CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 21536/S-033

Trade Name: **LEVEMIR**

Generic Name: **Insulin Detemir [rDNA Origin]**

Sponsor: **Novo Nordisk, Inc.**

Approval Date: 10/31/2013

Indications: LEVEMIR is a long-acting human insulin analog indicated to improve glycemic control in adults and children with diabetes mellitus.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21536/S-033

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21536/S-033

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21536/S-033

SUPPLEMENT APPROVAL

Novo Nordisk, Inc.
Attention: Robert B. Clark
Vice President, Regulatory Affairs
800 Scudders Mill Road
Plainsboro, NJ 08536

Dear Mr. Clark:

Please refer to your Supplemental New Drug Application (sNDA) dated and received December 15, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Levemir (insulin detemir [rDNA origin]) injection.

We acknowledge receipt of your amendments dated July 13, 2011, January 26, and March 2, 2012, February 13, March 22, April 19, May 22 and 30, August 26, and October 11 and 17, 2013.

The March 22, 2013, submission constituted a complete response to our March 20, 2012, action letter.

This Prior Approval supplemental new drug application provides for marketing of Levemir in the FlexTouch Pen device.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert, and Instructions For Use), with the addition of any labeling changes in

pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008).* Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 21536/S-033**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

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

If you have any questions, call Callie Cappel-Lynch, Regulatory Project Manager, at (301) 796 8436.

Sincerely,

{See appended electronic signature page}

Jean-Marc Guettier, MD
Director, Acting
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling (Package Insert, Patient Package Insert, and Instructions for Use)
Carton and Container Labeling for FlexTouch Pen device

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/s/

JEAN-MARC P GUETTIER
10/31/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21536/S-033

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020986/S-061
NDA 021536/S-033

COMPLETE RESPONSE

Novo Nordisk Inc.
Attention: Anne Phillips, M.D.
Corporate Vice President, Clinical, Medical and Regulatory Affairs
100 College Road West
Princeton, NJ 08540

Dear Dr. Phillips:

Please refer to your Supplemental New Drug Applications (sNDAs) dated and received December 15, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for: Novolog (insulin aspart [rDNA origin] injection) and Levemir (insulin detemir [rDNA origin] injection).

We acknowledge receipt of your amendments dated July 13, 2011, and January 26, March 2 (S-033) and 8 (S-061), 2012.

The July 13, 2011, submissions constituted a complete response to our August 20, 2010, action letter.

These "Prior Approval" supplemental new drug applications provide for the addition of PDS290 prefilled pen (FlexTouch), a new prefilled, multiple-dose, disposable insulin delivery device.

We have completed the review of your applications, as amended, and have determined that we cannot approve these applications in their present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

DEVICE

Bench Testing:

The dose accuracy testing submitted does not comply with ISO 111608-1, Pen-Injectors for Medical Use-Part 1: Pen-injectors- Requirements and Test Methods. This standard requires that the "Pen injector shall indicate, by visual, audible or tactile means or any combination of these, that the injection stroke has been completed." Dose accuracy testing must be measured using the volume that has been expelled from the device when the scale drum reaches zero. You have

measured dose accuracy 6 seconds after the scale drum has returned to zero. Provide a drug delivery device which is ISO 11608-1 compliant.

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the supplemental application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants", May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

These products may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change before approval of this supplemental application.

If you have any questions, call Rachel Hartford, Regulatory Project Manager, at (301) 796-0331.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

MARY H PARKS
03/20/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020986/S-061
(b) (4)
NDA 021536/S-033

COMPLETE RESPONSE

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

Dear Dr. McElligott:

Please refer to your Supplemental New Drug Applications (sNDAs) dated and received December 15, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for:

- Novolog (insulin aspart [rDNA origin] injection)
- (b) (4)
- Levemir (insulin detemir [rDNA origin] injection)

We acknowledge receipt of your amendments dated December 15, 2009, (b) (4)

These "Prior Approval" labeling supplemental new drug applications provide for the addition of a new prefilled multiple-dose disposable insulin delivery device, PDS290 prefilled pen (FlexTouch).

We have completed the review of your applications, as amended, and have determined that we cannot approve these applications in their present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

DEVICE

The requirements for Human Factors (HF) testing have not been satisfied.

Bench Testing:

1. While conducting the dose accuracy tests on the PDS-290 Pen Injector, you stated that two devices' push buttons were blocked. You clarified that one of these devices' push button failed after exposure to the cold environment, and the second failed after exposure to the hot environment. You also stated that the blockage of the push buttons was caused by (b) (4)

   Address the following:

   a. Review of your test summary indicates that the blockage did not hinder the delivery of the insulin dose. Further clarify the terminology that the "push buttons were blocked." Specifically, if the push button was blocked, then how was the dose delivered?
   b. Identify the function of the (b) (4) Also, identify the impact on the functionality of the device if the (b) (4) were removed. For example, does the device lose some tactile or audible feedback when the user (b) (4) a dose into the PDS-290 Pen injector?
   c. Provide performance data to demonstrate that the revised device met the requirements of ISO 11608, and passed the performance testing that it was subjected to.
   d. Identify whether human factors / usability testing was performed using the original device, or the revised device. If the original device was utilized in the human factors testing, but the revised device was not, explain your rationale for not testing the usability of the revised device.

Human Factors Testing:

Your final usability reports do not provide sufficient information to support a determination that your injectors and accessories have been designed such that they are safe and effective for their intended users. Of most concern is a lack of priority on risk associated with use, and lack of meaningful performance and subjective measures that pertain to critical aspects of device use. Note that study results consisting of general subjective measures of "ease of use," "acceptability," and the like, do not provide the necessary and sufficient information for successful review of your application.

The intent of the human factors validation study is to demonstrate that the device can be used by representative users under simulated conditions without patterns of failures or difficulties that could result in clinical impact to patients or, in some cases, to users themselves. To the extent that failures with use do occur, the study should collect sufficient and appropriate data such that these failures can be described in terms of their cause from the perspective of the representative

users. The test report should present a summary of these results within a discussion of whether or not and the extent to which failures found are due to aspects of the design of the device, its labeling, the content or proximity of training and whether modifications are necessary. If so, such modifications should be reevaluated to demonstrate that device use has been optimized with respect to safety and effectiveness. Note we may agree or disagree with this determination, and plans to modify design problems in future device versions for problems that impact safety are generally unacceptable.

2. Review the Center Guidance on Human Factors and Risk Management available at: http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094461.pdf

3. Relative priority of tasks: We need to understand the relative priority of the tasks you selected for testing in terms of the potential results of inadequate performance on these tasks. Indeed, the tasks selected for testing should be selected on this basis. You have not provided a rationale for selecting the tasks you tested. Provide this information, or if sufficient HF/Usability evaluation has not been performed, perform the evaluations necessary to do so.

4. Comprehensiveness of task set: We need to understand that the tasks you chose to test represent the extent of the tasks that could lead to use-related problems (as defined). Provide this information, or if sufficient analysis has not been performed, perform the evaluations necessary.

5. Realism of simulated use: Your reports did not discuss how the device system was used during the evaluations. Describe how the device was used by study participants and particularly the use scenarios involving critically important tasks.

6. Performance criteria: Your testing was based on rating scales and objectives. We expect users to perform critical tasks correctly 100% of the time. If errors occur on critical tasks, they should be counted as "failures." Each "failure" should be described with respect to its nature, its cause and what the result of the failure means with respect to inappropriate dosing or inadvertent injury with the injector.

7. Data analysis: Your analysis of performance and subjective data should be directed toward understanding user performance and particularly task failures. The analysis should determine the nature of failures based on subjective and objective evaluation data. Provide this information, or if sufficient HF/Usability evaluation has not been performed, perform the evaluations necessary to do so.

8. Training: You do not describe how training was involved in your evaluation or the extent to which it is necessary for professional or home users. Provide this information, or if sufficient HF/Usability evaluation has not been performed, perform the evaluations necessary to do so.

9. Users: We expect simulated use validation testing (Human Factors Validation) to be performed under simulated use conditions and involve a minimum of 15 representative device users for each distinct population of users. You have separated pediatric as well as elderly users in your initial studies; therefore your study would involve 15 for each of those groups as well as another group of 15 "typical" users.

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants", May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

This product may be considered to be misbranded under the FDCA if it is marketed with this change before approval of this supplemental application.

If you have any questions, call Rachel Hartford, Regulatory Project Manager, at (301) 796-0331.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21536	SUPPL-33	NOVO NORDISK INC	LEVEMIR
[redacted] (b) (4)			
NDA-20986	SUPPL-61	NOVO NORDISK INC	Aspart (NOVOLOG)

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/s/

MARY H PARKS
08/20/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21536/S-033

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use LEVEMIR® safely and effectively. See full prescribing information for LEVEMIR.

LEVEMIR® (insulin detemir [rDNA origin] injection) solution for subcutaneous injection
Initial U.S. Approval: 2005

----------RECENT MAJOR CHANGES----------
- Warnings and Precautions (5.8) 3/2013

----------INDICATIONS AND USAGE----------
LEVEMIR is a long-acting human insulin analog indicated to improve glycemic control in adults and children with diabetes mellitus. (1)

Important Limitations of Use:
- Not recommended for treating diabetic ketoacidosis. Use intravenous, rapid-acting or short-acting insulin instead.

----------DOSAGE AND ADMINISTRATION----------
- The starting dose should be individualized based on the type of diabetes and whether the patient is insulin-naïve (2.1, 2.2, 2.3)
- Administer subcutaneously once daily or in divided doses twice daily. Once daily administration should be given with the evening meal or at bedtime (2.1)
- Rotate injection sites within an injection area (abdomen, thigh, or deltoid) to reduce the risk of lipodystrophy (2.1)
- Converting from other insulin therapies may require adjustment of timing and dose of LEVEMIR. Closely monitor glucoses especially upon converting to LEVEMIR and during the initial weeks thereafter (2.3)

----------DOSAGE FORMS AND STRENGTHS----------
Solution for injection 100 Units/mL (U-100) in
- 3 mL LEVEMIR FlexPen®
- 3 ml LEVEMIR FlexTouch®
- 10 mL vial (3)

----------CONTRAINDICATIONS----------
- Do not use in patients with hypersensitivity to LEVEMIR or any of its excipients (4)

----------WARNINGS AND PRECAUTIONS----------
- Dose adjustment and monitoring: Monitor blood glucose in all patients treated with insulin. Insulin regimens should be modified cautiously and only under medical supervision (5.1)
- Administration: Do not dilute or mix with any other insulin or solution. Do not administer subcutaneously via an insulin pump, intramuscularly, or intravenously because severe hypoglycemia can occur (5.2)
- Hypoglycemia is the most common adverse reaction of insulin therapy and may be life-threatening (5.3, 6.1)
- Allergic reactions: Severe, life-threatening, generalized allergy, including anaphylaxis, can occur (5.4)
- Renal or hepatic impairment: May require adjustment of the LEVEMIR dose (5.5, 5.6)
- Fluid retention and heart failure can occur with concomitant use of thiazolidinediones (TZDs), which are PPAR-gamma agonists, and insulin, including LEVEMIR (5.8)

----------ADVERSE REACTIONS----------
Adverse reactions associated with LEVEMIR include hypoglycemia, allergic reactions, injection site reactions, lipodystrophy, rash and pruritus (6)

To report SUSPECTED ADVERSE REACTIONS, contact Novo Nordisk Inc. at 1-800-727-6500 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
- Certain drugs may affect glucose metabolism requiring insulin dose adjustment and close monitoring of blood glucose (7)
- The signs of hypoglycemia may be reduced or absent in patients taking anti-adrenergic drugs (e.g., beta-blockers, clonidine, guanethidine, and reserpine) (7)

----------USE IN SPECIFIC POPULATIONS----------
Pediatric: Has not been studied in children with type 2 diabetes. Has not been studied in children with type 1 diabetes < 2 years of age (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 10/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

LEVEMIR is indicated to improve glycemic control in adults and children with diabetes mellitus.

Important Limitations of Use:

- LEVEMIR is not recommended for the treatment of diabetic ketoacidosis. Intravenous rapid-acting or short-acting insulin is the preferred treatment for this condition.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing

LEVEMIR is a recombinant human insulin analog for once- or twice-daily subcutaneous administration.

Patients treated with LEVEMIR once-daily should administer the dose with the evening meal or at bedtime.

Patients who require twice-daily dosing can administer the evening dose with the evening meal, at bedtime, or 12 hours after the morning dose.

The dose of LEVEMIR must be individualized based on clinical response. Blood glucose monitoring is essential in all patients receiving insulin therapy.

Patients adjusting the amount or timing of dosing with LEVEMIR should only do so under medical supervision with appropriate glucose monitoring *[see Warnings and Precautions (5.1)]*.

In patients with type 1 diabetes, LEVEMIR must be used in a regimen with rapid-acting or short-acting insulin.

As with all insulins, injection sites should be rotated within the same region (abdomen, thigh, or deltoid) from one injection to the next to reduce the risk of lipodystrophy *[see Adverse Reactions (6.1)]*.

LEVEMIR can be injected subcutaneously in the thigh, abdominal wall, or upper arm. As with all insulins, the rate of absorption, and consequently the onset and duration of action, may be affected by exercise and other variables, such as stress, intercurrent illness, or changes in co-administered medications or meal patterns.

When using LEVEMIR with a glucagon-like peptide (GLP)-1 receptor agonist, administer as separate injections. Never mix. It is acceptable to inject LEVEMIR and a GLP-1 receptor agonist in the same body region but the injections should not be adjacent to each other.

2.2 Initiation of LEVEMIR Therapy

The recommended starting dose of LEVEMIR in patients with type 1 diabetes should be approximately one-third of the total daily insulin requirements. Rapid-acting or short-acting, pre-meal insulin should be used to satisfy the remainder of the daily insulin requirements.

The recommended starting dose of LEVEMIR in patients with type 2 diabetes inadequately controlled on oral antidiabetic medications is 10 Units (or 0.1-0.2 Units/kg) given once daily in the evening or divided into a twice daily regimen.

The recommended starting dose of LEVEMIR in patients with type 2 diabetes inadequately controlled on a GLP-1 receptor agonist is 10 Units given once daily in the evening.

LEVEMIR doses should subsequently be adjusted based on blood glucose measurements. The dosages of LEVEMIR should be individualized under the supervision of a healthcare provider.

2.3 Converting to LEVEMIR from other insulin therapies

If converting from insulin glargine to LEVEMIR, the change can be done on a unit-to-unit basis.

If converting from NPH insulin, the change can be done on a unit-to-unit basis. However, some patients with type 2 diabetes may require more LEVEMIR than NPH insulin, as observed in one trial *[see Clinical Studies (14)]*.

As with all insulins, close glucose monitoring is recommended during the transition and in the initial weeks thereafter. Doses and timing of concurrent rapid-acting or short-acting insulins or other concomitant antidiabetic treatment may need to be adjusted.

3 DOSAGE FORMS AND STRENGTHS

LEVEMIR solution for injection 100 Unit per mL is available as:

- 3 mL LEVEMIR FlexPen®
- 3 mL LEVEMIR FlexTouch®
- 10 mL vial

4 CONTRAINDICATIONS

LEVEMIR is contraindicated in patients with hypersensitivity to LEVEMIR or any of its excipients. Reactions have included anaphylaxis [*see Warnings and Precautions (5.4) and Adverse Reactions (6.1)*].

5 WARNINGS AND PRECAUTIONS

5.1 Dosage adjustment and monitoring

Glucose monitoring is essential for all patients receiving insulin therapy. Changes to an insulin regimen should be made cautiously and only under medical supervision.

Changes in insulin strength, manufacturer, type, or method of administration may result in the need for a change in the insulin dose or an adjustment of concomitant anti-diabetic treatment.

As with all insulin preparations, the time course of action for LEVEMIR may vary in different individuals or at different times in the same individual and is dependent on many conditions, including the local blood supply, local temperature, and physical activity.

5.2 Administration
LEVEMIR should only be administered subcutaneously.

Do not administer LEVEMIR intravenously or intramuscularly. The intended duration of activity of LEVEMIR is dependent on injection into subcutaneous tissue. Intravenous or intramuscular administration of the usual subcutaneous dose could result in severe hypoglycemia [*see Warnings and Precautions (5.3)*].

Do not use LEVEMIR in insulin infusion pumps.

Do not dilute or mix LEVEMIR with any other insulin or solution. If LEVEMIR is diluted or mixed, the pharmacokinetic or pharmacodynamic profile (e.g., onset of action, time to peak effect) of LEVEMIR and the mixed insulin may be altered in an unpredictable manner.

