the pen cap. The pens will be provided with a solid dark blue pen cap (the background color) without the graphic. This will ensure that none of the pens contain the contrasting color-codes.

With this submission, it is our understanding that FDA has received all information necessary for the approval of this product. We remain committed to working with FDA to ensure a rapid approval, and are ready to provide any additional information as necessary to meet this goal.

Please call Lisa Suttner, Assistant Director, Regulatory Affairs at (609) 987-5877 if you have any questions or comments regarding this information.

Sincerely,

NOVO NORDISK PHARMACEUTICALS, INC.

Barry Reitz, PhD
Vice President, Regulatory Affairs

151

April 13, 2000

John Jenkins, M.D., Acting Director
Division of Metabolic and Endocrine
Drug Products (HFD-510)
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 609-921-6082

Re: NDA 21-148, Norditropin® Cartridges
[Somatropin (rDNA origin) for injection]
Amendment – Response to FDA request for information

Dear Dr. Jenkins:

Please refer to the subject NDA, our submission of revised specifications and test methods dated 4/6/00, a fax from the chemistry reviewer dated 4/11/00, and a conference call between Dr. Ysern and Novo Nordisk representatives on 4/12/00.

In the specifications submitted on 4/6/00, Novo Nordisk included both the —— and —— tests as identity tests. Dr. Ysern commented the following response in the 4/11/00 fax:

If the proposed —— is capable of discriminating somatropin from somatropin-related compounds that have similar molecular weight to somatropin (i.e., —— the —— method is an adequate identification test. In this case, the use of the —— method would not be required, unless the applicant desires to retain it as an additional identification test. On the contrary, if the —— method lacks this discrimination power, the —— method is not an acceptable test for identification, and consequently, the —— method will be the [only] acceptable method for identification.

In the subsequent phone call, Novo Nordisk agreed that the ——test has more separation power and would be the only method for identification. The —— test would be retained as the test for biologically active forms.

As agreed in the phone call, we are hereby providing the revised specifications, which include only the —— test method as an identity test.

Please call Lisa Suttner, Assistant Director, Regulatory Affairs at (609) 987-5877 if you have any questions or comments regarding this information.

Sincerely,

NOVO NORDISK PHARMACEUTICALS, INC.

Barry Reit, PhD
Vice President, Regulatory Affairs

Health Care Quality Quality Site Gentofte 5-2070-02		Date: Version No.: Status: Page:	April 12, 2000 3 Final 1 of 1

Novo Nordisk

Quality specifications US

Liquid Norditropin 5 mg

Test parameter	Test method (Analysis no.)	Specification limits
Description		
Appearance	Visual inspection, Ph.Eur.	
Clarity	Visual inspection, Ph.Eur.	≤ Ph.Eur., lim II
Particulate matter		
pH		
Identity		
Assay of biologically active forms		
Content of		
and related substances of higher molecular mass		
Bacterial endotoxins		
Sterility	USP	Sterile

FAX TRANSMISSION

Novo Nordisk Pharmaceuticals Inc.
100 Overlook Center, Suite 200
Princeton, New Jersey 08540

Telephone: (609) 987-5877

Fax: (609) 987-3916

Please contact addressee for delivery as soon as possible.
Thank you.

TO: **Crystal King, FDA**

FAX #: **301-443-9282**

FROM: **Lisa Suttner**

DATE: **April 13, 2000**

PAGE 1 OF 5 PAGE(S)

COMMENTS:

RE: Norditropin Liquid NDA 21-148

Dear Crystal,
Attached are the revised product specifications in response to Dr. Ysern's fax dated 4/11 and our conference call on 4/12. We agreed to include only the — — test as the identity test. The revised specifications have been adjusted accordingly. Please forward this to Dr. Ysern.

The official copies are in the mail.

I hope to resolve the name and labeling issues tomorrow (we received your fax today, thanks). Thanks for hanging in there!

Best regards. Lisa

Novo Nordisk

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

April 11, 2000

John Jenkins, M.D., Acting Director
Division of Metabolic and Endocrine
Drug Products (HFD-510)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 21-148, Norditropin® SimpleXx™ Cartridges
[Somatropin (rDNA origin) for subcutaneous injection]
Amendment – Revised Draft Labeling – Device Instruction Manuals

Dear Dr. Jenkins:

Please refer to the subject NDA and amendments submitted March 23 and April 5, 2000. In those submissions, Novo Nordisk provided revised pages for the NordiPen™ 5, 10 and 15 instruction manuals. In submitting the revised pages, Novo Nordisk generated the changes to updated draft proofs rather than as direct edits to the hand-edited pages from the Original NDA.

In a subsequent phone call, FDA requested that the revised pages be resubmitted on the hand-modified versions reflected in the Original NDA. Otherwise, the completely revised brochures would need to be reviewed against the Original NDA versions in their entirety.

Therefore, we are hereby submitting revised pages of the NordiPen™ 5, 10, and 15mg device instruction manuals, based on the Original NDA pages. The revisions incorporate the FDA requested statements concerning the importance of using the correct cartridge with its corresponding color-coded injection pen. The pages reflect the same numbering as in the Original NDA, and this amendment supersedes both the 3/23 (device brochure pages only) and the 4/5/2000 amendments.

