# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**21-148**

# ADMINISTRATIVE DOCUMENTS

**Information About Patents Relating To Norditropin SimpleXx**

The patents mentioned below are the known U.S. patents which cover Norditropin SimpleXx and the method of use of Norditropin SimpleXx. The patent belongs to the company Novo Nordisk A/S, DK-2880 Bagsvaerd, Denmark. The applicant of the present New Drug Application No. 21-148, Novo Nordisk Pharmaceutical Inc., 100 Overlook Center, Suite 200, Princeton, New Jersey 08540, is a subsidiary of Novo Nordisk A/S.

The following U.S. patents are issued:

**U.S. Patent No.:** 5,679,552
**Expiration date:** October 21, 2014
**Type of patent:** recombinant hGH
**Owner:** Novo Nordisk A/S
**Patent agent:** Graham & James LLP
**U.S. agent authorized to receive notice of patent certification:**

Steve T. Zelson, Esq.
Director of Corporate Patents
Novo Nordisk of North America, Inc.
405 Lexington Avenue Suite 6400
New York, New York 10174-6401

**U.S. Patent No.:** 5,849,700 & 5,849,704
**Expiration date:** October 21, 2014
**Type of patent:** hGH stabilized with histidine in a specific ratio
**Owner:** Novo Nordisk A/S
**Patent agent:** Novo Nordisk of North America, Inc.
**U.S. agent authorized to receive notice of patent certification:**

Steve T. Zelson, Esq.
Director of Corporate Patents
Novo Nordisk of North America, Inc.
405 Lexington Avenue Suite 6400
New York, New York 10174-6401

# PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

| | | | |
|---|---|---|---|
| **NDA/BLA Number:** | 21148 | **Trade Name:** | NORDITROPIN/~~SIMPLEXX~~(SOMATROPIN (RDNA ORIGIN) |
| **Supplement Number:** | | **Generic Name:** | SOMATROPIN (RDNA ORIGIN)~~SUBCUTANEOUS~~ INJ |
| **Supplement Type:** | | **Dosage Form:** | Injectable; Injection |
| **Regulatory Action:** | AP | **Proposed Indication:** | long-term treatment of children who have growth failure due to inadequate secretion of endogenous growth hormone |

**ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?**

YES, Pediatric data exists for at least one proposed indication which supports pediatric approval

**What are the INTENDED Pediatric Age Groups for this submission?**

____NeoNates (0-30 Days ) ____Children (25 Months-12 years)

____Infants (1-24 Months) ____Adolescents (13-16 Years)

| | |
|---|---|
| **Label Adequacy** | Adequate for ALL pediatric age groups |
| **Formulation Status** | NEW FORMULATION developed with this submission |
| **Studies Needed** | - |
| **Study Status** | - |

**Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission?** YES

**COMMENTS:**

Phase 4 study needed to compare liquid formulation with existing formulation (powder) in terms of adverse experiences. At least 50 patients per treatment group, followed for one year.

**This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, CRYSTAL KING**

ISI

Signature

5/30/00

Date

# PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

**NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.**

~~BLA~~ # 21-148 Supplement # ____ Circle one SE1 SE2 SE3 SE4 SE5 SE6

For 510 Trade and generic names/dosage form: Norditropin SimpleXx Action: AP AE NA

Applicant Novo Nordisk Therapeutic Class growth hormone

Indication(s) previously approved GROWTH HORMONE DEFICIENCY IN children

Pediatric information in labeling of approved indication(s) is adequate ✓ inadequate ___

Proposed indication in this application long term treatment of children who have growth failure due to inadequate secretion of endogenous GH.

**FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.**

**IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS?** ___Yes (Continue with questions) ___No (Sign and return the form)

**WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED?** (Check all that apply)

___Neonates (Birth-1month) ___Infants (1month-2yrs) ___Children (2-12yrs) ___Adolecents(12-16yrs)

✓ **1. PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___ **2. PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

___ **3. PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

___ c. The applicant has committed to doing such studies as will be required.

___ (1) Studies are ongoing,

___ (2) Protocols were submitted and approved.

___ (3) Protocols were submitted and are under review.

___ (4) If no protocol has been submitted, attach memo describing status of discussions.

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

✓ **4. PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

___ **5. If none of the above apply, attach an explanation, as necessary.**

**ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER?** ✓ Yes ___No

**ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.**

This page was completed based on information from medical team leader (e.g., medical review, medical officer, team leader)

[signature] 4/4/00

Signature of Preparer and Title Date

Orig NDA/~~BLA~~ # 21-148

HFD-510 /Div File

NDA/~~BLA~~ Action Package

HFD-006/ KRoberts

(revised 10/20/97)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD-6 (ROBERTSK)

**Norditropin® Somatropin (rDNA origin) for subcutaneous injection**
**SimpleXx™ 5mg, 10mg, and 15 mg cartridges**

**NDA 21-148**

**Debarment Statement**

In accordance with the requirements of the Generic Drug Enforcement Act of 1992, Novo Nordisk Pharmaceuticals, Inc. did not use in any capacity, the services of any person debarred under Section 306 of the Federal, Food, Drug, and Cosmetic Act in connection with this submission.

# Exclusivity Checklist

| | | | | |
|---|---|---|---|---|
| **NDA:** 21-148 | | | | |
| **Trade Name:** Norditropin cartridges | | | | |
| **Generic Name:** Somatropin (rDNA origin) injection | | | | |
| **Applicant Name:** Novo Nordisk | | | | |
| **Division:** HFD-510 Metabolic + Endocrine Drug Products | | | | |
| **Project Manager:** Crystal King | | | | |
| **Approval Date:** 06/20/00 | | | | |
| | | | | |
| **PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?** | | | | |
| 1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission. | | | | |
| a. Is it an original NDA? | Yes | ✓ | No | |
| b. Is it an effectiveness supplement? | Yes | | No | ✓ |
| c. If yes, what type? (SE1, SE2, etc.) | N/A | | | |
| Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.") | Yes | | No | ✓ |
| If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study. | | | | |
| Explanation: Bioequivalence was assessed between the new solution and the approved, lyophilized powder for re-constitution. | | | | |
| If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data: | | | | |
| Explanation: | | | | |
| d. Did the applicant request exclusivity? | Yes | | No | ✓ |
| If the answer to (d) is "yes," how many years of exclusivity did the applicant request? | | | | |
| **IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS.** | | | | |
| 2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? | Yes | | No | ✓ |
| If yes, NDA # | | | | |
| Drug Name: | | | | |

| | | | | |
|---|---|---|---|---|
| **BLOCKS.** | | | | |
| 3. Is this drug product or indication a DESI upgrade? | Yes | | No | ✓ |
| **IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS (even if a study was required for the upgrade).** | | | | |
| | | | | |
| **PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES** | | | | |
| (Answer either #1 or #2, as appropriate) | | | | |
| 1. Single active ingredient product. | Yes | ✓ | No | |
| Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety. | Yes | ✓ | No | |
| If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s). | | | | |
| Drug Product | Norditropin (somatropin [r DNA origin] for injection) | | | |
| NDA # | 19-721 | | | |
| Drug Product | Nutropin AQ (somatropin [r DNA origin] injection) | | | |
| NDA # | 20-522 | | | |
| Drug Product | (and others) | | | |
| NDA # | | | | |
| 2. Combination product. N/A | Yes | | No | |
| If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.) | Yes | | No | |
| If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s). | | | | |
| Drug Product | | | | |
| NDA # | | | | |
| Drug Product | | | | |
| NDA # | | | | |
| Drug Product | | | | |
| NDA # | | | | |

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| **IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS. IF "YES," GO TO PART III.** | | | | |
| | | | | |
| **PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS** | | | | |
| To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes." | | | | |
| 1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation. | Yes | | No | ✓ |
| **IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS.** | | | | |
| 2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application. For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies. | | | | |
| a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement? | Yes | | No | |
| If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCKS.** | | | | |
| Basis for conclusion: | | | | |
| b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application? | Yes | | No | |
| 1) If the answer to 2 b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO. | Yes | | No | |
| If yes, explain: | | | | |

| | | | | |
|---|---|---|---|---|
| 2) If the answer to 2 b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product? | Yes | | No | |
| If yes, explain: | | | | |
| c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval: | | | | |
| Investigation #1, Study #: | | | | |
| Investigation #2, Study #: | | | | |
| Investigation #3, Study #: | | | | |
| 3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application. | | | | |
| a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.") | | | | |
| Investigation #1 | Yes | | No | |
| Investigation #2 | Yes | | No | |
| Investigation #3 | Yes | | No | |
| If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon: | | | | |
| Investigation #1 -- NDA Number | | | | |
| Investigation #2 -- NDA Number | | | | |
| Investigation #3 -- NDA Number | | | | |
| b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product? | | | | |
| Investigation #1 | Yes | | No | |
| Investigation #2 | Yes | | No | |
| Investigation #3 | Yes | | No | |
| If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on: | | | | |
| Investigation #1 -- NDA Number | | | | |
| Investigation #2 -- NDA Number | | | | |
| Investigation #3 -- NDA Number | | | | |
| If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"): | | | | |

| | | | | |
|---|---|---|---|---|
| Investigation #2 | | | | |
| Investigation #3 | | | | |

