CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-536

ADMINISTRATIVE DOCUMENTS

12/20/04 submission

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
21-536

NAME OF APPLICANT / NDA HOLDER
Novo Nordisk Inc.
100 College Road West
Princeton, NJ 08540 USA

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
To Be Assigned

ACTIVE INGREDIENT(S)	STRENGTH(S)
insulin detemir	100 units/ml

DOSAGE FORM
injectable; subcutaneous

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5,750,497	5/12/1998	5/12/2015

d. Name of Patent Owner	Address *(of Patent Owner)*	
Novo Nordisk A/S	Novo Alle	
	City/State: 2880 Bagsvaerd	
	ZIP Code: Denmark	FAX Number *(if available)*
	Telephone Number: 45 444 48888	E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☒ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3	If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7	If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3	If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for* each *patent claim claiming a method of using the pending drug product for which approval is being sought. For* each *method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No

4.2 Patent Claim Number *(as listed in the patent)*	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?		
95		☒ Yes	☐ No

4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.

Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*

Use of insulin detemir for once or twice-daily subcutaneous administration in the treatment of patients with diabetes mellitus who require basal (long acting coverage) insulin for the control of hyperglycemia

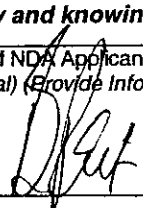
5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

6. Declaration Certification

The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	12/20/04

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Barry Reit, Ph.D.	
Address 100 College Road West	City/State Princeton, NJ
ZIP Code 08540	Telephone Number 609-987-5822
FAX Number *(if available)* 609-987-3916	E-Mail Address *(if available)* brei@nnpi.com

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

NDA NUMBER
21-536

NAME OF APPLICANT / NDA HOLDER
Novo Nordisk Inc
100 College Road West
Princeton, NJ 08540 USA

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
To Be Assigned

ACTIVE INGREDIENT(S)	STRENGTH(S)
insulin detemir	100 units/ml

DOSAGE FORM
Injectable; subcutaneous

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the tent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5,866,538	2/2/1999	6/20/2017

d. Name of Patent Owner
Novo Nordisk A/S

Address *(of Patent Owner)*
Novo Alle

City/State
2880 Bagsvaerd

ZIP Code
Denmark

FAX Number *(if available)*

Telephone Number
45 444 48888

E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address *(of agent or representative named in 1.e.)*

City/State

ZIP Code

FAX Number *(if available)*

Telephone Number

E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☒ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3	If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7	If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3	If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
4.2	Patent Claim Number *(as listed in the patent)*	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☐ No	
4.2a	If the answer to **4.2** is "Yes," *identify with specificity* the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	12/29/04

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Barry Reit, Ph.D.	
Address 100 College Road West	City/State Princeton, NJ
ZIP Code 08540	Telephone Number 609-987-5822
FAX Number *(if available)* 609-987-3916	E-Mail Address *(if available)* brei@nnpi.com

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
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PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

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NDA NUMBER
21-536

NAME OF APPLICANT / NDA HOLDER
Novo Nordisk Inc.
100 College Road West
Princeton, NJ 08540 USA

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
To Be Assigned

ACTIVE INGREDIENT(S)	STRENGTH(S)
insulin detemir	100 units/ml

DOSAGE FORM
injectable; subcutaneous

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1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
6,011,007	1/4/2000	9/16/2014

d. Name of Patent Owner	Address *(of Patent Owner)*	
Novo Nordisk A/S	Novo Alle	
	City/State 2880 Bagsvaerd	
	ZIP Code Denmark	FAX Number *(if available)*
	Telephone Number 45 444 48888	E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☒ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

Drug Substance (Active Ingredient)

...1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3	If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7	If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

Drug Product (Composition/Formulation)

	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3	If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for* each *patent claim claiming a method of using the pending drug product for which approval is being sought. For* each *method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2	Patent Claim Number *(as listed in the patent)* 85	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No	
4.2a	If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* Use of insulin detemir for once or twice-daily subcutaneous administration in the treatment of patients with diabetes mellitus who require basal (long acting coverage) insulin for the control of hyperglycemia	

5. No Relevant Patents

	For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to ...h a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in ...anufacture, use, or sale of the drug product.	☐ Yes

6 Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	12/20/04

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Barry Reit, Ph.D.	
Address 100 College Road West	City/State Princeton, NJ
ZIP Code 08540	Telephone Number 609-987-5822
FAX Number *(if available)* 609-987-3916	E-Mail Address *(if available)* brei@nnpi.com

Time Sensitive Patent Information pursuant to 21 C.F.R. 314.53 for NDA#21-536

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name:	**To Be Assigned**
Active Ingredient(s):	**INSULIN DETEMIR**
Strength(s):	100 UNITS/ML
Dosage Form:	Injectable; Subcutaneous
Approval Date:	To Be Determined

A. This information should be provided for each individual patent submitted.

U.S. Patent Number: **5,750,497**

Expiration Date: **May 12, 2015**
Type of Patent -- Indicate all that apply:

Drug Substance (Active Ingredient) X Y __N
Drug Product (Composition/Formulation) X Y __N
Method of Use X Y __N

i. If patent claims method(s) of use, please specify approved method(s) of use or method(s) of use for which approval is being sought that are covered by Patent:

A method of treating diabetes

Name of Patent Owner: Novo Nordisk A/S
Bagsvaerd, Denmark

U.S. Agent (if patent owner or applicant does not reside or have place of business in the US):

B. Declaration Statement Required by 21 CFR 314.53

The undersigned declares that the above stated United States Patent Number **5,750,497** covers the composition, formulation and/or method of use of **INSULIN DETEMIR**. This product is:

- currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act

OR

- _X_ the subject of this application for which approval is being sought.

Signed: Richard Bock

Date: November 7, 2002

Title (optional): Senior Patent Attorney

Telephone Number (optional): 609-919-7824

Appears This Way
On Original

Time Sensitive Patent Information pursuant to 21 C.F.R. 314.53 for NDA#21-536

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name:	**To Be Assigned**
Active Ingredient(s):	**INSULIN DETEMIR**
Strength(s):	100 UNITS/ML
Dosage Form:	Injectable; Subcutaneous
Approval Date:	To Be Determined

A. This information should be provided for each individual patent submitted.

U.S. Patent Number: **6,011,007**

Expiration Date: **September 16, 2014**

Type of Patent -- Indicate all that apply:

Drug Substance (Active Ingredient) X Y __N
Drug Product (Composition/Formulation) X Y __N
Method of Use X Y __N

i. If patent claims method(s) of use, please specify approved method(s) of use or method(s) of use for which approval is being sought that are covered by Patent:

A method of treating diabetes

Name of Patent Owner: Novo Nordisk A/S
Bagsvaerd, Denmark

U.S. Agent (if patent owner or applicant does not reside or have place of business in the US):

B. Declaration Statement Required by 21 CFR 314.53

The undersigned declares that the above stated United States Patent Number **6,011,007** covers the composition, formulation and/or method of use of **INSULIN DETEMIR**. This product is:

- __ currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act

OR

- _X_ the subject of this application for which approval is being sought.

Signed: Richard Bork

Date: November 7, 2002

Title (optional): Senior Patent Attorney

Telephone Number (optional): 609-919-7824

Appears This Way
On Original

Time Sensitive Patent Information pursuant to 21 C.F.R. 314.53 for NDA#21-536

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name:	**To Be Assigned**
Active Ingredient(s):	**INSULIN DETEMIR**
Strength(s):	100 UNITS/ML
Dosage Form:	Injectable; Subcutaneous
Approval Date:	To Be Determined

A. This information should be provided for each individual patent submitted.

U.S. Patent Number: **5,866,538**

Expiration Date: **June 20, 2017**

Type of Patent -- Indicate all that apply:

Drug Substance (Active Ingredient) __Y __N
Drug Product (Composition/Formulation) X Y __N
Method of Use _Y __N

ii. If patent claims method(s) of use, please specify approved method(s) of use or method(s) of use for which approval is being sought that are covered by Patent:

Name of Patent Owner: Novo Nordisk A/S
Bagsvaerd, Denmark

U.S. Agent (if patent owner or applicant does not reside or have place of business in the US):

B. Declaration Statement Required by 21 CFR 314.53

The undersigned declares that the above stated United States Patent Number **5,866,538** covers the composition, formulation and/or method of use of **INSULIN DETEMIR**. This product is:

- ___currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act

OR

- _X_ the subject of this application for which approval is being sought.

Signed: Richard Bork

Date: November 7, 2002

Title (optional): Senior Patent Attorney

Telephone Number (optional): 609-919-7824

EXCLUSIVITY SUMMARY

NDA # 21-536 SUPPL # n/a HFD # 510

Trade Name Levemir

Generic Name Insulin detemir [rDNA origin] injection

Applicant Name Novo Nordisk

Approval Date, If Known June 16, 2005

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy 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 a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) 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.

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:

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (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.

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).

NDA#

NDA#

NDA#

2. Combination product.

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).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs 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 ON PAGE 8.

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.

(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 BLOCK ON PAGE 8:

(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:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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 ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

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 ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) 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"):

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 !

IND # YES ☐ ! NO ☐

! Explain:

Investigation #2 !

IND # YES ☐ ! NO ☐

! 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 ☐ Explain:	! NO ☐ ! Explain:
Investigation #2 YES ☐ Explain:	! ! ! NO ☐ ! 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:

Name of person completing form:
Title:
Date:

Name of Office/Division Director signing form:
Title:

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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
6/17/05 04:29:34 PM

In DFS waiting for concurrence
6/16/05 sr

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA #: 21-536 **Supplement Type (e.g. SE5):** n/a **Supplement Number:**

Stamp Date: December 5, 2002 **Action Date:** June 16, 2005 **HFD-510**

Trade and generic names/dosage form: Levemir (insulin detemir [rDNA origin] injection)

Applicant: Novo Nordisk **Therapeutic Class:** 1S

Indication(s) previously approved: None

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Levemir is indicated for once or twice-daily subcutaneous administration in the treatment of adult patients with diabetes mellitus who require basal (long acting) insulin for the control of hyperglycemia.

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: ___Partial Waiver __x__Deferred __x__Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min____	**kg**____	**mo.**____	**yr.**____	**Tanner Stage**____
Max____	**kg**____	**mo.**____	**yr.**____	**Tanner Stage**____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____	**kg**_____	**mo.**_____	**yr.** Birth	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.** 5	**Tanner Stage**_____

Reason(s) for deferral:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
X **Adult studies ready for approval**
☐ **Formulation needed**
Other:_____

Date studies are due (mm/dd/yy): June30, 2009

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

ction D: Completed Studies

Age/weight range of completed studies:

Min _____	**kg**_____	**mo.**_____	**yr.** 6	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.** 17	**Tanner Stage**_____

Comments: NDA 21-878 was submitted on December 20, 2004, providing pediatric data.

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: **NDA 21-536**
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

NDA 21-536 Insulin Detemir CTD Module 1 Debarment Statement	Response	Date:	December 20, 2004	**Novo Nordisk**

Debarment Statement

Novo Nordisk Inc. hereby certifies that it did not and will 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 application.

Pamela Morgan for B. Reit, Ph.D.

Barry Reit, Ph.D.
Vice President
Regulatory Affairs & Quality Assurance

Debarment Statement

Novo Nordisk Pharmaceuticals Inc. hereby certifies that it did not and will 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 application.

M. Ellyott for B Reit

Barry Reit, Ph.D.
Vice President
Regulatory Affairs & Quality Assurance

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA: 21-536	Efficacy Supplement Type SE-	Supplement Number: NA	
Drug: *Levemir (insulin detemir [rDNA origin] injection)*		Applicant: *Novo Nordisk*	
RPM: *Julie Rhee*		HFD-510	Phone #: *827-6424*

Application Type: (**X**) 505(b)(1) ( ) 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) **If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.** ( ) Confirmed and/or corrected	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):

❖ Application Classifications:	
• Review priority	(**X**) Standard ( ) Priority
• Chem class (NDAs only)	1
• Other (e.g., orphan, OTC)	*NA*
User Fee Goal Dates	*June 20, 2005*
❖ Special programs (indicate all that apply)	(**X**) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review ( ) CMA Pilot 1 ( ) CMA Pilot 2
❖ User Fee Information	
• User Fee	(**X**) Paid UF ID number: *4451*
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other (specify)
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) ( ) Other (specify)
Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (**X**) No
• This application is on the AIP	( ) Yes (**X**) No

• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(X) Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	(X) Verified
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ( ) Verified 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	
• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).*	( ) N/A (no paragraph IV certification) ( ) Verified
• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for each paragraph IV certification: (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))). *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).* (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (3).* (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? (Note: This can be determined by confirming whether the Division has	( ) Yes ( ) No ( ) Yes ( ) No ( ) Yes ( ) No

received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))). *If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*	
(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? *If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "No," continue with question (5).*	( ) Yes ( ) No
(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	( ) Yes ( ) No
❖ Exclusivity (approvals only)	
• Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	*No*
• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	( ) Yes, Application #_____ **(X)** No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	ADRA: Review #1 (10/2/03) RPM: Review #1 (5/24/05)

General Information	
Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	AE (10/2/03)
• Status of advertising (approvals only)	(x) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes (x) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(x) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	*Included (sent to Novo 5/19)*
• Most recent applicant-proposed labeling	*Pending*
• Original applicant-proposed labeling	*Included*
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	*Included*
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	*Included (Lantus from Aventis)*
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	*Included*
• Applicant proposed	*Pending*
• Reviews	*Included*
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	??
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	*Included*
❖ Memoranda and Telecons	*Included*
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	*Included (7/22/99)*
• Pre-NDA meeting (indicate date)	*Included (6/11/02)*
• Pre-Approval Safety Conference (indicate date; approvals only)	
• Other	
❖ Advisory Committee Meeting	
• Date of Meeting	*N/A*
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	*N/A*

Summary Review	
Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	*Pending*
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	*Pending*
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	*N/A*
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	*Pending*
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	*N/A*
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	
❖ Demographic Worksheet *(NME approvals only)*	*N/A*
❖ Statistical review(s) *(indicate date for each review)*	*Included (5/13/05)*
❖ Biopharmaceutical review(s) *(indicate date for each review)*	*Included (5/13/05)*
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	*N/A*
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	*Pending*
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	*Completed (AP, 5/3/05)*
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	*CMC review #1, 9/9/03*
• Review & FONSI *(indicate date of review)*	
• Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	*AP (7/22/03)*
❖ Facilities inspection (provide EER report)	Date completed: *9/25/03* (**x**) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested (**x**) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	*AP (9/5/03)*
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	*No*
❖ CAC/ECAC report	*No*

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: June 13, 2005

FROM: David G. Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products

TO: NDA 21-536
Levemir (insulin detemir [rDNA origin] injection)
Novo Nordisk
Treatment of type 1 and type 2 diabetes mellitus

SUBJECT: NDA review issues and recommended action

I. Background

This is the second review cycle for this fatty-acid modified recombinant human insulin analogue, intended for use as a "basal" or long-acting insulin in type 1 and type 2 diabetes. Please see the division director memo in DFS entered 9/24/03 and co-signed by Dr. Meyer 9/25/03 summarizing the findings of the initial review cycle. An "approvable" action was taken on October 2, 2003, citing clinical and CMC deficiencies. The clinical deficiencies were summarized as follows:

> 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 as — and not by the conventional (e.g., U-100) nomenclature used for all other insulin products.

Additional studies in type 1 and type 2 diabetes were deemed necessary to address the deficiencies. In the case of DM1, an additional U.S. trial was required to corroborate the findings of trial 1448, the single phase 3 study in DM1 that met its objective of non-inferiority of

detemir to NPH, as well as to characterize the efficacy and safety of insulin detemir in whites versus non-whites. For DM2, an additional U.S. trial was required to establish the non-inferior glucose-lowering effect of detemir compared to NPH and to examine the efficacy and safety of detemir in DM2 as a function of race/ethnicity.

Additionally, in order to manage risk around practitioner and patient confusion related to the dose of detemir compared to other basal insulins, evidence was required to provide assurance that equivalent volumes of detemir and U-100 long-acting insulin products would have comparable glucose-lowering effects in clinical use.

Finally, a list of chemistry, manufacturing, and controls information necessary for approval was included in the action letter.

The complete response to the AE letter was submitted on December 20, 2004. The biopharmaceutics package included the results of a race-effect study examining dose-exposure and dose-response relationships of insulin detemir and NPH insulin in Blacks, Hispanics, and Whites, with DM2. Additionally, two iso-glycemic clamp studies, one in DM1 and one in DM2, examined the molar dose ratio for glucose utilization equivalence of insulin detemir to NPH insulin. The clinical package included the results of 3 clinical studies in DM1 and 2 clinical studies in DM2. The CMC information required by the action letter was submitted and reviewed.

II. Clinical efficacy and safety findings

Dr. Pian (statistical reviewer) has summarized the trials contained in the resubmission in her concise and clear review. Table 1 of her review shows the demographics and baseline characteristics and numbers of patients enrolled.

Efficacy in DM1

The results of the clinical studies are discussed in the medical and statistical reviews. Three clinical studies in DM1 were submitted. Study 1372 was a 26-week, open-label, randomized, insulin glargine-controlled trial with insulin aspart (Novolog) as the bolus insulin in both treatment groups, with a non-inferiority efficacy objective. Study 1374 was an 18-week, open-label comparison of insulin detemir plus bolus insulin aspart to NPH insulin plus bolus human regular insulin with a superiority efficacy objective. Study 1375 was an open-label, two period crossover study comparing the frequency of hypoglycemia in patients treated with insulin detemir versus NPH insulin. Each period lasted 16-weeks which included a 6-week titration phase followed by a 10-week maintenance phase.