Please call Lisa Suttner, Assistant Director, Regulatory Affairs at (609) 987-5877 if you have any questions or comments regarding this information.

Sincerely,

NOVO NORDISK PHARMACEUTICALS, INC.

Barry Reit, PhD
Vice President, Regulatory Affairs

DUPLICATE

April 7, 2000

John Jenkins, M.D., Acting Director
Division of Metabolic and Endocrine
Drug Products (HFD-510)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Novo Nordisk

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

Re: NDA 21-148, Norditropin® SimpleXx™ Cartridges
[Somatropin (rDNA origin) for subcutaneous injection]
Amendment – Response to FDA request for information
Post Approval Commitment

Dear Dr. Jenkins:

Please refer to the subject NDA and to a conference call held between Novo Nordisk and FDA on March 22, 2000.

During the conference call, FDA requested that Novo Nordisk commit to conduct a post approval safety study to compare Norditropin SimpleXx to Norditropin 4 mg or 8 mg in terms of adverse experiences reported. We hereby commit to conduct the study as requested, with 50 patients per treatment group who will be followed for one year, at quarterly visits.

We intend to initiate the study on October 1, 2000 (FPFV), with enrollment continuing until October 1, 2001 (LPFV). The study will therefore be completed on October 1, 2002 (LPLV), and the final report will be available on April 1, 2003.

Please call Lisa Suttner, Assistant Director, Regulatory Affairs at (609) 987-5877 if you have any questions or comments regarding this information.

Sincerely,

NOVO NORDISK PHARMACEUTICALS, INC.

Barry Reit, PhD
Vice President, Regulatory Affairs

April 6, 2000

John Jenkins, M.D., Acting Director
Division of Metabolic and Endocrine
Drug Products (HFD-510)
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 21-148, Norditropin® SimpleXx™ Cartridges
[Somatropin (rDNA origin) for subcutaneous injection]
Amendment – Response to FDA request for information

Dear Dr. Jenkins:

Please refer to the subject NDA and to FDA's fax from Drs. X. Ysern and N. Sweeney that was received on 3/27/00. The fax communicated FDA requests for information regarding chemistry, labeling and microbiology. Novo Nordisk provided a response to the microbiology questions on April 3, 2000 and responded to the labeling request in a submission dated March 23, 2000. Responses to the chemistry questions are provided below.

As requested by Dr. Ysern, we are providing a package that includes each final product test method and corresponding validation report from the original NDA submission plus the methods and validations for the additional parameters as requested in the items below.

We are hereby providing responses to the chemistry questions:

1. Regulatory Specifications:

a) [redacted] is not an adequate technique for identification purposes because it does not discriminate between somatropin and somatropin-related compounds that have similar molecular weight (i.e. [redacted] Please provide an alternative "identity" specification test. Identity Determination using [redacted] methodology is suggested.

Response:

We consider the [redacted] method an adequate method for identity, however, as requested, we have included the [redacted] method as a method for identity (p. 139). The validation of this method is ongoing and will be completed by May, 2000.

b) Although products retain the biological activity, as they are main degradation products, limits for should be provided as part of the Drug Product Specifications. Please provide specifications for the determination of both content and content.

Response:

Although we have shown and to be product-related substances, we have now included these parameters in the product specifications for Norditropin SimpleXx. We are hereby providing Quality Specifications for the Norditropin SimpleXx 5mg, 10mg and 15mg products including specifications for both content (pp. 1-3). Also provided are the method of analysis for for (p. 78) and method of analysis for Validation of method for and validation of method for are provided in Validation Report: Norditropin Liquid – Further Validation of Methods Applied (p. 288).

For a specification limit of is proposed. The stability data show that the batches contain up to at the end of shelf life (see stability study 433-0030-60 in Original NDA, Vol. 1.4, p. 196). The initial content of was approximately for the batches. However, the initial content could be as high as as the shelf life specification limit for in the active ingredient is Thus, when taking into consideration that the initial content can be approximately higher than the stability batches and also allowing for a slight increase during shipping, a limit of is found to be justified.

For the stability data show that the batches contain up to at the end of shelf life (see the above referenced report). The initial content of was approximately for the batches, while the shelf life specification limit for the active ingredient is Hence, for the specification limit is proposed.

Please call Lisa Suttner, Assistant Director, Regulatory Affairs at (609) 987-5877 if you have any questions or comments regarding this information.

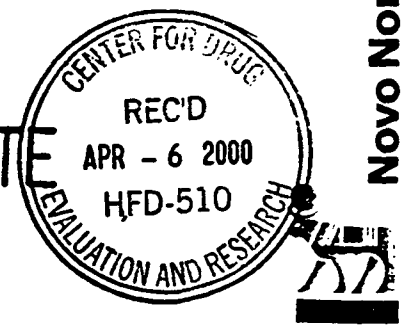
Sincerely,

NOVO NORDISK PHARMACEUTICALS, INC.