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a. For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

| | | | | |
|---|---|---|---|---|
| Investigation #1 | Yes | | No | |
| IND#: | | | | |
| Explain: | | | | |
| Investigation #2 | Yes | | No | |
| IND#: | | | | |
| Explain: | | | | |
| Investigation #3 | Yes | | No | |
| IND#: | | | | |
| Explain: | | | | |

b. For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

| | | | | |
|---|---|---|---|---|
| Investigation #1 | Yes | | No | |
| IND#: | | | | |
| Explain: | | | | |
| Investigation #2 | Yes | | No | |
| IND#: | | | | |
| Explain: | | | | |
| Investigation #3 | Yes | | No | |
| IND#: | | | | |
| Explain: | | | | |

c. Notwithstanding an answer of "yes" to (a) or (b), are there

| | | | | |
|---|---|---|---|---|
| other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.) | Yes | | No | |
| If yes, explain: | | | | |

BACK TO TOP

(b)(1)

Signature of PM/CSO
Date: 4/4/00

(b)(1)

Signature of Division Director
Date:

cc:
Original NDA
Division File
HFD-93 Mary Ann Holovac

BACK TO TOP

**MEMORANDUM**

DATE: June 16, 2000

FROM: John K. Jenkins, M.D.
Acting Director
Division of Metabolic and Endocrine Drug Products, HFD-510
Director
Office of Drug Evaluation II, HFD-102

TO: NDA 21-148

SUBJECT: Overview of review issues

Administrative

NDA 21-148 for Norditropin (somatropin [rDNA origin] injection) Cartridges was submitted by Novo Nordisk Pharmaceuticals on July 1, 1999. The application was assigned a standard review. The current user fee 12-month goal date for this application is July 1, 2000.

Clinical/Statistical

This application supports a new formulation of Norditropin that is a ready-to-inject solution (5 mg/1.5 ml, 10 mg/1.5 ml, and 15 mg/1.5 ml) rather than the currently approved lyophilized powder that must be reconstituted prior to injection. As such it is primarily a convenience formulation and the clinical data to support approval was provided by a showing of bioequivalence to the currently approved product. No new clinical trials were submitted and none were required for approval.

The application also requests approval of a new delivery device called the NordiPen (5, 10, and 15) that is specifically designed for use with the Norditropin Cartridge. The individual NordiPen devices are identical to one another with the exception that each is specifically calibrated for dosing based on the concentration of somatropin contained in the corresponding strength cartridge. Unfortunately, the cartridges are interchangeable within the three devices; i.e., there are no physical barriers to prevent a patient from inserting a 15 mg/ml cartridge into the NordiPen 5 device. This raises the possibility of medication errors and was the primary concern raised by the medical reviewer, Dr. Malozowski. A review of other approved growth hormone products revealed that other products raise similar concerns about interchangeability of cartridges and devices. A review of postmarketing adverse event reports contained in the MEDWATCH system did not reveal any signal of significant adverse events resulting from device-related dosing errors for these products. Therefore, it was determined that it would be acceptable to approve the current, though less than optimal, configuration with appropriate labeling,

including color-coordination of devices and cartridges, designed to minimize the risk of patient errors in dosing.

The application is approvable from a clinical/statistical standpoint.

Pharmacology/Toxicology

The primary pharmacology/toxicology issues raised by this application are related to the change in excepients from the currently approved formulation. The sponsor was requested to address the implication of these changes on the stability of the drug product, the activity and immunogenicity of the product at the end of the proposed shelf life, and the safety of the new excepients for chronic human subcutaneous injection. Please refer to the reviews prepared by Drs. Hertig and Steigerwalt for a detailed summary of the findings of the studies submitted by the sponsor to address these concerns. In summary, the pharmacologic activity and immunogenicity of the degraded solution product were determined to be comparable to those of the intact formulation. With regard to the safety of the new excepients (primary concern was poloxamer 188), the sponsor evaluated poloxamer 188 in a battery of in vitro and animal studies to evaluate its potential for genotoxicity, general toxicologic, and reproductive toxicologic effects. The results of these studies supported the safe use of this new excepient for chronic human subcutaneous dosing.

The application is approvable from a pharmacology/toxicology perspective.

CMC/Devices

The proposed new formulation is a solution in cartridges that are ready for injection. Please refer to the CMC review prepared by Dr. Ysern for a detailed summary of the data submitted in support of this new formulation. There are no outstanding CMC deficiencies. The NordiPen device was reviewed by CDRH and determined to be substantially equivalent to the currently marketed NovoPen, which is used for their line of insulin formulations. CDRH did not raise any deficiencies, but did note the potential concern for medication errors due to interchangeability of pens and cartridges as noted above.

The application is approvable from a CMC/Device perspective.

Clinical Pharmacology and Biopharmaceutics

As noted above, the basis for demonstration of the safety and effectiveness of the new formulation of somatropin was a showing of bioequivalence between the new and old formulations. Please refer to the review prepared by Dr. Wakelkamp-Barnes for details of the PK program. In summary, the PK study demonstrated that the systemic exposure to GH following injections of the two formulations were equivalent using standard bioequivalence intervals. Since the drug substance is the same between the two products, there are no new concerns regarding antigenicity as may arise with "generic" versions of

GH. Thus the showing of systemic bioequivalence is adequate to demonstrate the safety and effectiveness of the new formulation without need for additional clinical trials.

This application is approvable from a clinical pharmacology and biopharmaceutics perspective.

Data Integrity

No clinical studies were performed, thus no DSI audits were requested.

Labeling

The sponsor originally requested approval of the tradename "Norditropin SimpleXx for this product. This name was unacceptable to the Division, DDMAC, and OPDRA. The current proposed name, "Norditropin Cartridges" is acceptable. The draft labeling submitted by the sponsor on May 25, 2000, adequately addresses the Division's and OPDRA's concerns regarding the interchangeability of the devices and cartridges. Otherwise, the proposed labeling is generally identical to that of the approved Norditropin formulation and is acceptable.

Conclusions

This application may be approved. The sponsor will be reminded of their phase 4 commitment to conduct a comparative clinical trial to assess any differences in adverse event profile between the two formulations of Norditropin.

cc:

NDA 21-148
HFD-510/Division File
HFD-510/King
HFD-102/Jenkins

DEPARTMENT OF HEALTH & HUMAN SERVICES Food and Drug Administration

Memorandum

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Date: 4/4/00

From: Saul Malozowski, Medical Team Leader

Subject: NDA 21-148, Norditropin SimpleXx Cartridges. Medical Officer Review and Recommendations

To: The file

I concur with the biopharm recommendation to approve this product. We need, however, to solve the pending problem regarding the adequacy of the proposed name.

DEPARTMENT OF HEALTH & HUMAN SERVICES Food and Drug Administration

Memorandum

Date: 3/21/00

151

From: Saul Malozowski

Subject: NDA 21-148, Norditropin SimpleXx Cartridges. Phase 4 recommendations

To: The file

The current NDA has been approved on the basis of bioequivalence studies. In order to further gain insights into the safety profile of this product I recommend that as part of the approval package we request from the sponsor a small study to assess the comparative safety of this product with the previously approved. The goal is to better define whether the local reactions, due to the different formulations, following the injections are distinct for any of these products.

For this purpose we should request a one-year study in 50 subjects per arm (Norditropin vs. Norditropin SimpleXx) to collect the desired information. The study could be —— and during quarterly visits the attending physicians will —— to address the Agency's concerns. We could request that the commitment be fulfilled —— after the product is launched.

In addition, the sponsor should commit to solve the cartridge interchangeability issue ASAP to avoid potential mixes of the three approved strengths. This should be done in a

APPEARS THIS WAY
ON ORIGINAL

Redacted 1

pages of trade

secret and/or

confidential

commercial

information

Memorandum

Date: 3/7/00 (51

From: Saul Malozowski

Subject: NDA 21-148, Norditropin SimpleXx Cartridges. Labeling amendment. Medical Officer Recommendations

To: The file

This amendment received on February 28, 2000 provides wording to cover information in different sections of the label. Some of the proposals are adequate, some are unsubstantiated, and some may be construed as efficacy claims for a product not yet approved for some indications in the US. This memo will cover all proposals and make recommendations on what should be allowed and what should not.

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] s 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 [redacted] statement is adequate.

The above listed recommendations should be communicated to the sponsor.

DEPARTMENT OF HEALTH & HUMAN SERVICES Food and Drug Administration

Memorandum

Date: 2/14/00

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From: Saul Malozowski

Subject: NDA 21-148, Norditropin SimpleXx Cartridges. Certification of Financial Interests

To: The file

Adequate documentation regarding the certification of financial interests was provided by the sponsor.