5.3 Hypoglycemia
Hypoglycemia is the most common adverse reaction of insulin therapy, including LEVEMIR. The risk of hypoglycemia increases with intensive glycemic control.

When a GLP-1 receptor agonist is used in combination with LEVEMIR, the LEVEMIR dose may need to be lowered or more conservatively titrated to minimize the risk of hypoglycemia *[see Adverse Reactions (6.1)]*.

All patients must be educated to recognize and manage hypoglycemia. Severe hypoglycemia can lead to unconsciousness or convulsions and may result in temporary or permanent impairment of brain function or death. Severe hypoglycemia requiring the assistance of another person or parenteral glucose infusion, or glucagon administration has been observed in clinical trials with insulin, including trials with LEVEMIR.

The timing of hypoglycemia usually reflects the time-action profile of the administered insulin formulations. Other factors such as changes in food intake (e.g., amount of food or timing of meals), exercise, and concomitant medications may also alter the risk of hypoglycemia *[see Drug Interactions (7)]*.

The prolonged effect of subcutaneous LEVEMIR may delay recovery from hypoglycemia.

As with all insulins, use caution in patients with hypoglycemia unawareness and in patients who may be predisposed to hypoglycemia (e.g., the pediatric population and patients who fast or have erratic food intake). The patient's ability to concentrate and react may be impaired as a result of hypoglycemia. This may present a risk in situations where these abilities are especially important, such as driving or operating other machinery.

Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as longstanding diabetes, diabetic neuropathy, use of medications such as beta-blockers, or intensified glycemic control [*see Drug Interactions (7)*]. These situations may result in severe hypoglycemia (and, possibly, loss of consciousness) prior to the patient's awareness of hypoglycemia.

5.4 Hypersensitivity and allergic reactions
Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products, including LEVEMIR.

5.5 Renal Impairment
No difference was observed in the pharmacokinetics of insulin detemir between non-diabetic individuals with renal impairment and healthy volunteers. However, some studies with human insulin have shown increased circulating insulin concentrations in patients with renal impairment. Careful glucose monitoring and dose adjustments of insulin, including LEVEMIR, may be necessary in patients with renal impairment [*see Clinical Pharmacology (12.3)*].

5.6 Hepatic Impairment
Non-diabetic individuals with severe hepatic impairment had lower systemic exposures to insulin detemir compared to healthy volunteers. However, some studies with human insulin have shown increased circulating insulin concentrations in patients with liver impairment. Careful glucose monitoring and dose adjustments of insulin, including LEVEMIR, may be necessary in patients with hepatic impairment [*see Clinical Pharmacology (12.3)*].

5.7 Drug interactions
Some medications may alter insulin requirements and subsequently increase the risk for hypoglycemia or hyperglycemia *[see Drug Interactions (7)]*.

5.8 Fluid retention and heart failure with concomitant use of PPAR-gamma agonists
Thiazolidinediones (TZDs), which are peroxisome proliferator-activated receptor (PPAR)-gamma agonists, can cause dose-related fluid retention, particularly when used in combination with insulin. Fluid retention may lead to or exacerbate heart failure. Patients treated with insulin, including LEVEMIR, and a PPAR-gamma agonist should be observed for signs and symptoms of heart failure. If heart failure develops, it should be managed according to current standards of care, and discontinuation or dose reduction of the PPAR-gamma agonist must be considered.

6 ADVERSE REACTIONS
The following adverse reactions are discussed elsewhere:
- Hypoglycemia *[see Warnings and Precautions (5.3)]*
- Hypersensitivity and allergic reactions *[see Warnings and Precautions (5.4)]*

6.1 Clinical trial experience
Because clinical trials are conducted under widely varying designs, the adverse reaction rates reported in one clinical trial may not be easily compared to those rates reported in another clinical trial, and may not reflect the rates actually observed in clinical practice.

The frequencies of adverse reactions (excluding hypoglycemia) reported during LEVEMIR clinical trials in patients with type 1 diabetes mellitus and type 2 diabetes mellitus are listed in Tables 1-4 below. See Tables 5 and 6 for the hypoglycemia findings.

In the LEVEMIR add-on to liraglutide+metformin trial, all patients received liraglutide 1.8 mg + metformin during a 12-week run-in period. During the run-in period, 167 patients (17% of enrolled total) withdrew from the trial: 76 (46% of withdrawals) of these patients doing so because of gastrointestinal adverse reactions and 15 (9% of withdrawals) doing so due to other adverse events. Only those patients who completed the run-in period with inadequate glycemic control were randomized to 26 weeks of add-on therapy with LEVEMIR or continued, unchanged treatment with liraglutide 1.8 mg + metformin. During this randomized 26-week period, diarrhea was the only adverse reaction reported in ≥5% of patients treated with liraglutide 1.8 mg + metformin (11.7%) and greater than in patients treated with liraglutide 1.8 mg and metformin alone (6.9%).

In two pooled trials, a total of 1155 adults with type 1 diabetes were exposed to individualized doses of LEVEMIR (n=767) or NPH (n=388). The mean duration of exposure to LEVEMIR was 153 days, and the total exposure to LEVEMIR was 321 patient-years. The most common adverse reactions are summarized in Table 1.

Table 1: Adverse reactions (excluding hypoglycemia) in two pooled clinical trials of 16 weeks and 24 weeks duration in adults with type 1 diabetes (adverse reactions with incidence ≥ 5%)

	LEVEMIR, % (n = 767)	**NPH, % (n = 388)**
Upper respiratory tract infection	26.1	21.4
Headache	22.6	22.7
Pharyngitis	9.5	8.0
Influenza-like illness	7.8	7.0
Abdominal Pain	6.0	2.6

A total of 320 adults with type 1 diabetes were exposed to individualized doses of LEVEMIR (n=161) or insulin glargine (n=159). The mean duration of exposure to LEVEMIR was 176 days, and the total exposure to LEVEMIR was 78 patient-years. The most common adverse reactions are summarized in Table 2.

Table 2: Adverse reactions (excluding hypoglycemia) in a 26-week trial comparing insulin aspart + LEVEMIR to insulin aspart + insulin glargine in adults with type 1 diabetes (adverse reactions with incidence ≥ 5%)

	LEVEMIR, % (n = 161)	**Glargine, % (n = 159)**
Upper respiratory tract infection	26.7	32.1
Headache	14.3	19.5
Back pain	8.1	6.3
Influenza-like illness	6.2	8.2
Gastroenteritis	5.6	4.4
Bronchitis	5.0	1.9

In two pooled trials, a total of 869 adults with type 2 diabetes were exposed to individualized doses of Levemir (n=432) or NPH (n=437). The mean duration of exposure to LEVEMIR was 157 days, and the total exposure to LEVEMIR was 186 patient-years. The most common adverse reactions are summarized in Table 3.

Table 3: Adverse reactions (excluding hypoglycemia) in two pooled clinical trials of 22 weeks and 24 weeks duration in adults with type 2 diabetes (adverse reactions with incidence ≥ 5%)

	LEVEMIR, % (n = 432)	**NPH, % (n = 437)**
Upper respiratory tract infection	12.5	11.2
Headache	6.5	5.3

A total of 347 children and adolescents (6-17 years) with type 1 diabetes were exposed to individualized doses of LEVEMIR (n=232) or NPH (n=115). The mean duration of exposure to LEVEMIR was 180 days, and the total exposure to LEVEMIR was 114 patient-years. The most common adverse reactions are summarized in Table 4.

Table 4: Adverse reactions (excluding hypoglycemia) in one 26-week clinical trial of children and adolescents with type 1 diabetes (adverse reactions with incidence ≥ 5%)

	LEVEMIR, % (n = 232)	**NPH, % (n = 115)**
Upper respiratory tract infection	35.8	42.6
Headache	31.0	32.2
Pharyngitis	17.2	20.9
Gastroenteritis	16.8	11.3
Influenza-like illness	13.8	20.9
Abdominal pain	13.4	13.0
Pyrexia	10.3	6.1
Cough	8.2	4.3
Viral infection	7.3	7.8
Nausea	6.5	7.0
Rhinitis	6.5	3.5
Vomiting	6.5	10.4

Pregnancy

A randomized, open-label, controlled clinical trial has been conducted in pregnant women with type 1 diabetes. [*see Use in Specific Populations (8.1)*]

- *Hypoglycemia*

Hypoglycemia is the most commonly observed adverse reaction in patients using insulin, including LEVEMIR *[see Warnings and Precautions (5.3)]*.

Tables 5 and 6 summarize the incidence of severe and non-severe hypoglycemia in the LEVEMIR clinical trials.

For the adult trials and one of the pediatric trials (Study D), severe hypoglycemia was defined as an event with symptoms consistent with hypoglycemia requiring assistance of another person and

associated with either a plasma glucose value below 56 mg/dL (blood glucose below 50 mg/dL) or prompt recovery after oral carbohydrate, intravenous glucose or glucagon administration. For the other pediatric trial (Study I), severe hypoglycemia was defined as an event with semi-consciousness, unconsciousness, coma and/or convulsions in a patient who could not assist in the treatment and who may have required glucagon or intravenous glucose.

For the adult trials and pediatric Study D, non-severe hypoglycemia was defined as an asymptomatic or symptomatic plasma glucose < 56 mg/dL (or equivalently blood glucose <50 mg/dL as used in Study A and C) that was self-treated by the patient. For pediatric Study I, non-severe hypoglycemia included asymptomatic events with plasma glucose <65 mg/dL as well as symptomatic events that the patient could self-treat or treat by taking oral therapy provided by the caregiver.

The rates of hypoglycemia in the LEVEMIR clinical trials (see Section 14 for a description of the study designs) were comparable between LEVEMIR-treated patients and non-LEVEMIR-treated patients (see Tables 5 and 6).

Table 5: Hypoglycemia in Patients with Type 1 Diabetes

		Severe Hypoglycemia		Non-Severe Hypoglycemia	
		Percent of patients with at least 1 event (n/total N)	Event/patient/ year	Percent of patients (n/total N)	Event/patient/ year
Study A Type 1 Diabetes Adults 16 weeks In combination with insulin aspart	Twice-Daily LEVEMIR	8.7 (24/276)	0.52	88.0 (243/276)	26.4
	Twice-Daily NPH	10.6 (14/132)	0.43	89.4 (118/132)	37.5
Study B Type 1 Diabetes Adults 26 weeks In combination with insulin aspart	Twice-Daily LEVEMIR	5.0 (8/161)	0.13	82.0 (132/161)	20.2
	Once-Daily Glargine	10.1 (16/159)	0.31	77.4 (123/159)	21.8
Study C Type 1 Diabetes Adults 24 weeks In combination with regular insulin	Once-Daily LEVEMIR	7.5 (37/491)	0.35	88.4 (434/491)	31.1
	Once-Daily NPH	10.2 (26/256)	0.32	87.9 (225/256)	33.4
Study D Type 1 Diabetes Pediatrics 26 weeks In combination with insulin aspart	Once- or Twice Daily LEVEMIR	15.9 (37/232)	0.91	93.1 (216/232)	31.6
	Once- or Twice Daily NPH	20.0 (23/115)	0.99	95.7 (110/115)	37.0
Study I	Once- or	1.7	0.02	94.9	56.1

Type 1 Diabetes Pediatrics 52 weeks In combination with insulin aspart	Twice Daily LEVEMIR	(3/177)		(168/177)	
	Once- or Twice Daily NPH	7.1 (12/170)	0.09	97.6 (166/170)	70.7

Table 6: Hypoglycemia in Patients with Type 2 Diabetes

		Study E Type 2 Diabetes Adults 24 weeks In combination with oral agents		Study F Type 2 Diabetes Adults 22 weeks In combination with insulin aspart		Study H Type 2 Diabetes Adults 26 weeks in combination with Liraglutide and Metformin	
		Twice-Daily LEVEMIR	Twice-Daily NPH	Once- or Twice Daily LEVEMIR	Once- or Twice Daily NPH	Once Daily LEVEMIR + Liraglutide + Metformin	Liraglutide + Metformin
Severe hypoglycemia	Percent of patients with at least 1 event (n/total N)	0.4 (1/237)	2.5 (6/238)	1.5 (3/195)	4.0 (8/199)	0	0
	Event/patient/year	0.01	0.08	0.04	0.13	0	0
Non-severe hypoglycemia	Percent of patients (n/total N)	40.5 (96/237)	64.3 (153/238)	32.3 (63/195)	32.2 (64/199)	9.2 (15/163)	1.3 (2/158*)
	Event/patient/year	3.5	6.9	1.6	2.0	0.29	0.03

*One subject is an outlier and was excluded due to 25 hypoglycemic episodes that the patient was able to self-treat. This patient had a history of frequent hypoglycemia prior to the study

- *Insulin Initiation and Intensification of Glucose Control*

Intensification or rapid improvement in glucose control has been associated with a transitory, reversible ophthalmologic refraction disorder, worsening of diabetic retinopathy, and acute painful peripheral neuropathy. However, long-term glycemic control decreases the risk of diabetic retinopathy and neuropathy.

- *Lipodystrophy*

Long-term use of insulin, including LEVEMIR, can cause lipodystrophy at the site of repeated insulin injections. Lipodystrophy includes lipohypertrophy (thickening of adipose tissue) and lipoatrophy (thinning of adipose tissue), and may affect insulin absorption. Rotate insulin injection sites within the same region to reduce the risk of lipodystrophy *[see Dosage and Administration (2.1)]*.

- *Weight Gain*

Weight gain can occur with insulin therapy, including LEVEMIR, and has been attributed to the anabolic effects of insulin and the decrease in glucosuria [see *Clinical Studies (14)*].

- *Peripheral Edema*

Insulin, including LEVEMIR, may cause sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

- *Allergic Reactions*

Local Allergy

As with any insulin therapy, patients taking LEVEMIR may experience injection site reactions, including localized erythema, pain, pruritus, urticaria, edema, and inflammation. In clinical studies in adults, three patients treated with LEVEMIR reported injection site pain (0.25%) compared to one patient treated with NPH insulin (0.12%). The reports of pain at the injection site did not result in discontinuation of therapy.

Rotation of the injection site within a given area from one injection to the next may help to reduce or prevent these reactions. In some instances, these reactions may be related to factors other than insulin, such as irritants in a skin cleansing agent or poor injection technique. Most minor reactions to insulin usually resolve in a few days to a few weeks.

Systemic Allergy
Severe, life-threatening, generalized allergy, including anaphylaxis, generalized skin reactions, angioedema, bronchospasm, hypotension, and shock may occur with any insulin, including LEVEMIR, and may be life-threatening *[see Warnings and Precautions (5.4)]*.

- *Antibody Production*

All insulin products can elicit the formation of insulin antibodies. These insulin antibodies may increase or decrease the efficacy of insulin and may require adjustment of the insulin dose. In phase 3 clinical trials of LEVEMIR, antibody development has been observed with no apparent impact on glycemic control.

6.2 Postmarketing experience
The following adverse reactions have been identified during post approval use of LEVEMIR. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Medication errors have been reported during post-approval use of LEVEMIR in which other insulins, particularly rapid-acting or short-acting insulins, have been accidentally administered instead of LEVEMIR *[see Patient Counseling Information (17)]*. To avoid medication errors between LEVEMIR and other insulins, patients should be instructed always to verify the insulin label before each injection.

7 DRUG INTERACTIONS
A number of medications affect glucose metabolism and may require insulin dose adjustment and particularly close monitoring.

The following are examples of medications that may increase the blood-glucose-lowering effect of insulins including LEVEMIR and, therefore, increase the susceptibility to hypoglycemia: oral antidiabetic medications, pramlintide acetate, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, propoxyphene, pentoxifylline, salicylates, somatostatin analogs, and sulfonamide antibiotics.

The following are examples of medications that may reduce the blood-glucose-lowering effect of insulins including LEVEMIR: corticosteroids, niacin, danazol, diuretics, sympathomimetic agents (e.g., epinephrine, albuterol, terbutaline), glucagon, isoniazid, phenothiazine derivatives, somatropin, thyroid

hormones, estrogens, progestogens (e.g., in oral contraceptives), protease inhibitors and atypical antipsychotic medications (e.g. olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts, and alcohol may either increase or decrease the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.