Barry Reil, PhD
Vice President, Regulatory Affairs

BC

DUPLICATE



Novo Nordisk

April 5, 2000

John Jenkins, M.D., Acting Director
Division of Metabolic and Endocrine
Drug Products (HFD-510)
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 21-148, Norditropin® SimpleXx™ Cartridges
[Somatropin (rDNA origin) for subcutaneous injection]
Amendment – Revised Draft Labeling

Dear Dr. Jenkins:

Please refer to the subject NDA and amendment submitted March 23, 2000. In that submission, Novo Nordisk provided revised pages for the NordiPen™ 15 instruction manual and explained that the NordiPen™ 5 and 10 instruction manuals would be revised accordingly. In a subsequent phone call, FDA requested that the revised pages be submitted for all three NordiPen™ devices.

We are hereby submitting revised pages of the NordiPen™ 5, 10, and 15mg device brochures. The revisions incorporate the FDA requested statements concerning the importance of using the correct cartridge with its corresponding color-coded injection pen.

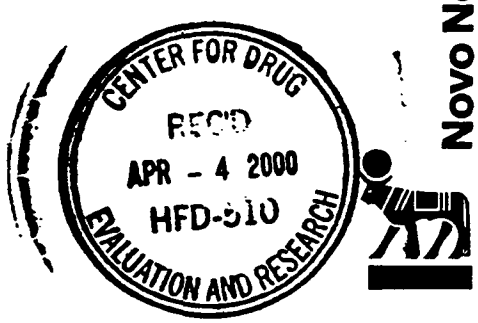
Please call Lisa Sutter, Assistant Director, Regulatory Affairs at (609) 987-5877 if you have any questions or comments regarding this information.

Sincerely,

NOVO NORDISK PHARMACEUTICALS, INC.

Barry Reit, PhD
Vice President, Regulatory Affairs

ORIGINAL



Novo Nordisk

April 3, 2000

John Jenkins, M.D., Acting Director
Division of Metabolic and Endocrine
Drug Products (HFD-510)
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 21-148, Norditropin® SimpleXx™ Cartridges
[Somatropin (rDNA origin) for subcutaneous injection]
Amendment – Response to FDA request for information

Dear Dr. Jenkins:

Please refer to the subject NDA and to FDA's fax from Drs. X. Ysern and N. Sweeney that was received on 3/27/00. The fax communicated FDA requests for information regarding chemistry, labeling and microbiology.

We are hereby providing responses to the microbiology questions:

1. **Regarding [redacted] of containers, closures, equipment, and components:**

   a) The [redacted] of [redacted] were not specified in the "Norditropin SimpleXx Validation Data Summary, [redacted] Sterilization" report.

Response:

Attachment A contains an amendment to the report, "Norditropin SimpleXx Validation Data Summary, [redacted] Sterilization," that provides the requested information for the [redacted] used in the validation study.

   b) No [redacted] validation information was included in the submission.

Response:

Attachment B contains a Summary Report, "Norditropin SimpleXx, Validation Data Summary, [redacted]

2. Regarding the [redacted]

[redacted]

Please call Lisa Suttner, Assistant Director, Regulatory Affairs at (609) 987-5877 if you have any questions or comments regarding this information.

Sincerely,

NOVO NORDISK PHARMACEUTICALS, INC.

Barry Reit, PhD
Vice President, Regulatory Affairs

[redacted]

BL

April 3, 2000

John Jenkins, M.D., Acting Director
Division of Metabolic and Endocrine
Drug Products (HFD-510)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Novo Nordisk

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

Re: NDA 21-148, Norditropin® SimpleXx™ Cartridges
[Somatropin (rDNA origin) for subcutaneous injection]
Amendment – Revised Draft Labeling

Dear Dr. Jenkins:

Please refer to the subject NDA, and to the submission of draft labeling dated 3/23/00.

On 3/29/00 we received a call from FDA requesting the following changes. These changes have been incorporated into the proposed package insert, and the revised package insert is attached.

1. In the package insert section, "Contraindications," third paragraph, we have added the term "growth hormone" so it now reads, "Anti-malignancy treatment must be complete with evidence of remission prior to the institution of growth hormone therapy."

2. Regarding the package insert section, "Pregnancy:" we inadvertently deleted "Pregnancy Category C." in the last version. The attached document has been revised to re-include "Pregnancy: Pregnancy Category C. Animal reproduction studies..."

Please call Lisa Suttner, Assistant Director, Regulatory Affairs at (609) 987-5877 if you have any questions or comments regarding this information.

Sincerely,

NOVO NORDISK PHARMACEUTICALS, INC.

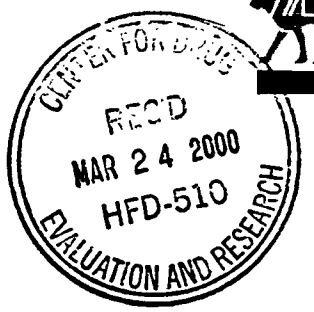
Barry Reit, PhD
Vice President, Regulatory Affairs

[redacted]

BV

March 23, 2000

Novo Nordisk



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

John Jenkins, M.D., Acting Director
Division of Metabolic and Endocrine
Drug Products (HFD-510)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 21-148, Norditropin® SimpleXx™ Cartridges
[Somatropin (rDNA origin) for subcutaneous injection]
Amendment – Revised Draft Labeling

Dear Dr. Jenkins:

Please refer to the subject NDA, the faxes received from FDA dated 3/20/00 and 3/22/00. and the conference call held on 3/22/00. The FDA faxes communicated FDA's comments regarding the additional proposed safety statements and various modifications requested to the proposed Norditropin SimpleXx package insert. During the 3/22/00 conference call, Novo Nordisk agreed to FDA's requested changes and committed to sending the changes as an official submission to the NDA.