**CONSULTATION RESPONSE**
**Office of Post-Marketing Drug Risk Assessment**
**(OPDRA; HFD-400)**

| DATE RECEIVED: 1/ 18/ 2000 | DUE DATE: 4/ 11/ 2000 | OPDRA CONSULT #: 00-0017 |
|---|---|---|

**TO:**

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

**THROUGH:**

Crystal King
Project Manager
(HFD-510)

| **PRODUCT NAME:** | **MANUFACTURER:** Novo Nordisk Pharmaceuticals Inc. |
|---|---|
| Norditropin SimpleXx (Somatropin (rDNA origin) Injection)<br><br>**NDA #:** 21-148 | |

**SAFETY EVALUATOR:** Lauren Lee, Pharm.D.

**OPDRA RECOMMENDATION:**

OPDRA does not recommend the use of the term, SimpleXx, as part of the proprietary name.

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Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 480-8173

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Peter Honig, MD
Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

**Office of Post-Marketing Drug Risk Assessment**
**HFD-400; Rm. 15B-03**
**Center for Drug Evaluation and Research**

**PROPRIETARY NAME REVIEW**

**DATE RECEIVED:** January 18, 2000

**NDA#:** 21-148

**NAME OF DRUG:** Norditropin SimpleXx (Somatropin (rDNA origin) Injection)

**NDA HOLDER:** Novo Nordisk Pharmaceuticals Inc.

## I. INTRODUCTION:

This OPDRA consult is in response to a January 18, 2000 request by the Division of Metabolic and Endocrine Drug Products, to review the name, Norditropin SimpleXx. Container(cartridge) label and carton labeling were also reviewed for possible interventions in minimizing medication errors.

Norditropin was approved on May 8, 1995 under the NDA 19-721 for 4 mg and 8 mg vials. On June 30, 1999, Novo Nordisk submitted a new dosage form of Somatropin (rDNA origin) for subcutaneous injection. The proposed product is a liquid formulation of somatropin in 5 mg, 10 mg, and 15 mg cartridges for use with NordiPen injection devices.

According to the Division, the concern is that Norditropin SimpleXx 5mg, 10 mg , and 15 mg are interchangeable in the NordiPen 5, 10, 15 injection devices. A color coding system is used to identify which cartridge pertains to which pen. In addition, since two other products, Humatrope and Genotropin, are given using similar devices, the Division requested a post-marketing review of medication error reports, if any, related to the use of an incorrect cartridge.

PRODUCT INFORMATION

Somatropin is a polypeptide hormone of recombinant DNA origin. The hormone is synthesized by a special strain of E.coli bacteria that has been modified by the addition of a plasmid which carries the gene for human growth hormone. Norditropin SimpleXx is indicated for the long-term treatment of children who have growth failure due to inadequate secretion of endogenous growth hormone. The usual recommended dosage is ——— mg/kg by subcutaneous injection 6-7 times a week. Norditropin SimpleXx is supplied in 5 mg, 10 mg, and 15 mg cartridges which must be administered using the corresponding color-coded NordiPen injection pen.

| SOMATOTROPIN | | |
|---|---|---|
| Norditropin | Powder for injection, lyophilized: 4 mg (≈ 12 IU)/ vial | In vials with diluent |
| | Powder for injection, lyophilized: 8 mg (≈ 24 IU)/ vial | |
| Norditropin SimpleXx | Injection: 5 mg/ 1.5 mL, 10 mg/ 1.5 mL, and 15 mg/ 1.5 mL | In 5 mg, 10 mg and 15 mg cartridges |

| | | |
|---|---|---|
| Genotropin | Powder for injection, lyophilized: 1.5 mg (≈ 4 IU)/ mL | In 1.5 mg Intra-Mix two-chamber cartridge with pressure-release needle. In 5s. |
| | Powder for injection, lyophilized: 5.8 mg (≈ 15 IU)/ mL | In 5.8 mg Intra-Mix two-chamber cartridge and pressure-release needle. In 1s, 5s. |
| | | For use with Genotropin Pen 5 or Genotropin Mixer |
| | Powder for injection, lyophilized: 13.8 mg (≈ 36 IU)/ mL | For use with Genotropin Pen 12 or Genotropin Mixer |
| | Powder for injection, lyophilized: fixed volume of 0.25 mL regardless of strength | 0.2 mg, 0.4 mg, 0.6 mg, 0.8 mg, 1 mg, 1.2 mg, 1.4 mg, 1.6 mg, 1.8 mg, and 2 mg in two-chamber cartridges |
| Humatrope | Powder for injection, lyophilized: 5 mg (≈ 15 IU)/ vial | In vials with 5 mL diluent |
| | Powder for injection, lyophilized: 2.08 mg /mL | In 6 mg cartridge with prefilled syringe of diluent |
| | Powder for injection, lyophilized: 4.17 mg/ mL | In 12 mg cartridge with prefilled syringe of diluent |
| | Powder for injection, lyophilized: 8.33 mg/ mL | In 24 mg cartridge with prefilled syringe of diluent |
| Nutropin | Powder for injection, lyophilized: 5 mg (≈ 13 IU)/ vial | In cartons of 2 vials with a 10 mL multiple-dose vial of diluent. |
| | Powder for injection, lyophilized: 10 mg (≈ 26 IU)/ vial | In cartons of 2 vials with two 10 mL multiple-dose vials of diluent. |
| Nutropin AQ | Injection: 10 mg (≈ 30 IU)/ vial | In cartons of 6 vials with one 2 mL vial (5 mg/ mL) |
| Serostim | Powder for injection, lyophilized: 5 mg (≈ 15 IU)/ vial | In vials with diluent. |
| | Powder for injection, lyophilized: 6 mg (≈ 18 IU)/ vial | In single-use vials with diluent. |
| Saizen | Powder for injection, lyophilized: 5 mg (≈ 15 IU)/ vial rDNA origin | In vials with diluent. |

HumatroPen is available for use with Humatrope 6 mg, 12 mg, and 24 mg cartridges. Genotropin can be given using Genotropin Pen 5, Genotropin Pen 12, Genotropin MiniQuick, Genotropin Mixer, and Genotropin Intra-Mix.

## II. RISK ASSESSMENT

A.

B. In addition, SimpleXx is also objectionable as part of the proprietary name because the term, "Xx", could be misinterpreted as a numerical number, twenty, and could misconstrued as a dose.

C. Searches in the Adverse Event Reporting System (AERS) and Drug Quality Reporting System (DQRS) databases were conducted to find any previously reported medication errors for somatropin. The AERS database was searched for reports using the Meddra term, DRUG MALADMINISTRATION, for somatropin, Norditropin, Genotropin, Humatrope, Serostim, Saizen, and Nutropin. The proprietary and established names were used for the above listed drugs in searching the DQRS database. *There were no reports located using this search related to the inadvertent substitution of different strength cartridges.*

However, NordiPens are different than the devices used for Humatrope and Genotropin. HumatroPen is available for use with Humatrope 6 mg, 12 mg, and 24 mg cartridges, but the device is designed so that all three strength cartridges can be used as long as the dosing chart is used to determine the proper dose. Furthermore, the cartridges that fit Genotropin Pen 5 and Genotropin Pen 12 are not interchangeable because they do not fit properly. Other devices for Genotropin already contain the active drug and diluent in the device and therefore, the user could not easily place the wrong strength cartridge in the device. However, Norditrope 5 mg, 10 mg, and 15 mg strengths cartridges are interchangeable in NordiPen 5, NordiPen 10, and NordiPen 15, and the user must place the cartridges in the pens. If the cartridge strength and the pen do not match in color, the user could potentially receive an improper amount of the drug. In addition, since more than one Nordipen may be required during dose titration, medication errors could occur if a user decides to purchase the higher strength cartridges and not the corresponding pens with the assumption that he/she already has a pen device. From a safety perspective, we recommend that the device or the size of the cartridge be altered so that the pens only accommodate the corresponding cartridge strength. For example, NordiPen 5 should only fit the 5 mg cartridge and not 10 mg or 15 mg strength cartridges.

Although there were no medication error reports related to the inadvertent substitution of different strength cartridges for Humatrope and Genotropin, many medication error reports were identified for the various somatropins, and are listed below per Division's request. However, we do not have any recommendations at this time pertaining to these reports:

**HUMATROPE**

1. ISR# 3332139-6 (Date of Event
   A 27 year old man experienced dehydration and hypotension while receiving somatropin (**Humatrope**). Ten months after starting the drug, the patient was brought to the ER with hypotension, weakness, fever, vomiting, and diarrhea for 2 days. In the opinion of the investigator, the events were not related to the study drug or protocol, but were probably due to viral gastroenteritis. The patient continued with somatotropin. Fifteen months later, the patient was hospitalized with psychosis. The investigator stated that the psychosis was possibly related to somatropin, as the decompensation may have occurred because he missed some injections of somatropin and hydrocortisone.