Study 1372 met its objective of demonstrating non-inferior glycemic control with a detemir/aspart regimen compared to a glargine/aspart regimen, and importantly the result was not confounded by differences between groups in the amount of bolus insulin used. Therefore, this study corroborates the findings of study 1448 and serves as a second study demonstrating efficacy in DM1. Study 1374 met its objective of demonstrating superior efficacy of a regimen of twice daily detemir plus bolus aspart to twice daily NPH plus bolus regular insulin, without apparent confounding by differences in the amount of bolus insulin, though this unblinded trial

using drugs that are titrated to effect, and in which the bolus insulins were also different does not support clinical superiority of detemir to NPH. The ratios of volumes of insulin detemir to comparator basal insulin in these trials were 1.14 and 1.37 in trial 1372 and trial 1374, respectively, thus better informing the dose comparisons for patients who might switch from another basal insulin to detemir.

Efficacy in DM2

The results of 2 clinical studies in DM2 were also submitted. Study 1385 compared a detemir/aspart regimen to an NPH/regular insulin regimen over 22 weeks in an unblinded trial. Study 1530 was a 26-week, open-label, non-inferiority comparison of detemir twice daily to NPH twice daily in patients treated with oral agents (OAD).

In study 1530, detemir and NPH were similarly effective in the control of glycemia, with 1.5 times the volume of detemir needed compared to NPH. Study 1385 met its non-inferiority objective, without apparent confounding by differences in the amounts of bolus insulin used between treatment groups (though the bolus insulins were different types) and with the average volume of detemir used approximately 1.4 times the average volume of NPH. Thus, these trials provide adequate support for the use of detemir in DM2 and inform labeling of the product with regard to dose comparisons to NPH.

III. Safety

Immunogenicity

The frequency of anti-insulin antibodies was higher in detemir-treated patients than in NPH-treated patients, though there were no apparent clinical consequences.

Secondary Effects associated with insulin therapy

Hypoglycemia

Insulin therapy is associated with a risk of hypoglycemia with increasing dose and with progressive improvements in overall glucose control. In addition, for any given dose of insulin, based on the kinetics of its absorption and clearance, risk of hypoglycemia will be impacted by the timing and quantity of meals. Comparisons between treatment groups in trials of hypoglycemic agents, like insulin, specifically regarding rates of hypoglycemia, must be interpreted in the context of trial design, randomization, blinding, differences in glycemic control between treatment groups, methods of ascertainment of events, endpoint criteria (i.e., definition of hypoglycemic events), confounding medications, and must acknowledge possible bias introduced by many other unknown variables. In trials of insulin detemir, all studies were open-label; in only some of the studies was glycemic control statistically comparable between treatment groups (or superior for the detemir groups); the vast majority of events were minor hypoglycemic events not involving another party (thus patient reported and lacking "hard" documentation); and in many trials there was confounding by imbalances in the amounts of bolus insulin (or differences in the types of bolus insulin) used between treatment groups. As a result of these facts, even considerations of comparisons of rates of hypoglycemia must be restricted to trials which met their efficacy objectives without confounding by differences between treatment groups in the type or amount of bolus insulin used, and major hypoglycemic events should be the only events considered. In the detemir application, only trial 1448 in DM1 from the original

submission showed non-inferiority of detemir to NPH for glycemic control and was not confounded by differences between groups in the amount of bolus insulin used, though this was an open-label trial. In the resubmission, study 1372 was a randomized, open-label study comparing detemir/aspart to glargine/aspart in DM1 which met its non-inferiority efficacy objective. In the original application, no trial in DM2 met a non-inferiority objective without confounding by differences between treatment groups in the amount of bolus insulin used. In the resubmission, studies 1385 and 1530 met their efficacy objectives and were considered valid for conclusions of the efficacy of detemir in support of labeling. The restriction to major events is consistent with our reviews of other applications and labeling of other drugs in this therapeutic area.

Dr. Misbin has discussed the hypoglycemia findings at length in his review. He relies on the results of trial 1375, the open-label crossover study in DM1 comparing detemir to NPH in two 16-week periods, and to the results of trial 1530, a 22-week, open-label comparison of detemir to NPH in insulin-naïve DM2 patients treated with oral agents, to conclude that detemir appears to cause less hypoglycemia than NPH. I do not believe there is a firm basis to conclude that detemir causes less hypoglycemia than NPH, as will be discussed.

Study 1375 in DM1 tallied all reported hypoglycemic events and categorized them as either "minor" or "major", the latter defined as requiring the intervention of another party. There was no apparent confounding by differences in glycemic control between the two treatment groups during either period of the crossover study. For both of the categories of hypoglycemia, reports were significantly fewer with detemir than with NPH. While this is perhaps intriguing, in the absence of blinding and in the context of a crossover study, this finding is at best only suggestive of a difference in the safety profile of detemir and NPH and would require corroboration in an appropriately designed hypothesis-testing study.

Examination of the results of the "pivotal" efficacy trials in DM1 is warranted. In study 1448, a 16-week trial showing non-inferiority of detemir to NPH in DM1 that was not confounded by differences between treatment groups in the amount of bolus insulin used, major hypoglycemic events occurred during the last 12 weeks (maintenance period) of treatment in 4.4% of patients on detemir q12, 7.8% of patients on NPH and 8.0% of patients on detemir morning + hs. Expressed as total number of episodes, 9 major hypoglycemic episodes occurred in the 127 patients on detemir q12hr, 12 major hypoglycemic episodes occurred in the 120 patients on NPH, and 24 major hypoglycemic episodes occurred in the 127 patients on detemir morning + hs. In sum, there was no consistent difference in hypoglycemia between Detemir and NPH.

By contrast, in study 1372, a 26-week, open-label trial showing non-inferiority of detemir/aspart to glargine/aspart in DM1 in which use of bolus insulin was balanced across treatment groups, major hypoglycemia was reported by 7.8% of glargine patients (15 events total among 12 patients) compared to 1.9% of detemir patients (4 episodes total among 3 patients) during the 20-week maintenance phase. It is notable that the percentage of detemir patients reporting major hypoglycemic events in trial 1372 was approximately 25% that in trial 1448, while the percentage of glargine patients reporting major hypoglycemia was similar to the percentages of detemir and NPH patients reporting it in trial 1448.

In sum, there are no consistent findings with regard to difference in hypoglycemia between detemir and comparator basal insulins in DM1, even ignoring the lack of blinding of the trials.

"Pivotal" study 1530 in DM2 patients on oral agents tallied hypoglycemic events and found a relative risk for any hypoglycemic episode of 0.53 for detemir vs. NPH. There were 8 major episodes of hypoglycemia in 6 patients on NPH and no episodes in patients on detemir (the medical officer re-adjudicated the one reported event associated with detemir use and deemed it not a major hypoglycemic episode; no detailed information is included in the MOR on the 8 cases in NPH-treated patients). These significance of these results is impossible to interpret; the number of episodes of major hypoglycemia was small, and since this, too, was an open-label trial, bias (e.g., differences in instructions by the sites impacting the patients' risk) cannot be excluded as a contributor to the difference in occurrence of hypoglycemia.

As in the DM1 trials, the second "pivotal" efficacy trial in DM2 yields a different result. In trial 1385, a 22-week study comparing detemir/aspart to NPH/regular insulin showing non-inferiority of detemir to NPH, there were 2 episodes of major hypoglycemia in 2/65 patients on detemir compared to 1 episode among 70 patients treated with NPH.

In sum, the results of two pivotal, non-blinded trials in DM1 and of two pivotal, non-blinded trials in DM2 were discrepant regarding comparative hypoglycemia risk. Furthermore, all the trials in this NDA, including the crossover study 1375, were open-label. Even if one were to ignore the potential biases (e.g., even minor differences in instructions to patients across treatment groups) that might arise as a result of lack of blinding (which cannot be ignored), in the absence of consistent findings across trials, there is no basis for a conclusion of reduced risk of hypoglycemia with detemir compared to NPH or to other basal insulins.

In conclusion, the superiority of detemir to comparator basal insulins with regard to risk of severe hypoglycemia is not supported by the clinical trial data, and no actual or implied claims of such superiority should be permitted in labeling or promotion.

Weight gain

Effective treatment of diabetes, whether DM1 or DM2 is often associated with weight gain, as calories otherwise lost in the urine are stored as a result of insulin action. Additionally, in patients using insulin or insulin secretagogues, there is a vicious cycle of "chasing" insulin-induced hypoglycemia with food followed by "chasing" meal-associated hyperglycemia with insulin or secretagogue, and so on, engendering excess energy storage and weight gain. While weight is an objective endpoint measure, weight change, either positive or negative, is ultimately a function of patient behavior, for example with regard to their use of drug, their caloric intake, meal composition, and exercise. As a result of this, comparisons between treatment groups regarding change in weight must be carefully considered in the context of study design, randomization, blinding, differences in glycemic control between treatment groups, confounding medications, and further must acknowledge potential influencing, for example, behavioral variables. In trials of insulin detemir, all trials were open-label; in only some of the studies was glycemic control statistically comparable between treatment groups (or superior for the determir

groups); in many trials there was confounding by imbalances in the amounts of bolus insulin (or differences in the types of bolus insulin) used between treatment groups; and no diet records were maintained to determine whether differences between treatment groups in eating behavior may have contributed to any observed differences in weight from baseline to endpoint.

Dr. Misbin cites the weight change results of studies 1447, 1448, and 1374 in DM1 and study 1530 in DM2 in support of his conclusion that detemir treatment was associated with weight loss or less weight gain compared to NPH. He cites these trials as those in which detemir was non-inferior to NPH for glycemic control. As discussed above, the pivotal trials in DM1 and DM2 showing non-inferior glycemic control of Detemir to comparator not confounded by differences between groups in amount or type of bolus insulin used were trials 1448, 1372 (glargine comparator) in DM1 and trials 1385 and 1530 in DM2. Nevertheless, to summarize the data cited by the MO, across the 3 trials (of different durations, it is acknowledged) in type 1, NPH insulin treatment was associated with changes in weight from +0.1 kg to +0.7 kg while detemir was associated with changes in weight from -0.8 to +0.2. Even ignoring potential bias due to lack of blinding, and confounding by differences in the types of bolus insulin used (1374), these differences are not clearly clinically meaningful. In study 1372 mean weight gain was 0.5 kg on detemir and 1.0 kg on glargine.

In trial 1530, the average change in weight was +1.2 kg for the detemir group and +2.8 kg for the NPH group. In trial 1385, patients treated with detemir/aspart gained an average of 0.52 kg and those treated with NPH/human regular insulin gained an average of 1.15 kg. Again, these trials are non-blinded and there are no controls on behavioral variables that might influence weight change from baseline.

In sum, the findings with regard to weight changes by treatment group vary from trial to trial in the clinical database for insulin detemir, and given lack of blinding and the potential biases thereby introduced (e.g., differences in emphasis and instructions to patients regarding diet and exercise), confounding by differences between treatment groups in type or amount of bolus insulin used, definitive conclusions about differences in change in body weight in patients treated with detemir and NPH (or detemir and glargine) are not possible. Therefore, implied or actual claims of superiority in this regard of detemir should not be permitted in labeling or promotion.

Pediatric studies
Pediatric studies have been submitted and are under review.

IV. Manufacturing
Microbiology
Approval is recommended based on product quality microbiology review. There are no deficiencies noted and no phase 4 commitments recommended.

Device review
There are no issues raised by CDRH as the devices and designated cartridges are already approved.

Chemistry
The ONDC reviewer recommends approval with no phase 4 commitments.

Environmental Assessment
A categorical exclusion from the requirement to prepare an environmental assessment report was requested and granted ONDC.

Establishment Inspections
Overall recommendation: acceptable

V. Data integrity/DSI audits
Study 1448: One site in the Netherlands inspected.
Study 1530: 2 sites in Poland inspected.
DSI recommends that data from these sites are acceptable for review.

VI. Biopharmaceutics
In response to the AE letter, the sponsor submitted the results of three biopharmaceutics studies. These are reviewed in the OCPB review by Dr. Qui. Study 1439 was a PK/PD study comparing dose-exposure and dose-response relationships (glucose utilization) between detemir and NPH in Blacks, Hispanics, and Whites with DM2. The critical analysis was of dose response for glucose uptake in an isoglycemic clamp study. This showed no statistical differences in the dose-response to three different doses of each insulin between the three racial groups, thereby addressing one of the deficiencies in the AE letter.

In addition, study 1419 in DM1 using the isoglycemic clamp technique showed a no statistical difference in 24 hour glucose utilization (AUC for glucose infusion rate) between 1 IU of NPH and 1 U of detemir. Therefore the molar dose ratio of detemir to NPH in DM1 was 4. This addressed one of the issues in the AE letter and informs labeling regarding dosage.

In study 1439 (DM2), the molar dose ratio of detemir to NPH was also determined. Across the three racial groups, the pharmacodynamic response to 1.57 U detemir was similar to the response to 1 IU NPH. Therefore the molar dose ratio of insulin detemir to NPH in DM2 was 6.28. This addressed one of the issues in the AE letter and informs labeling regarding dosage.

OCPB finds the biopharmaceutics package acceptable and has made labeling recommendations.

VII. Pharmacology
There were no pharmacology/toxicology data in the 12-20-04 submission.

VIII. ODS/DDMAC
Labeling/tradename issues
DDMAC has made labeling comments on the PI. ODS/DSRCS has made comments on the PPI. ODS/DMETS recommends against the proprietary name, Levemir because of potential look-alike sound-alike confusion with marketed drugs. These include Lovenox (enoxaparin sodium injection) and Luveris (lutropin alpha injection). The former is indicated for DVT prophylaxis

after surgery in specified high-risk patient groups and is therefore used at least initially in the setting of hospitalization. Luveris is for the stimulation of follicular development in female infertility. While the look-alike confusion potential is apparent, the indicated uses are totally unrelated and there is common recognition among patients of all types (not just patients with diabetes) that insulin is for diabetes only. Since the products will also be labeled with the chemical names of the actives, it seems unlikely that patients requiring either Lovenox or Luveris will unintentionally receive Levemir, or vice versa.

The division recommends acceptance of the tradename Levemir.

Risk management
No specific risk management plan is proposed or recommended by the division. The issue of appropriate dosing of Levemir relative to other human insulin (as it is less potent per mass of insulin) is "managed" by formulating it in a molar concentration 4 times that of other insulin. As such, as confirmed by the isoglycemic clamp studies, one U of Levemir is approximately equivalent for glucose lowering as one IU of human insulin.

In addition, the division finds the use of the term "unit" acceptable for Levemir, since although it is defined differently than an IU of human insulin, any confusion in the nomenclature will not pose safety problems, since the default will be to use one "unit" of Levemir interchangeably with one "IU" or "unit" of human insulin. As discussed above, the unit-to-unit ratio of glucose-lowering activities of insulin detemir to NPH human insulin is lower in type 1 patients compared to type 2 patients. However, this difference at most would mean that a DM2 patient switched from NPH and dosed on a unit-to-unit basis might be somewhat "underdosed" in the short-run until upward dose adjustment to glycemic goals was accomplished. Such short-term underdosing would clearly not pose a safety issue.

IX. Product Labeling
The division is in receipt of revised labeling from the sponsor and is continuing to modify the package insert. As above, further revisions are likely to be necessary to address

X. Phase 4 commitments
Dr. Misbin recommends that

— oe a condition of approval of this product. He considers there to be a "lingering question" about ethnic differences in responsiveness to detemir, despite the results of study 1439. I do not believe there is a "lingering question" and I see no reason to exact a phase 4 commitment to

XI. Recommendation
Adequate information has been presented to support the conclusion that detemir, properly dosed, as a basal insulin, is similarly effective to NPH and insulin glargine. The questions at the end of the first review cycle regarding the molar dose ratios of detemir to NPH in DM1 and DM2 have been satisfactorily answered, as has the question about possible racial differences in pharmacodynamic response, and the drug can be labeled for safe and effective use. There are no

safety issues unique to insulin detemir among long-acting insulins (or for that matter among insulins more generally). The fact that all trials were open-label, that many were confounded by differences between treatment groups in the amount or type of bolus insulin used, and that insulin is titrated to effect, makes definitive conclusions about [redacted]. Therefore, any implied or actual claims of [redacted] should not be permitted in labeling or promotion.

Insulin detemir is clearly a safe and effective "basal" insulin for use once or twice daily in DM1 or DM2 and should be approved.

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

/s/

David Orloff
6/14/05 01:55:02 PM
MEDICAL OFFICER

Robert Meyer
6/16/05 10:32:15 AM
MEDICAL OFFICER
I am in full agreement with Dr. Orloff's memo, which will serve as the official memo of record for approval

4 Page(s) Withheld

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

___ § 552(b)(5) Deliberative Process

___ § 552(b)(5) Draft Labeling

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date: June 8, 2005

From: Dr. Stephen Moore, Chemistry Team Leader, CDER/OPS/ONDC/DNDC2/DMEDP (HFD-510)

Subject: Color Branding for NDA 21-536 Levemir (insulin detemir [rDNA origin] injection), Novo Nordisk, Inc.

To: NDA 21-536 File

Background

Novo Nordisk, Inc. has submitted proposed carton, vial, cartridge and pen labeling in the original NDA 21-536 for Levemir (insulin detemir [rDNA origin] injection) for review by the Agency. The proposed labeling includes color branding. The labeling recommendations from DMETS for NDA 21-536 (see labeling review dated 18-MAY-2005) were previously communicated to Novo Nordisk (see Agency's FAX communication, dated 31-MAY-2005), except those items pertaining to the color branding.

Recommendation

I have reviewed the submitted labeling for NDA 21-536 (submissions dated 5-DEC-2002, 20-DEC-2004 and 1-JUN, 2005) and have the following recommendations to be communicated to Novo Nordisk on the color branding on the cartons, vials, cartridges and pens. These recommendations are designed to enhance label readability and product differentiation. Also, these recommendations are consistent with previously negotiated and approved labeling for two of Novo's other insulin products, namely, Novolog (NDA 20-986/S-019) and Novolog 70/30 (NDA 21-172/S-013) (see Agency's approval letter, dated 08-OCT-2004).

Notes: The above recommendations were previously outlined in an e-mail sent to Drs. Robert Misbin (OND/DMEDP), David Orloff (OND/DMEDP) and Robert Meyer (OND/ODE2) on 01-JUN-2005 requesting response of any objections or comments. They responded favorably to this approach. The above recommendations were discussed today in person with Kristina Arnwine (ODS/DMETS) and Carol Holquist (ODS/DMETS). They also responded favorably to this approach.