We are hereby submitting the revised, marked up labeling incorporating the changes as agreed. We are also providing the affected pages of the NordiPen™ 15mg device brochure to show the changes that will be incorporated into the three device brochures, 5mg, 10mg, and 15mg.

Please call Lisa Suttner, Assistant Director, Regulatory Affairs at (609) 987-5877 if you have any questions or comments regarding this information.

Sincerely,

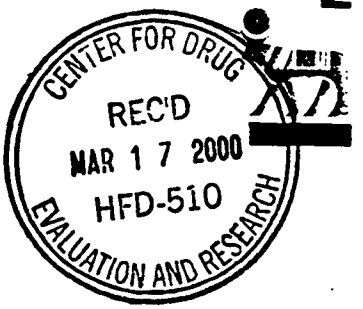
NOVO NORDISK PHARMACEUTICALS, INC.

Barry Reit, PhD
Vice President, Regulatory Affairs

[redacted]

DC

March 16, 2000



John Jenkins, M.D., Acting Director
Division of Metabolic and Endocrine
Drug Products (HFD-510)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Novo Nordisk

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

Re: NDA 21-148, Norditropin® SimpleXx™ Cartridges
[Somatropin (rDNA origin) for subcutaneous injection]
Amendment – Response to FDA Request for Information

Dear Dr. Jenkins:

Please refer to the subject NDA and to questions from Dr. Monique Wakelkamp, which were received via e-mail on March 9, 2000.

The questions and responses are as follows:

1) **Volume 1.19 page 5, the Validation summary sheet by [redacted] This page only provides with inter- and intra-assay precision data. Could you provide me with inter- and intra-assay ACCURACY data for the quality controls as mentioned on this page? I would need to see the mean accuracy value, as well as the range for both inter- and intra-assay accuracy for all three quality controls.**

Response:
The mean accuracy value, as well as the range for both inter- and intra-assay accuracy for all three quality controls are provided in the [redacted] eport, "HGH Advantage Validation," in APPENDIX 1. Intra-assay accuracy data is provided in Table 4.4 and inter batch accuracy is provided in Section 5 of that report.

2) **I have the same request for the additional data you sent me by fax yesterday (03/08/2000), page 7, 8 and 9 of this fax. These pages show overall inter-assay precision for 3 quality controls during the actual assay of the 14/UK study. However, there is no information what the nominal content was of these quality controls, i.e. what value they should be in theory, nor is there information about the accuracy. So, could you provide me with:**

a) the nominal values of these three quality controls.

Response 2a:
The nominal (assigned) values of the three quality controls ( ) are shown in the spread sheet in Appendix 1 and are included at the top of the spreadsheet in APPENDIX 2. These values were supplied by for the particular lot and make of the QC material used, which was manufactured by

b) the accuracy of each QC data point on this 3-page spreadsheet.

Response 2b:
The accuracy of each QC data point are now calculated and listed on the spreadsheet in APPENDIX 2.

c) the mean accuracy for each assay day (i.e. intra-assay accuracy) as shown by the dates on the spreadsheet and the mean overall inter-assay accuracy.

Response 2c:
The mean accuracy for each assay day and the mean overall inter-assay accuracy are now provided on the spreadsheet in APPENDIX 2.

d) intra-assay precision for each assay day (as shown by the dates on the spreadsheet).

Response 2d:
Intra-assay precision for each assay day are now provided on the spreadsheet in APPENDIX 2.

3) **Your reply to my question from March 1, 2000, whether inter-assay and intra-assay accuracy and precision were calculated for the lower limit of quantitation (LLOQ) was yes and you referred to page 5 of volume 1.19. However, I do not see this information on this particular page. If intra-assay and inter-assay accuracy and precision were calculated for the LLOQ, I would appreciate if you could supply it. This would give me information about a low QC value (your faxed spreadsheet refers to the three quality controls as being high QC results).**

Response:
The LLOQ information is provided in Section 3 of the "HGH Advantage Validation" report in APPENDIX 1. The LLOQ for this assay was as described in the assay validation, on an inter-assay basis only. Additional discussion of the LLOQ is provided in the response to item 4 below.

4) **Why was the LLOQ of the method as used by more than 10-fold higher than the LLOQ from the manufacturer of the See volume 1.19, page 5.**

Response:

The LLOQ is not the same as the sensitivity limit that [redacted] reports to be *'calculated as* [redacted]'. Indeed, the LLOQ study described in Section 3 of the [redacted] "HGH Advantage Validation" report in APPENDIX 1 shows that while the assay can *distinguish* between [redacted] µ/mL, precision at this level as C. of V. is [redacted] The lowest level at which [redacted] can attain acceptable precision is [redacted] The number of significant decimal places for this assay has previously been set at [redacted] and therefore, reportable units are to the nearest [redacted] Taking this into account, [redacted] defaulted to a cut-off and rounding value of [redacted] as described in the validation. This assay was initially validated as a diagnostic/monitoring test and taking physiological factors such as intra-individual variation into account, this is more than adequate.