2. ISR# 3112815-0 (Date of Report 7/29/98)
   A 17 month old with a history of hyperbilirubinemia with phototherapy treatment and hyaline membrane disease received somatotropin (**Humatrope**) at home. An abscess/ cellulitis occurred at the injection site. The patient was hospitalized and the abscess was incised and drained under general anesthesia. The patient's surgeon believed that the event was due to the technique used to administer the drug.

3. ISR# C1936950 (Date of Even
   Due to problems with the HumatroPen and the patient's own wish, a 51 year old man was given disposable syringes for the injection of **Humatrope**. A mistake was made in calculating the dose and the patient consequently took 0.5 mL (=2.86 unit) instead of 0.2 mL. He experienced dizziness, edema, and sweating. After five days, he corrected the dose himself to the correct dose and contacted the treating physician and nurse.

4. ISR# C1946174 (Date Received 1/31/97)
   A pharmacist reported that **Humatrope** was accidentally diluted with sodium acetate solution instead of their usual bacteriostatic normal saline which has been used for years as diluent. The injection site was red and swollen, and the child experienced extreme pain.

5. ISR# C1806696 (Date of Event
   Due to a change in sample dosage (from 4 IU to 16 IU per vial) of **Humatrope**, a 16 year old patient was injected 4 times the prescribed dose because the family kept the same volume. The patient was injected 6 times a week since 7/29/96. *(The date of the report was 8/27/96)* The patient presented with headaches and hypercalcemia. A physician discovered the overdose.

6. ISR# C1743701 (Date of Event
A 21 year old patient was inadvertently prescribed 2 times the amount of injectable study drug (**Humatrope**) that she should have been prescribed based on her weight and protocol. The patient took 0.84 mL 6 times a week instead of 0.42 mL 6 times a week. This occurred from 3/16/95 to 6/19/95. No serious events were reported.

7. ISR# C1743706 (Date of Event
A 19 year old patient was inadvertently prescribed 2 times the amount of injectable study drug (**Humatrope**) that she should have been prescribed based on her weight and protocol. The patient took 1 mL 6 times a week instead of 0.5 mL 6 times a week. This occurred from 3/16/95 to 6/19/95. No serious events were reported.

8. ISR# C1571325 (Date of Event
A 40 year old woman was discarding a medication from a syringe **[Humatrope]** into a sink and smelled a strong, pungent odor. She became lightheaded and nauseous. She left the room and recovered.

## GENOTROPIN

1. ISR# 3258588-2 (Date of Event
A physician from Japan reported that a 14 year old discontinued **Genotropin** at the patient's request due to noncompliance. The boy was receiving 10 IU/week instead of 21 IU/week. Two months after discontinuation, he was hospitalized for melena. H. pylori was detected along with anemia and gastric ulcer. The event had resolved by the time the firm received the report. The reporting physician assessed the event as unrelated to Genotropin.

2. ISR# 3170142-X (Date Received 10/28/98)
A 15 year old with a history of argile syndrome, hepatic transplant , renal aplasia/dysplasia started **Genotropin** 12/1/95 for chronic renal failure. Genu valgum (diagnosed prior to hepatic transplant) progression noticed in . Genotropin treatment was discontinued 9/1/98. The investigator assessed that the event was probably drug-related and serious since intervention was required to prevent permanent impairment or damage.

3. U# 24746 (Date of Event
A caregiver reported breaking the cartridge for **Genotropin** while changing the cartridge. The caregiver did not unwind the PEN device.

4. U# 24747 (Date of Event
Upon third attempt, the caregiver successfully changed the cartridge for **Genotropin** in the Pen-12 device. The reporter stated that the instructional video was not clear about unwinding the PEN.

5. U# 24654 (Date of Event
Genotropin squirted out immediately after loading into Pen-5 device. The device was probably not unwound prior to loading the cartridge.

6. U# 24651 (Date of Event
When **Genotropin** was loaded into Pen-5 device, the drug squirts out of cartridge. The mother failed to unwind the Pen-5 device prior to loading the cartridge.

7. U# 24655 (Date of Event
A caregiver attempted to load the **Genotropin** cartridge into the Pen-5 device and the cartridge broke. Pen-5 device was not unwound prior to changing the cartridge.

8. U# 24652 (Date of Event
The caregiver reported that **Genotropin** squirts out of cartridge after loading into the Pen-5 device. The caregiver feared that the wrong proportion of medicine to diluent remained in the cartridge to be administered. Pen-5 probably not unwound prior to loading the cartridge.

## NUTROPIN AQ

1. ISR# 3468627-8 (Date of Event
A 52 year old man experienced atrial flutter during participation in the National Cooperative Somatropin Surveillance Study for collection of safety and efficacy information about Nutropin and **Nutropin AQ**. The patient began Nutropin AQ and on the following day was reported to have a pulse rate of 160 beats/minute which later

converted to normal sinus rhythm after the patient was put on Betapace and Coumadin. A repeat episode of atrial flutter occurred with another dose of Nutropin AQ, which was discontinued. The patient reported that his endocrinologist indicated that the event was possible related to **Nutropin AQ** therapy. The investigator further stated that both CAD and stress could have accounted for the event. At the time of this report, the patient's condition was improving.

2. ISR# 3373921-9 (Date of Event —
   A 50 year old woman developed a benign colon tumor during therapy with **Nutropin AQ** for growth hormone deficiency. The patient underwent 2 partial colectomy. The treating physician told the patient that he does not know whether the growth hormone had any relation to the patient's condition.

3. D# 25854 (Date of Event —
   A 10 year old (20.4 kg) patient with a history of congenital heart disease started **Nutropin AQ** on 10/28/98 with the dose of 1 mg six times per week. A reporter stated that the pain at injection site occurred randomly after subcutaneous injection of the leg. It occurred randomly at no set pattern or location. It was severe enough to cause the patient to cry.

4. ISR# 3013585-7 (Date of Event
   A 9 year old with a chronic seizure disorder who began **Nutropin AQ** therapy for growth hormone deficiency experienced a grand mal seizure approximately one month later followed by 2 more seizures over the next 2 weeks. Nutropin AQ was discontinued. When Nutropin was restarted in 9/97, the patient experience another seizure in — The patient had not experienced a grand mal seizure for 5-6 years before starting growth hormone therapy. Her Depakene dosage was lowered around the time that she started the growth hormone therapy. The mother understands that the seizures may be related to the reduction in the patient's Depakene dose.

5. D# 22971 (Date Received 7/10/96)
   A patient complained of injections that "sting too much" and wanted to switch to lyophilized Nutropin.

6. D# 22762 (Date Received 5/10/96)
   A mother of a child reported an increase in pain upon injection of **Nutropin AQ**.

7. U# 22761 (Date of Event —
   A child experienced an increasing pain and bruising upon switching from lyophilized **Nutropin AQ** to aqueous product. The child tried 2 plus weeks to see if the pain would abate, but it did not. The sample was returned to the manufacturer.

8. U# 22537 (Date of Event —
   A 10 year old patient who was taking the growth hormone for 6+ years was recently switched to **Nutropin AQ**. The patient reported that the shots bled longer and were painful. The drug also oozed from the sight.

**SEROSTIM**

1. ISR# 3383496-6 (Date of Event —
   A consumer with a history of HIV reported that he started taking Diflucan and **Serostim**. He experienced a darkening of his skin pigmentation. The patient was hospitalized on — to receive amphotericin B and was discharged. As of — , the patient's darkening pigmentation has worsened.

## III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container label, carton and insert labeling of Norditropin SimpleXx, OPDRA has attempted to focus on safety issues relating to possible medication errors. OPDRA has reviewed the current container (cartridge) label and carton and insert labeling and has identified several areas of possible improvement, which might minimize potential user error.

A. **CONTAINER LABEL** (5 mg, 10 mg, & 15 mg)

1. We recommend the following presentation for the proprietary and established names on the container label (cartridge), carton labeling, and package insert:

   [redacted]

   (Somatropin (rDNA origin) Injection)

2. We recommend adding "Use only with NordiPen 5 injection pen" on the cartridge label.

3. The strength of the product should be stated in mg/ mL (e.g. 5 mg/ 1.5 mL). We also recommend increasing the prominence of the strength.

B. **CARTON LABELING** (5 mg, 10 mg, & 15 mg)

1. The " [redacted] " statement should be revised to read:

   Each 1.5 mL contains: somatropin 5 mg...

2. We recommend increasing the prominence of the statement, "For use with NordiPen 5 injection pen."

3. See comments under CONTAINER LABEL.

C. **PEN DEVICE**

1. Since different colors are used to differentiate the three strengths, we do not recommend having all three colors on the pen cap. We recommend that the use of the color differentiation be consistent on the entire device.

2. We recommend increasing the prominence of the strength on the NordiPen.

## IV. RECOMMENDATIONS:

A. OPDRA does not recommend the use of the term, SimpleXx, as part of the proprietary name.

B. OPDRA recommends the above labeling revisions that might lead to safer use of the product.

OPDRA would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Lauren Lee, Pharm.D. at 301-827-3243.