{see appended electronic signature page}
Stephen Moore, Ph.D.,
Chemistry Team Leader

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

/s/

Stephen Moore
6/8/05 05:58:56 PM
CHEMIST

4/18/05

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Meeting Cancellation Form

(Use this form to cancel a meeting that was granted and scheduled after which time the sponsor or FDA has subsequently cancelled.)

Please remember to update the Meeting Status field in IMTS for this cancellation.

Complete the information below and check form into DFS.

Application Type	NDA
Application Number	21-536
DATE Meeting Cancelled (per communication with requester)	April 8, 2005
Scheduled Meeting Date	April 11, 2005
Reason for Cancellation	The sponsor is satisfied with our responses to their questions in the meeting background material dated March 10, 2005. April 8, 2005, meeting cancellation request from the sponsor is attached to this form.
Project Manager	Julie Rhee, DMEDP

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED:	**DESIRED COMPLETION DATE:**	**ODS CONSULT #:** 02-0222-2
January 26, 2005	April 22, 2005 **PDUFA DATE:** May 20, 2005	

TO: David Orloff, MD
Director, Division of Metabolic and Endocrine Drug Products
HFD-510

THROUGH: Julie Rhee
Project Manager, Division of Metabolic and Endocrine Drug Products
HFD-510

PRODUCT NAME:	**NDA SPONSOR:** Novo Nordisk, Inc.
Levemir **Levemir FlexPen** **Levemir Innolet** [Insulin Detemir (rDNA origin) Injection] 100 Units/mL **NDA#:** 21-536	

SAFETY EVALUATOR: Kristina C. Arnwine, PharmD

RECOMMENDATIONS:

1. DMETS does not recommend the use of the proprietary name, Levemir.

2. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.

3. DDMAC finds the proprietary name Levemir acceptable from a promotional perspective.

/S/ /S/

Denise P. Toyer, PharmD
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Carol Holquist, RPh
Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; PKLN Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: February 18, 2005

NDA#: 21-536

NAME OF DRUG: Levemir, Levemir FlexPen, Levemir Innolet [Insulin Detemir (rDNA origin) Injection] 100 Units/mL

NDA HOLDER: Novo Nordisk, Inc.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Metabolic and Endocrine Drug Products (HFD-510), for a final review of the proprietary name, Levemir, regarding potential name confusion with other proprietary or established drug names. Container labels, carton and insert labeling were provided for review and comment.

The proposed proprietary name was initially found unacceptable by DMETS on June 4, 2003 (see ODS Consult 02-0222) due to the potential for name confusion between Levemir and Lovenox. A rebuttal submitted by the sponsor did not provide persuasive evidence to diminish DMETS' concerns regarding the potential for confusion between Levemir and Lovenox. Thus, the proposed proprietary name, Levemir, was again found unacceptable (see ODS Consult 02-0222-1, dated February 6, 2004). However, the Division is going forth with the name and has requested a re-review of the proposed name.

PRODUCT INFORMATION

Levemir is the proposed name for Insulin Detemir [rDNA origin] Injection. Levemir is a long-acting insulin analog produced by a process that includes expression of recombinant DNA in *Saccharomyces cerevisiae* followed by chemical synthesis. It differs from human insulin in that the amino acid molecule in position B30 has been omitted, and a 14-C fatty acid chain has been attached to position B29. One unit of insulin detemir corresponds to one international unit (IU) of human insulin. The indication of use is for the treatment of patients with diabetes mellitus who require basal insulin for the control of hyperglycemia. Levemir may be administered once or twice daily. When given twice daily the evening dose can be administered either with the evening meal, at bedtime, or 12 hours after the morning dose. Levemir will be marketed as a 10 mL vial, 3 mL PenFill cartridge, 3 mL InnoLet, and 3 mL FlexPen. The PenFill cartridges may be used with Novo Nordisk 3 mL PenFill cartridge compatible insulin delivery devices and NovoFine disposable needles.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound-alike or look-alike to Levemir to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[4]. The Saegis[5] Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Levemir. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proposed proprietary name, Levemir, acceptable from a promotional perspective.

2. Since DMETS' initial review (02-0222, dated June 4, 2003) the Expert Panel identified two additional proprietary names that were thought to have the potential for confusion with Levemir. These products are listed in table 1 (see below), along with the dosage forms available and usual dosage.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Levemir	Insulin Determir [DNA origin] Injection 100 Units/mL	0.1 - 0.2 U/kg once daily or 10 U twice daily and titrated to glycemic control	
Luveris	Lutropin Alfa Powder for Injection 75 IU	75 IU SC once daily, concurrently with follitropin alfa; treatment does not usually exceed 14 days	LA
Denavir	Penciclovir Cream 1 %	Apply every 2 hours while awake for 4 days beginning within 1 hours of onset of symptoms	LA

*Frequently used, not all-inclusive.
**L/A (look-alike), S/A (sound-alike)

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[1] MICROMEDEX Integrated Index, 2005, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.
[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.
[3] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-05, and the electronic online version of the FDA Orange Book.
[4] WWW location http://www.uspto.gov/tmdb/index.html.
□ Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. All names considered to have significant phonetic or orthographic similarities to Levemir were discussed by the Expert Panel (EPD).

C. SAFETY EVALUATOR RISK ASSESSMENT

The proposed proprietary name, Levemir, was initially found unacceptable by DMETS in two previous reviews due to potential confusion with Lovenox. Since those reviews, DMETS identified two additional proprietary names, Luveris and Denavir, as having potential look-alike and sound-alike confusion with Levemir. The name Denavir was not reviewed further due to a lack of convincing look-alike/sound-alike similarities with Levemir in addition to numerous differentiating product characteristics such as the product strength, indication for use, frequency of administration, route of administration and dosage formulation. Since the look-alike concerns regarding Lovenox were discussed in DMETS' two previous reviews, only the look-alike concern with Luveris will be discussed in this review.

Levemir and Luveris can look similar when scripted. Luveris is a recombinant human luteinizing hormone (r-hLH) indicated for the stimulation of follicular development in infertile hypogonadotropic hypogonadal women with profound LH deficiency (LH < 1.2 IU/L). The primary contributions to the look-alike characteristics of the names stem from the beginning letters of Levemir and Luveris ('Leve' vs. 'Luve'), and similar length (seven letters). The last two letters of each name ('ir' vs. 'is') can also look similar depending on how they are scripted, especially if the letter 's' is written in cursive (see below). Levemir and Luveris overlap with respect to route of administration (subcutaneous) and could potentially overlap in dosing frequency (once daily). Furthermore, Levemir and Luveris can also have overlapping numerals in their strength and similarity in their dosing units (7.5 Units vs. 75 IU). International units is sometimes abbreviated as 'U,' and the word 'units' is often abbreviated in prescriptions by writing the letter 'U,' which further adds to the potential for confusion. Levemir is supplied as an injection and Luveris is supplied as a powder for injection. However, the dosage form of the final dispensed product for both medications, if specified on the prescription, will be injection for Levemir and Luveris. Additionally, since both Levemir and Luveris are only supplied as one dosage form, with one strength, the dosage form and strength may be omitted on a prescription order. With all of these similar product characteristics taken into account, it is possible to receive prescriptions for Levemir and Luveris that look similar (Levemir 7.5 U SC, qd vs. Luveris 75 IU SC, qd).

If confused, there is an increased potential for harm. An overdose of Levemir can cause hypoglycemia which can result in coma and/or death. Meanwhile, if a pregnant patient is given Luveris (pregnancy category X) it is possible for the postnatal survival and growth of the newborn to be affected. Overall, the orthographic similarities between the two names with overlapping product characteristics, coupled with the increased potential for harm due to a medication error

between Levemir and Luveris, increase the potential for medication errors due to name confusion between this name pair.

III. COMMENTS TO THE SPONSOR:

As noted in our initial review and responses to your rebuttal, DMETS does not recommend the use of the proprietary name Levemir due to its similarity to Lovenox. In re-reviewing the proprietary name, Levemir, DMETS notes an additional look-alike concern with Luveris. The look-alike concerns with Lovenox were previously noted, thus only the look-alike conerns with Luveris are noted below.

Levemir and Luveris can look similar when scripted. Luveris is a recombinant human luteinizing hormone (r-hLH) indicated for the stimulation of follicular development in infertile hypogonadotropic hypogonadal women with profound LH deficiency (LH < 1.2 IU/L). The primary contributions to the look-alike characteristics of the names stem from the beginning letters of Levemir and Luveris ('Leve' vs. 'Luve'), and similar length (seven letters). The last two letters of each name ('ir' vs. 'is') can also look similar depending on how they are scripted, especially if the letter 's' is written in cursive (see below). Levemir and Luveris overlap with respect to route of administration (subcutaneous) and could potentially overlap in dosing frequency (once daily). Furthermore, Levemir and Luveris can also have overlapping numerals in their strength and similarity in their dosing units (7.5 Units vs. 75 IU). International units is sometimes abbreviated as 'U,' and the word 'units' is often abbreviated in prescriptions by writing the letter 'U,' which further adds to the potential for confusion. Levemir is supplied as an injection and Luveris is supplied as a powder for injection. However, the dosage form of the final dispensed product for both medications, if specified on the prescription, will be injection for Levemir and Luveris. Additionally, since both Levemir and Luveris are only supplied as one dosage form, with one strength, the dosage form and strength may be omitted on a prescription order. With all of these similar product characteristics taken into account, it is possible to receive prescriptions for Levemir and Luveris that look similar (Levemir 7.5 U SC, qd vs. Luveris 75 IU SC, qd).

If confused, there is an increased potential for harm. An overdose of Levemir can cause hypoglycemia which can result in coma and/or death. Meanwhile, if a pregnant patient is given Luveris (pregnancy category X) it is possible for the postnatal survival and growth of the newborn to be affected. Overall, the orthographic similarities between the two names with overlapping product characteristics, coupled with the increased potential for harm due to a medication error between Levemir and Luveris, increase the potential for medication errors due to name confusion between this name pair.

In the review of the Levemir container labels, carton and package insert labeling, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

A. General Comments

1. Increase the prominence of the established name so that is at least half the size of the proprietary name.

7 Page(s) Withheld

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

____ § 552(b)(5) Deliberative Process

____ § 552(b)(5) Draft Labeling

J. Innolet Patient Information

1. How Should I take Levemir Section

   a. Revise the statement, "The effect of an injected insulin injected into your upper arm, abdomen...," to read, "...into your upper arm *or* abdomen (stomach area)..."

   b. Revise the statement, "Change (rotate) injection sites..." as well as injection sites within body areas.

2. Revise all references to hyperglycemia and hypoglycemia so that they are consistent [e.g. hypoglycemia (too low blood sugar) **or**], but do not interchange both wordings] (e.g. page 3, "What are the possible side effects of Levemir," section).

3. Pages 7 through 11

   a. Currently, there is no name for this section. Label this section, "Levemir Innolet for Use."

   b. Number the, "Preparing the Levemir Innolet," section as number 1, followed by "Setting the Dose," as number 2, "Giving the Injection," as number 3, and so on, in order to ensure that patients are informed that they need to prepare the Innolet before each injection.

   c. List instructions in a step-by-step format (e.g. "Preparing the Levemir Innolet" Section, letters a and b) rather than

   For example: Levemir Innolet Instructions for Use
   1. Preparing the Levemir Innolet
      a. Pull off the cap
      b. Wipe the rubber membrane with an alcohol swab.
      c. Remove the protective tab from the disposable needle...
   2. Setting the Dose

   d. Revise the labeling of the figures so that they correspond with the particular step in the instructions, (e.g. the figure currently labeled 1A, should be labeled 1C.) Additionally, place the figure so that it appears directly below the corresponding step of instruction.

   e. Revise any statements regarding to read "priming," so that is consistent with the information regarding the Innolet found on the NovoNordisk website. In addition, define "priming" in consumer-friendly terms on all labels and labeling.

K. Penfill Cartridge and Vial Patient Information

1. See comment J-1 and J-2.

2. How Should I Take Levemir Section

The statement, ' — oes not appear in the package insert. If this statement is correct, include it in the package insert (see page 2).

3. Using the Levemir 3 mL PenFill cartridge Section

   See comment J-3-e.

4. After the first use of PenFill cartridge Section

   See comment J-3-e.

5. FlexPen Patient Information

See comments J-1, J-3-c, J-3-d, and J-3-e.

IV. RECOMMENDATIONS:

A. DMETS does not recommend the use of the proprietary name Levemir.

B. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.

C. DDMAC finds the proprietary name Levemir acceptable from a promotional perspective

DMETS 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 Diane Smith, project manager, at 301-827-1998.

/S/

Kristina C. Arnwine, PharmD
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur: /S/

Linda Kim-Jung, PharmD
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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

/s/

Kristina Arnwine
5/18/05 11:49:13 AM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
5/18/05 11:59:43 AM
DRUG SAFETY OFFICE REVIEWER
Signing for Carol Holquist, Director DMETS in her absence

MEMORANDUM OF MEETING MINUTES

MEETING DATE: December 9, 2003

TIME: 12:00 – 1:00 pm

LOCATION: Parklawn Building 3rd floor c/r "B"

APPLICATION: NDA 21-536 Insulin detemir

TYPE OF MEETING: General Post AE Action Mtg

MEETING CHAIR: David Orloff, M.D.

MEETING RECORDER: Julie Rhee

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

Name	Title	Division Name
Bob Meyer, M.D.	Director	Office of Drug Evaluation II
David Orloff, M.D.	Director	Division of Metabolic and Endocrine Drug Products
Bob Misbin, M.D.	Medical Officer	DMEDP
Todd Sahlroot, Ph.D.	Statistical Team Leader	OPSS/DBII/DMEDP
Lee Pian, Ph.D.	Statistician	OPSS/DBII/DMEDP
Julie Rhee	Regulatory Project Manager	DMEDP

EXTERNAL CONSTITUENT ATTENDEES AND TITLES: Novo Nordisk Pharmaceuticals, Inc (USA)

External Attendee	Title
Barry Reit, Ph.D.	Vice President, Regulatory Affairs
Mary Ann McElligott, Ph.D.	Sr. Director, Regulatory Affairs
Peter Aurup, M.D.	Vice President, Drug Development (Medical Affairs)
Bodil Elbroend, M.D.	Clinical Director
Elizabeth Tan, Ph.D.	Asst. Director, Regulatory Affairs

EXTERNAL CONSTITUENT ATTENDEES AND TITLES: Novo Nordisk A/S (Denmark)

Hanne Henriksen, M. Sc.	Project Manager, International Regulatory
Eberhard Draeger, Ph.D.	International Medical Officer
Peter Bonne Eriksen, M. Sc.	Sr. Vice President, Regulatory Affairs
Olga Santiago, M.D.	Project Vice President
Peter Kurtzals, Ph.D.	Vice President, Drug Discovery
Silvia Garcia Codony, M.Sc.	Biostatistician

BACKGROUND:

The sponsor (Novo Nordisk Pharmaceuticals) submitted an NDA (NDA 21-536) for insulin detemir (rDNA origin) which is a long-acting, soluble human insulin analog on December 5, 2002 (received December 5, 2002).

An approvable letter was issued on October 2, 2003, citing clinical and chemistry deficiencies.

This meeting was requested by the sponsor on October 22, 2003, to clarify some of the issues in the approvable letter.

The background material for the meeting was submitted on November 21, 2003.

DISCUSSION POINTS:

Question 1
New Study Information - Type 1 Diabetes
The enclosed Pre-Meeting Package of Information includes results from the newly completed trials in type 1 diabetes: Trials 1372, 1374, 1375 and 1379. Please refer to Sections 2 and 3.

Do you consider that these trials satisfy the request for additional information in type 1 diabetes and are the results adequate to support approval?

FDA's response:

Yes. Trials 1372, 1374, 1375 and 1379 satisfy the request for additional information in patients with type 1 diabetes. There is adequate data to support the efficacy of insulin detemir in patients with type 1 diabetes, except for the issue of race/ethnicity (see question 3).

Question 2
New Study Information - Type 2 Diabetes
The enclosed Pre-Meeting Package of Information includes results from the newly completed trial in type 2 diabetes: Trial 1385. Please refer to Sections 2 and 3.

Do you consider that this trial satisfies the request for additional information in type 2 diabetes and are the results adequate to support approval?

Discussion:

1. The November 21, 2003, meeting materials did not address our concern in the approvable letter concerning safe and efficacious use of the product in type 2 diabetes with the extra use of bolus insulin in insulin detemir group.
2. Responding to the Division's statement that insulin detemir is a different product from all other insulins, Novo stated that insulin detemir is not very different from other insulins other

than binding facility. Novo also stated that physical chemistry of insulin detemir is similar to other insulins.

3. A definitive trial with insulin detemir alone in patients with type 2 diabetes is needed to unequivocally demonstrate the efficacy of insulin detemir for these patients.

FDA's response:

No. The results of trial 1385 do not appear to establish the efficacy of insulin detemir in patients with type 2 diabetes. However, trial 1530 (ongoing) may provide sufficient data based on its design.

Question 3
Race/Ethnicity
It is unclear whether the observed difference in Trial 1337 is due to race/ethnicity or other factors such as previous treatment (see Section 5.3). We propose to further evaluate ethnicity as a post-approval commitment.

Until further information is available, we propose adding a statement in the *Special Populations, Ethnic Origin* section of the label that " —

—

Do you agree with this approach?

Discussion:

1. Study 1530 (along with other studies, see below) could be conducted in lieu of the requested clinical study that incorporated an examination of comparative race/ethnicity effect in the approvable letter.

2. Novo proposed two PK/PD studies to address race/ethnicity issue. The Division reminded Novo that they need to go over methodology of PK/PD studies so the studies can provide appropriate information for race/ethnicity.