[redacted] reports that intra-individual variation is almost certainly greater than their value of [redacted]

To give further information regarding the precision of this method over the analytical period and over a wider concentration range, [redacted] has provided an additional table in APPENDIX 2 (last two pages), tabulating raw data [redacted] for the [redacted] which are run at different intervals. This data demonstrates the ability of the method to reproduce actual chemical response to the relevant concentrations of HGH over time. This proves not only reagent integrity and stability but also overall reproducibility of the assay. This table shows the [redacted] in the pre-study validation (12/10/97-1/5/98), in comparison to the on-study results (1/9/98-1/20/98) and some data produced subsequently post-study (2/5/98-3/4/98).

This post-validation data shows that the method has performed over a [redacted] period with a reproducibility in [redacted] as compared with the validation data of [redacted]. The assay also shows the accuracy of the other QC material of [redacted] over the study period, making it difficult to improve on the assay performance. For growth hormone, [redacted] overall inter-batch CVs of [redacted] are more than twice as good as any automated or manual procedure they are aware of for this assay.

Please call Lisa Suttner, Assistant Director, Regulatory Affairs at (609) 987-5877 if you have any questions or comments regarding this information.

Sincerely,

NOVO NORDISK PHARMACEUTICALS, INC.

Barry Reit, PhD
Vice President, Regulatory Affairs

March 8, 2000

John Jenkins, M.D., Acting Director
Division of Metabolic and Endocrine
Drug Products (HFD-510)
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 21-148, Norditropin® SimpleXx™ Cartridges
[Somatropin (rDNA origin) for subcutaneous injection]
Amendment – Responses to FDA Request for Information

Dear Dr. Jenkins:

Please refer to the subject NDA and to questions from Dr. Monique Wakelkamp, which were received via e-mail on March 1, 2000 and March 5, 2000.

The questions and responses are as follows:

Question 1:

Was the analytical method for Human Growth Hormone as used by [redacted] for the GHPHKIN/BPD/14/UK study modified in any way as compared to the method described by [redacted]? If so, were these modifications validated? In that case would like to see additional validation data. Note also that the date on the method description by [redacted] volume 1.20, page 240) was later than the date on the validation summary sheet by [redacted]

Response 1:

The analytical method for Human Growth Hormone as used by [redacted] for the GHPHKIN/BPD/14/UK study was not modified in any way as compared to the method described by [redacted] (volume 1.20, page 240-258).

Please note that an Amendment to the Final Clinical Trial Report was provided in front of the Clinical Trial Report for GHPHKIN/BPD/14/UK, in NDA 21-148, Volume 1.19, pages 1-5. The Amendment, dated May 25, 1999, provided the correct pre-study validation summary by [redacted] for the [redacted] Human Growth Hormone assay, dated 1/7/98, which was later than the date on the method description by [redacted]

Question 2:

Specificity: description of cross-reactivity (page 255) does not mention the degradation products of HGH. Does the method distinguish between HGH and the degradation products

Response 2:

It is our understanding that no standard HGH assay for human samples can distinguish between HGH and the different HGH degradation products in question. The applied analytical method for HGH from is referenced to the Norditropin® SimpleXx is a new formulation of the somatropin product Norditropin® and both are biosynthetic somatropin produced by recombinant DNA technology. No novel HGH degradation products are present in Norditropin® SimpleXx compared to the current Norditropin® product. Thus, similar to previous HGH bioequivalence studies a standard method was applied, with a specificity appropriate to measure "bioactive" HGH in the samples from GHPHKIN/BPD/14/UK.

Question 3:

The summary of the Human Pharmacokinetics and Bioavailability section only briefl mentions these degradation products on page 166 (volume1.1). Could you supply me with a comparative list of the relative content of degradation products between Norditropin and Norditropin Simplexx and their respective biological activities

Response 3:

The relative content of degradation products are listed in the report "Degradation Profiles-Norditropin 4mg/8mg Compared With Liquid Norditropin At End Of Shelf Life, (report GKK2045 item 3.4.5.4), Appendix B, Tables 1-3. (NDA 21-148, Volume 1.3, pages 40-41)

Biological activities of the degradation products are given in the report "Chemical and Biological Characterization of Liquid Norditropin, (report HHS2078(US), item 3.4.5.4, Table 4.(NDA 21-148, Volume 1.3, page 14)

Question 4:

What was the Lower Limit of Quantitation (LOQ) of the assay method (as used b ' Were inter-assay and intra-assay accuracy and precision calculated for the LOQ

Response 4:

The Lower Limit of Quantification of the assay method as used by —— was —— Inter-assay and intra-assay accuracy and precision were calculated for the LOQ, please refer to the pre-study validation summary by —— for the GHPHKIN/BPD/14/UK, dated 01.07.1998 (NDA 21-148, Volume 1.19, page 5).

Question 5:

The inter-assay and intra-assay accuracy and precision data on the —— summar sheet are not entirely clear to me. E.g. it is not clear why the quoted inter-assay or intra-assay data should have a CV. Also, do these summarized data represent the entire analysis of study 14/UK samples?