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Lauren Lee, Pharm.D.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur:

Jerry Phillips, RPh
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

CC:

NDA: 21-148
Office Files
HFD-510; DivFiles; Crystal King, Project Manager
HFD-510; John Jenkins, Acting Division Director
HFD-042, Mark Askine, Senior Regulatory Review Officer, DDMAC (Electronic Only)
HFD-400; Lanh Green, Safety Evaluator, DDRE II, OPDRA
HFD-400; Jerry Phillips, Associate Director, OPDRA
HFD-400; Peter Honig, Director, OPDRA (Electronic Only)
HFD-002; Mac Lumpkin, Deputy Center Director for Review Management
(Electronic Only)

FILING MEETING AGENDA

Drug/Application: NDA 21-148 NovoNordisk: Norditropin SimpleXx

1. Filing Discussion:

- Clinical – no filing issues per Saul Malozowski

- Pharmacology – no filing issues regarding the Norditropin component of the product per Dave Hertig and Ronald Steigerwalt. However, if the sponsor has long-term toxicity data or, alternatively, carcinogenicity data on the poloxamer, the sponsor should supply it. ***Crystal King will request this from the firm.*** This could be an approval issue or might be handled as a Phase 4 commitment depending upon the available data.

- Micro – no filing issues per Patricia Hughes (e-mail attached).

- Devices – no filing issues per Von Nakayama. Several problems were noted, however. The device as presented cannot be evaluated—it appears that a part may be missing (a cap on the cartridge). ***Crystal King will request a workable unit to be forwarded to Von.*** There are two possible issues regarding the barrel of the injector. One is the exclusive use of the Norditropin cartridge. The second is that the samples of injectors that we had could accommodate a "standard" 3mL cartridge. As Norditropin is to be available in a 1.5mL cartridge, an injector that can fit a 3mL cartridge raises a question. These will be addressed in the review process.

- Chemistry – no filing issues per Bill Berlin.

- Biopharmaceutics – no filing issues per Rob Shore and Hae-Young Ahn. ***Crystal King will forward Rob's comments to sponsor from review document dated 8/5/99.***

- Biostatistics – N/A

- DSI – N/A

- Regulatory – Crystal King noted that the sponsor did not believe the financial disclosure regulations pertained to this application. Clarification from Linda Carter indicated that foreign bioequivalence studies not conducted under an IND were still considered covered studies. (The fact that the rule is silent on this does not exclude such studies. If the approval relies on a BE or BA study, then it is a covered study.)

The acknowledgement letter

requested submission of pediatric waiver. Finally, annotated labeling will be requested.

2. Priority or Standard Review schedule: ~~Priority~~ Standard

3. Clinical Audit sites (list): N/A

4. Advisory Committee Meeting: ~~Yes~~ No

5. Review Timelines/Review Goal Date (with labeling): MS Project timelines for the entire project and for individual disciplines were distributed. The $UF_{10}$ for this standard submission is May 1, 2000. Office level review is NOT required. ***Each discipline agreed that all reviews, with labeling, would be signed and delivered to Crystal King on or before March 23, 2000. (All consults will be signed and delivered by March 9, 2000.***

Due to the recent implementation of pre-Rounds, a full team meeting will not be scheduled for at least two months, unless necessary.

ACCEPTED FOR FILING

/S/ /S/

Crystal King, Regulatory Project Manager Saul Malozowski, Medical Team Leader

Attachments:
(1) e-mail from Patricia Hughes
(2) Filing memo from Robert Shore
(3) IR memo to Novo from Crystal King

cc: Original NDA 21-148
HFD510: C.King/S.Malozowski/D.Hertig/R.Steigerwalt/W.Berlin/
S.Moore/R.Shore/H.Ahn/
HFD-160: P.Hughes
HFZ-480: V.Nakayama

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ENVIRONMENTAL ASSESSMENT
NDA 21-148

The request for Categorical Exclusion is deemed suitable and consequently granted. See Chemistry Review page 23, section D.

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ATTACHMENT 3

**HFD-510 DMEDP**

# 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**

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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

# Meeting Minutes

| | |
|---|---|
| **NDA # and Drug Name:** | 19-721 Norditropin |
| **Meeting Date:** | April 7, 1999 |
| **Time:** | 9:30 am |
| **Location:** | Parklawn Conference Room "M" |
| **Indication:** | Short stature due to growth hormone deficiency |
| **Sponsor:** | Novo Nordisk |
| **Type of Meeting:** | Pre-NDA |
| **Meeting Facilitator:** | Saul Malozowski, M.D., Ph.D., Medical Team Leader (Acting) |
| **Sponsor Participant Lead:** | Barry Reit, Ph.D., VP Regulatory Affairs, USA |
| **Regulatory Project Manager:** | Crystal King, P.D., M.G.A. |
| **FDA Participants:** | Stephen Moore, Ph.D., Chemistry Team Leader |
| | William Berlin, Ph.D., Chemistry Reviewer |
| | Ronald Steigerwalt, Ph.D., Pharmacology Team Leader |
| | Dave Hertig, Pharmacology Reviewer |
| | Robert Shore, Pharm.D., Biopharmaceutics Reviewer |
| | David Hussong, Ph.D., Microbiology Reviewer |
| **Sponsor Participants:** | Lisa Suttner, Assistant Director, Regulatory Affairs, USA |
| | Lars Nordholm, Ph.D., Project Director, Project Planning & Management, Denmark |
| | Hans Holmegaard Sørensen, MSc., Manager, Protein Chemistry, Denmark |
| | Annie Hoelgaard, Ph.D., Project Manager, Production Development Management, Denmark |
| | Ulla Brønnum, MSc., Manager, Regulatory Affairs, Denmark |
| | Michael Højby RasmussenM.D., Ph.D., Manager, Clinical Drug Development, Denmark |

**Meeting Objective:** To discuss the submission plans for: (1) new NDA for a new liquid formulation of Norditropin and pen injector system; and (2) [redacted]

**Background:** Norditropin received approval on 05/08/95 as a lyophilized powder.

**Discussion:** Novo presented material to further clarify the preliminary material . Points to note include:

- Referring to Novo's '— validations, approvals and implementation" (Attachment B, page 10), B. Berlin explained that the comparison of — — s the most relevant and should be clearly indicated.
- Regarding the implementation of the WHO reference standard, B. Berlin suggested that Novo give consideration to changing the acceptance limits for potency rather than changing the actual dose. Labeling and dosing will be affected. All agreed that further discussion of this may be necessary.

  **ACTION: Novo will send a data package.**
- Regarding the drug product specifications, S. Moore indicated that a specification for main peak purity should be included.
- Regarding labeling, S. Moore indicated that the labeling may need to include the —
- Referring to Novo's comparison of SimpleXx degradation products to freeze-dried Norditropin (Attachment B, page 17), B. Berlin noted that Novo will be asked to calculate an appropriate limit specific for the somatropin — peak (HPLC), and to set appropriate limits for product related substances.
- R. Steigerwalt noted that Novo would need to provide evidence that carcinogenicity studies are not necessary for this product, including the excipient, or would need to provide the data.
- The Division voiced concern that the Norditropin cartridges would be interchangeable in the different dosage pen devices. The Division believed that color coding system alone was not sufficient and strongly encouraged Novo to additionally modify the devices (knobs on cartridge, etc.) so that ONLY the appropriate dosage cartridge could be accepted by the pen device. (Other products are not compatible with the pen device.)

**Agenda Item 1:** Does FDA agree with the proposed format for submitting the information in the — NDA?

**Agreements:**

- Clinical
  - We will require documentation for safety of the new formulation.
    - S. Malozowski noted that the AEs should compare the new formulation to the current.
- Biopharm
  - If the formulation of the powder will change, a bioequivalence study is needed.
  - The bioequivalence study needs to report AUC and Cmax with 90% confidence intervals.
  - Are all the growth hormone products used in the bioequivalence study from commercial size batches?
    - This data will be included with the submission.

- An 'outlier' is identified in the bioequivalence study summary. Is this subject 52 or 62? How was it determined that this subject is an 'outlier'? Please provide bioequivalence analysis both with and without this 'outlier'.
  - Subject 62.

♦ Pharmacology

- We need available toxicity information on Poloxamer 188.
- Is there a control group (or portion of the 3-month toxicity study) with un-degraded product?
  - Both have degraded and un-degraded product.
- What are the long-term experiences vs. the short-term experiences with the new excipient? Further toxicity studies may be required.

♦ Device

- Is the device new or a modification to an existing one? Does the Sponsor expect to file as a "combination" device under the NDA?
  - The pen is a modified insulin device; the device will be filed as a combination device under the NDA.
- Can the device demonstrate accuracy in dosing and performance for the life of the pen?
- What unique features are present to assure that other cartridges are not interchangeable?

♦ Chemistry

- What evidence exists that the container closure system is suitable for the liquid formulation—leaching, absorption—vs. the powder?
- We need liquid formulation stability protocols ASAP.
- /

♦ Microbiology

- The meeting package refers to [redacted] The CMC section needs sterility, as well as validation of the [redacted]
  - D. Hussong mentioned that the micro section for the NDA will need to be new; [redacted]

**Agenda Item 2:** Are there any special considerations which would make the submission easier to review?

**Agreements:**

♦ Raw data for bioequivalence should be provided on diskette.