The signs of hypoglycemia may be reduced or absent in patients taking anti-adrenergic drugs such as beta-blockers, clonidine, guanethidine, and reserpine.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

Risk Summary

The background risk of birth defects, pregnancy loss, or other adverse events that exists for all pregnancies is increased in pregnancies complicated by hyperglycemia. Female patients should be advised to tell their physician if they intend to become, or if they become pregnant while taking LEVEMIR. A randomized controlled clinical trial of pregnant women with type I diabetes using LEVEMIR during pregnancy did not show an increase in the risk of fetal abnormalities. Reproductive toxicology studies in non-diabetic rats and rabbits that included concurrent human insulin control groups indicated that insulin detemir and human insulin had similar effects regarding embryotoxicity and teratogenicity that were attributed to maternal hypoglycemia.

Clinical Considerations

The increased risk of adverse events in pregnancies complicated by hyperglycemia may be decreased with good glucose control before conception and throughout pregnancy. Because insulin requirements vary throughout pregnancy and in the post-partum period, careful monitoring of glucose control is essential in pregnant women.

Human Data

In an, open-label, clinical study, women with type 1 diabetes who were (between weeks 8 and 12 of gestation) or intended to become pregnant were randomized 1:1 to LEVEMIR (once or twice daily) or NPH insulin (once, twice or thrice daily). Insulin aspart was administered before each meal. A total of 152 women in the LEVEMIR arm and 158 women in the NPH arm were or became pregnant during the study (Total pregnant women = 310). Approximately one half of the study participants in each arm were randomized as pregnant and were exposed to NPH or to other insulins prior to conception and in the first 8 weeks of gestation. In the 310 pregnant women, the mean glycosylated hemoglobin (HbA_{1c}) was < 7% at 10, 12, and 24 weeks of gestation in both arms. In the intent-to-treat population, the adjusted mean HbA_{1c} (standard error) at gestational week 36 was 6.27% (0.053) in LEVEMIR-treated patient (n=138) and 6.33% (0.052) in NPH-treated patients (n=145); the difference was not clinically significant.

Adverse reactions in pregnant patients occurring at an incidence of ≥5% are shown in Table 7. The two most common adverse reactions were nasopharyngitis and headache. These are consistent with findings from other type 1 diabetes trials (see Table 1, Section 6.1.), and are not repeated in Table 7.

The incidence of adverse reactions of pre-eclampsia was 10.5% (16 cases) and 7.0% (11 cases) in the LEVEMIR and NPH insulin groups respectively. Out of the total number of cases of pre-eclampsia, eight (8) cases in the LEVEMIR group and 1 case in the NPH insulin group required hospitalization. The rates of pre-eclampsia observed in the study are within expected rates for pregnancy complicated by diabetes. Pre-eclampsia is a syndrome defined by symptoms, hypertension and proteinuria; the definition of pre-eclampsia was not standardized in the trial making it difficult to establish a link between a given treatment and an increased risk of pre-eclampsia. All events were considered unlikely related to trial treatment. In all nine (9) cases requiring hospitalization the women had healthy infants. Events of hypertension, proteinuria and edema were reported less frequently in the LEVEMIR group than in the NPH insulin group as a whole. There was no difference between the treatment groups in mean blood pressure during pregnancy and there was no indication of a general increase in blood pressure.

In the NPH insulin group there were 6 serious adverse reactions in four mothers of the following placental disorders, 'Placenta previa', 'Placenta previa hemorrhage', and 'Premature separation of placenta' and 1 serious adverse reaction of 'Antepartum haemorrhage'. There were none reported in the LEVEMIR group.

The incidence of early fetal death (abortions) was similar in LEVEMIR and NPH treated patients; 6.6% and 5.1%, respectively. The abortions were reported under the following terms: 'Abortion spontaneous', 'Abortion missed', 'Blighted ovum', 'Cervical incompetence' and 'Abortion incomplete'.

Table 7: Adverse reactions during pregnancy in a trial comparing insulin aspart + LEVEMIR to insulin aspart + NPH insulin in pregnant women with type 1 diabetes (adverse reactions with incidence ≥ 5%)*

	LEVEMIR, % (n = 152)	**NPH, % (n = 158)**
Anemia	13.2	10.8
Diarrhea	11.8	5.1
Pre-eclampsia	10.5	7.0
Urinary tract infection	9.9	5.7
Gastroenteritis	8.6	5.1
Abdominal pain upper	5.9	3.8
Vomiting	5.3	4.4
Abortion spontaneous	5.3	2.5
Abdominal pain	5.3	6.3
Oropharyngeal pain	5.3	6.3

*Because clinical trials are conducted under widely varying designs, the adverse reaction rates reported in one clinical trial may not be easily compared to those rates reported in another clinical trial, and may not reflect the rates actually observed in clinical practice.

The proportion of subjects experiencing severe hypoglycemia was 16.4% and 20.9% in LEVEMIR and NPH treated patients respectively. The rate of severe hypoglycemia was 1.1 and 1.2 events per patient-year in LEVEMIR and NPH treated patients respectively. Proportion and incidence rates for non-severe episodes of hypoglycemia were similar in both treatment groups (Table 8).

Table 8: Hypoglycemia in Pregnant Women with Type 1 Diabetes

		Study G Type 1 Diabetes Pregnancy In combination with insulin aspart	
		LEVEMIR	NPH
Severe hypoglycemia*	Percent of patients with at least 1 event (n/total N)	16.4 (25/152)	20.9 (33/158)
	Events/patient/year	1.1	1.2
Non-severe hypoglycemia*	Percent of patients with at least 1 event (n/total N)	94.7 (144/152)	92.4 (146/158)
	Events/patient/year	114.2	108.4

* For definition regarding severe and non-severe hypoglycemia see section 6, Hypoglycemia.

In about a quarter of infants, LEVEMIR was detected in the infant cord blood at levels above the lower level of quantification (<25 pmol/L).

No differences in pregnancy outcomes or the health of the fetus and newborn were seen with LEVEMIR use.

Animal Data
In a fertility and embryonic development study, insulin detemir was administered to female rats before mating, during mating, and throughout pregnancy at doses up to 300 nmol/kg/day (3 times a human dose of 0.5 Units/kg/day, based on plasma area under the curve (AUC) ratio). Doses of 150 and 300 nmol/kg/day produced numbers of litters with visceral anomalies. Doses up to 900 nmol/kg/day (approximately 135 times a human dose of 0.5 Units/kg/day based on AUC ratio) were given to rabbits during organogenesis. Drug and dose related increases in the incidence of fetuses with gallbladder abnormalities such as small, bilobed, bifurcated, and missing gallbladders were observed at a dose of 900 nmol/kg/day. The rat and rabbit embryofetal development studies that included concurrent human insulin control groups indicated that insulin detemir and human insulin had similar effects regarding embryotoxicity and teratogenicity suggesting that the effects seen were the result of hypoglycemia resulting from insulin exposure in normal animals.

8.3 Nursing Mothers

It is unknown whether LEVEMIR is excreted in human milk. Because many drugs, including human insulin, are excreted in human milk, use caution when administering LEVEMIR to a nursing woman. Women with diabetes who are lactating may require adjustments of their insulin doses.

8.4 Pediatric Use

The pharmacokinetics, safety and effectiveness of subcutaneous injections of LEVEMIR have been established in pediatric patients (age 2 to 17 years) with type 1 diabetes *[see Clinical Pharmacology (12.3) and Clinical Studies (14)]*. LEVEMIR has not been studied in pediatric patients younger than 2 years of age with type 1 diabetes. LEVEMIR has not been studied in pediatric patients with type 2 diabetes.

The dose recommendation when converting to LEVEMIR is the same as that described for adults *[see Dosage and Administration (2) and Clinical Studies (14)]*. As in adults, the dosage of LEVEMIR must be individualized in pediatric patients based on metabolic needs and frequent monitoring of blood glucose.

8.5 Geriatric Use

In controlled clinical trials comparing LEVEMIR to NPH insulin or insulin glargine, 64 of 1624 patients (3.9%) in the type 1 diabetes trials and 309 of 1082 patients (28.6%) in the type 2 diabetes trials were ≥65 years of age. A total of 52 (7 type 1 and 45 type 2) patients (1.9%) were ≥75 years of age. No overall differences in safety or effectiveness were observed between these patients and younger patients, but small sample sizes, particularly for patients ≥65 years of age in the type 1 diabetes trials and for patients ≥75 years of age in all trials limits conclusions. Greater sensitivity of some older individuals cannot be ruled out. In elderly patients with diabetes, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemia. Hypoglycemia may be difficult to recognize in the elderly.

10 OVERDOSAGE

An excess of insulin relative to food intake, energy expenditure, or both may lead to severe and sometimes prolonged and life-threatening hypoglycemia. Mild episodes of hypoglycemia usually can be treated with oral glucose. Adjustments in drug dosage, meal patterns, or exercise may be needed.

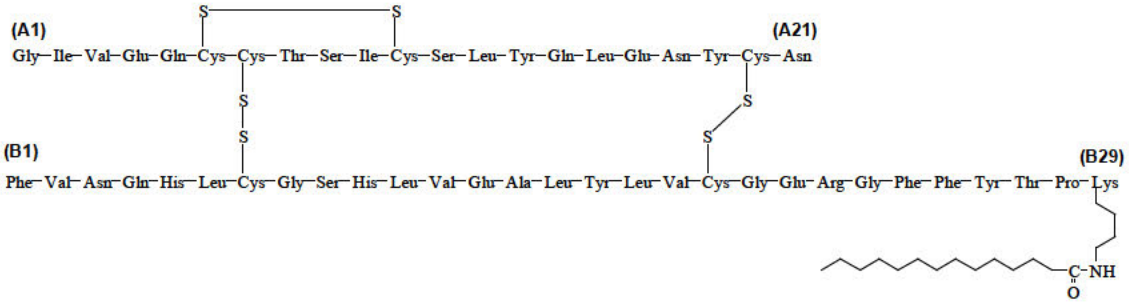
More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. After apparent clinical recovery from hypoglycemia, continued observation and additional carbohydrate intake may be necessary to avoid recurrence of hypoglycemia [*see Warnings and Precautions (5.3)*].

11 DESCRIPTION

LEVEMIR (insulin detemir [rDNA origin] injection) is a sterile solution of insulin detemir for use as a subcutaneous injection. Insulin detemir is a long-acting (up to 24-hour duration of action) recombinant human insulin analog. LEVEMIR is produced by a process that includes expression of recombinant DNA in *Saccharomyces cerevisiae* followed by chemical modification.

Insulin detemir differs from human insulin in that the amino acid threonine in position B30 has been omitted, and a C14 fatty acid chain has been attached to the amino acid B29. Insulin detemir has a molecular formula of $C_{267}H_{402}O_{76}N_{64}S_6$ and a molecular weight of 5916.9. It has the following structure:

Figure 1: Structural Formula of insulin detemir



LEVEMIR is a clear, colorless, aqueous, neutral sterile solution. Each milliliter of LEVEMIR contains 100 units (14.2 mg/mL) insulin detemir, 65.4 mcg zinc, 2.06 mg m-cresol, 16.0 mg glycerol, 1.80 mg phenol, 0.89 mg disodium phosphate dihydrate, 1.17 mg sodium chloride, and water for injection. Hydrochloric acid and/or sodium hydroxide may be added to adjust pH. LEVEMIR has a pH of approximately 7.4.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The primary activity of insulin detemir is the regulation of glucose metabolism. Insulins, including insulin detemir, exert their specific action through binding to insulin receptors. Receptor-bound insulin lowers blood glucose by facilitating cellular uptake of glucose into skeletal muscle and adipose tissue and by inhibiting the output of glucose from the liver. Insulin inhibits lipolysis in the adipocyte, inhibits proteolysis, and enhances protein synthesis.

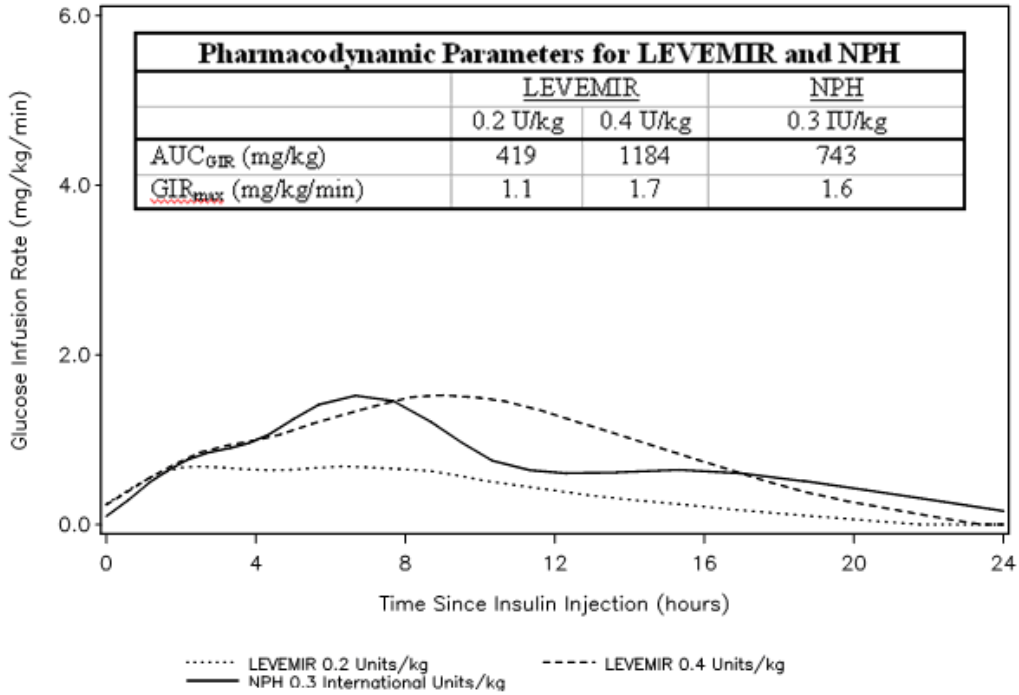
12.2 Pharmacodynamics

Insulin detemir is a soluble, long-acting basal human insulin analog with up to a 24-hour duration of action. The pharmacodynamic profile of LEVEMIR is relatively constant with no pronounced peak.

The duration of action of LEVEMIR is mediated by slowed systemic absorption of insulin detemir molecules from the injection site due to self-association of the drug molecules. In addition, the distribution of insulin detemir to peripheral target tissues is slowed because of binding to albumin.

Figure 2 shows results from a study in patients with type 1 diabetes conducted for a maximum of 24 hours after the subcutaneous injection of LEVEMIR or NPH insulin. The mean time between injection and the end of pharmacological effect for insulin detemir ranged from 7.6 hours to > 24 hours (24 hours was the end of the observation period).

Figure 2: Activity Profiles in Patients with Type 1 Diabetes in a 24-hour Glucose Clamp Study

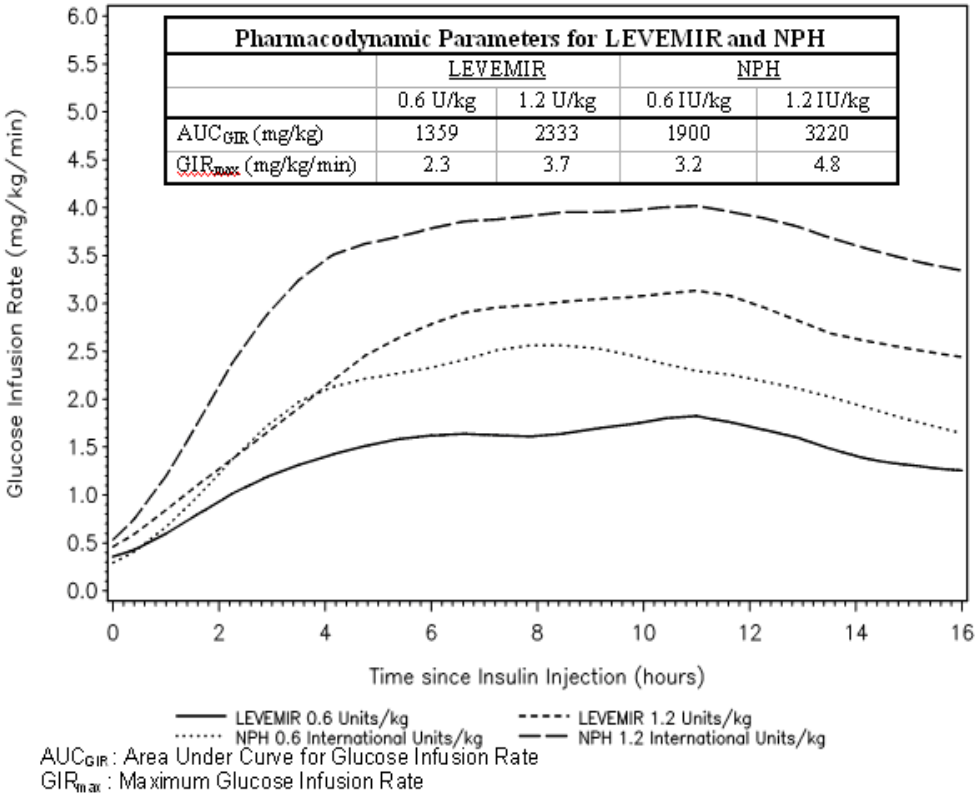


AUC_{GIR} : Area Under Curve for Glucose Infusion Rate
GIR_{max} : Maximum Glucose Infusion Rate

For doses in the interval of 0.2 to 0.4 Units/kg, insulin detemir exerts more than 50% of its maximum effect from 3 to 4 hours up to approximately 14 hours after dose administration.