Response 5:

The —— summary sheet, dated 01.07.1998, provided in NDA 21-148, Volume 1.19, page 5, is exclusively a pre-study validation summary by —— for the analyzer used for the GHPHKIN/BPD/14/UK and does not represent the entire analysis of stud 14/UK samples (please refer to answer 6 regarding the latter). —— has chosen to give the quoted (manufacturers) inter-assay and intra-assay with a CV, instead of the manufacturers QC ranges. However, the CV's for the quoted inter-assay and intra-assay data stated in the validation summary compares to the QC ranges in the attached document, page 4.

Question 6:

Could you supply me with a some more information with regard to the inter and intra-assay accuracy and precision data as shown on the —— validation summary sheet, e.g. how many quality controls were used at each time? On how many occasions was this determined

Response 6:

A summary of the quality control performance of the growth hormone assay used throughout the GHPHKIN/BPD/14/UK dated 25 May 1999 is attached. Quality controls with three different concentrations were used each day. A total of —— quality controls were performed over the —— ; the samples were assayed. The quality control with the medium level concentration was assayed approximately —— as frequently as the 2 other quality control concentration levels.

Question 7:

What were the acceptance criteria for linearity of the calibration curve, accuracy, precision, sensitivity and specificity?

Response 7:

Acceptance criteria for linearity of the calibration curve were set by the manufacturer (volume 1.20, page 240-258 and in the attached document). Accuracy and precision are also provided in the attached document. For sensitivity, please refer to the validation summary in NDA 21-148, Volume 1.19, page 5. Regarding specificity, the applied analytical method for HGH from is referenced to the . Please refer to volume 1.20, page 240-258.

Question 8:

Please see volume 1.19, page 186-187 (figures 1.1 through 1.4) and page 211-216 (figures 3.1 through 3.6). Do the error bars represent standard deviation, standard error of the mean or certain upper and lower percentiles

Response 8:

The error bars represent standard errors of the means (SEM). For each time point the error bar represents the approximate 95% confidence interval of the mean. The approximate 95% confidence limits are calculated by the mean plus-minus t(n-1,0.025) x SEM, where n is the number of subjects included.

Please call Lisa Suttner, Assistant Director, Regulatory Affairs at (609) 987-5877 if you have any questions or comments regarding this information.

Sincerely,

NOVO NORDISK PHARMACEUTICALS, INC.

Barry Reit, PhD
Vice President, Regulatory Affairs

DUPLICATE

BL.

February 25, 2000

John Jenkins, M.D., Acting Director
Division of Metabolic and Endocrine
Drug Products (HFD-510)
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 21-148, Norditropin® SimpleXx™ Cartridges
[Somatropin (rDNA origin) for subcutaneous injection]
Amendment – Revisions to Proposed Package Insert

Dear Dr. Jenkins:

Please refer to the subject NDA and to our submission to NDA 19-721 dated 2/14/00. In the 2/14/00 submission, Novo Nordisk proposed the addition of safety statements to the prescribing information for the Norditropin 4 mg and 8 mg products. In an effort to ensure that these additions will be reflected in the labeling for the Norditropin SimpleXx product, we are hereby submitting the same revisions as an amendment to the proposed SimpleXx prescribing information, which is currently under FDA review.

Attached is a revised draft annotated package insert in hard copy and on diskette that includes the following changes, which are noted in the revised draft package insert in green text:

Section: **Contraindications**

We propose to add the statement, "Norditropin® ——— should not be used or should be discontinued when there is any evidence of active malignancy. Anti-malignancy treatment must be complete with evidence of remission prior to the institution of ———

The reason for this change is that the US package insert currently addresses only intracranial tumors in hypopituitary children, however it is also prudent to contraindicate any active malignancies. The statement as proposed is consistent with the labeling of similar growth hormone products.

Change B - Section: **Precautions**

To be consistent with the labeling of similar growth hormone products, we propose to add the statement, ——— ' This sentence will be added directly after the statement, "Because growth hormone may induce a state of insulin resistance, patients should be observed for evidence of glucose intolerance."

John Jenkins, M.D., FDA
NDA 21-148, Norditropin® SimpleXx™ Cartridges
[Somatropin (rDNA origin) for subcutaneous injection]
Amendment – Revisions to Proposed Package Insert

Novo Nordisk Pharmaceuticals, Inc.
February 25, 2000

Section: **Precautions**

Following the statement, "Patients with endocrine disorders, including growth hormone deficiency, may develop slipped capital epiphyses more frequently," we propose to add,

An explanatory document entitled, "Norditropin and Aseptic Bone Necrosis," summarizing the known experience of this condition with growth hormone is attached.

Section: **Precautions**

We propose to add, '

Section: **Precautions**

To be consistent with similar growth hormone products, we propose to add, "

Progression of scoliosis can occur in children who experience rapid growth. Because growth hormone increases growth rate, patients with a history of scoliosis who are treated with growth hormone should be monitored for progression of scoliosis."

Section: **Adverse Reactions**

We propose to add the statement, "Fluid retention and peripheral edema may occur."

Edema in growth hormone treated patients is described in the attached New England Journal of Medicine review, Vance ML, Mauras N.: Growth hormone therapy in adults and children, N Engl J Med 1999; 341: 1206-1216.

