021536_OriginalApproval_Package.PDF

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
21-536

Trade Name:	Levemir
Generic Name:	Insulin detemir [rDNA origin] injection
Sponsor:	Novo Nordisk, Inc.
Approval Date:	June 16, 2005
Indications:	Provides for the use of Levemir (insulin detemir [rDNA origin] injection) for once or twice-daily subcutaneous administration in the treatment of adult patients with Type 1 or Type 2 diabetes mellitus who require basal (long-acting) insulin for the control of hyperglycemia.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-536

CONTENTS

Reviews / Information Included in this NDA Review.	
Approval Letter	X
Approvable Letter(s)	
Final Printed Labeling	X
Medical Review(s)	X
Chemistry Review(s)	X
EA/FONSI	
Pharmacology Review(s)	X
Statistical Review(s)	X
Microbiology Review(s)	X
Clinical Pharmacology/ Biopharmaceutics Review(s)	X
Administrative Document(s) and Correspondence	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-536

APPROVAL LETTER(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-536

Novo Nordisk Inc.
Attention: Mary Ann McElligott, Ph.D.
Associate Vice President, Regulatory Affairs
100 College Road West
Princeton, NJ 08540

Dear Dr. McElligott:

Please refer to your new drug application (NDA) dated December 5, 2002, received December 5, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Levemir (insulin detemir [rDNA origin] injection).

We acknowledge receipt of your submissions dated October 22, and November 21, 2003, May 21, June 22, and December 20, 2004, and January 21 and 24, March 10 and 21, April 4, 7, 8, and 26, May 11, and June 1, 10, 14 (2), 15, and 16 (2), 2005.

The December 20, 2004, submission constituted a complete response to our October 2, 2003, action letter.

This new drug application provides for the use of Levemir (insulin detemir [rDNA origin] injection) for once or twice-daily subcutaneous administration in the treatment of adult patients with Type 1 or Type 2 diabetes mellitus who require basal (long-acting) insulin for the control of hyperglycemia.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text and the editorial revision listed below:

> The "Sample Not For Resale" statement should be displayed prominently on all of the panels of the sample carton labeling for the vial, 3 mL PenFill cartridge, 3 mL FlexPen, and 3 mL InnoLet.

We remind you that the color used on the labels and labeling for Levemir, "Green C," should not be used for any other insulin product in the International Diabetes Foundation color coding scheme.

The final printed labeling (FPL) must be identical to the submitted labeling (text for the package insert and text for the patient package inserts submitted June 16, 2005; immediate container and carton labels submitted June 10, 2005) as edited above. Marketing the product with FPL that is

not identical to the approved labeling text as edited may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-536.**" Approval of this submission by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have fulfilled the pediatric study requirement for this application for ages 6 and above.

Additionally, we are deferring submission of your pediatric studies for ages birth through 5 years old until June 30, 2009.

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The status of this postmarketing study shall be reported annually according to 21 CFR 314.81. This commitment is listed below.

1. Deferred pediatric study under PREA for the treatment of diabetes in pediatric patients ages birth through 5 years old.

   Final Report Submission: June 30, 2009

Submit the final study report to this NDA. For administrative purposes, all submissions related to this pediatric postmarketing study commitment should be clearly designated "**Required Pediatric Study Commitments**".

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Metabolic and Endocrine Drug Products and two copies of both the promotional materials and the package inserts directly to:

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

Please submit one market package of the drug product when it is available.

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

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

Sincerely,

{See appended electronic signature page}

Robert J. Meyer, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Labeling pieces enclosed:

1. Physician Insert
2. Information For The Patient for 10 mL Vial and 3 mL PenFill Cartridge
3. Information For The Patient for 3 mL FlexPen
4. Information For The Patient for 3 mL InnoLet
5. Levemir FlexPen (3 mL) sample carton
6. Levemir FlexPen (3 mL) sample container
7. Levemir FlexPen (3 mL) trade carton
8. Levemir InnoLet (3 mL) sample carton
9. Levemir InnoLet (3 mL) sample container
10. Levemir InnoLet (3 mL) trade carton
11. Levemir PenFill (3 mL) sample carton
12. Levemir PenFill (3 mL) sample container
13. Levemir PenFill (3 mL) trade carton
14. Levemir vial (10 mL) sample carton
15. Levemir vial (10 mL) sample container
16. Levemir vial (10 mL) trade container