Figure 3 shows glucose infusion rate results from a 16-hour glucose clamp study in patients with type 2 diabetes. The clamp study was terminated at 16 hours according to protocol.

Figure 3: Activity Profiles in Patients with Type 2 Diabetes in a 16-hour Glucose Clamp Study



12.3 Pharmacokinetics

Absorption and Bioavailability

After subcutaneous injection of LEVEMIR in healthy subjects and in patients with diabetes, insulin detemir serum concentrations had a relatively constant concentration/time profile over 24 hours with the maximum serum concentration (Cmax) reached between 6-8 hours post-dose. Insulin detemir was more slowly absorbed after subcutaneous administration to the thigh where AUC_{0-5h} was 30-40% lower and AUC_{0-inf} was 10% lower than the corresponding AUCs with subcutaneous injections to the deltoid and abdominal regions.

The absolute bioavailability of insulin detemir is approximately 60%.

Distribution and Elimination

More than 98% of insulin detemir in the bloodstream is bound to albumin. The results of *in vitro* and *in vivo* protein binding studies demonstrate that there is no clinically relevant interaction between insulin detemir and fatty acids or other protein-bound drugs.

Insulin detemir has an apparent volume of distribution of approximately 0.1 L/kg. After subcutaneous administration in patients with type 1 diabetes, insulin detemir has a terminal half-life of 5 to 7 hours depending on dose.

Specific Populations

Children and Adolescents- The pharmacokinetic properties of LEVEMIR were investigated in children (6-12 years), adolescents (13-17 years), and adults with type 1 diabetes. In children, the insulin detemir

plasma area under the curve (AUC) and C_{max} were increased by 10% and 24%, respectively, as compared to adults. There was no difference in pharmacokinetics between adolescents and adults.

Geriatrics- In a clinical trial investigating differences in pharmacokinetics of a single subcutaneous dose of LEVEMIR in young (20 to 35 years) versus elderly (≥68 years) healthy subjects, the insulin detemir AUC was up to 35% higher among the elderly subjects due to reduced clearance. As with other insulin preparations, LEVEMIR should always be titrated according to individual requirements.

Gender- No clinically relevant differences in pharmacokinetic parameters of LEVEMIR are observed between males and females.

Race- In two clinical pharmacology studies conducted in healthy Japanese and Caucasian subjects, there were no clinically relevant differences seen in pharmacokinetic parameters. The pharmacokinetics and pharmacodynamics of LEVEMIR were investigated in a clamp study comparing patients with type 2 diabetes of Caucasian, African-American, and Latino origin. Dose-response relationships for LEVEMIR were comparable in these three populations.

Renal impairment- A single subcutaneous dose of 0.2 Units/kg (1.2 nmol/kg) of LEVEMIR was administered to healthy subjects and those with varying degrees of renal impairment (mild, moderate, severe, and hemodialysis-dependent). In this study, there were no differences in the pharmacokinetics of LEVEMIR between healthy subjects and those with renal impairment. However, some studies with human insulin have shown increased circulating levels of insulin in patients with renal impairment. Careful glucose monitoring and dose adjustments of insulin, including LEVEMIR, may be necessary in patients with renal impairment [*see Warnings and Precautions (5.5)*].

Hepatic impairment- A single subcutaneous dose of 0.2 Units/kg (1.2 nmol/kg) of LEVEMIR was administered to healthy subjects and those with varying degrees of hepatic impairment (mild, moderate and severe). LEVEMIR exposure as estimated by AUC decreased with increasing degrees of hepatic impairment with a corresponding increase in apparent clearance. However, some studies with human insulin have shown increased circulating levels of insulin in patients with liver impairment. Careful glucose monitoring and dose adjustments of insulin, including LEVEMIR, may be necessary in patients with hepatic impairment [*see Warnings and Precautions (5.6)*].

Pregnancy- The effect of pregnancy on the pharmacokinetics and pharmacodynamics of LEVEMIR has not been studied [*see Use in Specific Populations (8.1*)].

Smoking- The effect of smoking on the pharmacokinetics and pharmacodynamics of LEVEMIR has not been studied.

Liraglutide -No pharmacokinetic interaction was observed between liraglutide and LEVEMIR when separate subcutaneous injections of LEVEMIR 0.5 Unit/kg (single-dose) and liraglutide 1.8 mg (steady state) were administered in patients with type 2 diabetes.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenicity, Mutagenicity, Impairment of Fertility

Standard 2-year carcinogenicity studies in animals have not been performed. Insulin detemir tested negative for genotoxic potential in the *in vitro* reverse mutation study in bacteria, human peripheral blood lymphocyte chromosome aberration test, and the *in vivo* mouse micronucleus test.
In a fertility and embryonic development study, insulin detemir was administered to female rats before mating, during mating, and throughout pregnancy at doses up to 300 nmol/kg/day (3 times a human dose of 0.5 Units/kg/day, based on plasma AUC ratio). There were no effects on fertility in the rat.

14 CLINICAL STUDIES

The efficacy and safety of LEVEMIR given once-daily at bedtime or twice-daily (before breakfast and at bedtime, before breakfast and with the evening meal, or at 12-hour intervals) was compared to that of once-daily or twice-daily NPH insulin in open-label, randomized, parallel studies of 1155 adults with type 1 diabetes mellitus, 347 pediatric patients with type 1 diabetes mellitus, and 869 adults with type 2 diabetes mellitus. The efficacy and safety of LEVEMIR given twice-daily was compared to once-daily insulin glargine in an open-label, randomized, parallel study of 320 patients with type 1 diabetes. The evening LEVEMIR dose was titrated in all trials according to pre-defined targets for fasting blood glucose. The pre-dinner blood glucose was used to titrate the morning LEVEMIR dose in those trials that also administered LEVEMIR in the morning. In general, the reduction in glycosylated hemoglobin (HbA_{1c}) with LEVEMIR was similar to that with NPH insulin or insulin glargine.

Type 1 Diabetes – Adult

In a 16-week open-label clinical study (Study A, n=409), adults with type 1 diabetes were randomized to treatment with either LEVEMIR at 12-hour intervals, LEVEMIR administered in the morning and bedtime or NPH insulin administered in the morning and bedtime. Insulin aspart was also administered before each meal. At 16 weeks of treatment, the combined LEVEMIR-treated patients had similar HbA_{1c} and fasting plasma glucose (FPG) reductions compared to the NPH-treated patients (Table 9). Differences in timing of LEVEMIR administration had no effect on HbA_{1c}, fasting plasma glucose (FPG), or body weight.

In a 26-week, open-label clinical study (Study B, n=320), adults with type 1 diabetes were randomized to twice-daily LEVEMIR (administered in the morning and bedtime) or once-daily insulin glargine (administered at bedtime). Insulin aspart was administered before each meal. LEVEMIR-treated patients had a decrease in HbA_{1c} similar to that of insulin glargine-treated patients.

In a 24-week, open-label clinical study (Study C, n=749), adults with type 1 diabetes were randomized to once-daily LEVEMIR or once-daily NPH insulin, both administered at bedtime and in combination with regular human insulin before each meal. LEVEMIR and NPH insulin had a similar effect on $HbA_{1c.}$

Table 9: Type 1 Diabetes Mellitus – Adult

	Study A		Study B		Study C	
Treatment duration	16 weeks		26 weeks		24 weeks	
Treatment in combination with	NovoLog® (insulin aspart)		NovoLog® (insulin aspart)		Human Soluble Insulin (regular insulin)	
	Twice-daily LEVEMIR	Twice-daily NPH	Twice-daily LEVEMIR	Once-daily insulin glargine	Once-daily LEVEMIR	Once-daily NPH
Number of patients treated	276	133	161	159	492	257
HbA1c (%)						
Baseline HbA1c	8.6	8.5	8.9	8.8	8.4	8.3
Adj. mean change from baseline	-0.8*	-0.7*	-0.6**	-0.5**	-0.1*	0.0*
LEVEMIR – NPH	-0.2		-0.0		-0.1	
95% CI for Treatment difference	(-0.3, -0.0)		(-0.2, 0.2)		(-0.3, 0.0)	
Basal insulin dose (units/day)						
Baseline mean	21	24	27	23	12	24
Mean change from baseline	16	10	10	4	9	2
Total insulin dose (units/day)						
Baseline mean	48	54	56	51	46	57
Mean change from baseline	17	10	9	6	11	3
Fasting blood glucose (mg/dL)						
Baseline mean	209	220	153	150	213	206
Adj. mean change from baseline	-44*	-9*	-38**	-41**	-30*	-9*
Body weight (kg)						
Baseline mean	74.6	75.5	77.5	75.1	76.5	76.9
Adj.Mean change from baseline	0.2*	0.8*	0.5**	1.0**	-0.3*	0.3*

*From an ANCOVA model adjusted for baseline value and country.
**From an ANCOVA model adjusted for baseline value and study site.

Type 1 Diabetes – Pediatric

Two open-label, randomized, controlled clinical studies have been conducted in pediatric patients with type 1 diabetes. One study was 26 weeks in duration and enrolled patients 6-17 years of age. The other study was 52 weeks in duration and enrolled patients 2-16 years of age. In both studies, LEVEMIR and NPH insulin were administered once- or twice-daily. Bolus insulin aspart was administered before each meal. In the 26-week study, LEVEMIR-treated patients had a mean decrease in HbA_{1c} similar to that of NPH insulin (Table 10). In the 52-week study, the randomization was stratified by age (2-5 years, n=82, and 6-16 years, n=265) and the mean HbA_{1c} increased in both treatment arms, with similar findings in the 2-5 year-old age group (n=80) and the 6-16 year-old age group (n=258) (Table 10).

Table 10: Type 1 Diabetes Mellitus – Pediatric

	Study D		Study I	
Treatment duration	26 weeks		52 weeks	
Treatment in combination with	NovoLog® (insulin aspart)		NovoLog® (insulin aspart)	
	Once- or Twice Daily LEVEMIR	Once- or Twice Daily NPH	Once- or Twice Daily LEVEMIR	Once- or Twice Daily NPH
Number of subjects treated	232	115	177	170
HbA1c (%)				
Baseline HbA1c	8.8	8.8	8.4	8.4

Adj. mean change from baseline	-0.7*	-0.8*	0.3**	0.2**
LEVEMIR – NPH	0.1		0.1	
95% CI for Treatment difference	-0.1; 0.3		-0.1; 0.4	
Basal insulin dose (units/day)				
Baseline mean	24	26	17	17
Mean change from baseline	8	6	8	7
Total insulin dose (units/day)				
Baseline mean	48	50	35	34
Mean change from baseline	9	7	10	8
Fasting blood glucose (mg/dL)				
Baseline mean	181	181	135	141
Adj. mean change from baseline	-39	-21	-10**	0**
Body weight (kg)				
Baseline mean	46.3	46.2	37.4	36.5
Adj.Mean change from baseline	1.6*	2.7*	2.7**	3.6**

*From an ANCOVA model adjusted for baseline value, geographical region, gender and age (covariate).
**From an ANCOVA model adjusted for baseline value, country, pubertal status at baseline and age (stratification factor).

Type 2 Diabetes – Adult

In a 24-week, open-label, randomized, clinical study (Study E, n=476), LEVEMIR administered twice-daily (before breakfast and evening) was compared to NPH insulin administered twice-daily (before breakfast and evening) as part of a regimen of stable combination therapy with one or two of the following oral antidiabetic medications: metformin, an insulin secretagogue, or an alpha–glucosidase inhibitor. All patients were insulin-naïve at the time of randomization. LEVEMIR and NPH insulin similarly lowered HbA_{1c} from baseline (Table 11).

In a 22-week, open-label, randomized, clinical study (Study F, n=395) in adults with type 2 diabetes, LEVEMIR and NPH insulin were given once- or twice-daily as part of a basal-bolus regimen with insulin aspart. As measured by HbA_{1c} or FPG, LEVEMIR had efficacy similar to that of NPH insulin.

Table 11: Type 2 Diabetes Mellitus – Adult

	Study E		Study F	
Treatment duration	24 weeks		22 weeks	
Treatment in combination with	oral agents		insulin aspart	
	Twice-daily LEVEMIR	Twice-daily NPH	Once- or Twice Daily LEVEMIR	Once- or Twice Daily NPH
Number of subjects treated	237	239	195	200
HbA1c (%)				
Baseline HbA1c	8.6	8.5	8.2	8.1
Adj. mean change from baseline	-2.0*	-2.1*	-0.6**	-0.6**
LEVEMIR – NPH	0.1		-0.1	
95% CI for Treatment difference	(-0.0, 0.3)		(-0.2, 0.1)	
Basal insulin dose (units/day)				
Baseline mean	18	17	22	22
Mean change from baseline	48	28	26	15
Total insulin dose[1] (units/day)				
Baseline mean	-	-	22	22
Mean change from baseline	-	-	57	42
Fasting blood glucose[2] (mg/dL)				
Baseline mean	179	173	-	-

Adj. mean change from baseline	-69*	-74*	-	-
Body weight (kg)				
Baseline mean	82.5	82.3	82.0	79.6
Adj.Mean change from baseline	1.2*	2.8*	0.5**	1.2**

[1]Study E – Conducted in insulin-naïve patients
[2]Study F - Fasting blood glucose data not collected
*From an ANCOVA model adjusted for baseline value, country and oral antidiabetic treatment category.
**From an ANCOVA model adjusted for baseline value and country.

Combination Therapy with Metformin and Liraglutide

This 26-week open-label trial enrolled 988 patients with inadequate glycemic control (HbA1c 7-10%) on metformin (≥1500 mg/day) alone or inadequate glycemic control (HbA1c 7-8.5%) on metformin (≥1500 mg/day) and a sulfonylurea. Patients who were on metformin and a sulfonylurea discontinued the sulfonylurea then all patients entered a 12-week run-in period during which they received add-on therapy with liraglutide titrated to 1.8 mg once-daily. At the end of the run-in period, 498 patients (50%) achieved HbA1c <7% with liraglutide 1.8 mg and metformin and continued treatment in a non-randomized, observational arm. Another 167 patients (17%) withdrew from the trial during the run-in period with approximately one-half of these patients doing so because of gastrointestinal adverse reactions *[see Adverse Reactions (6.1)]*. The remaining 323 patients with HbA1c ≥7% (33% of those who entered the run-in period) were randomized to 26 weeks of once-daily LEVEMIR administered in the evening as add-on therapy (N=162) or to continued, unchanged treatment with liraglutide 1.8 mg and metformin (N=161). The starting dose of LEVEMIR was 10 units/day and the mean dose at the end of the 26-week randomized period was 39 units/day. During the 26-week randomized treatment period, the percentage of patients who discontinued due to ineffective therapy was 11.2% in the group randomized to continued treatment with liraglutide 1.8 mg and metformin and 1.2% in the group randomized to add-on therapy with LEVEMIR.

Treatment with LEVEMIR as add-on to liraglutide 1.8 mg + metformin resulted in statistically significant reductions in HbA1c and FPG compared to continued, unchanged treatment with liraglutide 1.8 mg + metformin alone (Table 12). From a mean baseline body weight of 96 kg after randomization, there was a mean reduction of 0.3 kg in the patients who received LEVEMIR add-on therapy compared to a mean reduction of 1.1 kg in the patients who continued on unchanged treatment with liraglutide 1.8 mg + metformin alone.