Please call Lisa Suttner, Assistant Director, Regulatory Affairs at (609) 987-5877 if you have any questions or comments regarding this information.

Sincerely,

NOVO NORDISK PHARMACEUTICALS, INC.

Ann Marie Elliott for Barry Reit

Barry Reit, PhD
Vice President, Regulatory Affairs

6 pages redacted from this section of the approval package consisted of draft labeling

February 24, 2000

Monique Wakelkamp, PhD, Reviewer
Division of Pharmaceutical Evaluation II (HFD-870)
Floor 13B-17, Room 46
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 21-148, Norditropin® SimpleXx™ Cartridges
[Somatropin (rDNA origin) for subcutaneous injection]
Response to FDA Request for Information

Dear Dr. Wakelkamp:

Please refer to the subject NDA and to your phone call on 2/24/00 requesting an electronic copy of the bioequivalence study report GHPHKIN/BPD/14/UK that was included in the Original NDA in Volume 1.19. We are hereby providing the requested report on the enclosed computer diskette.

Please call Lisa Suttner, Assistant Director, Regulatory Affairs at (609) 987-5877 if you have any questions or comments regarding this information.

Sincerely,

NOVO NORDISK PHARMACEUTICALS, INC.

Barry Relt, PhD
Vice President, Regulatory Affairs

C: Crystal King, CSO (Desk Copy)

ORIGINAL

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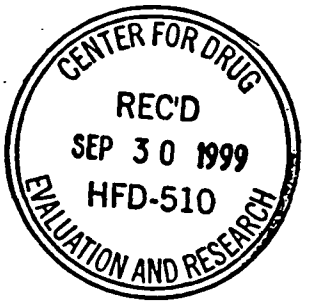


September 29, 1999

Solomon Sobel, M.D., Director
Division of Metabolic and Endocrine
Drug Products (HFD-510)
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 21-148, Norditropin® SimpleXx™ Cartridges
[Somatropin (rDNA origin) for subcutaneous injection]
Response to FDA Request for Information

Dear Dr. Sobel:

Please refer to the subject NDA and to FDA's fax requesting additional information dated 8/18/99. We are hereby responding to those requests.

1. If you have long-term toxicity data or, alternatively, carcinogenicity data, on the poloxamer, please supply it.

In the NDA for Norditropin SimpleXx, a 13 week study in rats in provided in volume 1.13 and a 13 week study in dogs is provided in volume 1.15. The reason for not performing a carcinogenicity study is explained in the statement below which is reproduced from the Original NDA volume 1.17, page 1:

Statement:

Poloxamer 188
Evaluation of Carcinogenic Potential

Poloxamer 188 is a polymer comprising polyoxypropylene and polyoxyethylene used in a wide range of products due to its — properties. In the Liquid Norditropin formulation Poloxamer 188 is included as an excipient. The expected human load of Poloxamer 188 is in the magnitude of 2.25 mg/patient/day.

Polymers are normally considered not to be genotoxic even though the monomers might be. After subcutaneous administration Poloxamer 188 is fully reabsorbed from the subcutaneous tissue and excreted mainly via the kidneys without being metabolized. Poloxamer 188 might therefore be considered non-genotoxic.

Repeated Dose Toxicity studies up to and including 13 week studies in rat and dogs showed reaction at the injection site and renal lesions in extreme subcutaneous dosages. These changes were reversible, and consequently there is no indication for a carcinogenic potential from the general toxicological studies.

The mutagenic potential of Poloxamer 188 has been investigated in three in vitro studies and one in vivo study indicating no mutagenic or clastogenic effects.

Based on the above it can be concluded that in vivo carcinogenicity studies on the excipient are not expected to add to the safety evaluation of Liquid Norditropin for the applied indication.

2. The device as presented cannot be evaluated--it appears that a part may be missing (a cap on the cartridge). Please send one working unit as soon as possible.

Please refer to our submission dated September 2, 1999 in which we provided the requested device/cartridge.

3. How does the lot/batch size and production site/method of Norditropin SimpleXx used in study GHPHKIN/BPD/14/UK compare with the proposed commercial lot/batch size and production method/site?

Please be referred to volume 6 of the Original NDA 21-148, page 173, the report "Liquid Norditropin: Investigational formulations". This report gives information about the batches used for the clinical trial GHPHKIN/BPD/14/UK:

Liquid Norditropin 5mg	batch no. 317701	batch size —
Liquid Norditropin 10 mg	batch no. 317703	batch size —
Liquid Norditropin 15 mg	batch no. 317706	batch size —

All batches are ———— The batch sized of the product scale bates is — — Hence, the size of the pilot batches used for the clinical trial is at least — of the production scale batch size. The compositions of the Liquid Norditropin batches used in the clinical trial are identical to the formulations of the products to be marketed.

Both — ———— batches are produced at Site Gentofte, Novo Nordisk, Denmark. The production method for ———— batches is the same with minor differences in the equipment used due to the difference in batch size.

4. Please submit labeling on disk (preferably in WORD format) that clearly distinguishes portion of approved product labeling from portions that are proposed for Norditropin SimpleXx (e.g., different colored text or underlining/strikeouts). Eight disks are requested.