3. Novo proposed a clamp study only in patients with type 1 diabetes, as they felt a study in type 2 patients would lead to difficulties in recruitment. The Division agreed to have an internal meeting and to get back to Novo within a week *

* The following comments were conveyed to the sponsor on December 10, 2003:
"A submission of the results of (1) a clamp study in DM1 patients to explore racial/ethnic differences in pharmacodynamic response to NPH and detemir and (2) study 1530 will be considered a complete response to the clinical deficiencies in the October 2, 2003, AE letter. However, the conduct and submission of an analogous clamp study in DM2 will ultimately be required, whether prior to or after approval (depending upon findings on review of the other data). Therefore, we advise that this study be implemented ASAP."

Additional e-mails between Novo and the Division are attached to this meeting minutes.

FDA's response:

No. The possibility that the response to insulin detemir may be dependent on race/ethnicity must be evaluated prior to approval.

Question 4
Unit Definition
The volume equivalence of the 2400 nmol/mL formulation of insulin detemir and 600 nmol/mL formulation of NPH insulin is supported in the recently completed dose-response clamp Trials 1491 and 1538 (type 1 and type 2 diabetes, respectively)(see Section 4). Taken together with the results from phase 3/3b clinical investigations, including results from recently completed phase 3b trials (type 1 diabetes: Trials 1374, 1375, 1372, 1379; type 2 diabetes: Trial 1385, Section 3), the data available provide support for the use of unit nomenclature.

The insulin detemir dose ranges used at end of trial in phase 3/3b clinical trials, reflecting the actual insulin requirements, will be included in the label to instruct on potential doses needed. This information could be presented in — *Dosage and Administration* sections.

Do you agree with this approach?

Discussion:

1. Novo stated that they will have a definition for "Unit". However, the Division responded that they do not agree with the use of "Unit" for insulin detemir since a "Unit" for insulin detemir has inconsistent molar ratio for type 1 and type 2 diabetes (and potentially for different racial groups).

2. The Division suggested Novo to consider how much insulin detemir needs to be taken instead of how many units of insulin to take.

3. One of the suggested terminologies by Novo wa — The Division reminded Novo that the terminology has to be patient friendly.

4. This issue needs to have further discussion before the product is approved.

5. The Division asked how insulin detemir is labeled in other countries. Novo stated that insulin detemir is approved in Switzerland and agreed to provide the approved labeling in Switzerland.

FDA's response:

No. The PD data submitted in the November 21, 2003, package (trials 1491 and 1538) suggest that the molar ratio of insulin detemir to NPH is 2.7 in type 1 diabetes and 5.6 in type 2 diabetes. It is not appropriate to define a "unit" that varies among different patient populations.

Question 5
Risk Management
Based on the dosing outcomes from clinical trials, we propose a one-to-one dose transfer for patients previously on basal insulin. The one-to-one unit correspondence of the to-be-marketed preparation of insulin detemir is most clearly apparent in Trial 1375, a two-period cross-over trial (16 weeks per period) in subjects with type 1 diabetes, where non-inferiority was shown with similar basal and bolus doses used in both treatments (see Section 3, Table 2). A description of the insulin detemir dose range used at end of trial in phase 3/3b clinical trials, reflecting the actual insulin requirements, will be added in the *Dosage and Administration* section to instruct on potential doses needed. This will ensure a safe dose transfer when switching from another basal insulin, and will allow for an appropriate dose titration to individual treatment goals.
The general recommendation on glucose monitoring previously included in the NDA applies: "as with all insulin preparations, close glucose monitoring is recommended during the transition and in the initial weeks thereafter."

Do you agree with this approach?

FDA's response:

A discussion of appropriate risk management consideration is better deferred until full review of the response to our action letter, closer to an approval action.

Question 6
Pediatric Trial
Trial 1379 is a supportive trial in type 1 diabetes, where pediatric subjects were evaluated (see Section 3 and Appendix 2).

FDA's response:

Question 7
Approvability
The new data provided in the Pre-Meeting Package of Information are considered adequate to support labeling for: '

Do you agree with this approach?

Alternatively, does the Agency consider the data adequate to support labeling for '

Do you agree with this approach?

FDA's response:

No.

DECISIONS (AGREEMENTS) REACHED:

Clamp study in patients with Type 1 or Type 2 diabetes is acceptable to address race/ethnicity issue.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

Unit definition needs further discussion. Meantime, Novo is to provide the approved labeling for insulin detemir from Switzerland.

Enclosure: Three e-mail responses (from DMEDP) dated December 10, 12, 16 and 17, 2003

MEETING MINUTES

Ripper, Leah W

om: Morse, David E
Sent: Wednesday, October 01, 2003 4:18 PM
To: Ripper, Leah W; Meyer, Robert J; Rhee, H Julie
Subject: RE: Status of your reviews?

I have no PT issues for the NDA 21536 action package (Insulin Detemir). There are some general comments about the label, but no specifics at this time since it is an AE action. I should have my review in DFS tomorrow AM.

David

No review by D. Morse in DFS.
6/16/05

-----Original Message-----
From: Ripper, Leah W
Sent: Monday, September 29, 2003 2:06 PM
To: Morse, David E
Subject: RE: Status of your reviews?

We are not putting labeling comments in letter. If asking for some major rewrite of labeling, we could convey that separately in a DR letter.

Lee

W. Ripper
sociate Director for Regulatory Affairs
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: 301-827-5921
Fax: 301-480-6644
Email: ripper@cder.fda.gov

-----Original Message-----
From: Morse, David E
Sent: Monday, September 29, 2003 2:05 PM
To: Ripper, Leah W
Subject: RE: Status of your reviews?

Mostly done. No issues spotted so far, except some labeling terminology. But the latter is moot at this time. Correct?

David

-----Original Message-----
From: Ripper, Leah W
Sent: Monday, September 29, 2003 1:30 PM
To: Wu, Duu Gong; Morse, David E
Subject: Status of your reviews?

w are your reviews of insulin detemir going? We would like to issue the AE letter on or before Thursday, Oct 2, since Bob Meyer, the PM and I all have plans to be elsewhere on Friday.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO (Division/Office):
irector, Division of Medication Errors and
echnical Support (DMETS), HFD-420
PKLN Rm. 6-34

FROM: Julie Rhee, DMEDP, HFD-510

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
September 23, 2003		21-536	Correspondence	September 19, 2003

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Insulin detemir (rDNA origin)			December 31, 2003

NAME OF FIRM: Novo Nordisk Pharmaceuticals, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: Trade name review

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
'PE A OR B NDA REVIEW) OF PHASE II MEETING JNTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:

This correspondence is in response to your previous recommendation (ODS Consult # 02-0222) rejecting the sponsor's first choice of tradename "Levemir". In this submission dated 9/19/03, Novo is requesting you to re-consider "Levemir" as a trade name for insulin detemir. Do you agree with Novo's request?

Draft approvable letter, along with the action package, is currently in ODE II.

DATE: **October 5, 2003**

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

RECORD OF TELEPHONE CONVERSATION/MEETING	Date: August 28, 2003
Submission date: December 5, 2002 (tradename consult) ********** I called Dr. Tan and informed her that DMETS does not recommend the use of their proposed tradename "Levemir" but has no objections to the use of — Dr. Tan asked me why DMETS objected the use of "Levemir". I responded that it's because there is a product ("Lovenox") that is look-alike to "Levemir" available on the U.S. market. I mentioned that "Lovenox" is a low molecular weight heparin. I also informed her that tradename has to be re-evaluated just before the approval of the application. --- **Name: Julie Rhee**	**NDA#:** 21-536 **Telecon/Meeting initiated by:** FDA **By:** Telephone **Product Name:** — ™ (insulin detemir) **Firm Name:** Novo Nordisk **Name and Title of Person with whom conversation was held:** Elizabeth Tan, Ph.D. Regulatory Affairs **Phone:** (609) 987-5940

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

/s/

Julie Rhee
8/29/03 08:57:47 AM
CSO

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: December 11, 2002	**DUE DATE:** July 30, 2003	**ODS CONSULT #:** 02-0222

TO: David Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products
HFD-510

THROUGH: Julie Rhee
Project Manager
HFD-510

PRODUCT NAME:	**NDA SPONSOR:**
Levemir and — **(alternate)** (Insulin Delemir [rDNA origin] Injection) 100 units per mL **NDA:** 21-536	Novo Nordisk Pharmaceuticals

SAFETY EVALUATOR: Denise P. Toyer, Pharm.D.

SUMMARY: In response to a consult from the Division of Metabolic and Endocrine Drug Products (HFD-510), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed roprietary names "Levemir and — to determine the potential for confusion with approved proprietary and established names as well as pending names.

RECOMMENDATIONS:

this info was forwarded to Dodo on 8/28/02 t-con

1. DMETS does not recommend use of the proprietary name Levemir. However, DMETS has no objections to the use of the proprietary name — This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names from this date forward.
2. DMETS recommends implementation of the labeling revisions outlined in Section III of this review.
3. DDMAC finds the proprietary names Levemir and — cceptable from a promotional perspective.

/S/

Carol Holquist, RPh
Deputy Director,
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

/S/

Jerry Phillips, RPh
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; Parklawn Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: June 4, 2003

NDA # 21-536

NAME OF DRUG: Levemir and — alternate)
(Insulin Delemir [rDNA origin] Injection)
100 units per mL

NDA HOLDER: Novo Nordisk Pharmaceuticals

I. INTRODUCTION:

This consult was written in response to a request from the Division of Metabolic and Endocrine Drug Products (DMEDP), to review the proprietary names Levemir and — regarding potential name confusion with other proprietary and established drug names. The draft container labels, carton, patient information and package insert labeling were also submitted for review of possible interventions to minimize medication errors. The container labels and carton labeling for the PenFill cartridges, FlexPen, or InnoLet were not submitted for review.

PRODUCT INFORMATION

Levemir — is the proposed name for Insulin Delemir [rDNA origin] Injection. Levemir/ — is a long-acting insulin analog produced by a process that includes expression of recombinant DNA in *Saccharomyces cerevisiae* followed by chemical synthesis. It differs from human insulin in that the amino acid molecule in position B30 has been omitted, and a 14-C fatty acid chain has been attached to position B29. One unit of insulin detemir corresponds to one international unit (IU) of human insulin. The indication of use is for the treatment of patients with diabetes mellitus who require basal insulin for the control of hyperglycemia. Levemir — may be administered once or twice daily. When given twice daily the evening dose can be administered either with the evening meal, at bedtime, or 12 hours after the morning dose. Levemir — will be marketed as a 10 mL vial, 3 mL PenFill cartridge, 3 mL InnoLet, and 3 mL FlexPen. The PenFill cartridges may be used with — delivery devices.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound-alike or look-alike to "Levemir and — to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted.[4] The Saegis[5] Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies for each name, consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary names "Levemir and — Potential concerns regarding drug marketing and promotion related to the proposed names were also discussed. The members of this panel include DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. The Expert Panel identified the proprietary name Lovenox as having the potential for confusion with Levemir. This products is listed in Table 1 (see Page 4), along with the dosage forms available and usual dosage.

3. DDMAC did not have concerns about the names Levemir or — with regard to promotional claims.

[1] MICROMEDEX Integrated Index, 2003, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[3] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-03, and the electronic online version of the FDA Orange Book.

[4] WWW location http://www.uspto.gov/main/trademarks.htm

[5] Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

Table 1 Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel			
Product Name	**Dosage form(s), Established name**	**Usual adult dose***	**Other****
Levemir®	Insulin Detemir [rDNA origin] Injection 100 units per mL	Dose needs to be individualized* Clinical trial starting dose 0.1 to 0.2 units per kilogram once daily.	N/A
Lovenox	Enoxaparin Sodium Injection Ampules: 30 mg per 0.3 mL Prefilled Syringe: 30 mg per 0.3 mL Graduate Prefilled Syringe 60 mg per 0.6 mL 80 mg per 0.8 mL 100 mg per 1 mL	30 mg to 40 mg once a twice a day	LA

• / Frequently used, not all-inclusive.
** L/A (look-alike), S/A (sound-alike)

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies for Levemir and — were conducted within FDA for the proposed proprietary names to determine the degree of confusion of Levemir or — with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. Each study employed a total of 106 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Levemir or — (see page 5). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

a. Levemir Prescriptions

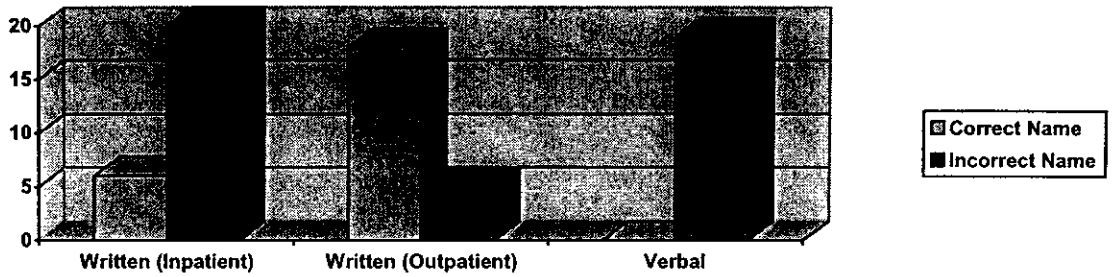
HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: Levemir ud #1	The fourth prescription is Levemir, Use as directed, Dispense One
Inpatient RX: Levemir 25 units SC qHS	

2. Prescription Results

a. Levemir results are summarized in Table I.

Table I

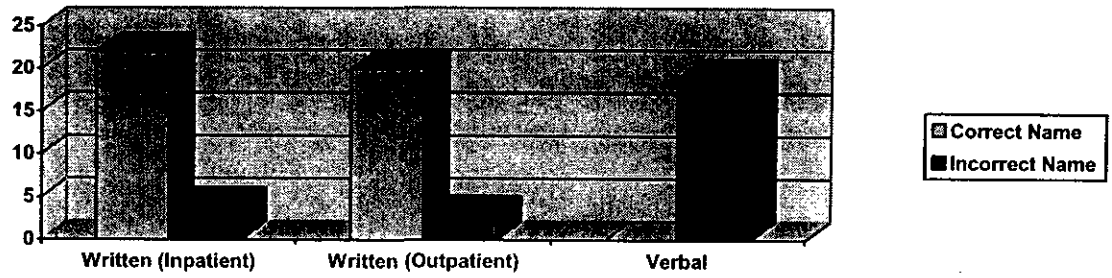
Study	# of Participants	# of Responses (%)	Correctly Interpreted	Incorrectly Interpreted
Written Inpatient	39	26 (67%)	6 (23%)	20 (77%)
Written Outpatient	35	23 (66%)	18 (78%)	5 (22%)
Verbal	32	19 (59%)	0	19 (100%)
Total	106	68 (64%)	24 (35%)	44 (65%)



In the written inpatient study 6 of the 26 (23%) participants interpreted Levemir correctly. The misinterpretations were misspelled variations of Levemir. The misinterpretations included Lenemir (7), Leriemir (4), Leuemir (2), Lenemin (2), Levemin (1), Lesumir (1), Lerumir (1), Lenemia (1), and L Insulin (1). None of the misinterpreted names represented a currently marketed product, although L Insulin could represent Lente Insulin.

In the written outpatient study 18 of 23 (78%) participants interpreted Levemir correctly. The five incorrect name interpretations were misspelled variations of Levemir. The misinterpretations included Levimir, Levemin, Levenier, Levenir, and Uvemir. None of the misinterpreted names represented a currently marketed product.

In the verbal prescription study, none of the participants interpreted Levemir correctly. The majority of the misinterpretations were phonetic variations of Levemir. The misinterpretations included Levamur (3), Levamir (3), Levamere (2), Levamier (1), Levomere (1), Lamavir (1), Lavamure (1), Lavemir (1), Lavimir (1), Levamirror (1), Levamuir (1), Levonear (1), Levonir (1), and Loveamir (1). None of the misinterpreted names represented a currently marketed product.



C. SAFETY EVALUATOR RISK ASSESSMENT

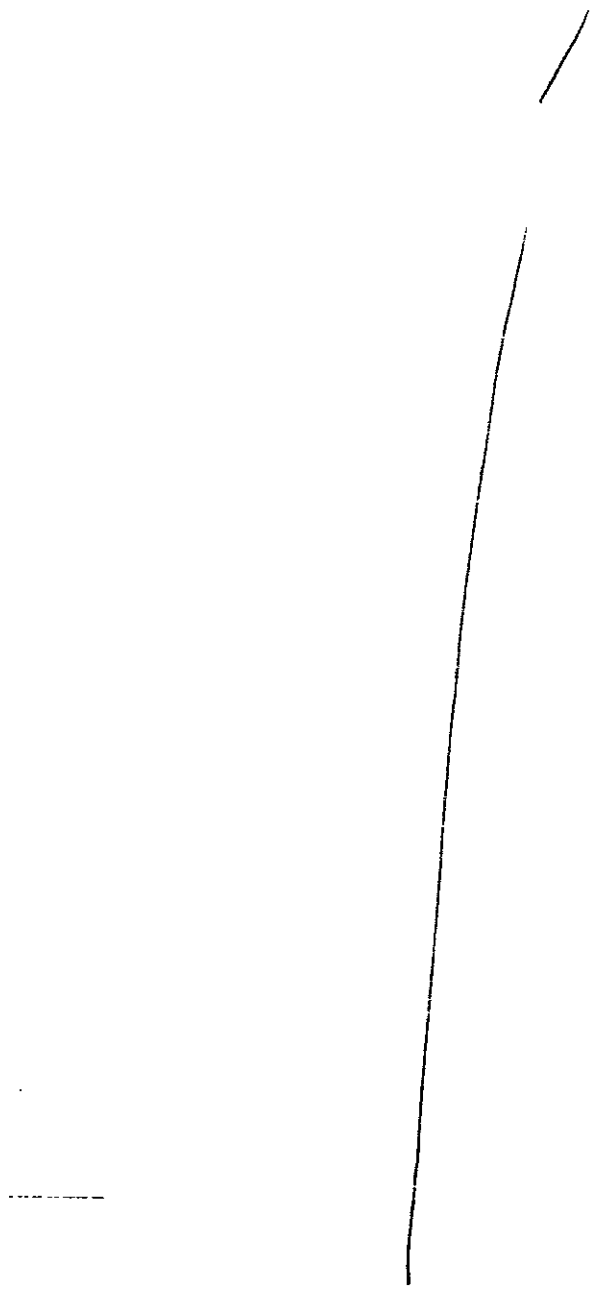
1. Levemir

In reviewing the proprietary name Levemir, the primary concerns raised were related to Lovenox, a look-alike name that currently exists in the U.S. market.