♦ [redacted]

- Is an electronic submission being planned?
  - No. Diskettes will be provided.

**Agenda Item 3:** Will Norditropin® SimpleXx™ be an acceptable tradename for the ready to use liquid formulation?

**Agreements:**

- Chemistry will submit the name; however, it may not be acceptable due to its suggestive nature.

**Agenda Item 4:** Will NordiPen be acceptable for the pen delivery system (for the ready to use liquid formulation)?

**Agreements:**

- See previous Device section (Question 1).

The sponsor agreed to provide all requested information in the submissions and appreciated the Division's input.

Although FDA minutes are the official documentation of the meeting, we note that Sponsor minutes have not been provided at this time, therefore no discrepancies are noted.

Prepared by: _____, Regulatory Project Manager
Crystal King, P.D., M.G.A. date

Concurrence: _____, Meeting Facilitator
Saul Malozowski, M.D., Ph.D. date

Concurrence: RShore 04.23.99/WBerlin 04.27.99/RSteigerwalt, DHertig, Dhussong, SMoore 04.28.99

Attachments:
A. Background package submitted March 5, 1999
B. Sponsor presentation
C. Overhead Agenda Questions/Answers

cc: NDA 19-721
Division File
HFD-510: SMalozowski/SMoore/WBerlin/RSteigerwalt/DHertig/RShore/
HFD-160: DHussong
HFZ-480: VNakayama

| RECORD OF TELEPHONE CONVERSATION/MEETING | Date: April 27, 2000 |
|---|---|
| I spoke with Ms. Suttner to relay the following comments.<br>1. The use of '— in the name, as ' ——— as submitted on April 17, 2000, will not be acceptable. If the sponsor wishes to add a suffix, it should be informative as to how the particular formulation differs from available formulations of the same drug. Another option is to simply use the name Norditropin.<br>2. Once we have agreed upon a name, all labeling will need to be officially submitted reflecting that name.<br>3. We do not anticipate taking action prior to May 1, 2000, but will continue to work towards an action before the UF 12 date.<br>4. Responses to Chemistry and Micro deficiencies were acceptable.<br>5. Regarding the device labeling submitted on April 17, 2000, all corrections will need to be corrected without any hand corrections to post on the internet. (There were several corrections by hand on this submission.) Further, the following additional corrections are necessary:<br>a) The Xx — graphic should be removed from all labeling.<br>b) All strengths (e.g., —) should be re-written and expressed as mg/mL (e.g., 5mg/1.5mL) in all labeling. The strength expressed in the name of the device (e.g., NordiPen 5) is acceptable as is.<br>c) All device labeling will need to have corrected product name.<br><br>Ms. Suttner agreed that all these issues could be addressed; some are already in progress. She pointed out that removing the Xx — graphic from the labeling was not a problem; however, the actual pen device and the device case have already been manufactured with this graphic in preparation for launch. She was unsure of the supply already on hand.<br><br>After speaking with Dr. Jenkins (acting Division Director), I conveyed to Ms. Suttner that we would permit Novo to launch with the graphic as long as they agreed to delete the graphic within six months. She agreed this would be acceptable to Novo.<br><br>151<br><br>Crystal King, P.D., M.G.A., Regulatory Project Mgr. | NDA#: 21-148<br><br>**Telecon/Meeting initiated by:**<br><br>○ Applicant/Sponsor<br>● FDA<br>**By:** Telephone<br><br>**Product Name:**<br>Norditropin SimpleXx<br><br>**Firm Name:**<br>Novo Nordisk<br><br>**Name and Title of Person with whom conversation was held:**<br>Lisa Suttner, Regulatory Affairs<br><br>**Phone:** 609-987-5877 |

cc: NDA 21-148
Div Files

| RECORD OF TELEPHONE CONVERSATION/MEETING | Date: 18-APR-2000 |
|---|---|
| I spoke to Ms. Lisa Suttner regarding Novo Nordisk NDA 21-148 April 11, 2000, communication. The communication provides changes to the NordiPen® Manual, but as expected by the date of the document, does not include the changes suggested by the Agency in our Phone Conversation with the applicant on April 12, 2000.<br><br>The applicant has revised the NordiPen Manual incorporating the Agency comments. The new version of the NordiPen Manual is dated 17-APR-2000 and according to the applicant has been sent to the Agency.<br><br>As mentioned by Lisa Suttner, the document dated 11-APR-2000 should be disregarded because it will be superseded by the NordiPen Manual new version dated 17-APR-2000.<br><br>filename: nda/21148tc1.doc<br><br>**Name:** Xavier Ysern HFD-510 | **NDA#:** 21-148<br><br>**Telecon/Meeting initiated by:**<br><br>Applicant/Sponsor<br>✓ FDA<br><br>**By:** Telephone<br><br>**Product Name:** Norditropin Cartridges 5 mg/1.5 mL, 10 mg/1.5 mL and 15 mg/1.5 mL<br><br>**Firm Name:** Novo Nordisk<br><br>**Name and Title of Person with whom conversation was held:**<br>Ms. Lisa Suttner, Assistant Director, Regulatory Affairs<br><br>**Phone:** (609) 987-5877 |

| **RECORD OF TELEPHONE CONVERSATION/MEETING** | **Date: April 12, 2000** |
|---|---|
| FDA participants:<br>Saul Malozowski, M.D., Ph.D., Medical Team Leader<br>Xavier Ysern, Ph.D., Chemistry Reviewer<br>Crystal King, P.D., M.G.A., Regulatory Project Manager<br><br>**Purpose:** to relay comments regarding injection device and proposed trade name.<br><br>**Device**<br>1. Although we recommend altering the device and/or cartridges so that the cartridges are not interchangeable with the different dosing pens, we will not require physical modification.<br>2. We do not agree with Novo's position that the NordiPen is similar to existing marketed pens.<br>3. We will require the following additional label modifications in lieu of physical alterations:<br>a) Cartridge Carton (5, 10, and 15 mg):<br>1) Add language that this cartridge must only be used with the proper color-coded pen.<br>2) Increase the prominence of the strength.<br>3) Revise the statement [redacted] " to read: "Each 1.5mL contains: somatropin Xmg..." (where X is the strength).<br>b) Cartridge Container (5, 10, and 15 mg):<br>1) Add "For use only with NordiPen X injection pen" (where X is the strength).<br>2) Express the strength of the product in mg/mL (e.g., 5 mg/1.5 mL).<br>3) Increase the prominence of the strength.<br>c) NordiPen Instruction Booklet (-5, -10, and -15):<br>1) Under **Important Things to Know**, delete the [redacted] | **NDA#: 21-148**<br><br>**Telecon/Meeting initiated by:**<br><br>○ Applicant/Sponsor<br>● FDA<br>**By:** Telephone<br><br>**Product Name:**<br>Norditropin SimpleXx<br><br>**Firm Name:**<br>Novo Nordisk<br><br>**Name and Title of Person with whom conversation was held:**<br>Lisa Suttner, Regulatory Affairs<br><br>**Phone:** 609-987-5877 |

4. On each of the three NordiPen devices:
   a) Increase the prominence of the strength.
   d) Do not use the three different strength colors in the spots on the pen cap; this is confusing with the color coding system. Use only the single applicable color.

**Tradename**

The proposed term SimpleXx is not acceptable as part of the proprietary name. The term is objectionable because of safety and promotional concerns. "Xx" could be misinterpreted as a numerical number, twenty, and could be misconstrued as a dose.

Novo may choose to submit an alternate name.

**Addendum**

At Ms. Suttner's request, following the conversation, we determined that the application may be approved without a tradename. We would need to monitor any tradename used after approval. If objectionable, we would seek regulatory action against the product as being misbranded.

/S/

**Saul Malozowski**

/S/

**Xavier Ysern**

/S/

**Crystal King**

cc: NDA 21-148
Div Files
HFD-510: S.Malozowski/X.Ysern/C.King

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: April 30, 2000*
*See OMB Statement on page 2.*

**FOR FDA USE ONLY**

APPLICATION NUMBER

## APPLICANT INFORMATION

| NAME OF APPLICANT | DATE OF SUBMISSION |
|---|---|
| Novo Nordisk Pharmaceuticals, Inc. | 5/25/00 |
| 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<br>Suite 200<br>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) 21-148

| ESTABLISHED NAME (e.g., Proper name, USP/USAN name) | PROPRIETARY NAME (trade name) IF ANY |
|---|---|
| Somatropin (rDNA origin) injection | Norditropin® |
| CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) | CODE NAME (If any) Laboratory Code: BhGH |

| DOSAGE FORM: | STRENGTHS: | ROUTE OF ADMINISTRATION: |
|---|---|---|
| Liquid | 5mg/1.5mL, 10mg/1/5mL and 15mg/1.5mL | Subcutaneous injection |

(PROPOSED) INDICATION(S) FOR USE: Long-term treatment of children who have growth failure due to inadequate secretion of endogenous growth hormone.