The requested disk is provided in Attachment 1. The information from the approved Norditropin package insert is shown in black text, the information specific to Norditropin SimpleXx is shown in blue text. The reference information (annotation) is shown in red text.

5. Please provide seven copies of annotated labeling.

The requested information is provided in Attachment 1.

6. Please provide one packet of all labeling referred to in the Table of Contents (clean, annotated, other).

The requested information is provided in Attachment 2.

7. The cover letter stated that financial disclosure information was not submitted. Please note that foreign studies not conducted under an IND may still be considered as covered studies. The fact that the rule is silent does not exclude such studies. If the approval relies on a bioequivalence or bioavailability study, it is a covered study.

We were able to obtain the required financial disclosure information and are now enclosing Form FDA 3454 in Attachment 3.

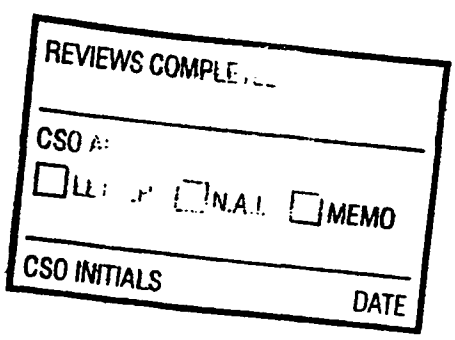
We believe we have answered all of FDA's questions to this point. We look forward to working with FDA to obtain the approval of this product.

Please call Lisa Suttner, Assistant Director, Regulatory Affairs at (609) 987-5877 if you have any questions or comments regarding this submission.

Sincerely,

NOVO NORDISK PHARMACEUTICALS, INC.

Barry Reit, PhD
Vice President, Regulatory Affairs



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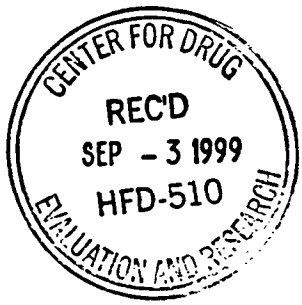
NEW CORRESP

September 2, 1999



Solomon Sobel, M.D., Director
Division of Metabolic and Endocrine
Drug Products (HFD-510)
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 21-148, Norditropin® SimpleXx™ Cartridges
[Somatropin (rDNA origin) for subcutaneous injection]
Partial Response to FDA Request for Information

Dear Dr. Sobel:

Please refer to the subject NDA and to FDA's memo dated 8/18/99. In response to request #2 of that memo for a replacement device, we have enclosed one (1) NordiPen™ 10 injection device and four (4) Norditropin SimpleXx 10 mg cartridges.

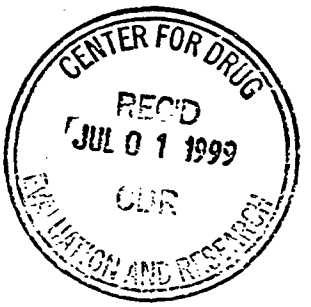
We are currently working with our Denmark offices to provide FDA with responses to the remaining requests of the August 18 memo.

Please call Lisa Suttner, Assistant Director, Regulatory Affairs at (609) 987-5877 if you have any questions or comments regarding this submission.

Sincerely,

NOVO NORDISK PHARMACEUTICALS, INC.

Barry Reit, PhD
Vice President, Regulatory Affairs



June 30, 1999

Novo Nordisk

Solomon Sobel, M.D., Director
Division of Metabolic and Endocrine
Drug Products (HFD-510)
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 21-148, Norditropin® SimpleXx™ Cartridges
[Somatropin (rDNA origin) for subcutaneous injection]
Original NDA

Dear Dr. Sobel:

In accordance with 21 CFR 314.50, Novo Nordisk is hereby submitting an NDA for Norditropin® SimpleXx™, as a new dosage form of Novo Nordisk's Somatropin (rDNA origin) for subcutaneous injection. The Norditropin SimpleXx drug product is formulated from somatropin bulk drug substance, which is fully described in Novo Nordisk's NDA 19-721.

Norditropin SimpleXx is the name being proposed for this product, which is a liquid formulation of somatropin in 5 mg, 10 mg, and 15 mg cartridges. The cartridges are ready to administer when inserted into the NordiPen™ injection devices. This application contains full documentation pertaining to the NordiPen 5, 10, and 15 injection devices as a drug/device combination product.

The Norditropin SimpleXx 5 mg, 10 mg, and 15 mg cartridges are interchangeable in the NordiPen 5, 10 and 15 injection devices. As discussed with FDA at the Pre-NDA meeting on April 7, 1999, a color coding system is used to identify which cartridge pertains to which pen. Based on the discussions at the Pre-NDA meeting, the Benefit/Risk Summary of this application provides further explanation for the color coding system and its safety.

Please note that forms FDA 3454 or 3455 are not included in this submission regarding Financial Disclosure because no "covered clinical studies" were conducted under the US IND in support of this application.

Please call Lisa Suttner, Assistant Director, Regulatory Affairs at (609) 987-5877 if you have any questions or comments regarding this submission.

Sincerely,

NOVO NORDISK PHARMACEUTICALS, INC.

Barry Reit, PhD
Vice President, Regulatory Affairs