DMETS conducted prescription studies to simulate the prescription ordering process. There was no confirmation that Levemir could be confused with Lovenox. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to small sample size. The majority of the interpretations from the verbal and written prescription studies were phonetic or spelling misinterpretations of the drug name Levemir.

Lovenox and Levemir may look-alike depending upon how they are scripted. Lovenox is a low molecular weight heparin, which has antithrombotic properties. Lovenox is indicated for prophylaxis and treatment of deep vein thrombosis and prophylaxis treatment of ischemic complications of unstable angina and non-Q-wave myocardial infarction, when concurrently administered with aspirin. Both names contain seven letters and three syllables. The letters 'Love' and 'Leve' may look similar when scripted. Additionally, the beginning letters of the third syllable of each name 'n' and 'm' may also look similar when scripted. Although the endings of each name is different (ox vs. ir), this may not distinguish the names if the last two letters are not clearly scripted. Both products are injectables and share the same route of administration (subcutaneous) and

dosing intervals (once or twice a day). The products have different indications of use, prescribing strengths (milligrams vs. units), and storage conditions (room temperature vs. refrigeration). However, the dose of Lovenox and Levemir may overlap since the dose of Levemir must be individualized. Thus 30 or 40 units of Levemir could be misinterpreted as Lovenox 30 or 40 milligrams, especially if the increments of measure (units vs. milligrams) are omitted. Overall the similarities with the two names and the overlapping product characteristics increase the potential for name confusion between Lovenox and Levemir.



III. COMMENTS TO THE SPONSOR

DMETS does not recommend the use of the proprietary name, Levemir. However, DMETS has no objections to the use of the proprietary name. — In reviewing the proprietary name Levemir, the primary concerns raised were related to Lovenox, a look-alike name that currently exists in the U.S. market.

Lovenox and Levemir may look-alike depending upon how they are scripted. Lovenox is a low molecular weight heparin, which has antithrombotic properties. Lovenox is indicated for prophylaxis and treatment of deep vein thrombosis and prophylaxis treatment of ischemic complications of unstable angina and non-Q-wave myocardial infarction, when concurrently administered with aspirin. Both names contain seven letters and three syllables. The letters 'Love' and 'Leve' may look similar when scripted. Additionally, the beginning letters of the third syllable of each name 'n' and 'm' may also look similar when scripted. Although the endings of each name is different (ox vs. ir), this may not distinguish the names if the last two letters are not clearly scripted. Both products are injectables and share the same route of administration (subcutaneous) and dosing intervals (once or twice a day). The products have different indications of use, prescribing strengths (milligrams vs. units), and storage conditions (room temperature vs. refrigeration). However, the dose of Lovenox and Levemir may overlap since the dose of Levemir must be individualized. Thus 30 or 40 units of Levemir could be misinterpreted as Lovenox 30 or 40 milligrams, especially if the increments of measure (units vs. milligrams) are omitted. Overall the similarities with the two names and the overlapping product characteristics increase the potential for name confusion between Lovenox and Levemir.

In the review of the container labels, carton, insert and patient information labeling of Levemir/ — DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

A. CONTAINER LABELS (10 mL Vial)

1.

B. CARTON LABELING (10 mL Vial)

C. INSERT LABELING

1. Precautions Section, Mixing of Insulin Subsection

From the information presented, DMETS is unclear whether it is acceptable to mix Levemir — with other currently marketed insulin products. If mixing is acceptable,

If mixing is unacceptable, this section should be revised for clarity. The Patient Information Sheet should also contain statements referring to the mixing of Levemir/ —

2. Dosage and Administration Section

The last paragraph states: —

D. PATIENT INFORMATION SHEET

See Comment C-1.

IV. RECOMMENDATIONS:

1. DMETS does not recommend use of the proprietary name Levemir. However, DMETS has no objections to the use of the proprietary name — This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names from this date forward.

2. DMETS recommends implementation of the labeling revisions outlined in Section III of this review.

3. DDMAC finds the proprietary names Levemir and — . acceptable from a promotional perspective.

DMETS 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 Sammie Beam, project manager, at 301-827-3242.

Denise P. Toyer, Pharm.D.
Safety Evaluator/Team Leader
Division of Medication Errors and Technical Support

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

/s/

Denise Toyer
8/6/03 04:15:07 PM
PHARMACIST

Carol Holquist
8/6/03 04:22:08 PM
PHARMACIST

Jerry Phillips
8/7/03 09:02:22 AM
DIRECTOR

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 27, 2003

TO: David Orloff, M.D., Director
Division of Metabolic and Endocrine Drug Products
HFD-510

VIA: Julie Rhee, Regulatory Health Project Manager,
Division of Metabolic and Endocrine Drug Products
HFD-510

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Toni Piazza-Hepp, Pharm. D., Acting Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: DSRCS Review of Patient Labeling for insulin detemir [rDNA origin], NDA 21-536

The attached patient labeling (clean copies) represent part of the revised risk communication materials for insulin detemir [rDNA origin], NDA 21-536 (FlexPen, InnoLet, 3mL Penfill Cartridge, and 10 mL Vial). They have been reviewed by our office and by DDMAC. We have simplified the wording, made them consistent with the PI, removed promotional language and other unnecessary information (the purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications), and put them in the format that we are recommending for all patient information. Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds. Comments to the review division are bolded, underlined and italicized. We can provide marked-up and clean copies of the revised documents in Word if requested by the review division.

We also have the following comment:

1. ODS/DSRCS has noted that existing PPIs for insulin products are quite varied and most are written at a reading comprehension level that is too high to be understood by low literacy

readers. The review division may want to consider initiating class PPI labeling in the future for insulin products utilizing the following suggestions:

1. Follow a question and answer format with the contents ordered similarly to Medication Guides. Alternative formats are discouraged without supportive data for their communication effectiveness from studies such as label comprehension testing.

2. Simplify the vocabulary and sentence structure for low literacy readers. A 6-8th grade reading comprehension level is optimal.

3. Keep information on the medical conditions brief. Patient information leaflets (PPIs) are to enhance appropriate use of medications and provide important risk information. Education of underlying medical conditions should be separated.

4. Remove any promotional language per DDMAC guidelines.

Please let us know if you have any questions.

35 Page(s) Withheld

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

____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

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

/s/

Jeanine Best
5/27/03 09:47:05 AM
CSO

Toni Piazza Hepp
5/28/03 08:49:31 AM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: September 12, 2003

FROM: David G. Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products

TO: NDA 21-536
— (insulin detemir)
Novo Nordisk
Treatment of types 1 and 2 diabetes mellitus

SUBJECT: NDA review issues and recommended action

Background
Insulin detemir is a modified human insulin proposed for the treatment of type 1 and type 2 diabetes mellitus. It has a single amino acid deletion (B30 Thr) and B29 Lys is covalently modified with a myristic acid moiety (C14). As such, detemir is bound to serum albumin (and probably to proteins in the subcutis) and has a delayed release after injection and a prolonged duration of action. In addition, the trials suggest that, injected SQ, detemir has approximately one-fourth the potency per mole as native human insulin. Finally, detemir has differential activity across different species studied. Both of these last characteristics make it unique among insulin products, all of which possess equivalent glucose-lowering activity per mass of insulin.

The standard of efficacy for approval of a new insulin is the demonstration of effect in improving glycemic control in patients with types 1 and 2 DM. For a long-acting insulin, a comparison to NPH insulin with demonstration of non-inferior glycemic control without augmented hypoglycemic risk is acceptable. The principle of risk versus benefit for diabetes therapies bears further clarification. Part and parcel of the therapy of diabetes is the unavoidable reality that with efforts at improved glycemic control, with a goal of reducing diabetic sequelae (mostly microvascular and neuropathic) comes increased risk of hypoglycemia. Thus, notwithstanding any intrinsic toxicities of a new antidiabetic agent or immunogenicity of a new insulin, it is important to characterize the risk of hypoglycemia with the new therapy compared to an approved, effective therapy, for a given degree of glycemic control. This comparison obviously requires, in the ideal, that new therapy (and old therapy) be "effective" in the context of the pivotal trial (i.e., HbA1c must be lowered from baseline and must be in the "desirable" range), and that effect of new therapy be statistically and clinically non-inferior to existing approved therapy.

Additionally, it is further necessary, in order to interpret the results of such trials, that the use of other antidiabetic drugs, particular bolus (regular or rapid-acting) insulin, be balanced at baseline and on treatment, such that effects on glycemia, both beneficial (lowering HbA1c) and

potentially harmful (hypoglycemia) can be considered in the context of an unconfounded trial. Indeed, at the end-of-phase 2 meeting for detemir on July 22, 1999, the division specifically noted in their response to Question 5 by the sponsor, that the dose of regular insulin across treatment groups must be considered in the interpretation of any finding of apparent non-inferiority to comparator.

Clinical efficacy and safety

The clinical safety and efficacy data have been reviewed by Dr. Misbin, and Dr. Pian has conducted a thorough statistical review of the efficacy data. This memo will touch on the salient issues raised by those reviews.

In brief, efficacy (based on non-inferiority to NPH) has been satisfactorily demonstrated in a single trial in patients with type 1 DM. By contrast, in 3 phase 3 trials in type 2 DM, non-inferiority has not been demonstrated. Each trial is flawed/confounded either by inadequate improvement in glycemic control to render an evaluable study or by the use of excess bolus insulin in the detemir group.

While there is ample evidence in the application that detemir is an active insulin, the failure to demonstrate consistently non-inferior efficacy to NPH, the variable data addressing the relative potency of detemir to NPH, at the very least, lead to a conclusion that there is currently inadequate information to 1) determine the effective dose(s) of detemir either in absolute terms or compared to other basal insulins and 2) to understand fully the safety (re: hypoglycemia) of detemir relative to NPH. In addition, while "unit" of detemir was defined for the purposes of the clinical trials (and had to be changed as development proceeded and it became clear that at least 4 times the molar dose of detemir was needed to approach the effect of NPH), there is sufficient inconsistency of clinical activity of detemir relative to NPH to suggest that, in the end, detemir will be labeled as — and not by the conventional (e.g., U100) nomenclature used for all other insulin products. —

/

Finally, against a background of cross-species differences in potency (unique among human insulin and insulin analog products), the finding of apparent increased efficacy among the small number of non-Caucasians in one trial in type 2 DM, leads to a recommendation for further exploration of this phenomenon, as it may have implications for appropriate, safe dosing of the drug across races.

Efficacy

Type 1 diabetes

There were 5 phase 3 trials in type 1 diabetes. These are summarized in table 1 on page 4 of Dr. Pian's review. Note that all trials in both type 1 and type 2 were open-label in nature due to the fact that NPH insulin is a suspension and detemir is a clear solution.

Two trials, 1181 and 1205, were 6 months in length and each was followed by a 6-month extension study. These trials utilized a formulation of detemir that was double the concentration of U-100 human insulin (1200mmol/mL vs 600 mmol/mL) with twice daily dosing of both

detemir and the comparator, NPH insulin. Three other trials utilized a formulation of detemir with a concentration of 2400 mmol/mL (ultimately proposed for marketing). Two of these, 1447 and 1448, were virtually identical in design and enrolled approximately 140 patients in each of three arms, NPH BID, detemir BID q 12 h, and detemir BID q am and q hs. The molar starting dose of detemir was recommended (to trial investigators) as 2.8 times the molar dose of pre-study basal insulin. Insulin dose in all treatment groups was titrated to protocol-defined target fasting and 90-minute postprandial blood glucose concentrations. Basal insulin dose was to be adjusted during the first 4 weeks, with adjustments of both basal and bolus insulin to occur subsequently to achieve optimum control. Studies 1447 and 1448 were designed to test for superiority of detemir to NPH and did not meet that objective. However, in both cases, nominal non-inferiority of detemir dosed according to either regimen to NPH dosed BID was established. That is, the upper bound of the 95% CI for the difference in change from baseline in HbA1c (NPH minus detemir) was < 0.4 HbA1c percentage units. Only in trial 1448, however, was this result not confounded by higher average daily doses of bolus (mealtime) insulin in the detemir group.

In sum, in a single trial (of 5 total) in type 1 diabetes, using a detemir product 4 times the molar concentration of existing human insulin products, dosed twice daily, glycemic control non-inferior to that obtained with BID NPH was demonstrated in the context of nearly equivalent daily doses of bolus (mealtime) insulin across the treatment groups. This trial (and trial 1447) suggests that a molar daily dose of detemir approximately 4-4.5 times that of NPH will effect similar glycemic control to NPH, when both are dosed BID. The trial is evaluable from the standpoint of safety/hypoglycemia (see below).

An additional US trial (none so far has been conducted in the US) in type 1 diabetes to corroborate this result and to better inform dosing/method of use of detemir is recommended by the MO and I concur.

Type 2 diabetes

Three phase 3 trials were conducted in type 2 diabetes comparing detemir to NPH insulin (see Dr. Pian's table 2 on page 4 of her review). Two were conducted using the 2400 mmol/mL concentration of detemir. One of these (1336) was a study of BID dosing of both basal insulins used in conjunction with mealtime bolus insulin. The second (1337) was a study of once-a-day dosing of both basal insulins in conjunction with metformin at maximum tolerated doses. Nominal non-inferiority of detemir BID to NPH BID was achieved in study 1336 in the context of minor (≤ 0.3 percentage unit) reductions in HbA1c in both treatment groups with a higher mean daily dose of bolus insulin in the detemir group. In studies 1166 and 1337, the non-inferiority standard was not met, even nominally.

An analysis of the effects of detemir vs. NPH as a function of race in trial 1337 was, however, conducted and is summarized in table 46 on page 45 of Dr. Pian's review. Among the Caucasian patients, the mean reduction in HbA1c from baseline to 24 weeks was 0.9% with detemir (n=181) vs. 1.6% with NPH (n=89). By contrast, among non-Caucasians, mostly Hispanic and Black, the mean effects of detemir and NPH on HbA1c were similar (~1.3% reduction from baseline to 24 weeks). Considering that the sample size was so much larger for the Caucasian subgroup, this post hoc finding is striking and bears further investigation.

In sum, no phase 3 trial in type 2 diabetes demonstrated in a convincing fashion non-inferior efficacy of detemir to NPH, regardless of BID or QD dosing, alone or in combination with metformin or rapid acting mealtime insulin, and in spite of the use of mean daily molar doses of detemir up to 5 times those of NPH.

An additional study in type 2 diabetes to establish the non-inferiority of detemir to NPH dosed BID and to explore the efficacy of detemir as a function of race is recommended by the MO and I concur.

Safety

In phase 3, approximately 1550 type 1 diabetics were exposed to detemir with approximately 350 continued in extension studies with exposures out to 12 months. Approximately 900 type 2 diabetics were exposed to detemir in phase 3 in 6-month trials. The safety of detemir with regard to hypoglycemia appears no different than that of NPH, though the recommended additional trials in type 1 and type 2 diabetes will need to continue to characterize this risk. The clinical significance of the antigenicity of detemir has been adequately characterized. As per Dr. Misbin's review, detemir is more antigenic than NPH but there is no evidence of clinically significant immune response (i.e., neutralization of clinical effect). Dr. Misbin has suggested a protocol for detecting detemir-specific and cross-reacting antibodies to be applied in insulin-naïve patients with type 2 diabetes. This is described on page 53 of his review.

Additional studies

Dr. Misbin recommends the following:

Type 1 DM

A two-period, open-label study, 6 months in duration. During the first period, all patients will be treated in order to achieve goal HbA1c $\leq$ 7.5% with detemir along with mealtime bolus insulin. Responders (HbA1c $\leq$ 7.5%) are then randomized in the second period to detemir or NPH, both given BID. The primary comparison is the change from baseline at the start of period 2 to endpoint ($\geq$ 3 months) between treatment groups with a test for non-inferiority of detemir to NPH. Randomization should be stratified by race/ethnicity. Non-responders after period 1 and/or dropouts for lack of efficacy on detemir should be switched to NPH and the response assessed (descriptive analysis only). The analysis of response in period 1 should be descriptive as well.

I concur with this basic trial design as a means 1) to corroborate the finding of non-inferior efficacy of detemir to NPH and 2) to characterize the response/safety of detemir in whites vs. non-whites with type 1 DM.

Type 2 DM

A 6-month, open-label comparison of detemir to NPH. Following a 1-2 week washout of other antidiabetic medications (as necessary), patients meeting entry criteria will be randomized to detemir or NPH both dosed qd or BID with titration to goal FPG. No other antidiabetic meds permitted. Patients should be naïve to insulin. The primary comparison is the change from baseline to endpoint in HbA1c between treatment groups with a test of non-inferiority of detemir to NPH. Randomization should be stratified by race/ethnicity.

I concur with this basic trial design as a means 1) to establish, in an unconfounded trial, the non-inferior efficacy of detemir to NPH and 2) the prospectively investigate the impact of race/ethnicity on the response to detemir.

Labeling
No labeling has been discussed with the sponsor at this time and the division recommends that no comments be conveyed with this action.

Biopharmaceutics
Dr. Misbin discusses the results of euglycemic clamp studies in patients with types 1 and 2 diabetes on page 15 of his review. In short, the data on glucose utilization stimulated by insulin detemir compared to human insulin suggest that detemir is one tenth to one twelfth as potent per mole as human insulin. As above, in clinical use (SQ injection), 4-5 moles of detemir appears to be the dose equivalent to one mole of NPH.

OCPB finds the package acceptable and has two comments for the sponsor, on page 2 of Dr. Wei's review.

Pharmacology/Toxicology
As for all insulins, the primary toxicity of detemir relates to its hypoglycemic action and its safety profile in animals appears similar to other insulins. Labeling recommendations are contained in Dr. Rhee's review.