Table 12: Results of a 26-week open-label trial of LEVEMIR as add on to liraglutide + metformin compared to continued treatment with liraglutide + metformin alone in patients not achieving HbA1c < 7% after 12 weeks of Metformin and Liraglutide

	Study H	
	LEVEMIR + Liraglutide +Metformin	**Liraglutide+ Metformin**
Intent-to-Treat Population (N)[a]	162	157
HbA_{1c} (%) (Mean)		
Baseline (week 0)	7.6	7.6
Adjusted mean change from baseline	-0.5*	0*

Difference from liraglutide + metformin arm (LS mean) [b] 95% Confidence Interval	-0.5*** (-0.7, -0.4)	
Percentage of patients achieving A_{1c} <7%	43**	17**
Fasting Plasma Glucose (mg/dL) (Mean)		
Baseline (week 0) Adjusted mean change from baseline	166 -38*	159 -7*
Difference from liraglutide + metformin arm (LS mean) [b] 95% Confidence Interval	-31*** (-39 , -23)	

[a]Intent-to-treat population using last observation on study
[b]Least squares mean adjusted for baseline value
*From an ANCOVA model adjusted for baseline value, country and previous oral antidiabetic treatment category.
**From a logistic regression model adjusted for baseline HbA1c.
***p-value <0.0001

Pregnancy
A randomized, open-label, controlled clinical trial has been conducted in pregnant women with type 1 diabetes. [*see Use in Specific Populations (8.1)*]

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

LEVEMIR is available in the following package sizes: each presentation containing 100 Units of insulin detemir per mL (U-100).

3 mL LEVEMIR FlexPen® NDC 0169-6439-10
3 mL LEVEMIR FlexTouch® NDC 0169-6438-10
10 mL vial NDC 0169-3687-12

FlexPen and FlexTouch can be used with NovoFine® or NovoTwist® disposable needles. Each FlexPen or FlexTouch is for use by a single patient. LEVEMIR FlexPen and LEVEMIR FlexTouch should never be shared between patients, even if the needle is changed.

16.2 Storage:

Unused (unopened) LEVEMIR should be stored in the refrigerator between 2° and 8°C (36° to 46°F). Do not store in the freezer or directly adjacent to the refrigerator cooling element. **Do not freeze. Do not use LEVEMIR if it has been frozen.**

Unused (unopened) LEVEMIR can be kept until the expiration date printed on the label if it is stored in a refrigerator. Keep unused LEVEMIR in the carton so that it stays clean and protected from light.

If refrigeration is not possible, unused (unopened) LEVEMIR can be kept unrefrigerated at room temperature, below 30°C (86°F) as long as it is kept as cool as possible and away from direct heat and light. Unrefrigerated LEVEMIR should be discarded 42 days after it is first kept out of the refrigerator, even if the FlexPen, FlexTouch or vial still contains insulin.

Vials:

After initial use, vials should be stored in a refrigerator, never in a freezer. If refrigeration is not possible, the in-use vial can be kept unrefrigerated at room temperature, below 30°C (86°F) as long as it is kept as cool as possible and away from direct heat and light. Refrigerated LEVEMIR vials should be discarded 42 days after initial use. Unrefrigerated LEVEMIR vials should be discarded 42 days after they are first kept out of the refrigerator.

LEVEMIR FlexPen or LEVEMIR FlexTouch:
After initial use, the LEVEMIR FlexPen or LEVEMIR FlexTouch must NOT be stored in a refrigerator and must NOT be stored with the needle in place. Keep the opened (in use) LEVEMIR FlexPen or LEVEMIR FlexTouch away from direct heat and light at room temperature, below 30°C (86°F). Unrefrigerated LEVEMIR FlexPen or LEVEMIR FlexTouch should be discarded 42 days after they are first kept out of the refrigerator.

The storage conditions are summarized in Table 13:

Table 13: Storage Conditions for LEVEMIR FlexPen, LEVEMIR FlexTouch, and vial

	Not in-use (unopened) **Refrigerated**	**Not in-use (unopened)** **Room Temperature (below 30°C)**	**In-use (opened)**
3 mL LEVEMIR FlexPen	Until expiration date	42 days*	42 days* Room Temperature (below 30°C) **(Do not refrigerate)**
3 mL LEVEMIR FlexTouch	Until expiration date	42 days*	42 days* Room Temperature (below 30°C) **(Do not refrigerate)**
10 mL vial	Until expiration date	42 days*	42 days* Refrigerated or Room Temperature (below 30°C)

*The total time allowed at room temperature (below 30°C) is 42 days regardless of whether the product is in-use or not in-use.

16.3 Preparation and handling
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. LEVEMIR should be inspected visually prior to administration and should only be used if the solution appears clear and colorless.

Mixing and diluting: LEVEMIR must NOT be mixed or diluted with any other insulin or solution [See *Warnings and Precautions* (5.2)].

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (Patient Information and Instructions for Use)

17.1 Instructions for Patients

Patients should be informed that changes to insulin regimens must be made cautiously and only under medical supervision. Patients should be informed about the potential side effects of insulin therapy, including hypoglycemia, weight gain, lipodystrophy (and the need to rotate injection sites within the same body region), and allergic reactions. Patients should be informed that the ability to concentrate and react may be impaired as a result of hypoglycemia. This may present a risk in situations where these abilities are especially important, such as driving or operating other machinery. Patients who have frequent hypoglycemia or reduced or absent warning signs of hypoglycemia should be advised to use caution when driving or operating machinery.

Accidental mix-ups between LEVEMIR and other insulins, particularly short-acting insulins, have been reported. To avoid medication errors between LEVEMIR and other insulins, patients should be instructed to always check the insulin label before each injection.

LEVEMIR must only be used if the solution is clear and colorless with no particles visible. Patients must be advised that LEVEMIR must NOT be diluted or mixed with any other insulin or solution.

Patients should be instructed on self-management procedures including glucose monitoring, proper injection technique, and management of hypoglycemia and hyperglycemia. Patients should be instructed on handling of special situations such as intercurrent conditions (illness, stress, or emotional disturbances), an inadequate or skipped insulin dose, inadvertent administration of an increased insulin dose, inadequate food intake, and skipped meals.

Patients should receive proper training on how to use Levemir. Instruct patients that when injecting Levemir, they must press and hold down the dose button until the dose counter shows 0 and then keep the needle in the skin and count slowly to 6. When the dose counter returns to 0, the prescribed dose is not completely delivered until 6 seconds later. If the needle is removed earlier, they may see a stream of insulin coming from the needle tip. If so, the full dose will not be delivered (a possible under-dose may occur by as much as 20%), and they should increase the frequency of checking their blood glucose levels and possible additional insulin administration may be necessary.

- If 0 does not appear in the dose counter after continuously pressing the dose button, the patient may have used a blocked needle. In this case they would **not** have received **any** insulin – even though the dose counter has moved from the original dose that was set.
- If the patient did have a blocked needle, instruct them to change the needle as described in Section 5 of the Instructions for Use and repeat all steps in the IFU starting with Section 1: Prepare your pen with a new needle. **Make sure the patient selects the full dose needed.**

Patients with diabetes should be advised to inform their healthcare professional if they are pregnant or are contemplating pregnancy. Refer patients to the LEVEMIR "Patient Information" for additional information.

17.2 Never Share a LEVEMIR FlexPen or LEVEMIR FlexTouch Between Patients

Counsel patients that they should never share a LEVEMIR FlexPen or LEVEMIR FlexTouch with another person, even if the needle is changed. Sharing of the FlexPen or FlexTouch between patients may pose a risk of transmission of infection.

Manufactured by:
Novo Nordisk A/S
DK-2880 Bagsvaerd, Denmark

For information about LEVEMIR contact:
Novo Nordisk Inc.
800 Scudders Mill Road
Plainsboro, New Jersey 08536
1-800-727-6500

www.novonordisk-us.com

Patient Information
LEVEMIR® (LEV–uh-mere)
(insulin detemir [rDNA origin] injection)

What is Levemir?
- Levemir is a man-made insulin that is used to control high blood sugar in adults and children with diabetes mellitus.
- Levemir is not meant for use to treat diabetic ketoacidosis.

Who should not take Levemir?
Do not take Levemir if you:
- have an allergy to Levemir or any of the ingredients in Levemir.

Before taking Levemir, tell your healthcare provider about all your medical conditions including, if you are:
- pregnant, planning to become pregnant, or are breastfeeding.
- taking new prescription or over-the-counter medicines, vitamins, or herbal supplements.

Before you start taking Levemir, talk to your healthcare provider about low blood sugar and how to manage it.

How should I take Levemir?
- **Read the Instructions for Use** that come with your Levemir.
- Take Levemir exactly as your healthcare provider tells you to.
- Know the type and strength of insulin you take. **Do not** change the type of insulin you take unless your healthcare provider tells you to. The amount of insulin and the best time for you to take your insulin may need to change if you take different types of insulin.
- **Check your blood sugar levels.** Ask your healthcare provider what your blood sugars should be and when you should check your blood sugar levels.
- **Do not share your Levemir FlexPen, FlexTouch or needles with another person.** You may give another person an infection or get an infection from them.
- **Never** inject Levemir into a vein or muscle.

What should I avoid while taking Levemir?
While taking Levemir do not:
- Drive or operate heavy machinery, until you know how Levemir affects you.
- Drink alcohol or use prescription or over-the-counter medicines that contain alcohol.

What are the possible side effects of Levemir?
Levemir may cause serious side effects that can lead to death, including:
Low blood sugar (hypoglycemia). Signs and symptoms that may indicate low blood sugar include:
- dizziness or light-headedness
- sweating
- confusion
- headache
- blurred vision
- slurred speech
- shakiness
- fast heart beat
- anxiety, irritability, or mood changes
- hunger

Your insulin dose may need to change because of:
- change in level of physical activity or exercise
- weight gain or loss
- increased stress
- illness
- change in diet

Other common side effects of Levemir may include:
- Reactions at the injection site, itching, rash, serious allergic reactions (whole body reactions), skin thickening or pits at the injection site (lipodystrophy), weight gain, and swelling of your hands and feet.

Get emergency medical help if you have:
- trouble breathing, shortness of breath, fast heartbeat, swelling of your face, tongue, or throat, sweating, extreme drowsiness, dizziness, confusion.

These are not all the possible side effects of Levemir. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

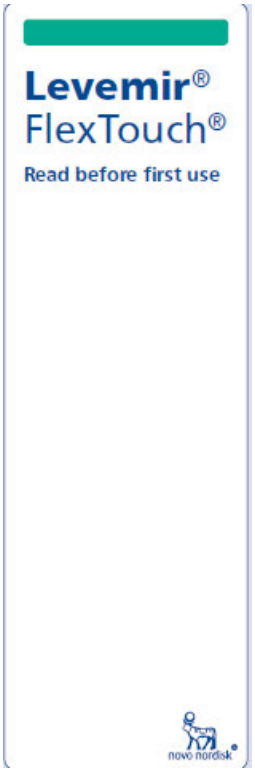
General information about the safe and effective use of Levemir.
Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. You can ask your pharmacist or healthcare provider for information about Levemir that is written for health professionals. Do not use Levemir for a condition for which it was not prescribed. Do not give Levemir to other people, even if they have the same symptoms that you have. It may harm them.

What are the ingredients in Levemir?
Active Ingredient: insulin detemir (rDNA origin)
Inactive Ingredients: zinc, m-cresol, glycerol, phenol, disodium phosphate dihydrate, sodium chloride and water for injection. Hydrochloric acid or sodium hydroxide may be added.
Manufactured by:
Novo Nordisk A/S
DK-2880 Bagsvaerd, Denmark
For more information, go to www.novonordisk-us.com or call 1-800-727-6500.

This Patient Information has been approved by the U.S. Food and Drug Administration

Revised: 10/2013

For more information go to
www.levemirflextouch.com



Instructions for Use

Levemir® (LEV–uh-mere) FlexTouch® Pen

(insulin detemir [rDNA origin] injection)

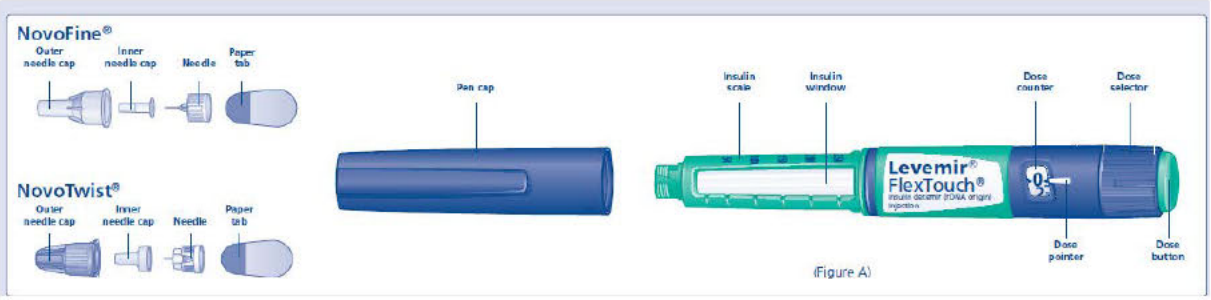
- **Levemir FlexTouch Pen ("Pen") is a prefilled disposable pen** containing 300 units of U-100 Levemir (insulin detemir [rDNA origin] injection) insulin. You can inject from 1 to 80 units in a single injection.
- **Do not share your Levemir FlexTouch Pen with another person. You may give an infection to them or get an infection from them.**
- **This Pen is not recommended for use by the blind or visually impaired without the assistance of a person trained in the proper use of the product.**

Supplies you will need to give your Levemir injection:

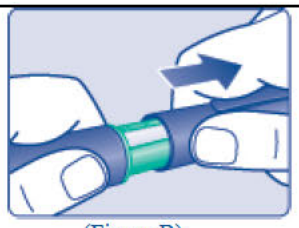
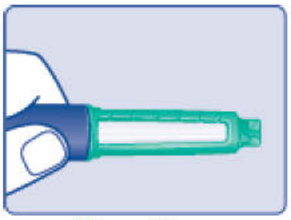
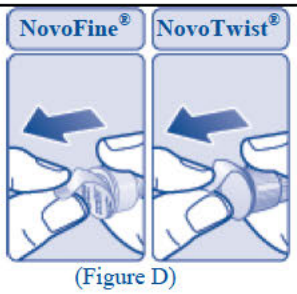
- Levemir FlexTouch Pen
- a new NovoFine or NovoTwist needle
- alcohol swab
- 1 sharps container for throwing away used Pens and needles. **See "Disposing of used Levemir FlexTouch Pens and needles" at the end of these instructions.**

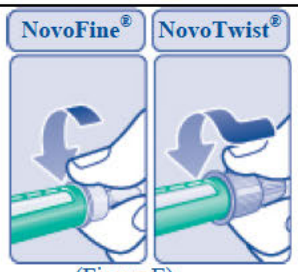
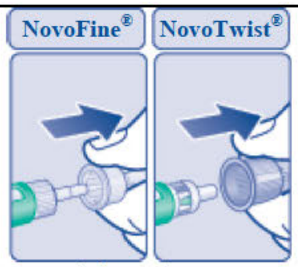
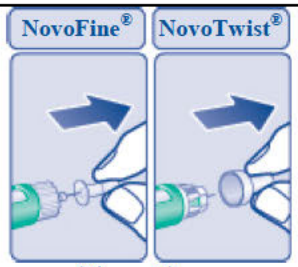
Preparing your Levemir FlexTouch Pen:

- Wash your hands with soap and water.
- **Before you start to prepare your injection, check the Levemir FlexTouch Pen label to make sure you are taking the right type of insulin. This is especially important if you take more than 1 type of insulin.**
- Levemir should look clear and colorless. **Do not** use Levemir if it is thick, cloudy, or is colored.
- **Do not** use Levemir past the expiration date printed on the label or 42 days after you start using the Pen.
- **Always use a new needle for each injection to help ensure sterility and prevent blocked needles.**

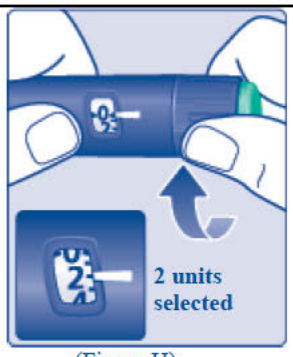


(Figure A)

Step 1: • Pull Pen cap straight off (See Figure B)	 (Figure B)
Step 2: • **Check the liquid in the Pen** (See Figure C). Levemir should look clear and colorless. **Do not** use it if it looks cloudy or colored.	 (Figure C)
Step 3: • **Select a new needle.** • Pull off the paper tab from the outer needle cap (See Figure D).	 (Figure D)

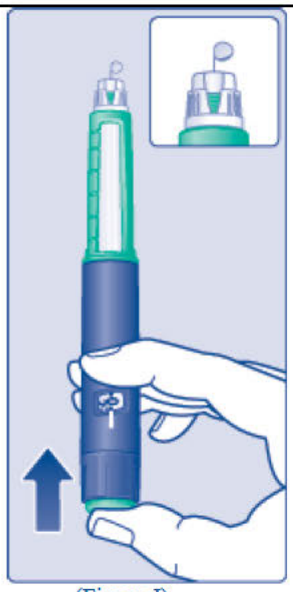
Step 4: • Push the capped needle straight onto the Pen and twist the needle on until it is tight (See Figure E).	 (Figure E)
Step 5: • Pull off the outer needle cap. **Do not** throw it away (See Figure F).	 (Figure F)
Step 6: • Pull off the inner needle cap and throw it away (See Figure G).	 (Figure G)

Priming your Levemir FlexTouch Pen:

Step 7: • Turn the dose selector to **select 2 units** (See Figure H).	 (Figure H)
Step 8: • Hold the Pen with the needle pointing up. Tap the top of the Pen gently a few times to let any air bubbles rise to the top (See Figure I).	 (Figure I)

Step 9:

- **Hold the Pen with the needle pointing up.** Press and hold in the dose button until the dose counter shows "0". The "0" must line up with the dose pointer.
- A drop of insulin should be seen at the needle tip (See Figure J).
  - If you **do not** see a drop of insulin, repeat steps 7 to 9, no more than 6 times.
  - If you **still do not** see a drop of insulin, change the needle and repeat steps 7 to 9.