Labeling pieces not enclosed:

1. Levemir FlexPen (3 mL) trade container
2. Levemir InnoLet (3 mL) trade container
3. Levemir PenFill (3 mL) trade container
4. Levemir vial (10 mL) trade carton

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-536

APPROVABLE LETTER(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-536

10/2/03

AE

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

Dear Dr. Reit:

Please refer to your new drug application (NDA) dated December 5, 2002, received December 5, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prydectia™ (insulin detemir [rDNA origin] injection).

We acknowledge receipt of your submissions dated January 15 and 24, February 21, March 3 and 7, April 2, 3, 7, 16, 17, and 23, May 1, June 26, July 2, August 5, and September 17 and 19, 2003.

We have completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to adequately address the following deficiencies.

Clinical Safety and Efficacy:

Of the five Phase 3 trials submitted in patients with type 1 diabetes, only one trial conclusively demonstrated non-inferiority of insulin detemir to NPH insulin when both were administered twice daily (this trial used an insulin detemir formulation four times the molar concentration of standard human insulin products).

In patients with type 2 diabetes, no Phase 3 trial demonstrated non-inferior efficacy of insulin detemir to NPH. However, the non-white subgroup in trial 1337 (in contrast to the majority white subgroup and hence the overall results) appeared to show efficacy of insulin detemir comparable to that of NPH, suggesting differential efficacy in non-white patients compared to Caucasians.

While there is evidence in your application that insulin detemir is an active insulin, the failure to consistently demonstrate efficacy (as defined by non-inferiority to NPH), a lack of conclusive data establishing the relative potency of insulin detemir to human insulin, and the

finding of potential differences in responsiveness to insulin detemir by race/ethnic group lead to the following conclusions:

- For the proposed target populations of patients with type 1 and type 2 diabetes, the effective dose(s) of insulin detemir has not been established, particularly compared to other basal insulins.
- For the proposed target populations of patients with type 1 and type 2 diabetes, the safe dose(s) of insulin detemir has not been established, particularly compared to other basal insulins.
- A "unit" of insulin detemir was defined for the purposes of the clinical trials. However, there is inconsistency in the clinical activity of insulin detemir relative to NPH, which suggests that insulin detemir should be labeled a[illegible]e and not by the conventional (e.g., U-100) nomenclature used for all other insulin products.

Information necessary to address these deficiencies is listed below. You are strongly encouraged to confer with the Division of Metabolic and Endocrine Drug Products prior to design and initiation of studies designed to address these deficiencies.

1. Additional trials in patients with type 1 and type 2 diabetes should be conducted in the U.S. and attempts should be made to enroll African-American, Latino, and Caucasian patients in approximately equal proportions. Collection of data on potential genetic markers of risk or response, as well as on environmental and dietary factors that might affect insulin effect are recommended.

    a. Type 1 diabetes:

    An additional U.S. trial in patients with type 1 diabetes is required to corroborate the findings of trial 1448, to characterize the response to and safety of insulin detemir in whites versus non-whites, and to better inform dosing and the method of use of insulin detemir in the broad patient population of patients with type 1 diabetes mellitus.