Chemistry/ Microbiology
The chemistry, manufacturing, and controls are satisfactory and the application is approvable from the standpoint of ONDC, pending satisfactory response to certain deficiencies identified. Dr. Brown lists multiple items to be resolved in order to address the AE recommendation from ONDC, starting on page 145 of her review.
A satisfactory cGMP inspection of facilities used to manufacture drug substance and drug product is also required and final recommendation for Compliance is still pending.
A categorical exclusion from the environmental assessment was requested by the sponsor and granted by the Agency.
Microbiological review recommendation: Approval

DSI/Data Integrity
No clinical site audits were requested or conducted for this NDA as all sites were overseas and the recommendation was to be AE on this cycle as per the clinical deficiencies above. Additional clinical studies will be needed to address these deficiencies and clinical site audits will be requested on the second review cycle.

Financial disclosure
The financial disclosure information is in order. The sponsor has certified that no investigator received outcome payments, that no investigator disclosed a proprietary interest in the product or an equity interest in the company, and that no investigator was the recipient of significant payments of other sorts.

ODS/nomenclature
The originally proposed proprietary name Levemir was not acceptable due to potential for confusion with Lovenox (low molecular weight heparin) which would be associated with clinical risk. The alternative name proposed. , is acceptable.

Recommendation
Approvable, pending addressing the clinical and CMC deficiencies.

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/s/

David Orloff
9/24/03 04:52:16 PM
MEDICAL OFFICER

Robert Meyer
9/25/03 09:29:17 AM
MEDICAL OFFICER
I am in agreement with Dr. Orloff's memorandum and this will serve as the ODE level memo for this review cycle.

DEPARTMENT OF HEALTH AND HUMAN SERVICES **MEMORANDUM**

Food and Drug Administration
Office of Device Evaluation -CDRH
9200 Corporate Blvd
Rockville, Maryland 20850

CONSULTATION REVIEW

Date: April 29, 2003

To: CDER - Division of Metabolic and Endocrine Drug Products (HFD-510)

Thru: Branch Chief, HFZ-480

From: Reviewer

Document No: NDA 21-536
Company Name: Novo Nordisk
Devices: FlexPen® containing PenFill® 3ml cartridge
InnoLet® containing PenFill® 3ml cartridge
Indications for Use:
The treatment of diabetes mellitus.

I. Purpose

This is a review of the sponsor's responses to a request for additional information about the InnoLet and FlexPen injector devices that are proposed for use to inject Insulin Detemir, proposed trade name Levemir™ (insulin detemir [rDNA origin] injection). Insulin Detemir is a long-acting, soluble human insulin analog.

II. Review:

Background: The information provided is part of the New Drug Application for Insulin Detemir (NDA 21-536) that includes two packaging presentations called the FlexPen® containing PenFill® 3ml cartridge and the InnoLet® containing PenFill® 3ml cartridge. The information requested and sponsor response, were:

REQUEST #1: A statement, comparable to that required in a device premarket notification, indicating how the FlexPen is similar to and/or different from the NovoPen3/NovoPen Junior. This statement should compare the design, features, operating mechanism, and final assembly procedures between the FlexPen and the NovoPen 3/ NovoPen Junior. Where appropriate, the statement should be supported by data. A similar statement should be provided for the InnoLet and the Innovo which are different devices from the FlexPen and the NovoPen 3/NovoPen Junior.

RESPONSE: The InnoLet and FlexPen are currently approved for the administration of insulin, and are compatible with the 3mL cartridge. The InnoLet was approved December 10, 2001 in NDA 19-938/S029; the FlexPen was approved on January 19, 2001 in NDA 20-986/S001.

For Consulting Center Use Only:

Date Received: _____
Assigned to: _____
Date Assigned: _____
Assigned by: _____

Completed date: 4/29/03
Reviewer Initials: _____
Supervisory Concurrence: _____

Intercenter Request for Consultative or Collaborative Review Form

To (Consulting Center):
Center: CDRH
Division: ODE/DAGID
Mail Code: HF Z-480
Consulting Reviewer Name: Von Nakayama
Building/Room #: CORP RM 340N
Phone #: 594-1287
Fax #:
Email Address:
RPM/CSO Name and Mail Code:

From (Originating Center):
Center: CDER
Division: DMEDP
Mail Code: HFD-510
Requesting Reviewer Name: Julie Rhee
Building/Room #: Parklawn 14B04
Phone#: 827-6424
Fax #: 443-9282
Email Address: rheej@cder.fda.gov
RPM/CSO Name and Mail Code: Julie Rhee, HFD-510
Requesting Reviewer's Concurring Supervisor's Name: Kati Johnson

Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.

Date of Request: April 23, 2003

Requested Completion Date: June 30, 2003

Submission/Application Number: NDA 21-536
(Not Barcode Number)

Submission Type: NDA
(510(k), PMA, NDA, BLA, IND, IDE, etc.)

Type of Product: ☑ Drug-device combination ☐ Drug-biologic combination ☐ Device-biologic combination ☐ Drug-device-biologic combination ☐ Not a combination product

Submission Receipt Date: April 18, 2003

Official Submission Due Date: August 7, 2003

Name of Product: Insulin detemir

Name of Firm: Novo Nordisk

Intended Use: Treatment of patients with diabetes mellitus

Brief Description of Documents Being Provided (e.g., clinical data – include submission dates if appropriate):
The sponsor's response to your information request. Please review whether or not the response is acceptable. I have attached a copy of the fax that was sent to the sponsor. When you complete the review, could you please forward your review to me as an e-mail attachment? Thanks.

Documents to be returned to Requesting Reviewer? ☐ Yes ☑ No

Complete description of the request. Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

Type of Request: ☑ Consultative Review ☐ Collaborative Review

(940 characters max -- use additional sheet if necessary)

Rhee, H Julie

From: Nakayama, Von
Sent: Wednesday, April 02, 2003 5:14 AM
To: Rhee, H Julie
Cc: Cricenti, Patricia
Subject: RE: NDA 21-536 Novo insulin pen

Julie,

Although the four devices use the same cartridges, they are not the same devices as the sponsor seems to imply. They have known, and perhaps unknown differences that have not been explained. The FlexPen and InnoLet are likely okay, but the documents that we reviewed don't have the data to show that.

VON

-----Original Message-----
From: Rhee, H Julie
Sent: Tuesday, April 01, 2003 4:47 PM
To: Cricenti, Patricia; Nakayama, Von
Cc: Brown, Janice; Moore, Stephen K
Subject: RE: NDA 21-536 Novo insulin pen

Pat and Von,

Thanks for the review.

FlexPen and InnoLet Pen are disposable prefilled syringe that are discarded when the cartridge is empty. But NovoPen 3/NovoPen Junior are reusable device and replace the cartridge when it is empty. All four devices use a same type of cartridges.

Do you still need me to send your comment #1 to the sponsor?

Thanks,

Julie

-----Original Message-----
From: Cricenti, Patricia
Sent: Tuesday, April 01, 2003 1:38 PM
To: Rhee, H Julie
Subject: FW: NDA 21-536 Novo insulin pen

I concur with this review
Pat Cricenti
Chief GHDB

-----Original Message-----
From: Nakayama, Von
Sent: Tuesday, April 01, 2003 1:38 PM
To: Cricenti, Patricia
Subject: NDA 21-536 Novo insulin pen

Pat,

E-version to forward to Julie Rhee. Hard copy will be mailed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES **MEMORANDUM**

Food and Drug
Administration
Office of Device
Evaluation -CDRH
9200 Corporate Blvd
Rockville, Maryland 20850

CONSULTATION REVIEW

Date: April 1, 2003

To: CDER/Division of Metabolic and Endocrine Drug Products (HFD-510)

Thru: Branch Chief, HFZ-480 Patricia Cricenti

From: Reviewer

Document No: NDA 21-536
Company Name: Novo Nordisk
Devices: FlexPen® containing PenFill® 3ml cartridge
InnoLet® containing PenFill® 3ml cartridge
Indications for Use:
The treatment of diabetes mellitus.

I. Purpose

This consult is for the review of two pen injector devices that are proposed for use to inject Insulin Detemir, proposed trade name Levemir™ (insulin detemir [rDNA origin] injection), a new molecular entity that is a long-acting, soluble human insulin analog.

II. Review:

Background: The device-related information provided for us to review is part of the New Drug Application for Insulin Detemir (NDA 21-536 cover letter document, volumes 3/12 and 7/12 of module 3 volume 1.3) that includes two packaging presentations called the FlexPen® containing PenFill® 3ml cartridge and the InnoLet® containing PenFill® 3ml cartridge. The FlexPen and the InnoLet are pen injectors Class II medical devices, classification 21CFR880.5860: Piston Syringe, Product code FMF.

The FlexPen is a single patient use, disposable pen injector preloaded with a PenFill cartridge containing 3 milliliters of 100U/ml Insulin Detemir. The FlexPen is designed to deliver 1 to 60 units of insulin in 1 unit increments using a screw drive mechanism and a combination dose knob/push button. The InnoLet is a single patient use, disposable pen injector preloaded with a PenFill cartridge containing 3 milliliters of 100U/ml Insulin Detemir. The InnoLet is designed to deliver 1 to 50 units of insulin in 1 unit increments using a rack-and-pinion drive, dose dial, and a separate push button. Both have proposed shelf lives of [redacted] and draft labeling directing the user to throw the injector away 42 days after first use.

The sponsor stated that the technical description and assembly documents for the FlexPen are in NDA 20-986/S001, approved January 19, 2001. The implication is that the FlexPen has the same design, intended use, and fundamental technology as the sponsor's legally marketed NovoPen 3 and NovoPen Junior. The FlexPen has two identifiable differences: it is a disposable device with a dose range of 1 to 60 units in 1 unit increments, unlike the reusable NovoPen 3 which has a range of 2 to 70 units in 1 unit increments, or the dose range of 1 to 35 units in 0.5 unit increments of the NovoPen Junior. The FlexPen, NovoPen 3, and NovoPen Junior use screw drives and dose knobs.

Documentation for the InnoLet is contained in NDA 19-938/S029, approved December 10, 2001. The implication is that the InnoLet has the same, design, intended use, and fundamental technology as the Innovo pen injector. There are two differences: the InnoLet is a disposable device with a dose range of 1 to 50 units of insulin in 1 unit increments; the Innovo/InDuo is a reusable device with a dose range of 1 to 70 units in 1 unit increments. The pen injector used in the InDuo device, cleared for marketing by the CDRH as K011616 is identical to the Innovo pen injector that was cleared as K010359.

Testing of device: The sponsor evaluated and verified the functions and dose accuracy of the FlexPen and InnoLet devices to the requirements of ISO/DIS Standard 11608-1, "Pen injectors for Medical Use - Part 1: Requirements and Test Methods, December 2000." This ISO standard is not currently in the FDA Consensus Standards Program. The sponsor will include a dose accuracy test at the ——— dose level as a release test.

III. Conclusion:

Unable to recommend approval, based upon the information provided. The FlexPen and InnoLet appear to be the sponsor's legally marketed pen injectors that have been modified for use with Insulin Detemir. The modifications appear to be different dose ranges, reuse capability, and assembly from the original pen injectors. Although these modifications do not change the intended use of the devices or fundamental technologies that would raise new questions of safety and effectiveness, the sponsor did not provide technical information about these modifications or provide the comparisons with a predicate device that would permit an evaluation of safety and effectiveness. The device information contained in other documents, as referenced by the sponsor, are not sufficient to evaluate the safety and effectiveness of the FlexPen® containing PenFill® 3ml cartridge and the InnoLet® containing PenFill® 3ml cartridge for the subcutaneous administration of the proposed new insulin Levemir™ (insulin detemir [rDNA origin] injection)].

The insulin detemir dose appears to be based upon volume, not the conventional insulin "unit" although the sponsor is using the "unit" convention in the submission. The sponsor did not identify what modifications to the dose setting mechanism of the original devices may have been required by dosing on "an equal volume approach" instead of a "unit" approach.

The sponsor should be asked to provide:

A statement, comparable to that required in a device premarket notification, indicating how the FlexPen is similar to and/or different from the NovoPen3/NovoPen Junior. This statement should compare the design, features, operating mechanism, and final assembly procedures between the FlexPen and the NovoPen 3/ NovoPen Junior. Where appropriate, the statement should be supported by data. A similar statement should be provided for the InnoLet and the Innovo which are different devices from the FlexPen and the NovoPen 3/NovoPen Junior.

A discussion about what modifications to the dose setting mechanism of the FlexPen and InnoLet to administer insulin detemir by volumes rather than in units. This discussion should include an evaluation of the effects of these modifications on device performance and dose accuracy testing.

Von Nakayama

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

/s/

Julie Rhee
4/3/03 01:53:30 PM
CSO

2/4/03

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-536
Trade Name: Levemir (insulin detemir [rDNA origin] injection)
Generic Name: NN304
Strengths: U-100

Applicant: Novo Nordisk

Date of Application: *December 5, 2002*
Date of Receipt: *December 9, 2002*
Date clock started after UN: *N/A*
Date of Filing Meeting: *January 27, 2003*
Filing Date: *February 3, 2003*
Action Goal Date (optional): **User Fee Goal Date:** *October 5, 2003*

Indication(s) requested: *For the treatment of diabetes mellitus.*

Type of Application: *Original (b)(1) NDA*

Therapeutic Classification: *S*
Resubmission after a withdrawal? *NO* **Resubmission after a refuse to file?** *NO*
Chemical Classification: (1,2,3 etc.) *1*
Other (orphan, OTC, etc.) *N/A*

User Fee Status: *Paid*
Form 3397 (User Fee Cover Sheet) submitted: *YES*
User Fee ID # *4451*
Clinical data? *YES*

Is there any 5-year or 3-year exclusivity on this active moiety in either a (b)(1) or a (b)(2) application? *NO*
If yes, explain:

Does another drug have orphan drug exclusivity for the same indication? *NO*
If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

Is the application affected by the Application Integrity Policy (AIP)? *NO*
If yes, explain.
If yes, has OC/DMPQ been notified of the submission?

- **Does the submission contain an accurate comprehensive index?** *YES*

- **Was form 356h included with an authorized signature?** *YES*
  If foreign applicant, both the applicant and the U.S. agent must sign.

- **Submission complete as required under 21 CFR 314.50?** *YES*
  If no, explain:

- **If an electronic NDA, does it follow the Guidance?** *N/A*
  If an electronic NDA, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format? *CRT and Labeling*

  Additional comments:

- **If in Common Technical Document format, does it follow the guidance?** *YES*

- **Is it an electronic CTD?** *NO*
  If an electronic CTD, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

  Additional comments:

- **Patent information included with authorized signature?** *YES*

- **Exclusivity requested?** *NO*
  Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- **Correctly worded Debarment Certification included with authorized signature?** *YES*

  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: Debarment Certification must have correct wording, e.g.: "I, the undersigned, hereby certify that _____ Co. did not and will 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 the studies listed in Appendix ____." Applicant may not use wording such as "To the best of my knowledge . . . ."

- **Financial Disclosure information included with authorized signature?** *YES*
  (Forms 3454 and/or 3455 must be used and must be signed by the APPLICANT.)

- **Field Copy Certification (that it is a true copy of the CMC technical section)?** *YES*

Refer to 21 CFR 314.101(d) for Filing Requirements

- **PDUFA and Action Goal dates correct in COMIS?** *YES*
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- **Drug name/Applicant name correct in COMIS?** *YES*
  If not, have the Document Room make the corrections.

- **List referenced IND numbers:** *IND 51,789*

- **End-of-Phase 2 Meeting(s)?** *Date 7-22-99*
  If yes, distribute minutes before filing meeting.

- **Pre-NDA Meeting(s)?** *Date 6-11-02*
  If yes, distribute minutes before filing meeting.

Project Management

- **Package insert consulted to DDMAC?** *YES (1-24-03)*

- **Trade name (plus PI and all labels and labeling) consulted to ODS/Div. of Medication Errors and Technical Support?** *YES (12-11-02)*

- **MedGuide and/or PPI (plus PI) consulted to ODS/Div. of Surveillance, Research and Communication Support?** *YES (1-24-03)*

- **If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?** *N/A*

If Rx-to-OTC Switch application:

- **OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/ Div. of Surveillance, Research and Communication Support?** *N/A*

- **Has DOTCDP been notified of the OTC switch application?** *N/A*

Clinical

- **If a controlled substance, has a consult been sent to the Controlled Substance Staff?** *N/A*

Chemistry

- **Did applicant request categorical exclusion for environmental assessment?** *YES*
  If no, did applicant submit a complete environmental assessment? YES NO
  If EA submitted, consulted to Nancy Sager (HFD-357)? YES NO

- **Establishment Evaluation Request (EER) submitted to DMPQ?** *YES*

- **If parenteral product, consulted to Microbiology Team (HFD-805)?** *YES*

If 505(b)(2) application, complete the following section: *N/A*

- Name of listed drug(s) and NDA/ANDA #:

- Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

- Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs.) YES NO

- Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 314.101(d)(9). YES NO

- Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD? (See 314.54(b)(2)). If yes, the application should be refused for filing under 314.101(d)(9). YES NO

- Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

  ____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

  ____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

  ____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

  ____ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

  IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

  ____ 21 CFR 314.50(i)(1)(ii): No relevant patents.

  ____ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications.

  ____ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above.)
  ____ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

- Did the applicant:

    - Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference? YES NO

    - Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity? YES NO

    - Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug? N/A YES NO

    - Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).? N/A YES NO

- If the (b)(2) applicant is requesting exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

    - Certification that each of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a). YES NO

    - A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval. YES NO

    - EITHER
      The number of the applicant's IND under which the studies essential to approval were conducted. YES, IND # _____ NO
      OR
      A certification that it provided substantial support of the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted? N/A YES NO

- Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application? YES NO

Rhee, H Julie

'om: Pawar, Vinayak
Jent: Wednesday, January 29, 2003 10:02 AM
To: Rhee, H Julie
Subject: RE: Updated: FILE/NDA 21-536/Insulin Detemir/Novo

Hi Julie,
Here is the email I sent you. There are no microbiology issues. Thanks.
Vinnie

-----Original Appointment-----
From: Pawar, Vinayak
Sent: Friday, January 17, 2003 5:51 PM
To: Rhee, H Julie
Subject: Tentative: Updated: FILE/NDA 21-536/Insulin Detemir/Novo
When: Monday, January 27, 2003 10:00 AM-11:00 AM (GMT-05:00) Eastern Time (US & Canada).
Where: CDER PKLN 14B45 Conf Room -AR; CDER 510 Calendar

Hi Julie,
I looked through the document and it is filable from microbiological standpoint. If you have specifc issue please let me know and I can arrange to be at the meeting.
Vinnie

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

(Division/Office): Karen Lechter, HFD-410

FROM: Julie Rhee, DMEDP, HFD-510

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
January 24, 2003		21-536	Original NDA	December 5, 2002

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Insulin detemir			May 30, 2003

NAME OF FIRM:

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- BIOAVAILABILTY STUDIES
- PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Karen,

Could you please review the PPI and let me know of your comments? The proposed labelings are available thru EDR. Thanks,

Julie

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

(Division/Office): Marci Kiester, DDMAC, HFD-42

FROM: Julie Rhee, DMEDP, HFD-510

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
January 24, 2003		21-536	Original NDA	December 5, 2002

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Insulin detemir			May 30, 2003

NAME OF FIRM:

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE–NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- BIOAVAILABILTY STUDIES
- PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Marci,

The proposed labeling is available thru EDR. Thanks,

Julie

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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

/s/

Julie Rhee
1/24/03 03:41:13 PM

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 27, 2003

BACKGROUND:

Insulin detemir (NN304) is a long-acting human insulin analog without the threonine residue at position B30 of the human insulin molecule and a C_{14} fatty acid side-chain attached to position B29. Insulin detemir is fat soluble and 98-99% bound to albumin in plasma causing it to compete with insulin receptor.