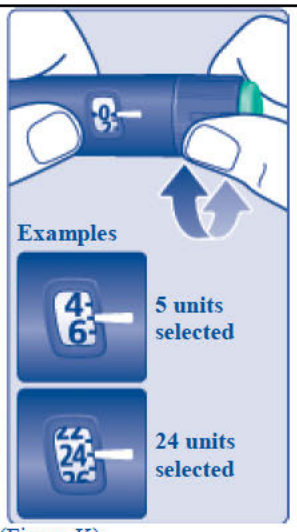


(Figure J)

Selecting your dose:

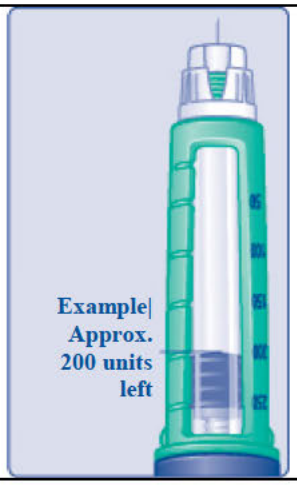
Step 10:

- **Turn the dose selector to select the number of units you need to inject.** The dose pointer should line up with your dose (See Figure K).
  - If you select the wrong dose, you can turn the dose selector forwards or backwards to the correct dose.
  - The **even** numbers are printed on the dial.
  - The **odd** numbers are shown as lines.



(Figure K)

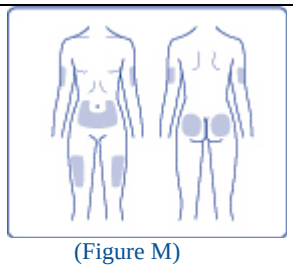
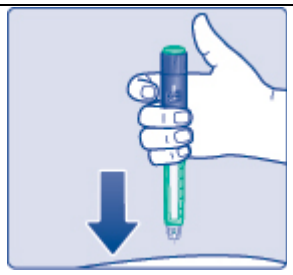
- The Levemir FlexTouch Pen insulin scale will show you how much insulin is left in your Pen (See Figure L).



	(Figure L)
• **To see how much insulin is left in your Levemir FlexTouch Pen:** o Turn the dose selector until it stops. The dose counter will line up with the number of units of insulin that is left in your Pen. If the dose counter shows 80, there are **at least 80** units left in your Pen. o If the dose counter shows **less than 80,** the number shown in the dose counter is the number of units left in your Pen.	

Giving your injection:

- Inject your Levemir exactly as your healthcare provider has shown you. Your healthcare provider should tell you if you need to pinch the skin before injecting.
- Levemir can be injected under the skin (subcutaneously) of your stomach area (abdomen), buttocks, upper legs (thighs) or upper arms.
- Change (rotate) your injection sites within the area you choose for each dose. **Do not** use the same injection site for each injection.

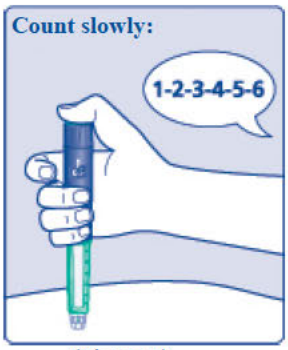
Step 11: • Choose your injection site and wipe the skin with an alcohol swab. Let the injection site dry before you inject your dose (See Figure M).	 (Figure M)
Step 12: • **Insert the needle into your skin** (See Figure N). o **Make sure you can see the dose counter. Do not** cover it with your fingers, this can stop your injection.	 (Figure N)

Step 13:

- **Press and hold down the dose button until the dose counter shows "0"** (See Figure O).
  - The "0" must line up with the dose pointer. You may then hear or feel a click.

(Figure O)

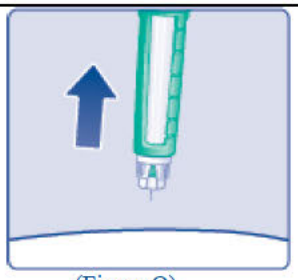
- **Keep the needle in your skin after** the dose counter has returned to "0" and **slowly count to 6** (See Figure P).
  - **When the dose counter returns to "0", you will not get your full dose until 6 seconds later.**
  - **If the needle is removed before you count to 6, you may see a stream of insulin coming from the needle tip.**
  - **If you see a stream of insulin coming from the needle tip you will not get your full dose. If this happens you should check your blood sugar levels more often because you may need more insulin.**



(Figure P)

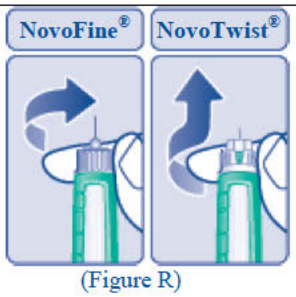
Step 14:

- **Pull the needle out of your skin** (See Figure Q).
  - If you see blood after you take the needle out of your skin, press the injection site lightly with a piece of gauze or an alcohol swab. **Do not** rub the area.

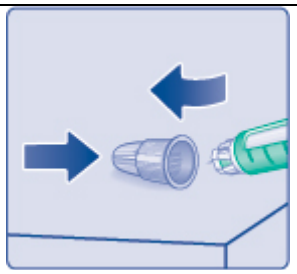
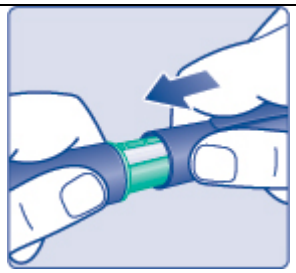

(Figure Q)

Step 15:

- **Carefully remove the needle from the Pen and throw it away** (See Figure R).
  - **Do not** recap the needle. Recapping the needle can lead to needle stick injury.
- If you **do not** have a sharps container, carefully slip the needle



(Figure R)

into the outer needle cap (See Figure S). Safely remove the needle and throw it away as soon as you can. o **Do not** store the Pen with the needle attached. Storing without the needle attached helps prevent leaking, blocking of the needle, and air from entering the Pen.	 (Figure S)
Step 16: • Replace the Pen cap by pushing it straight on (See Figure T).	 (Figure T)

After your injection:

- Put your used Levemir FlexTouch Pen and needles in a FDA-cleared sharps disposal container right away after use. Do not throw away (dispose of) loose needles and Pens in your household trash.
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
  - made of a heavy-duty plastic
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out
  - upright and stable during use
  - leak-resistant
  - properly labeled to warn of hazardous waste inside the container
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about the safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.
- Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.

How should I store my Levemir FlexTouch Pen?

- Store unused Levemir FlexTouch Pens in the refrigerator at 36°F to 46°F (2°C to 8°C).

- Store the Pen you are currently using out of the refrigerator below 86^{O}F.
- **Do not** freeze Levemir. **Do not** use Levemir if it has been frozen.
- Keep Levemir away from heat or light.
- Unused Pens may be used until the expiration date printed on the label, if kept in the refrigerator.
- The Levemir FlexTouch Pen you are using should be thrown away after 42 days, even if it still has insulin left in it.

General Information about the safe and effective use of Levemir.

- **Keep Levemir FlexTouch Pens and needles out of the reach of children.**
- **Always** use a new needle for each injection.
- **Do not** share Pens or needles.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured By:

Novo Nordisk A/S

DK-2880 Bagsvaerd, Denmark

Revised: 10/2013

Code centre line
Code: 100% Direction
Length: Max 295mm (100%)

Regulatory Operations
Carton: 22-521-00-301
Current 1.0
Lacquer free area:
Lacquerform: 30271-1

Colour:
PMS 280C
+ PMS 289C
+ Black
+ PMS Green C

USA
5 pcs

28

Warning
Any change of insulin should be made cautiously and only under medical supervision.
Levemir® FlexTouch® is for single patient use only.
See accompanying literature for dosage.
Needles not included.

For subcutaneous use.

Each mL contains 100 Units (14.20 mg/mL) of insulin detemir; glycerol, 16.0 mg; phenol, 1.80 mg; metacresol, 2.06 mg; zinc, 65.4 mcg; disodium phosphate dihydrate, 0.89 mg; sodium chloride, 1.17 mg, and water for injection.

NOT TO BE USED BARCODE
USED FOR VISUEL PLACEMENT
3 00000 00000 3

Novo Nordisk Inc.
Plainsboro, NJ 08536
www.novonordisk-us.com
1-800-727-6500

(Se habla español)

Manufactured by:
Novo Nordisk A/S
DK-2880 Bagsvaerd, Denmark

novo nordisk®

22-521-00

Levemir® FlexTouch®
insulin detemir (rDNA origin) injection
100 units/mL (U-100)
5x3 mL Prefilled Pens

NDC 0169-6438-10 List: 643810

Levemir® FlexTouch®

Insulin detemir (rDNA origin) injection

100 units/mL (U-100)
5x3 mL Prefilled Pens
For subcutaneous use only
Rx Only
Single patient use only

Recommended for use with NovoFine® or NovoTwist® disposable needles.
Keep in a cold place until first use.
Store at 2°- 8°C (36°- 46°F).
Avoid freezing.
Protect from light.

novo nordisk®

Expiry/Batch:

Levemir® FlexTouch®
Insulin detemir (rDNA origin) injection
100 units/mL (U-100)
5x3 mL Prefilled Pens

8-9508-31-301-x

Levemir® FlexTouch®
insulin detemir (rDNA origin) injection
100 units/mL (U-100)
5x3 mL Prefilled Pens

Reference ID: 3399164

Code centre line
Code: 100% Direction
Length: Max 295 mm (100%)

(b) (4)

2
8

Warning
Any change of insulin should be made cautiously and only under medical supervision.
Levemir® FlexTouch® is for single patient use only.

See accompanying literature for dosage.
Sample Kit includes:
• (1) Levemir® FlexTouch®
• (7) single use NovoFine® 32G Tip needles
For subcutaneous use.

Each mL contains 100 Units (14.20 mg/mL) of insulin detemir; glycerol, 16.0 mg; phenol, 1.80 mg; metacresol, 2.06 mg; zinc, 65.4 mcg; disodium phosphate dihydrate, 0.89 mg; sodium chloride, 1.17 mg, and water for injection.

Levemir® is covered by US Patent Nos. 5,750,497, 5,866,538, 6,011,007, 6,869,930 and other patents pending.

FlexTouch® pen is covered by US Patent Nos. 7,686,786, 6,899,699, and other patents pending.

NOT TO BE USED BARCODE
USED FOR VISUEL PLACEMENT

3 00000 00000 3

40x25

Novo Nordisk Inc.
Plainsboro,
NJ 08536
www.novonordisk-us.com
1-800-727-6500
(Se habla español)
Manufactured by:
Novo Nordisk A/S
DK-2880 Bagsvaerd, Denmark

novo nordisk®

22-520-00

Levemir® FlexTouch®
nsu n detem r (rDNA or g n) nject on
100 un ts/mL (U-100)
1x3 mL Pref ed Pen
Samp e. Not for Resa e

Levemir® FlexTouch®
Insulin detemir (rDNA origin) injection
100 units/mL (U-100)
1x3 mL Prefilled Pen
Sample. Not for Resale

8-9508-31-302-x

NDC 0169-6438-97 List: 643897

Levemir® FlexTouch®

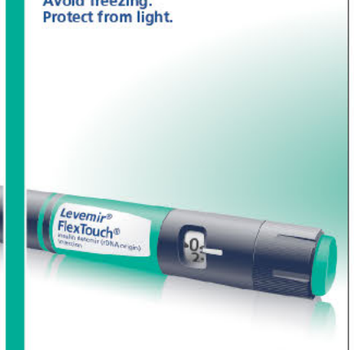
Insulin detemir (rDNA origin) injection

100 units/mL (U-100)
1x3 mL Prefilled Pen

For subcutaneous use only
Rx Only
Single patient use only
Sample. Not for Resale

Sample Kit includes:
• (1) Levemir® FlexTouch®
• (7) single use NovoFine® 32G Tip needles

Recommended for use with NovoFine® or NovoTwist® disposable needles.
Keep in a cold place until first use.
Store at 2°- 8°C (36°- 46°F).
Avoid freezing.
Protect from light.

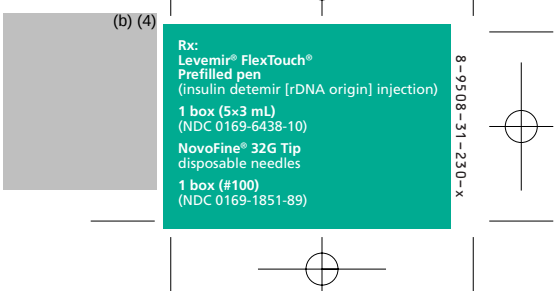


novo nordisk®

Levemir® FlexTouch®
nsu n detem r (rDNA or g n) nject on
100 un ts/mL (U-100)
1x3 mL Pref ed Pen
Samp e. Not for Resa e

Expiry/Batch:


(b) (4)
Area without lacquer
100 units/mL 3 mL Prefilled Pen
Levemir®
FlexTouch®
insulin detemir (rDNA origin)
injection
NDC 0169-6438-97 List: 643897
Rx Only. For subcutaneous use only
Sample. Not for Resale
For single patient use only
Novo Nordisk Inc.
Plainsboro, NJ 08536
1-800-727-6500
Expiry/
Batch:
8-9508-31-202-x
Center of Productbox
Overlap



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21536/S-033

CHEMISTRY REVIEW(S)

CHEMISTRY REVIEW #2	1. ORGANIZATION	2. NDA NUMBER
	ONDQA/DNDQA III/Branch IX	Bundled supplement- see below
3. NAME AND ADDRESS OF APPLICANT		**4. SUPPLEMENT NUMBER, DATE**
Novo Nordisk Inc. 100 College Road West Princeton, NJ 08540		N020986/S-061, 15-Dec-2009 N021536/S-033, 15-Dec-2009
5. PROPRIETARY NAME	**6. NAME OF THE DRUG**	**7. AMENDMENTS, REPORT, DATE**
NovoLog® Levemir®	Insulin aspart (rDNA Origin) injection Insulin detemir (rDNA Origin) injection	N020986/S-061, 22-Mar-2013 N021536/S-033, 22-Mar-2013
8. SUPPLEMENT PROVIDES INFORMATION FOR		
New PDS290 pre-filled pen device.		
9. PHARMACOLOGICAL CATEGORY	**10. HOW DISPENSED**	**11. RELATED IND, NDA, DMF**
Insulin analog for treatment of hyperglycemia	Rx	
12. DOSAGE FORM	**13. POTENCY**	
Injectable	100 U/mL	
14. CHEMICAL NAME AND STRUCTURE		
See Chemist's review notes on next page		

15. COMMENTS

The PDS290 prefilled pen is a new disposable insulin delivery device that contains the currently approved products NovoLog and Levemir, presented in the 3 mL PenFill cartridges respectively, as in the currently approved device FlexPen. The PDS290 pen is a similar pen device but it is improved in ergonomic design, function, and quality compared to FlexPen. It is designed for subcutaneous injection of insulin products, and it is intended to function with the standard range of applicant's disposable needles. The proposed proprietary names for PDS290 are NovoLog® FlexTouch® **and** Levemir® FlexTouch®.

The latest draft labeling and container/carton labeling in amendments submitted on 22-Mar-2013 were reviewed and found to be adequate from CMC review standpoint.

The Chemistry review #1 of the initial submission was completed on 14-May-2010 pending the CDRH review. The supplements as amended are recommended for approval since the CDRH review was completed on 22-Jul-2013.