## APPLICATION INFORMATION

APPLICATION TYPE *(check one)*
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 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)*
☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ 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)**

19-721

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: April 30, 2000*
*See OMB Statement on page 2.*

FOR FDA USE ONLY

APPLICATION NUMBER

## APPLICANT INFORMATION

| NAME OF APPLICANT | DATE OF SUBMISSION |
|---|---|
| Novo Nordisk Pharmaceuticals, Inc. | 4/11/00 |
| 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) 21-148

| ESTABLISHED NAME (e.g., Proper name, USP/USAN name) | PROPRIETARY NAME (trade name) IF ANY |
|---|---|
| Somatropin (rDNA origin) for injection | Norditropin® SimpleXx™ |

| CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) | CODE NAME (If any) |
|---|---|
| | Laboratory Code: BhGH |

| DOSAGE FORM: | STRENGTHS: | ROUTE OF ADMINISTRATION: |
|---|---|---|
| Liquid | 5mg, 10mg and 15mg | Subcutaneous injection |

(PROPOSED) INDICATION(S) FOR USE. Long-term treatment of children who have growth failure due to inadequate secretion of endogenous growth hormone.

## APPLICATION INFORMATION

APPLICATION TYPE *(check one)*
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 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)*
☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION Revised Draft Labeling - Device Instruction Manual

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ 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.

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19-721

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: April 30, 2000*
*See OMB Statement on page 2.*

FOR FDA USE ONLY

APPLICATION NUMBER

## APPLICANT INFORMATION

| NAME OF APPLICANT | DATE OF SUBMISSION |
|---|---|
| Novo Nordisk Pharmaceuticals, Inc. | 4/7/00 |
| **TELEPHONE NO.** *(Include Area Code)* | **FACSIMILE (FAX) Number** *(Include Area Code)* |
| (609) 987-5822 | (609) 987-3916 |
| **APPLICANT ADDRESS** *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* | **AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE |
| 100 Overlook Center<br>Suite 200<br>Princeton, New Jersey 08540 | |

## PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-148

| ESTABLISHED NAME (e.g., Proper name, USP/USAN name) | PROPRIETARY NAME (trade name) IF ANY |
|---|---|
| Somatropin (rDNA origin) for injection | Norditropin® SimpleXx™ |

| CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) | CODE NAME (If any) |
|---|---|
| | Laboratory Code: BhGH |

| DOSAGE FORM: | STRENGTHS: | ROUTE OF ADMINISTRATION: |
|---|---|---|
| Liquid | 5mg, 10mg and 15mg | Subcutaneous injection |

(PROPOSED) INDICATION(S) FOR USE: Long-term treatment of children who have growth failure due to inadequate secretion of endogenous growth hormone.

## APPLICATION INFORMATION

APPLICATION TYPE *(check one)*
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 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)*
☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION Post Approval Commitment

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

## ESTABLISHMENT INFORMATION

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

19-721



rkr

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: April 30, 2000*
*See OMB Statement on page 2.*

FOR FDA USE ONLY

APPLICATION NUMBER

## APPLICANT INFORMATION

| NAME OF APPLICANT | DATE OF SUBMISSION |
|---|---|
| Novo Nordisk Pharmaceuticals, Inc. | 4/6/00 |
| **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<br>Suite 200<br>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) 21-148

| ESTABLISHED NAME (e.g., Proper name, USP/USAN name) | PROPRIETARY NAME (trade name) IF ANY |
|---|---|
| Somatropin (rDNA origin) for injection | Norditropin® SimpleXx™ |

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any)

CODE NAME (If any) Laboratory Code: BhGH

| DOSAGE FORM: | STRENGTHS: | ROUTE OF ADMINISTRATION: |
|---|---|---|
| Liquid | 5mg, 10mg and 15mg | Subcutaneous injection |

(PROPOSED) INDICATION(S) FOR USE: Long-term treatment of children who have growth failure due to inadequate secretion of endogenous growth hormone.

## APPLICATION INFORMATION

APPLICATION TYPE *(check one)*
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 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)*
☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION Response to FDA Request for Information

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

## ESTABLISHMENT INFORMATION

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19-721



rkr

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: April 30, 2000*
*See OMB Statement on page 2.*

FOR FDA USE ONLY

APPLICATION NUMBER

## APPLICANT INFORMATION

| NAME OF APPLICANT | DATE OF SUBMISSION |
|---|---|
| Novo Nordisk Pharmaceuticals, Inc. | 4/5/00 |
| **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<br>Suite 200<br>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) 21-148

| ESTABLISHED NAME (e.g., Proper name, USP/USAN name) | PROPRIETARY NAME (trade name) IF ANY |
|---|---|
| Somatropin (rDNA origin) for subcutaneous injection | Norditropin® SimpleXx™ |

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any)

CODE NAME (If any) Laboratory Code: BhGH

| DOSAGE FORM: Liquid | STRENGTHS: 5mg, 10mg and 15mg | ROUTE OF ADMINISTRATION: Subcutaneous injection |
|---|---|---|

(PROPOSED) INDICATION(S) FOR USE: Long-term treatment of children who have growth failure due to inadequate secretion of endogenous growth hormone.

## APPLICATION INFORMATION

APPLICATION TYPE *(check one)*
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 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)*
☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

REASON FOR SUBMISSION Revised Draft Labeling

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

## ESTABLISHMENT INFORMATION

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19-721

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: April 30, 2000*
*See OMB Statement on page 2.*

FOR FDA USE ONLY

APPLICATION NUMBER

## APPLICANT INFORMATION

| NAME OF APPLICANT | DATE OF SUBMISSION |
|---|---|
| Novo Nordisk Pharmaceuticals, Inc. | 4/3/00 |
| **TELEPHONE NO.** *(Include Area Code)* | **FACSIMILE (FAX) Number** *(Include Area Code)* |
| (609) 987-5822 | (609) 987-3916 |
| **APPLICANT ADDRESS** *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* | **AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE |
| 100 Overlook Center<br>Suite 200<br>Princeton, New Jersey 08540 | |

## PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-148

| ESTABLISHED NAME (e.g., Proper name, USP/USAN name) | PROPRIETARY NAME (trade name) IF ANY |
|---|---|
| Somatropin (rDNA origin) for subcutaneous injection | Norditropin® SimpleXx™ |

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any)

CODE NAME (If any) Laboratory Code: BhGH

| DOSAGE FORM: | STRENGTHS: | ROUTE OF ADMINISTRATION: |
|---|---|---|
| Liquid | 5mg, 10mg and 15mg | Subcutaneous injection |

(PROPOSED) INDICATION(S) FOR USE: Long-term treatment of children who have growth failure due to inadequate secretion of endogenous growth hormone.

## APPLICATION INFORMATION

APPLICATION TYPE *(check one)*

☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)

☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 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)*

☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION

☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT

☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION Response to FDA Request for Information

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ 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)**

19-721

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: April 30, 2000*
*See OMB Statement on page 2.*

FOR FDA USE ONLY

APPLICATION NUMBER

## APPLICANT INFORMATION

| NAME OF APPLICANT | DATE OF SUBMISSION |
|---|---|
| Novo Nordisk Pharmaceuticals, Inc. | 3/23/00 |
| **TELEPHONE NO.** *(Include Area Code)* | **FACSIMILE (FAX) Number** *(Include Area Code)* |
| (609) 987-5822 | (609) 987-3916 |
| **APPLICANT ADDRESS** *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* | **AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE |
| 100 Overlook Center<br>Suite 200<br>Princeton, New Jersey 08540 | |

## PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-148

| ESTABLISHED NAME (e.g., Proper name, USP/USAN name) | PROPRIETARY NAME (trade name) IF ANY |
|---|---|
| Somatropin (rDNA origin) for subcutaneous injection | Norditropin® SimpleXx™ |

| CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) | CODE NAME (If any) |
|---|---|
| | Laboratory Code: BhGH |

| DOSAGE FORM: | STRENGTHS: | ROUTE OF ADMINISTRATION: |
|---|---|---|
| Liquid | 5mg, 10mg and 15mg | Subcutaneous injection |

(PROPOSED) INDICATION(S) FOR USE: Long-term treatment of children who have growth failure due to inadequate secretion of endogenous growth hormone.