The potency of insulin detemir is about one fourth that of human insulin on a molar basis.

The entire NDA is submitted using Common Technical Document format.

ATTENDEES:

David Orloff, M.D., DMEDP, HFD-510
Robert Misbin, M.D., DMEDP, HFD-510
Todd Sahlroot, Ph.D., DBII, HFD-715
Lee Pian, Ph.D., DBII, HFD-715
Stephen Moore, Ph.D., DNDC II, HFD-510
Janice Brown, DNDC II, HFD-510
Herman Rhee, DMEDP, HFD-510
Hae-Young Ahn, Ph.D., OPS/DPEII, HFD-870
Jim Wei, OPS/DPE II, HFD-870
Andrea Slavin, DSI, HFD-46
Sandy Birdsong, OPSS/DDRE, HFD-430
Julie Rhee, DMEDP, HFD-510

ASSIGNED REVIEWERS:

Medical:	Robert Misbin, M.D.
Statistical:	Lee Pian, Ph.D.
Pharmacology:	Herman Rhee, Ph.D.
Chemist:	Janice Brown
Biopharmaceutical:	Jim Wei, Ph.D.
Microbiology, sterility:	Vinnie Pawar, Ph.D.
DSI:	Andrea Slavin
Regulatory Project Manager:	Julie Rhee
Other Consults:	CDRH—Patricia Cricenti
	DDMAC (PI)—Marci Kiester
	ODS/DMETS—Sammie Beam
	OPSS/DDRE (PPI)—Jeanie Best

Per reviewers, are all parts in English or English translation? *YES*
If no, explain:

CLINICAL : ***FILE***

- Clinical site inspection needed: ***YES***

  DSI inspection is requested on Studies 1447 and 1448. DSI is to choose individual study site from these studies.

- Advisory Committee Meeting needed? ***NO***

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? ***N/A***

- Filing comments to be sent to the sponsor: ***YES***

MICROBIOLOGY: ***FILE***

- Filing comments to be sent to the sponsor: ***NO***

STATISTICS: ***FILE***

- Filing comments to be sent to the sponsor: ***NO***

BIOPHARMACEUTICS: ***FILE***

- Biopharm. inspection needed: ***NO***

- Filing comments to be sent to the sponsor: ***YES***

PHARMACOLOGY: ***FILE***

- GLP inspection needed: ***NO***

- Filing comments to be sent to the sponsor: ***NO***

CHEMISTRY: ***FILE***

- Establishment(s) ready for inspection? ***YES***

- Microbiology consult requested: ***YES***

- Filing comments to be sent to the sponsor: ***NO***

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

_____ The application is unsuitable for filing. Explain why:

__X__ The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

_____ No filing issues have been identified.

__X__ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. If RTF, notify everybody who already received a consult request of the RTF action. Cancel the EER.

2. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

3. Document filing issues/no filing issues conveyed to applicant by Day 74.

CONCLUSIONS:

1. The NDA is fileable.

2. DSI inspection is requested on Studies 1447 and 1448. DSI is to choose individual study site from these studies. Request a desk copy for Module 1 volume 1 for DSI.

3. Advisory Committee meeting is not needed.

4. Target date for the final review (with T/L's concurrence) is July 11, 2003.

5. Each discipline is to enter the filing comments into the DFS.

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

/s/

Julie Rhee
2/4/03 09:40:42 AM
CSO

MEMORANDUM OF MEETING MINUTES

MEETING DATE: June 11, 2002
TIME: 3:30 – 5:00 pm
LOCATION: Parklawn 3rd floor c/r "C"
APPLICATION: IND 51, 789 Insulin detemir (NN304)
TYPE OF MEETING: Pre-NDA
MEETING CHAIR: David Orloff, M.D.
MEETING RECORDER: Julie Rhee
FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

Name of FDA Attendee	Title	Division Name
David Orloff, M.D.	Director	Division of Metabolic and Endocrine Drug Products
Robert Misbin, M.D.	Medical Officer	DMEDP
Jeri El-Hage, Ph.D.	Pharm/Tox Team Leader	DMEDP
Herman Rhee, Ph.D.	Pharm/Tox Reviewer	DMEDP
Janice Brown, Ph.D.	Chemistry Reviewer	DMEDP
Lee Pian, Ph.D.	Statistical Reviewer	Division of Biometrics II
Jim Wei, Ph.D.	Biopharm Reviewer	DPE II
Justina Molzon, M.S.Pharm, J.D.	Associate Director for Internatioal Programs	CDER
Randy Levin, M.D.	Associate Director for Information Management	CDER
Julie Rhee	Project Manager	DMEDP

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

External Attendee	Title	Sponsor/Firm Name
Peter Bonne Eriksen	Senior VP, Project Management & Regulatory Affairs	Novo Nordisk A/S (Denmark)
Hanne Henriksen	Project Manager, International Regulatory	
Lisbeth Jabosen	Scientist, Clinical	
Allan Kristensen	Statistician, Biostatistics	
Peter Kurtzhals	VP, Discovery Management	
Eberhard Draeger	Project Manager, International Clinical	
Ulla Ribel	Scientist, Pharmacology	
Susanna Rugh	Project VP, Project Management	
Jerzy Kolaczynski	Associate Director, Medical	Novo Nordisk PI (USA)
Mary Ann McElligott	Senior Director, Regulatory Affairs	
Barry Reit	VP, Regulatory Affairs	
Olga Santiago	Director, Medical	
Elizabeth Tan	Assistant Director, Regulatory Affairs	

BACKGROUND:

Insulin detemir (NN304) is a long-acting human insulin analog without the threonine residue at position B30 of the human insulin molecule and a C_{14} fatty acid side-chain attached to position B29. Insulin detemir is fat soluble and 98-99% bound to albumin in plasma causing it to compete with insulin receptor.

Since it takes four times of insulin detemir dose to be equivalent with one human insulin dose, unit definition for insulin detemir is an issue and is one of the agenda items at the June 11, 2002, pre-NDA meeting.

The sponsor plans to include (1) 3 mL PenFill cartridges, (2) 3 mL disposable prefilled InnoLet syringes, (3) 3 mL disposable prefilled FlexPen syringes, and (4) 10 mL vials insulin presentations in the NDA.

The meeting background material was received and distributed on May 10, 2002.

QUESTIONS AND ANSWERS: The following is a list of the sponsor's questions and the Agency's responses:

Question 1: In-process control of drug substance

Testing of have been performed as in-process controls during development of the drug substance (for data please refer to Appendix 2).
In addition, these tests will be part of the process validation of the manufacturing-scale batches of drug substance, in order to confirm that routine in-process control testing of will not be necessary during continued manufacturing (data are included in Appendix 2).

Does the Agency concur with this strategy?

FDA's response:

Yes, as long as the results of future batch data do not change.

Question 2: Drug substance specification

Based upon data collected from clinical batches (please refer to DNA report in Appendix 3), the content of total has consistently been very low: typically µg/g (ppm), which is of the acceptance limit established during development. As corresponds to of drug product (assuming a maximal dose

of 1U/kg body weight), the — content in API is far below the generally accepted level. We propose omitting this parameter from the final specifications of the drug substance.

Does the Agency concur with this strategy?

FDA's response:

Yes, as long as the results of future batch data do not change.

Question 3: Stability of drug substance and drug product

At the time of filing, Novo Nordisk plans to submit drug substance stability data from batches made in the pilot plant and — stability data from batches made at the production plant. The drug products (cartridge and vial) will have varying amounts of data (—) from batches made in pilot and production plants. Does the Agency concur with our proposed strategy on the stability of drug substance and drug product?

FDA's response:

API – long term and — accelerated data at pilot scale and — long-term and accelerated full-scale data is acceptable. During the review process, updated stability data may be requested. This is based on the assumption that the API manufacturing process is identical at the Bagsvaerd and Kalundborg locations (Process C).

Drug Product
3-mL Cartridge – Pilot scale data and the full-scale data is acceptable.
10-mL Vial – see answer to question 4.

Question 4: Stability data of vial presentation

The formulation for the two drug product presentations is identical and the production process similar. Materials of both container closures are identical except for the presence of a — closure in the 3 ml cartridge. Consequently, the stability of the two presentations is expected to be comparable.
Assuming acceptable stability data, does the Agency agree that the stability data on the Penfill® cartridge and the vial formulations support simultaneous approval of both presentations with the longer shelf-life projected by the stability data obtained on the Penfill® cartridge?

FDA's response:

No, the proposal to use the cartridge stability data to support the vial presentation is not acceptable, even though the manufacturing processes and the container/closure materials of construction are similar. According to ICH Q1A, stability testing should be conducted on the dosage form in the container/closure proposed for marketing, two of the three batches should be at least pilot scale and the third can be smaller if justified.

(Notes: Stability data for the vial included — at laboratory scale and — full-scale batch.)

Question 5: Batch data for vial presentation

For the vial presentation, batch release data on one production scale batch will be included in the NDA. Novo Nordisk intends to provide release data on — additional production scale batches of the 10 ml vial presentation not later than 6 months after submission of the NDA. Is this acceptable to the Agency?

FDA's response: Yes.

Question 6: Bioassay

Reference is made to IND amendment No. 088 submitted February 13, 2002. It was a response to a question regarding the feasibility of developing an *in-vivo* bioassay to establish drug unit activity when compared to NPH and whether the bioassay could be correlated to a proposed free fat cell assay. Reference is also made to a March 14, 2002 submission containing a proposal on the next steps Novo Nordisk intends to take in addressing the question.

In a March 26, 2002 teleconference an agreement was reached that Novo Nordisk should proceed with conducting pilot and definitive studies using a modified Ph. Eur. mouse bioassay to document insulin detemir bioactivity. We propose submitting the data one to two months in advance of the NDA for the Agency's review. Is this acceptable?

We also plan to provide the data from the mouse bioassay in Module 3 of the CTD. Is this acceptable?

FDA's response:

1. *Yes. However, if there are problems with the bioassay, we are requesting to be notified immediately of your preliminary results.*

2. *Submit the bioassay data two months prior to the NDA submission.*
3. *It is acceptable to provide the data from the mouse bioassay in Module 3 of the CTD.*

Question 7: Description of human insulin production

Hence, the information provided on the — — are already approved world wide for human insulin production. We propose to cross reference NDA 19-938 in which the entire human insulin manufacturing process is detailed. Does the Agency agree with this proposal?

FDA's response:

Yes, only if — are identical.

Question 8: Carcinogenicity

Reference is made to January-February 1997 discussions wherein the Agency stated that carcinogenicity studies would not be required for NDA filing. Instead, Novo Nordisk was asked to submit studies that would follow up on the possibility of carcinogenic potential. At the July 22, 1999 End-of-Phase 2 meeting, the Agency agreed to the following proposal:

1) A study to determine IGF-1 receptor binding affinity of insulin detemir
2) A study to determine the mitogenic potential of detemir in human B10 osteosarcoma cells

To date we have submitted the following to the IND:

1) **Mitogenicity of NN304 (report with original IND)**
2) **Mitogenicity in MCF-7 cells (report, IND serial # 85 sent 1/7/02)**
3) **Binding of NN304 and NN344 to insulin and IGF-1 receptors of HepG2 cells (report in 7/14/99 – 7/13/00 Annual Report)**
4) **Binding to insulin receptor and IGF-1-receptor (report in 7/14/99 – 7/13/00 Annual Report)**
   Mitogenic Potency of insulin detemir in CHO-K1 cells (report in 7/14/99 – 7/13/00 Annual Report)
   Mitogenic potential of NN304 in human B10 osteosarcoma cells (report, IND serial #104 sent 04/02/02)

All studies have shown that insulin detemir has minimal or no mitogenic potential. Based on the results, Novo Nordisk believes a carcinogenicity study is not necessary. Does the Agency concur?

FDA's response:

Yes. However, the Division requires a one-year rat study for insulin analogues with a human insulin comparator arm as was conducted for NovoLog. The sponsor was advised to conduct a similar one-year rat study during the EOP 2 meeting that was held on July 22, 1999. The Division stated that they would waive one-year rat study for insulin detemir because of the lower binding affinity, potency, and mitogenic activity of this analog relative to native sequence human insulin.

Question 9: Hyperlipidemia and Renal and Hepatic Studies

At the End-of-Phase 2 meeting July 1999 (and later at a December 2000 teleconference) the Agency asked for an update regarding Novo Nordisk's plans to address the possibility that in some patients hyperlipidemia could displace insulin detemir from the albumin binding sites, with possible partitioning in the hydrophilic and lipophilic interphase, potential loss of biologic activity, or unpredictable release of insulin detemir. This hypothesis was proposed by the Agency. The Agency indicated that it was reasonable to address this problem with *in-vitro* studies.
Based upon this proposal, blood plasma samples were tested in an *in-vitro* experiment to determine drug displacement in hyperlipidemic serum. Final data was sent to Dr. Misbin 16. of April 2002, and the data is also included in the pre-NDA briefing package (Appendix 8). The results of the single-dose pharmacokinetic study in subjects with varying degrees of renal impairment and results of the single-dose pharmacokinetic study in subjects with various stages of hepatic impairment will also be included in the pre-NDA briefing document.
If the issue of hyperlipidemia has not been resolved by the *in-vitro* data, we would like to finalize an agreement at the pre-NDA meeting.

FDA response:

Additional data is not needed prior to the NDA submission.

Question 10: Non-inferiority claim in efficacy trials

The criterion for claiming non-inferiority in all phase III efficacy trials was defined as an upper limit of the two-sided 95% confidence interval for the difference in HbA_{1c} of less than 0.4% (absolute). The upper limit in the confidence interval for the final trials, which met the non-inferiority criterion is in the interval of 0.02 – 0.31%. An increase in bolus dosage was observed for the insulin detemir group as compared to the NPH group (the bolus doses in the insulin detemir groups were 6 – 18% higher than in the NPH groups). Please refer to the pre-NDA briefing package, clinical/statistical section, for

more information.

Does the Agency accept the claim of non-inferiority of insulin detemir with regard to NPH based on the findings described above?

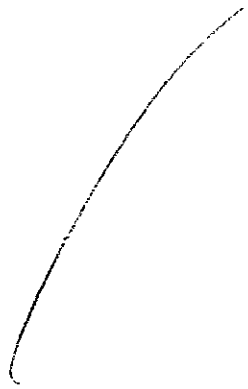
Discussion:

1. To be marketed concentration is 2,400 nmol/mL. The sponsor has conducted one study (Study 1335) with to be marketed concentration in patients with type 1 diabetes and two studies (Study 1336 and 1337) in patients with type 2 diabetes.
2. Study 1447 and 1448 included bolus dose at bedtime.

FDA response:

No, because bolus contributed to efficacy and more bolus dose was used in insulin detemir group. Non-inferiority claim is going to be handled as a review issue.

Question 11: Pediatric labeling



Discussion:

The sponsor plans to include PK/PD data in the NDA.

FDA response:

The submission of PK/PD data will meet the pediatric rule requirement.

Question 12: Proposal for unit definition

At the End-of-Phase 2 meeting (July 1999) and later at a follow-up teleconference December 2000, Novo Nordisk proposed the following unit definition to insulin detemir: In order for the patient to obtain a comparable metabolic effect per unit of the injected volume, one unit/ml (a "dosing unit"/ml) of insulin detemir (24 nmol/ml) equals one unit/ml of NPH insulin (6 nmol/ml). At the teleconference December 2000 the Agency agreed to the equal volume approach, but reserved the right to further discuss the proposed unit definition.

Does the Agency have any comments regarding the proposed unit definition?

FDA response:

1. *It is not acceptable to use "Unit" for insulin detemir. The Division does not agree with re-defining of "Unit" and asked the sponsor to come up with an alternate terminology, i.e.,* —
2. *USP definition of "Unit" is based on human insulin molecular structure.*

Question 13: Table of content and ISE/ISS requirements in CTD

The dossier of insulin detemir will be provided in the Common Technical Document (CTD) format and has considered country-specific requirements. Please see the pre-NDA information package for our proposed mapping of topics as evidenced by the basic outline of the Table of Content (TOC) in Appendices 5-7. Does the agency have any comments?

Novo Nordisk intends to provide a clinical written summary in module 2 which incorporates all elements of ISS and ISE. This should fulfill the requirements for the presentation of efficacy and safety for both EU and the US. Does the Agency have any comments to the above outlined strategy?