16. CONCLUSION AND RECOMMENDATION

The bundled supplements as amended are satisfactory from the CMC review standpoint. The subject supplements as amended are recommended for approval. The bundled supplements are OND managed.

17. NAME	18. REVIEWERS SIGNATURE	19. DATE COMPLETED
Pallaiah Thammana	See electronic signature sheet	23-Oct-2013

DISTRIBUTION: ORIGINAL JACKET CSO REVIEWER DIVISION FILE
DMEP

AP

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/s/

PALLAIAH THAMMANA
10/23/2013

RAMESH RAGHAVACHARI
10/23/2013

CHEMISTRY REVIEW	1. ORGANIZATION	2. NDA NUMBER
	ONDQA/DPE/Branch VII	Bundled supplement- see below
3. NAME AND ADDRESS OF APPLICANT		**4. SUPPLEMENT NUMBER, DATE**
Novo Nordisk Inc. 100 College Road West Princeton, NJ 08540		N021536/S-033, 15-Dec-2009 N020986/S-061, 15-Dec-2009 (b) (4)
5. PROPRIETARY NAME	**6. NAME OF THE DRUG**	**7. AMENDMENTS, REPORT, DATE**
Levemir® NovoLog® (b) (4)	Insulin detemir (rDNA Origin) injection Insulin aspart (rDNA Origin) injection (b) (4)	
8. SUPPLEMENT PROVIDES INFORMATION FOR		
New PDS290 pre-filled pen device		
9. PHARMACOLOGICAL CATEGORY	**10. HOW DISPENSED**	**11. RELATED IND, NDA, DMF**
Insulin analog for treatment of hyperglycemia	Rx	
12. DOSAGE FORM	**13. POTENCY**	
Injectable	100 U/mL	
14. CHEMICAL NAME AND STRUCTURE		
See Chemist's review notes on next page		

15. COMMENTS

The PDS290 prefilled pen is a new insulin delivery device that contains three currently approved products Levemir, NovoLog (b) (4) presented in the same 3 mL PenFill® cartridges as in the currently approved device FlexPen®. The PDS290 pen is similar but improved in ergonomic design, function, and quality compared to FlexPen. It is designed for subcutaneous injection of insulin, and it is intended to function with the standard range of applicant's disposable needles. The proposed proprietary names for PDS290 are Levemir® FlexTouch®, NovoLog® FlexTouch® (b) (4)

Since the formulation and filling of the drug products are the same as the current prefilled pens, the methods of analysis, container closure materials, proposed storage conditions and shelf-life remain the same. The drug product specifications remain the same except for the addition of PDS290 dose accuracy, which is specific to the pen. The stability statements for the proposed device remain the same as the approved FlexPen, and the stability sections in the three supplements were found to be adequate from CMC review standpoint. The draft labeling submitted was reviewed and found to be adequate from CMC review standpoint.

16. CONCLUSION AND RECOMMENDATION

The bundled supplements are satisfactory from a CMC review standpoint. The subject supplements are recommended for approval, pending a satisfactory CDRH review.

17. NAME	18. REVIEWERS SIGNATURE	19. DATE COMPLETED
Pallaiah Thammana	See electronic signature sheet	14-May-2010

DISTRIBUTION: ORIGINAL JACKET CSO REVIEWER DIVISION FILE
510

3 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20986	SUPPL-61	NOVO NORDISK INC	Aspart (NOVOLOG)
[redacted] (b) (4)			
NDA-21536	SUPPL-33	NOVO NORDISK INC	LEVEMIR

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

/s/

PALLAIAH THAMMANA
05/14/2010

JAMES D VIDRA
05/14/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21536/S-033

PROPRIETARY NAME REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Proprietary Name Review

Date:	August 19, 2012
Reviewer:	Reasol S. Agustin, PharmD Division of Medication Error Prevention and Analysis
Team Leader:	Yelena Maslov, PharmD Division of Medication Error Prevention and Analysis
Deputy Director:	Kellie Taylor, PharmD MPH Division of Medication Error Prevention and Analysis
Drug Name and Strength:	Levemir FlexTouch (Insulin Detemir), 100 units/mL (U-100)
Application Type/Number:	NDA 021536/S-033
Applicant/Sponsor:	Novo Nordisk
OSE RCM #:	2013-1266

*** This document contains proprietary and confidential information that should not be released to the public.***

CONTENTS

1 INTRODUCTION

This review evaluates the proposed proprietary name, Levemir FlexTouch, from a safety and promotional perspective. The sources and methods used to evaluate the proposed name are outlined in the reference section and Appendix A respectively.

1.1 REGULATORY HISTORY

The Division of Medication Error Prevention and Analysis (DMEPA) previously reviewed the proposed proprietary name Levemir FlexTouch, under NDA 021536/S-033 in OSE Review #2009-2454, dated March 15, 2010 and #2012-280, dated April 23, 2012. DMEPA found the root name, Levemir, and the proposed modifier, FlexTouch, acceptable.

1.2 PRODUCT INFORMATION

The Applicant stated that none of the proposed product characteristics have changed. The following product information is provided in the December 15, 2009 proprietary name submission.

- Active Ingredient: Insulin Detemir [rDNA]
- Indication of Use: For the treatment of adult and pediatric patients with Type 1 diabetes mellitus or adult patients with Type 2 diabetes mellitus who require basal (long acting) insulin for the control of hyperglycemia.
- Route of Administration: Subcutaneously
- Dosage Form: Injection in a prefilled pen
- Strength: 100 units/mL
- Dose and Frequency: The dose for insulin varies based on the patients' needs but usual starting dose is 0.1 units/kg to 0.2 units/kg once daily in the evening or 10 units once or twice daily in insulin naïve patients.
- How Supplied: 100 units/mL (U-100) in 3 mL FlexTouch disposable pen injector.
- Storage: The pens and the cartridges are stored between 2° and 8° C (36° and 46° F). After initial use, the product may be stored at room temperature, below 30° C (86° F) for up to four weeks.
- Container and Closure Systems: The disposable pen-injector is the PDS290 device

2. RESULTS

The following sections provide the information obtained and considered in the evaluation of the proposed proprietary name.

2.1 PROMOTIONAL ASSESSMENT

The Office of Prescription Drug Promotion (OPDP) determined the proposed name is acceptable from a promotional perspective. DMEPA and the Division of Metabolism and Endocrinology Products (DMEP) concurred with the findings of OPDP's promotional assessment of the proposed name.

2.2 SAFETY ASSESSMENT

The following aspects of the name were considered in the overall safety evaluation.

2.2.1 United States Adopted Names (USAN) SEARCH

On July 29, 2013 the United States Adopted Name (USAN) stem search, identified that a USAN stem is not present in the proposed proprietary name.

2.2.2 Components of the Proposed Proprietary Name

The Applicant, Novo Nordisk, noted that the root name, Levemir, was not derived from one particular concept and is a currently approved name of a drug. The Applicant also noted that the modifier "FlexTouch" represents the new delivery device. This modifier is a combination of "flexible" and "touch". "Flexible" represents flexible dosing available in the pen. "Touch" represents improvements upon the design of the current Levemir® FlexPen®. Therefore, the name is not trying to convey any specific meaning to the device or drug that could be misinterpreted at any point in the medication use process. Since the currently marketed device, FlexPen and the new device, FlexTouch are both prefilled pen-injectors used for the same indication of use, route of administration, concentration, quantity, and method of use, the sole purpose of the modifier FlexTouch is to differentiate this new device from the other products in the Levemir family (e.g. Levemir FlexPen, and Levemir vials).

The modifier, FlexTouch, was evaluated in conjunction with the proposed proprietary name, Levemir, as well as separately for vulnerabilities for confusion that could lead to medication errors under NDA 021536/S-033 in OSE Review #2009-2454 dated March 15, 2010 and #2012-280, dated April 23, 2012. The modifier was found acceptable. As a result, the name Levemir FlexTouch was found acceptable.

2.2.3 FDA Name Simulation Studies

Seventy-three practitioners participated in DMEPA's prescription studies. The interpretations did not overlap with any currently marketed products nor did the misinterpretations sound or look similar to any currently marketed products or any products in the pipeline. Twenty-five of the 30 outpatient participants responded correctly and the most common misinterpretation occurred with 2 participants misinterpreting the modifier "FlexTouch" for Flexpatch. Fifteen of the 22 inpatient participants responded correctly and the most common misinterpretation occurred with participants misinterpreting the modifier "FlexTouch" for Flextocide, Flextovel, Fl—Touch. Five of the 21 voice participants responded correctly and a common misinterpretation occurred with 5 participants misinterpreting the letter 'e' for 'a' (i.e. LevEmir misinterpreted as 'LevAmir') and 4 participants misinterpreting the letter 'e' for 'i' (i.e. LevEmir misinterpreted as 'LevImir'). We have considered these variations in our look-alike and sound-alike searches and analysis (see Appendix B). Appendix C contains the results of the verbal and written prescription studies.

2.2.4 Comments from Other Review Disciplines

In response to the OSE, July 10, 2013 e-mail, the Division of Metabolism and Endocrinology Products (DMEP) had no objections to the proposed name at the initial phase of the proprietary name review.

2.2.5 Failure Mode and Effects Analysis of Similar Names

Appendix B lists possible orthographic and phonetic misinterpretations of the letters used in the search for similar names to the proposed proprietary name, NovoLog FlexTouch. Since no new names were identified since the last two OSE reviews (#2009-2454 and #2012-280) and product characteristics remained the same, we determined that none of the previously identified names raises concerns related to orthographic or phonetic similarity to Levemir FlexTouch.

2.2.7 Communication of DMEPA's Final Decision to Other Disciplines

DMEPA communicated our findings to the Division of Metabolism and Endocrinology Products (DMEP) via e-mail on July 29, 2013. At that time we also requested additional information or concerns that could inform our review. Per e-mail correspondence from the Division of Metabolism and Endocrinology Products (DMEP) on July 30, 2013 they stated no additional concerns with the proposed proprietary name, Levemir FlexTouch.

3 CONCLUSIONS

The proposed proprietary name is acceptable from both a promotional and safety perspective.

If you have further questions or need clarifications, please contact Margarita Tossa, OSE project manager, at 301-796-4053.

3.1 COMMENTS TO THE APPLICANT

We have completed our review of the proposed proprietary name, Levemir FlexTouch, and have concluded that this name is acceptable.

The proposed proprietary name must be re-reviewed 90 days prior to approval of the NDA Supplement. The results are subject to change. If any of the proposed product characteristics as stated in your December 15, 2009 submission are altered, the name must be resubmitted for review.

4 REFERENCES

1. ***Micromedex Integrated Index (http://csi.micromedex.com)***

   Micromedex contains a variety of databases covering pharmacology, therapeutics, toxicology and diagnostics.

2. ***Phonetic and Orthographic Computer Analysis (POCA)***

   POCA is a database which was created for the Division of Medication Error Prevention and Analysis, FDA. 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. Likewise, an orthographic algorithm exists which operates in a similar fashion.

3. ***Drug Facts and Comparisons, online version, St. Louis, MO (http://factsandcomparisons.com)***

   Drug Facts and Comparisons is a compendium organized by therapeutic course; it contains monographs on prescription and OTC drugs, with charts comparing similar products. This database also lists the orphan drugs.

4. ***FDA Document Archiving, Reporting & Regulatory Tracking System [DARRTS]***

   DARRTS is a government database used to organize Applicant and Sponsor submissions as well as to store and organize assignments, reviews, and communications from the review divisions.

5. ***Division of Medication Errors Prevention and Analysis proprietary name consultation requests***

   This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention and Analysis from the Access database/tracking system.

6. ***Drugs@FDA (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm)***

   Drugs@FDA contains most of the drug products approved since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA approved brand name, generic drugs, therapeutic biological products, prescription and over-the-counter human drugs and discontinued drugs and "Chemical Type 6" approvals.

7. ***U.S. Patent and Trademark Office (http://www.uspto.gov)***

   USPTO provides information regarding patent and trademarks.

8. ***Clinical Pharmacology Online (www.clinicalpharmacology-ip.com)***

   Clinical Pharmacology contains full monographs for the most common drugs in clinical use, plus mini monographs covering investigational, less common, combination, nutraceutical and nutritional products. It also provides a keyword search engine.

9. ***Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at (www.thomson-thomson.com)***

   The Pharma In-Use Search database contains over 400,000 unique pharmaceutical trademarks and trade names that are used in about 50 countries worldwide. The data is provided under license by IMS HEALTH.

10. ***Natural Medicines Comprehensive Databases (www.naturaldatabase.com)***

    Natural Medicines contains up-to-date clinical data on the natural medicines, herbal medicines, and dietary supplements used in the western world.

11. ***Access Medicine (www.accessmedicine.com)***

    Access Medicine® from McGraw-Hill contains full-text information from approximately 60 titles; it includes tables and references. Among the titles are: Harrison's Principles of Internal Medicine, Basic & Clinical Pharmacology, and Goodman and Gilman's The Pharmacologic Basis of Therapeutics.

12. ***USAN Stems (http://www.ama-assn.org/ama/pub/about-ama/our-people/coalitions-consortiums/united-states-adopted-names-council/naming-guidelines/approved-stems.shtml)***

    USAN Stems List contains all the recognized USAN stems.

13. ***Red Book (www.thomsonhc.com/home/dispatch)***

    Red Book contains prices and product information for prescription, over-the-counter drugs, medical devices, and accessories.

14. ***Lexi-Comp (www.lexi.com)***

    Lexi-Comp is a web-based searchable version of the Drug Information Handbook.

15. ***Medical Abbreviations (www.medilexicon.com)***

    Medical Abbreviations dictionary contains commonly used medical abbreviations and their definitions.

16. ***CVS/Pharmacy (www.CVS.com)***

    This database contains commonly used over the counter products not usually identified in other databases.

17. Walgreens (www.walgreens.com)

This database contains commonly used over the counter products not usually identified in other databases.

18. Rx List (www.rxlist.com)

RxList is an online medical resource dedicated to offering detailed and current pharmaceutical information on brand and generic drugs.

19. Dogpile (www.dogpile.com)

Dogpile is a Metasearch engine that searches multiple search engines including Google, Yahoo! and Bing, and returns the most relevant results to the search.

APPENDICES

Appendix A

FDA's Proprietary Name Risk Assessment considers the promotional and safety aspects of a proposed proprietary name.. The promotional review of the proposed name is conducted by OPDP. OPDP evaluates proposed proprietary names to determine if they are overly fanciful, so as to misleadingly imply unique effectiveness or composition, as well as to assess whether they contribute to overstatement of product efficacy, minimization of risk, broadening of product indications, or making of unsubstantiated superiority claims. OPDP provides their opinion to DMEPA for consideration in the overall acceptability of the proposed proprietary name.

The safety assessment is conducted by DMEPA. DMEPA staff search a standard set of databases and information sources to identify names that are similar in pronunciation, spelling, and orthographically similar when scripted to the proposed proprietary name. Additionally, we consider inclusion of USAN stems or other characteristics that when incorporated into a proprietary name may cause or contribute to medication errors (i.e., dosing interval, dosage form/route of administration, medical or product name abbreviations, names that include or suggest the composition of the drug product, etc.). DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [1]

Following the preliminary screening of the proposed proprietary name, DMEPA gathers to discuss their professional opinions on the safety of the proposed proprietary name. This meeting is commonly referred to the Center for Drug Evaluation and Research (CDER) Expert Panel discussion. DMEPA also considers other aspects of the name that may be misleading from a safety perspective. DMEPA staff conducts a prescription simulation studies using FDA health care professionals. When provided, DMEPA considers external proprietary name studies conducted by or for the Applicant/Sponsor and incorporates the findings of these studies into the overall risk assessment.

The DMEPA primary reviewer assigned to evaluate the proposed proprietary name is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name. DMEPA bases the overall risk assessment on the findings of a Failure Mode and Effects Analysis (FMEA) of the proprietary name and misleading nature of the proposed proprietary name with a focus on the avoidance of medication errors.

DMEPA uses the clinical expertise of its staff to anticipate the conditions of the clinical setting where the product is likely to be used based on the characteristics of the proposed product. DMEPA considers the product characteristics associated with the proposed product throughout the risk assessment because the product characteristics of the proposed may provide a context for communication of the drug name and ultimately determine the use of the product in the *usual* clinical practice setting.

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[1] National Coordinating Council for Medication Error Reporting and Prevention. http://www nccmerp.org/aboutMedErrors html. Last accessed 10/11/2007.