## APPLICATION INFORMATION

APPLICATION TYPE *(check one)*
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 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)*
☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

REASON FOR SUBMISSION Response to FDA Request for Information

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

## ESTABLISHMENT INFORMATION

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19-721

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: April 30, 2000*
*See OMB Statement on page 2.*

FOR FDA USE ONLY

APPLICATION NUMBER

## APPLICANT INFORMATION

| NAME OF APPLICANT | DATE OF SUBMISSION |
|---|---|
| Novo Nordisk Pharmaceuticals, Inc. | 3/16/00 |
| **TELEPHONE NO.** *(Include Area Code)* | **FACSIMILE (FAX) Number** *(Include Area Code)* |
| (609) 987-5822 | (609) 987-3916 |
| **APPLICANT ADDRESS** *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* | **AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE |
| 100 Overlook Center<br>Suite 200<br>Princeton, New Jersey 08540 | |

## PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-148

| ESTABLISHED NAME (e.g., Proper name, USP/USAN name) | PROPRIETARY NAME (trade name) IF ANY |
|---|---|
| Somatropin (rDNA origin) for subcutaneous injection | Norditropin® SimpleXx™ |

| CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) | CODE NAME (If any) |
|---|---|
| | Laboratory Code: BhGH |

| DOSAGE FORM: | STRENGTHS: | ROUTE OF ADMINISTRATION: |
|---|---|---|
| Liquid | 5mg, 10mg and 15mg | Subcutaneous injection |

(PROPOSED) INDICATION(S) FOR USE: Long-term treatment of children who have growth failure due to inadequate secretion of endogenous growth hormone.

## APPLICATION INFORMATION

APPLICATION TYPE *(check one)*
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 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)*
☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION Response to FDA Request for Information

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

## ESTABLISHMENT INFORMATION

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19-721

**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: April 30, 2000*
*See OMB Statement on page 2.*

**FOR FDA USE ONLY**

APPLICATION NUMBER

21-148

## APPLICANT INFORMATION

| NAME OF APPLICANT | DATE OF SUBMISSION |
|---|---|
| Novo Nordisk Pharmaceuticals, Inc. | 06/30/99 |
| TELEPHONE NO. *(Include Area Code)* (609) 987-5877 | 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, NJ 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) 21-148

| ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)* | PROPRIETARY NAME *(trade name)* IF ANY |
|---|---|
| Somatropin (rDNA origin) for subcutaneous injection | Norditropin® SimpleXx™ |

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*

CODE NAME *(If any)*

| DOSAGE FORM: | STRENGTHS: | ROUTE OF ADMINISTRATION: |
|---|---|---|
| Liquid | 5mg, 10mg, 15mg | Subcutaneous Injection |

(PROPOSED) INDICATION(S) FOR USE: Long-term treatment of children who have growth failure due to inadequate secretion of endogenous growth hormone.

## APPLICATION INFORMATION

APPLICATION TYPE (check one)

☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)

☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

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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)

☒ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION

☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT

☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION Original application for new dosage form

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER-THE-COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 23

THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ 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.

Novo Nordisk A/S, Gentofte, Denmark

The facilities for both drug substance and drug product will be ready for inspection on November 1, 1999.

**ıss References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs and DMFs referenced in the current .plication)**

NDA 19-721

## Field Copy Certification

The undersigned certifies that the field copy of this document is an exact copy of that submitted to NDA 21-148.

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

**OFFICES OF DRUG EVALUATION**
**ORIGINAL NDA/NDA EFFICACY SUPPLEMENT**
**ACTION PACKAGE CHECKLIST**

NDA 21-148 Drug: Norditropin Cartridges + NordiPen

Applicant: Novo Nordisk Chem/Ther/other Types: 3S

CSO/PM: Crystal King Phone: 827-6423 MailCode: HFD-510

ACTION PERF. GOAL DATE: UE 12: 7/1/00 DATE CKLIST CMPLTD: 5/30/00

Arrange package in the following order (include a completed copy of this CHECKLIST): Check or Comment

1. ACTION LETTER with supervisory signatures — AP ✓ AE ___ NA ___
   Are there any Phase 4 commitments? — Yes ✓ No ___
2. Have all disciplines completed their reviews? — Yes ✓ No ___
   If no, what review(s) is/are still pending? ___
3. LABELING (package insert and carton and container labels). — Draft ✓
   (If final or revised draft, include copy of previous version with ODE's comments and state where in action package the Division's review is located. If Rx-to-OTC switch, include current Rx Package insert and HFD-312 and HFD-560 reviews of OTC labeling.) — Revised Draft ___ Final ___
4. PATENT INFORMATION ✓
5. EXCLUSIVITY CHECKLIST ✓
6. PEDIATRIC PAGE ✓
7. DEBARMENT CERTIFICATION (Copy of applicant's certification for all NDAs submitted on or after June 1, 1992). ✓
8. Statement on status of DSI's AUDIT OF PIVOTAL CLINICAL STUDIES — NN
   If AE or AP ltr, explain if not satisfactorily completed. Attach a COMIS printout of DSI status.
   If no audits were requested, include a memo expaining why.

9. REVIEWS & MEMORANDA:

| | | |
|---|---|---|
| DIVISION DIRECTOR'S MEMO | If more than 1 review for any | ✓ |
| GROUP LEADER'S MEMO | 1 discipline, separate reviews | ✓ |
| MEDICAL REVIEW | with a sheet of colored paper. | ✓ |
| SAFETY UPDATE REVIEW | Any conflicts between reviews | NN |
| STATISTICAL REVIEW | must have resolution documented | NN |
| BIOPHARMACEUTICS REVIEW | | 3/21/00 |
| PHARMACOLOGY REVIEW (Include pertinent IND reviews) | | 3/17/00 |
| Statistical Review of Carcinogenicity Study(ies) | | — |
| CAC Report/Minutes | | |
| CHEMISTRY REVIEW | | 3/14/00 |
| Labeling and Nomenclature Committee Review Memorandum | | — |
| Date EER completed 7/16/99 (attach signed form or CIRTS printout) | | OK ✓ No ___ |
| FUR needed — FUR requested — | | |
| Have the methods been validated? | | Yes (attach) — NN No — |
| Environmental Assessment Review / FONSI | | Review See review FONSI — |
| ODRH (devices) consult | | 3/7/00 |
| MICROBIOLOGY REVIEW | | 3/22/00 |
| What is the status of the monograph? | | — |
| OPDRA consult | | ✓ |

10. CORRESPONDENCE, MEMORANDA OF TELECONS, and FAXes ___
11. MINUTES OF MEETINGS ✓
    Date of End-of-Phase 2 Meeting ___
    Date of pre-NDA Meeting 4/7/99 IND # ___
12. ADVISORY COMMITTEE MEETING MINUTES — Minutes NA Info Alert —
    or, if not available, 48-Hour Info Alert or pertinent section of transcript. — Transcript — No mtg ___
13. FEDERAL REGISTER NOTICES; OTC or DESI DOCUMENTS — NN
14. If approval letter, has ADVERTISING MATERIAL been reviewed? — Yes — No —
    If no and this is an AP with draft labeling letter, has advertising material already been requested? — Yes, documentation attached ___ No, included in AP ltr ✓
15. INTEGRATED SUMMARY OF EFFECTIVENESS (from NDA) — NN

| | |
|---|---|
| 16. **INTEGRATED SUMMARY OF SAFETY** (from NDA) | NN |
| 17. **FDA LETTERS & MEMOS** | ✓ |
| 18. **APPLICANT'S LETTERS** | ✓ |
| 19. **CHARGE AND HISTORY CARD** | ✓ |

revision:1/16/98

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

# CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

*TO BE COMPLETED BY APPLICANT*

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

*Please mark the applicable checkbox.*

/ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

| Clinical Investigators | Studies: GHPHKIN/BPD/13/UK<br>GHPHKIN/BPD/14/UK |
|---|---|
| / | |

/ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

/ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

| NAME | TITLE |
|---|---|
| Barry Reit, PhD | Vice President, Regulatory Affairs |
| FIRM/ORGANIZATION<br>Novo Nordisk Pharmaceuticals, Inc.<br>100 Overlook Center, Suite 200, Princeton, NJ 08540 | |
| SIGNATURE | DATE |

**Paperwork Reduction Act Statement**

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

# LABELING REVIEW

| | |
|---|---|
| Application: | NDA 21-148 |
| Drug: | Norditropin (somatropin [rDNA origin]) injection) |
| Sponsor: | Novo Nordisk |
| Review of: | Final labeling submitted May 25, 2000 |
| Review date: | May 30, 2000 |
| Materials reviewed: | Comparison of FPL submission against original NDA submission of June 30, 1999, and all labeling comments and revisions as negotiated between reviewers and sponsor. |
| Summary: | This new liquid formulation of growth hormone will be provided in cartridges of three different dosages (5 mg/1.5 mL, 10 mg/1.5 mL, and 15 mg/1.5 mL) for use in a re-usable pen injector device. Evaluation includes the package insert and cartridge vial labels, cartridge box labels, pen device cartons, and pen device instructional for all three dosages. |

Medical Team Leader: (b)(4)

Chemistry Reviewer: (b)(4)

Chemistry Team Leader: (b)(4)

Pharmacology Reviewer: (b)(4)

Pharmacology Team Leader: (b)(4)

Biopharmaceutics Reviewer: (b)(4)

Biopharmaceutics Team Leader: (b)(4)

Regulatory Project Manager: (b)(4)

Chief, Project Management Staff: (b)(4)

cc: NDA 21-148
Division File