    While you are encouraged to discuss the protocol with the Division of Metabolic and Endocrine Drug Products prior to initiating such a study, the following summarizes a suggested trial design: a two-period, open-label study, 6 months in total duration. During the first 3-month period, all patients will be treated with insulin detemir and mealtime bolus insulin with a therapeutic goal of HbA1c $\leq$ 7.5%. Responders (HbA1c $\leq$ 7.5%) may then be randomized in the second 3-month period to insulin detemir or NPH, both given twice daily, again in addition to bolus insulin. The primary comparison is the change from baseline at the start of period 2 to end of study between treatment groups with a test for non-inferiority of insulin detemir to NPH. Randomization should be stratified by race/ethnicity. Patients who fail to achieve glycemic control during period 1 and/or dropouts for lack of efficacy on insulin detemir during period 2 should be switched to NPH and their response assessed (descriptive analysis only). The analysis of response in period 1 should be descriptive as well.

b. Type 2 diabetes:

At least one additional U.S. study in patients with type 2 diabetes is required to (1) establish, in an unconfounded trial, the non-inferiority of insulin detemir to NPH dosed twice daily, and (2) examine prospectively the efficacy and safety of insulin detemir in type 2 diabetes as a function of race/ethnicity.

The following summarizes a suggested trial design: a 6-month, open-label comparison of insulin detemir to NPH in patients who have not received insulin for at least three months. Patients with HbA1c >8% will be randomized to insulin detemir or NPH both dosed once daily or twice daily with titration to HbA1c $\leq$ 7.5%. No other antidiabetic medications are permitted during the last 3 months of the study. The primary comparison is the change from baseline to endpoint in HbA1c between treatment groups with a test of non-inferiority of insulin detemir to NPH. Randomization should be stratified by race/ethnicity. Antibodies to human insulin and to insulin detemir should be measured at endpoint.

2. Risk management proposals:

The potential for consumer and/or healthcare practitioner confusion and the resultant risk of under- or overdosing with insulin detemir when switching from another basal insulin must be adequately managed and needs to be better addressed. Your response should include sufficient evidence to provide assurance that the marketed concentration of insulin detemir is such that equivalent volumes of insulin detemir and U-100 long-acting human insulin products will have comparable glucose-lowering activities in clinical use. If differential clinical responses are confirmed amongst different patient subpopulations, some other reasonable method of informing practitioners and patients about appropriate dosing must be identified and supported. Proposals regarding patient and healthcare practitioner education including appropriately revised labeling should be submitted.

Chemistry, Manufacturing, and Controls:

3. A limited number — of clinical batches was used to present a correlation between the mouse blood glucose assay (MBG) and the free fat cell assay (FFCA) (activity ratio of MBG/FFC). The biological activity of insulin detemir should include the modified MBG assay until sufficient production scale batches have been manufactured to demonstrate a consistent correlation between these two assays.

4. Provide the in-process control acceptance criteria for the following attributes:

2 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

____ § 552(b)(5) Deliberative Process

____ § 552(b)(5) Draft Labeling

22. Submit the results from an in-use stability study to support storage of the 10 mL vial, 100 U/mL for 42 days at room temperature. The study should include testing for —

Labeling:

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

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Although not approvability issues, we have the following recommendations for your consideration:

Clinical Pharmacology and Biopharmaceutics:

A. Develop improved methodology in order to achieve a valid system with which to study insulin detemir action and degradation *in vitro*.

B. In rat liver microsomal studies, insulin detemir induced CYP1A family and CYP2E1 up to 30% as well as total cytochrome P450 activity up to 21%. It is known that diabetes itself also induces CYP2E1 activity. The activity of insulin detemir with regard to CYP induction should be further investigated in humans. Studies should include an *in vitro* induction study using human hepatocytes.

C. *In vitro* insulin degradation profiles have been well studied and the information is readily available from literature. The initial degradation product is an intact A chain with one or more cleavages in the B chain and an intact disulfide bond (*Duckworth et al., Endocrine Review 19(5):608-624, 1998*). However, the metabolic pathways you provided for human insulin, using your methodology, are very different from those available in the literature regarding the sequence and products. Since insulin detemir has many unique characteristics, a valid *in vitro* metabolic profile of insulin detemir needs to be established. You are encouraged to submit the protocol for review before the study is initiated.

Chemistry, Manufacturing, and Controls:

D. A stability update for the first three production-scale batches (—) of insulin detemir Penfill® 3 mL, 100 U/mL, should be provided.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

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

Sincerely,

{See appended electronic signature page}

Robert J. Meyer, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Meyer
10/2/03 03:55:49 PM