FDA response:

1. *The sponsor needs to follow CTD guidance document.*
2. *A clinical written summary in module 2, which incorporates ISS and ISE, is acceptable if it fits. However, the regulatory requirements for ISS and ISE are still required and the sponsor needs to follow the GUIDELINE FOR THE FORMAT AND CONTENT OF THE CLINICAL AND STATISTICAL SECTIONS OF NEW DRUG APPLICATIONS.*
3. *If ISS is not a summary, it cannot be placed in module 2.*
4. *Tab that identifies more than one element can be put under single tab.*
5. *The Agency stated that transitional CTD phase is until July 2003 and asked the sponsor to let the Agency know of any problems related to CTD.*

6. *It was suggested that the sponsor use sequential page numbers in addition to individual document page number. Each tab will start with page 1.*

Question 14: Location of analytical methods and validation reports repeated in modules 4 and 5

Some of the analytical methods and the associated validation reports are presented in modules 4 (Non-Clinical) and 5 (Clinical) of the CTD. Novo Nordisk proposes to submit a complete set of analytical methods and validation reports in each of modules 4 and 5, without any cross-references between the modules. Cross-referencing will be made within each module.

For module 2, cross-references to the summary of analytical methods and validation reports will be made either to module 4 or 5.

Does the FDA concur with this strategy?

FDA response:

Yes. However, each module needs to have Table of Contents.

Question 15: Electronic deliverables

Novo Nordisk proposes to electronically submit the following:
• Case record forms (death and serious adverse events) and individual patient listings. These files will be presented in a PDF format and can be delivered on CD-ROMs otherwise paper copies can be provided.
• Electronic derived data listings in SAS transport files for pivotal efficacy trials.
Are there any other documents that the FDA would like to receive electronically?

FDA response:

1. *The proposed electronic deliverables are acceptable. The Agency requested that the sponsor provide a paper copy for death and discontinuation in the trial as a part of trial summary.*
2. *There should be a separate microbiology volume when the NDA is submitted.*

Question 16: Advisory Committee Meeting

Can the Agency provide any projections regarding the likelihood of an Advisory Committee Meeting for insulin detemir?

FDA response:

This is going to be decided during the review of the NDA.

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

/s/

David Orloff
7/11/02 04:31:00 PM

MEMORANDUM OF MEETING MINUTES

Meeting Date: July 22, 1999
Time: 2:00 – 3:30 pm
Location: Parklawn Bldg 3rd fl c/r "K"
Application: IND 51, 789 NN304
Sponsor: Novo Nordisk Pharmaceuticals Inc.
Type of Meeting: End-of-Phase 2 meeting
Meeting Chair: Solomon Sobel, M.D.
Meeting Recorder: Julie Rhee
Attendees:
FDA:

John Jenkins, M.D., Director, ODE II
Solomon Sobel, M.D., Director, DMEDP
Saul Malozowski, M.D., Acting Medical Team Leader, DMEDP
Robert Misbin, M.D., Medical Officer, DMEDP
Ronald Steigerwalt, Ph.D., Pharmacology Team Leader, DMEDP
Herman Rhee, Ph.D., Pharmacology Reviewer, DMEDP
Stephen Moore, Ph.D., Chemistry Team Leader, DMEDP
William Berlin, Ph.D., Chemist, DMEDP
Hae-Young Ahn, Ph.D., Biopharm Team Leader, DPE II
Lee Pian, Ph.D., Statistician, DOB II

Novo Nordisk (Copenhagen):

Mads Axelsen, M.D., Director, Clinical Development
Jeppe Christensen, MS.C., Project Director
Allen Kristensen, Statistician
Peter Kurtzhals, Ph.D., Head of Diabetes Biology
Jesper Nelleman, D.D.S., Regulatory Affairs Project Manager

Novo Nordisk (Princeton):

Won-Chin Huang, Ph.D., Statistician
Jerzy Kolaczynski, M.D., Ph.D., Asscociate Medical Director
Mary Ann McElligott, Ph.D., Director, Regulatory Affairs
Peter Mueller, M.D., Director, Medical Affairs
Olga Santiago, M.D., Medical Director

Discussion Points:

1. The structure of NN 304 is similar to human insulin with a fatty acid chain modification at B-29 lysine and deletes of the terminal amino acid at B-30.
2. NN 304 does not have any patent conflict with Lilly's lyspro.
3. 98.8% of NN 304 is bound to protein in human plasma.

The following is a list of the sponsor's questions (bolded) and FDA's responses (italicized).

Question 1:

A comprehensive package of preclinial studies have been performed on insulin detemir, including pharmacology, pharmacokinetics/toxicokinetics, drug metabolism, toxicology, mitogenicity and immunogenicity (*see* Appendix A in Information Package). In general, all preclinical findings are in accordance with the expected primary pharmacological profile of insulin detemir. Does the agency concur that this preclinical package qualify insulin detemir as a candidate for an NDA?

FDA response:

1. *Basic pharm/tox package appears to be acceptable.*
2. *The Agency liked* —
   — · *and would like to see a similar study with NN 304.*
3. *Information on the status of one-year dog study and Segment III reproductive study is needed.***

** The sponsor responded that one-year dog study has been completed and the report is targeted in early fall. Segment III study is to be started in 9/99 and expected to finish next year. The report should be readied 6-mon after the study is completed.

Question 2:

The mitogenic potential of insulin detemir has been examined in CHO-K1 and MCF-7 cells. Both these studies indicated a lower mitogenic potential than that of human insulin, with or without tentative correction for albumin binding in the assays. Draft results appear from Section B.1-7, Table B.1-2, page 24.

The following studies are planned to further explore the receptor binding properties and mitogenic potential of insulin detemir:

1. A study to determine the IGF-1 receptor binding affinity of insulin detemir

2. A study to determine the mitogenic potential of insulin detemir in human B10 osteosarcoma cells. Human insulin, insulin B10Asp and IGF-1 will be included as reference substances.

Does the agency concur to the above strategy to investigate the mitogenic potential of insulin detemir?

FDA Response:

1. *Are these studies different from* —

** Novo responded that — . NN304 had mitogenic study done with the MCF-7 cell line. In addition to the MCF-7 cell line study, a Chinese hamster

ovary cell line study is done with NN304. The sponsor also proposes to do similar studies using human B10 osteosarcoma cells.

2. *Depending on the mitogenic data, the Agency may request one-year bioassay. The sponsor agreed to provide a rationale (if they are not able to conduct the assay) why they cannot conduct the assay.*

Question 3:

Preclinical in vivo studies have demonstrated large species differences in the pharmacological response to equi-molar s.c. doses of insulin detemir relative to human NPH insulin, e.g. in rodents up to 40 fold higher doses can be tolerated, whereas the insulin detemir and NPH insulin appear equally effective on a molar basis in dogs and pigs.

In accordance with the general species difference, clinical studies have demonstrated that insulin detemir and NPH insulin are not equally effective on a molar basis in humans. Results from clinical studies in patients with Type 1 diabetes have indicated that 2.2 - 2.5 times higher doses of insulin detemir (compared to NPH human insulin) are required to achieve similar glycaemic control. Furthermore, clinical studies have shown that patients with diabetes can safely and without loss of glycaemic control be transferred to 2X nmol of insulin detemir from X nmol of NPH insulin. As a consequence 1 U of insulin detemir will be defined as 12 nmol (compared to 6 nmol for human insulin). This unit definition will ensure consistency between insulin detemir and human NPH insulin in terms of 'efficacy per unit' and thereby minimise the risk of confusion for the patients. Does the agency concur with this unit definition for insulin detemir?

FDA response:

1. *The answer to this question will be decided after we have a chance to review the supporting data.*

2. *Redefining units remains to be problematic and the Agency needs to review the data before making the decision. The Agency tentatively agreed to allow a more concentrated solution on NN 304 so that the volume needed by patients would be the same as for NPH.*

3. *The potency issue will be handled during a labeling discussion.*

4. *Agency agrees that the concept of 'equivalent dose' should be communicated to the patient in the labeling.*

Question 4:

The overall patient exposure in the development programme comprises 2900 healthy subjects and diabetic patients. The number of subjects/patients exposed to insulin detemir is tabulated below:

Clinical Development Phase	No. of subjects/patients exposed to insulin detemir
Phase I	**240**
Phase II	**146**
Phase III	**1380**
Grand Total	**1766**

For the phase III programme a total of 2500 patients with Type 1 and Type 2 diabetes will be included (hereof 1380 on insulin detemir). The patients will be treated for 6 months in an open-label trial programme. In addition, a trial extension period of 6 months has been planned, including 200 patients on insulin detemir. Does the agency consider the number of patients and the extend of exposure sufficient?

FDA response:

1. *A recommended total exposure to new drug is 1,000 for Type 1 and 1,000 for Type 2 patients.*
2. *Two-hundred patients exposure at one-year is acceptable. However, the Agency is undecided if 200 patients exposure at one-year is acceptable at the time of NDA submission. The Agency will get back to the sponsor.*
3. *Proposed study duration of 6-months treatment period followed by 6-months extension is acceptable.*
4. *In lipidemia and nephrotic patients, multiple dose PK/PD studies are recommended.*
5. *In-vitro studies followed by a short-term study to evaluate the effect of high triglycerides are acceptable. If the sponsor could demonstrate that triglycerides do not affect the binding of NN304 to albumin, the Agency is willing to accept a sample size of 1,000 for Type 1 and 500 for Type 2 patients.*

6. *The sponsor stated that they have done single dose PK study in nephrotic patients. The Agency will decide whether or not PK/PD study in nephrotic patients needs to be repeated after reviewing the data.*

7. *The sponsor needs to provide information demonstrating the maximal bioactivity of NPH and NN304 is similar.*

Question 5

The phase III trial programme has been designed as an open-label programme, including patients with both Type 1 and Type 2 diabetes, where NPH insulin has been chosen as the active comparator and the primary endpoint is HbA_{c1}. However, additional analysis will investigate whether the potential HbA_{1c} reduction is gained at the expense of the numbers/frequency of hypoglycaemic episodes (*see* Section C.3 page 66). Does the agency offer any comments to the programme?

FDA response:

1. *The sponsor responded that they plan to seek non-inferiority claim.*

2. *If the sponsor is seeking non-inferiority claim, the delta has to be discussed. Delta needs to be decided and agreed a priori. Delta should be based on the starting point.*

3. *The Agency has not decided whether or not to accept the proposed delta of 0.4% and agreed to get back to the sponsor.*

4. *With non-inferiority claim, the regular insulin dose should be considered in addition to HbA1c and hypoglycemia.*

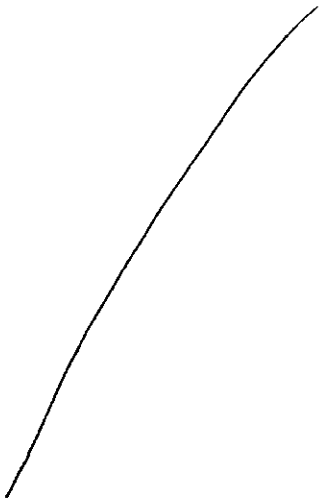
Question 6

To fulfil the paediatric labeling requirements and obtain exclusivity extension Novo Nordisk A/S is planning to conduct a PK trial in children. The trial will a include a total of 9-10 children in the age groups 6-11 and 12-17 years. Trial data will be included in the 120 days safety update. Does the agency concur to the proposal?.

If the above proposal is acceptable to the agency, Novo Nordisk will submit a formal pediatric study request together with the protocol.

FDA response:

The Agency recommends the following study design for Pediatric Exclusivity Written Letter:



9. *If the sponsor is not seeking Pediatric Exclusivity, a PK study in children is acceptable for pediatric labeling. Novo informed the Agency that they do not plan to seek Pediatric Exclusivity.*

Question 7

Clinical studies planned to further characterise the pharmacokinetics of insulin detemir in special populations / conditions are presented in Table 1. These trials will be part of the NDA submission package. Does the agency agree on the proposed programme?

FDA response:

1. *Ask the sponsor for any intramuscular injection data.** These data are needed to evaluate protein and fat binding.*
2. *The Agency recommends in vitro protein binding studies. The sponsor responded that they have conducted PK studies for protein binding.*
3. *Evaluation of serum lipids binding in patients with hyperlipidemia is needed.*

** This question has been conveyed to the sponsor and waiting for a response.

Question 8

Some of the pre-clinical studies were performed with NN304 prepared by process A and some of the studies were performed by the process C (process intended for phase III and launch). Based on the justification (*See* Section D, page 95) does the Agency consider the overall preclinical programme sufficient?

FDA response:

It appears to be acceptable.

Minutes Preparer: Julie Rhee

Chair Concurrence: Solomon Sobel, M.D.

Attachments: Overhead presentation

cc: Original
HFD-510/Div. Files
HFD-510/Malozowski/Misbin/HRhee/Steigerwalt
HFD-715/Pian
HFD-870/Ahn

Drafted by: JRhee 7-23-99
Initialed by: Steigerwalt 7-23-99/Malozowski 7-23-99/Misbin 7-26-99/Pian 8-4-99/Berlin 8-4-99/Moore 8-4-99/Ahn 8-5-99/Jenkins 8-16-99
final: JRhee 8-16-99

MEETING MINUTES

1 Page(s) Withheld

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

___ § 552(b)(5) Deliberative Process

___ § 552(b)(5) Draft Labeling

NDA 21-536 Levemir (insulin detemir [rDNA origin] injection) review status as of 5/20/05

PENDING:

1. Clinical Review:
2. DSI Inspection:
3. Division Director/Team Leader Memo:

COMPLETED:

1. **Micro:** AP (7/22/03)
2. **Pharm/Tox:** AP (9/5/03)
3. **DDMAC:** Completed (4/15/05)
4. **CMC:** AP (5/3/05)
   a. **EER:** Acceptable (9/25/03)
   b. **EA:** Categorical Exclusion (CMC review #1, 9/9/03)
5. **Biometrics:** Completed (5/13/05)
6. **Biopharm:** Acceptable (5/13/05)
7. **ODS/DMETS:** Completed (5/18/05)
   a. DMETS rejected the proposed tradename (Levemir) but DMEDP overruled DMETS recommendation.
   b. Labeling comments to be conveyed to Novo
8. **ODS/DSRCS:** Memo (1/28/05)

****

Labeling status:

1. Physician insert:

   --FDA revision #1 was e-mailed to Novo on 5/19/05

2. Patient package insert:

ADRA Review #2 of Action Package for NDA 21-536, Levemir (insulin detemir)

Reviewer: Lee Ripper, HFD-102
Date received: June 3, 2005
Date of Review: June 8, 2005

Date original NDA received: December 5, 2002
UF GOAL DATE: June 20, 2005

Indications: Tx of type 1 and type 2 diabetes mellitus

Action type: AP
RPM: Julie Rhee
Drug Classification: 1S
505(b)(1) application

Patent Info: 3542a Received
Debarment Certification: 12/20/04
Safety Update: SU for RS rec'd 4/4/05, see MOR page 73.
Clinical Inspection Summary: 2003: Inspections cancelled. New clinical studies requested in action letter. 2005: 3 inspections, data AC 6/6/05.
ODS/DMETS Review of Trade Name: Found Levemir to be UN on 8/7/03 and 5/18/05. DD review finds Levemir AC.
DDMAC Review of Trade Name: Per DMETS 8/7/03 and 5/18/05 reviews, DDMAC found Levemir to be AC from a promotional perspective.
DSRCS Review of PPIs: 5/23/03. No review of 12/20/04 version.
EA: Categorical exclusion AC
EER: AC 9/25/03. 2005: No facilities under potential OAI or OAI as of 6/15/05.
Financial Disclosure: 2003: AC. 2005: AC.

1. Minutes of PSC mtg need to be added to DFS and action package when completed.

Action packages to RMeyer, EDuffy, and KHastings on 6/8/05.

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/s/

Leah Ripper
6/16/05 06:36:11 PM
CSO

ADRA Review #1 of Action Package for NDA 21-536, — (insulin detemir)

Reviewer: Lee Ripper, HFD-102
Date received: September 12, 2003
Date of Review: September 22, 2003 *and October 2, 2003*

Date original NDA received: December 5, 2002
UF GOAL DATE: October 3, 2003

Indications: Tx of type 1 and type 2 diabetes mellitus

Action type: AE
RPM: Julie Rhee
Drug Classification: 1S
505(b)(1) application

Patent Info: Received
Debarment Certification: 9/16/03: asked Julie to obtain a revised debarment certification. *Received, dated 9/17/03*
Safety Update: 4/7/03, see page 51 of MOR
Clinical Inspection Summary: Inspections cancelled. New clinical studies requested in action letter.
ODS/DMETS Review of Trade Name: Found Levemir to be UN. No objections to —. *9/22: Julie says applicant has resubmitted the tradename Levemir.*
EA: Categorical exclusion AC
EER: Pending as of 9/22/03. *AC 9/25/03*
Financial Disclosure: AC

1. MOR *9/16/03*, team leader *(DD review stands as TL review)*, and DD *(9/25)* reviews ~~are pending~~. *MOR will serve as the ODE-level review.*

2. Since labeling comments are not being sent in the action letter, I recommend issuing a DR letter with the labeling comments from the various disciplines so that the applicant can consider and incorporate them into any resubmission.

3. See comments on letter. I will discuss BPh comments with H-YAhn. *Done, a few revisions to letter.*

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

/s/

Leah Ripper
10/2/03 03:19:08 PM
CSO
No action by FDR required

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement: See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

Novo Nordisk Pharmaceuticals, Inc.
100 College Road West
Princeton, NJ 08540

2. TELEPHONE NUMBER *(Include Area Code)*

(609) 987-5822

3. PRODUCT NAME

Insulin Detemir

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

NDA 21-536

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

NDA 21-536
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER

4451

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE **EXCLUSIONS**? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

☐ YES ☒ NO

(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, 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 for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

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.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Pamela Morgan for B. Reit	VP Regulatory Affairs & Quality Assurance	12/05/02

FORM FDA 3397 (4/01)

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30 Page(s) Withheld

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

✓ § 552(b)(5) Deliberative Process

____ § 552(b)(5) Draft Labeling