Typical product characteristics considered when identifying drug names that could potentially be confused with the proposed proprietary name include, but are not limited to; established name of the proposed product, proposed indication of use, dosage form, route of administration, strength, unit of measure, dosage units, recommended dose, typical quantity or volume, frequency of administration, product packaging, storage conditions, patient population, and prescriber population. DMEPA considers how these product characteristics may or may not be present in communicating a product name throughout the medication use system. Because drug name confusion can occur at any point in the medication use process, DMEPA considers the potential for confusion throughout the entire U.S. medication use process, including drug procurement, prescribing and ordering, dispensing, administration, and monitoring the impact of the medication.[2]

The DMEPA considers the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. DMEPA compares the proposed proprietary name with the proprietary and established name of existing and proposed drug products and names currently under review at the FDA. DMEPA compares the pronunciation of the proposed proprietary name with the pronunciation of other drug names because verbal communication of medication names is common in clinical settings. DMEPA examines the phonetic similarity using patterns of speech. If provided, DMEPA will consider the Sponsor's intended pronunciation of the proprietary name. However, DMEPA also considers a variety of pronunciations that could occur in the English language because the Sponsor has little control over how the name will be spoken in clinical practice. The orthographic appearance of the proposed name is evaluated using a number of different handwriting samples. DMEPA applies expertise gained from root-cause analysis of postmarketing medication errors to identify sources of ambiguity within the name that could be introduced when scripting (e.g.,"T" may look like "F," lower case 'a' looks like a lower case 'u,' etc). Additionally, other orthographic attributes that determine the overall appearance of the drug name when scripted (see Table 1 below for details).

Table 1. Criteria Used to Identify Drug Names that Look- or Sound-Similar to a Proposed Proprietary Name.

Type of Similarity	**Considerations when Searching the Databases**		
	Potential Causes of Drug Name Similarity	*Attributes Examined to Identify Similar Drug Names*	*Potential Effects*

[2] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006.

Look-alike	Similar spelling	Identical prefix Identical infix Identical suffix Length of the name Overlapping product characteristics	• Names may appear similar in print or electronic media and lead to drug name confusion in printed or electronic communication • Names may look similar when scripted and lead to drug name confusion in written communication
	Orthographic similarity	Similar spelling Length of the name/Similar shape Upstrokes Down strokes Cross-strokes Dotted letters Ambiguity introduced by scripting letters Overlapping product characteristics	• Names may look similar when scripted, and lead to drug name confusion in written communication
Sound-alike	Phonetic similarity	Identical prefix Identical infix Identical suffix Number of syllables Stresses Placement of vowel sounds Placement of consonant sounds Overlapping product characteristics	• Names may sound similar when pronounced and lead to drug name confusion in verbal communication

Lastly, DMEPA considers the potential for the proposed proprietary name to inadvertently function as a source of error for reasons other than name confusion. Post-marketing experience has demonstrated that proprietary names (or components of the proprietary name) can be a source of error in a variety of ways. Consequently, DMEPA considers and evaluates these broader safety implications of the name throughout this assessment and the medication error staff provides additional comments related to the safety of the proposed proprietary name or product based on professional experience with medication errors.

1. Database and Information Sources

DMEPA searches the internet, several standard published drug product reference texts, and FDA databases to identify existing and proposed drug names that may sound-alike or look-alike to the proposed proprietary name. A standard description of the databases used in the searches is provided in the reference section of this review. To complement the process, the DMEPA uses a computerized method of identifying phonetic and orthographic similarity between medication names. The program, Phonetic and Orthographic Computer Analysis

(POCA), uses complex algorithms to select a list of names from a database that have some similarity (phonetic, orthographic, or both) to the trademark being evaluated. Lastly, DMEPA reviews the USAN stem list to determine if any USAN stems are present within the proprietary name. The individual findings of multiple safety evaluators are pooled and presented to the CDER Expert Panel. DMEPA also evaluates if there are characteristics included in the composition that may render the name unacceptable from a safety perspective (abbreviation, dosing interval, etc.).

2. Expert Panel Discussion

DMEPA gathers gather CDER professional opinions on the safety of the proposed product and discussed the proposed proprietary name (Expert Panel Discussion). The Expert Panel is composed of Division of Medication Errors Prevention (DMEPA) staff and representatives from the Office of Prescription Drug Promotion (OPDP). We also consider input from other review disciplines (OND, ONDQA/OBP). The Expert Panel also discusses potential concerns regarding drug marketing and promotion related to the proposed names.

The primary Safety Evaluator presents the pooled results of the database and information searches to the Expert Panel for consideration. Based on the clinical and professional experiences of the Expert Panel members, the Panel may recommend additional names, additional searches by the primary Safety Evaluator to supplement the pooled results, or general advice to consider when reviewing the proposed proprietary name.

3. FDA Prescription Simulation Studies

Three separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of the proposed proprietary name with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. The studies employ healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The primary Safety Evaluator uses the results to identify orthographic or phonetic vulnerability of the proposed name to be misinterpreted by healthcare practitioners.

In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, inpatient medication orders and/or outpatient prescriptions are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. These orders are optically scanned and one prescription is delivered to a random sample of participating health professionals via e-mail. In addition, a verbal prescription is recorded on voice mail. The voice mail messages are 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 record their interpretations of the orders which are recorded electronically.

4. Comments from Other Review Disciplines

DMEPA requests the Office of New Drugs (OND) and/or Office of Generic Drugs (OGD), ONDQA or OBP for their comments or concerns with the proposed proprietary name, ask for any clinical issues that may impact the DMEPA review during the initial phase of the name review. Additionally, when applicable, at the same time DMEPA requests concurrence/non-

concurrence with OPDP's decision on the name. The primary Safety Evaluator addresses any comments or concerns in the safety evaluator's assessment.

The OND/OGD Regulatory Division is contacted a second time following our analysis of the proposed proprietary name. At this point, DMEPA conveys their decision to accept or reject the name. The OND or OGD Regulatory Division is requested to provide any further information that might inform DMEPA's final decision on the proposed name.

Additionally, other review disciplines opinions such as ONDQA or OBP may be considered depending on the proposed proprietary name.

5. Safety Evaluator Risk Assessment of the Proposed Proprietary Name

The primary Safety Evaluator applies his/her individual expertise gained from evaluating medication errors reported to FDA, considers all aspects of the name that may be misleading or confusing, conducts a Failure Mode and Effects Analysis, and provides an overall decision on acceptability dependent on their risk assessment of name confusion. Failure Mode and Effects Analysis (FMEA) is a systematic tool for evaluating a process and identifying where and how it might fail.[3] When applying FMEA to assess the risk of a proposed proprietary name, DMEPA seeks to evaluate the potential for a proposed proprietary name to be confused with another drug name because of name confusion and, thereby, cause errors to occur in the medication use system. FMEA capitalizes on the predictable and preventable nature of medication errors associated with drug name confusion. FMEA allows the Agency to identify the potential for medication errors due to orthographically or phonetically similar drug names prior to approval, where actions to overcome these issues are easier and more effective than remedies available in the post-approval phase.

In order to perform an FMEA of the proposed name, the primary Safety Evaluator must analyze the use of the product at all points in the medication use system. Because the proposed product is has not been marketed, the primary Safety Evaluator anticipates the use of the product in the usual practice settings by considering the clinical and product characteristics listed in Section 1.2 of this review. The Safety Evaluator then analyzes the proposed proprietary name in the context of the usual practice setting and works to identify potential failure modes and the effects associated with the failure modes.

In the initial stage of the Risk Assessment, the Safety Evaluator compares the proposed proprietary name to all of the names gathered from the above searches, Expert Panel Discussion, and prescription studies, external studies, and identifies potential failure modes by asking:

> ***"Is the proposed proprietary name convincingly similar to another drug name, which may cause practitioners to become confused at any point in the usual practice setting? And are there any components of the name that may function as a source of error beyond sound/look-alike?"***

An affirmative answer indicates a failure mode and represents a potential for the proposed proprietary name to be confused with another proprietary or established drug name because

[3] Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

of look- or sound-alike similarity or because of some other component of the name. If the answer to the question is no, the Safety Evaluator is not convinced that the names posses similarity that would cause confusion at any point in the medication use system, thus the name is eliminated from further review.

In the second stage of the Risk Assessment, the primary Safety Evaluator evaluates all potential failure modes to determine the likely *effect* of the drug name confusion, by asking:

> ***"Could the confusion of the drug names conceivably result in medication errors in the usual practice setting?"***

The answer to this question is a central component of the Safety Evaluator's overall risk assessment of the proprietary name. If the Safety Evaluator determines through FMEA that the name similarity would not ultimately be a source of medication errors in the usual practice setting, the primary Safety Evaluator eliminates the name from further analysis. However, if the Safety Evaluator determines through FMEA that the name similarity could ultimately cause medication errors in the usual practice setting, the Safety Evaluator will then recommend the use of an alternate proprietary name.

Moreover, DMEPA will object to the use of proposed proprietary name when the primary Safety Evaluator identifies one or more of the following conditions in the Overall Risk Assessment:

a. OPDP finds the proposed proprietary name misleading from a promotional perspective, and the Review Division concurs with OPDP's findings. The Federal Food, Drug, and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made or suggested by statement, word, design, device, or any combination thereof, whether through a PROPRIETARY name or otherwise [21 U.S.C 321(n); See also 21 U.S.C. 352(a) & (n)].

b. DMEPA identifies that the proposed proprietary name is misleading because of similarity in spelling or pronunciation to another proprietary or established name of a different drug or ingredient [CFR 201.10.(C)(5)].

c. FMEA identifies the potential for confusion between the proposed proprietary name and other proprietary or established drug name(s), and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.

d. The proposed proprietary name contains an USAN (United States Adopted Names) stem.

e. DMEPA identifies a potential source of medication error within the proposed proprietary name. For example, the proprietary name may be misleading or, inadvertently, introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug and another drug product but involve a naming characteristic that when incorporated into a proprietary name may be confusing, misleading, cause or contribute to medication errors.

If DMEPA objects to a proposed proprietary name on the basis that drug name confusion could lead to medication errors, the primary Safety Evaluator uses the FMEA process to identify strategies to reduce the risk of medication errors. DMEPA generally recommends that the Sponsor select an alternative proprietary name and submit the alternate name to the

Agency for review. However, in rare instances FMEA may identify plausible strategies that could reduce the risk of medication error of the currently proposed name. In that instance, DMEPA may be able to provide the Sponsor with recommendations that reduce or eliminate the potential for error and, thereby, would render the proposed name acceptable.

In the event that DMEPA objects to the use of the proposed proprietary name, based upon the potential for confusion with another proposed (but not yet approved) proprietary name, DMEPA will provide a contingency objection based on the date of approval. Whichever product, the Agency approves first has the right to use the proprietary name, while DMEPA will recommend that the second product to reach approval seek an alternative name.

The threshold set for objection to the proposed proprietary name may seem low to the Applicant/Sponsor. However, the safety concerns set forth in criteria a through e above are supported either by FDA regulation or by external healthcare authorities, including the Institute of Medicine (IOM), World Health Organization (WHO), the Joint Commission, and the Institute for Safe Medication Practices (ISMP). These organizations have examined medication errors resulting from look- or sound-alike drug names, confusing, or misleading names and called for regulatory authorities to address the issue prior to approval. Additionally, DMEPA contends that the threshold set for the Proprietary Name Risk Assessment is reasonable because proprietary drug name confusion is a predictable and preventable source of medication error that, in many instances, the Agency and/or Sponsor can identify and rectify prior to approval to avoid patient harm.

Furthermore, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to rectify post-approval. Educational and other post-approval efforts are low-leverage strategies that have had limited effectiveness at alleviating medication errors involving drug name confusion. Sponsors have undertaken higher-leverage strategies, such as drug name changes, in the past but at great financial cost to the Sponsor and at the expense of the public welfare, not to mention the Agency's credibility as the authority responsible for approving the error-prone proprietary name. Moreover, even after Sponsors' have changed a product's proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from practitioners' vocabulary, and as a result, the Agency has continued to receive reports of drug name confusion long after a name change in some instances. Therefore, DMEPA believes that post-approval efforts at reducing name confusion errors should be reserved for those cases in which the potential for name confusion could not be predicted prior to approval.

Appendix B: Letters with Possible Orthographic or Phonetic Misinterpretation

Letters in Name, Levemir FlexTouch	**Scripted may appear as**	**Spoken may be interpreted as**
Capital 'L'	I, S, T, or Z	w
lower case 'e'	l, p, any vowel	any vowel
lower case 'v'	n, u, r	b, f
lower case 'e'	l, p, any vowel	any vowel
lower case 'm'	rn, nn, n, v, w, vi, onc, z	'n'
lower case 'i'	any vowel	any vowel
lower case 'r'	s, n, m, e, v	
Capital 'F'	T	'P'
lower case 'l'	b, e, s, A, P, i	
lower case 'e'	l, p, any vowel	any vowel
lower case 'x'	f, k, r, t, or v	'cks'
Capital 'T'	F, I, or Z	'D' or 'B'
lower case 'o'	a, c, e, u	'Oh' or any vowel
lower case 'u'	a, e, c, i, or l	any vowel
lower case 'c'	a, e, s, or u	'k'
lower case 'h'	b, n, or k	--

Appendix C: Prescription Simulation Samples and Results

Figure 1. Levemir FlexTouch Study (Conducted on *June 14, 2013*)

Handwritten Requisition Medication Order	Verbal Prescription
Medication Order: Levemir FlexTouch 10 units subq at bedtime	Levemir FlexTouch Use as directed #2
Outpatient Prescription: Levemir Flextouch Sig: UAD Disp: #2	

FDA Prescription Simulation Responses (Aggregate 1 Rx Studies Report)

191 People Received Study

73 People Responded

Study Name: Levemir FlexTouch

Total	30	21	22	
INTERPRETATION	OUTPATIENT	VOICE	INPATIENT	TOTAL
LEAVAMEIR	0	1	0	1
LEVAMERE FLEX TOUCH	0	1	0	1
LEVAMERE FLEXTOUCH	0	1	0	1
LEVAMIR	1	1	0	2
LEVAMIR FLEX TOUCH	0	1	0	1
LEVAMIR FLEXTOUCH	0	2	0	2
LEVEMIR FLEX TOUCH	0	2	2	4
LEVEMIR FLEXPATCH	2	0	0	2
LEVEMIR FLEXTOCIDE	0	0	1	1
LEVEMIR FLEXTOUCH	25	3	13	41

LEVEMIR FLEXTOVEL	0	0	1	1
LEVEMIR FL--TOUCH	0	0	1	1
LEVEMIR FLUXTOUDE	0	0	1	1
LEVEMIRE FLEXTOUCH	0	0	1	1
LEVENIR FLEXTOUCH	0	0	1	1
LEVERMERE FLEX TOUCH	0	2	0	2
LEVERMERE FLEXTOUCH	0	1	0	1
LEVIMEAR FLEXTOUCH	0	1	0	1
LEVIMERE FLEX TOUCH	0	2	0	2
LEVIMERE FLEXTOUCH	0	1	0	1
LEVIMIR FLEXTOUCH	0	1	1	2
LEVONER FLEX TOUCH	0	1	0	1
SEVEMIR FLEXTOUCH	2	0	0	2

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

/s/

REASOL AGUSTIN
08/19/2013

YELENA L MASLOV
08/19/2013

KELLIE A TAYLOR
08/19/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Proprietary Name Review

Date:	April 23, 2012
Reviewer:	Reasol S. Agustin, PharmD Division of Medication Error Prevention and Analysis
Acting Team Leader	Yelena Maslov, PharmD Division of Medication Error Prevention and Analysis
Division Director	Carol Holquist, RPh Division of Medication Error Prevention and Analysis
Drug Name(s) and Strength(s):	Levemir (Insulin Detemir), 100 units/mL (U-100) FlexTouch Pen
Application Type/Number:	NDA 021536/S-033
Applicant/Sponsor:	Novo Nordisk
OSE RCM #:	2012-280

*** This document contains proprietary and confidential information that should not be released to the public.***

CONTENTS

1 INTRODUCTION

This review evaluates the proposed proprietary name, Levemir FlexTouch, from a safety and promotional perspective. The sources and methods used to evaluate the proposed name are outlined in the reference section and Appendix A respectively.

1.1 REGULATORY HISTORY

The Division of Medication Error Prevention and Analysis (DMEPA) previously reviewed the proposed proprietary name Levemir FlexTouch, under NDA 021536/S-033 in OSE Review #2009-2454, dated March 15, 2010. DMEPA found the root name, Levemir and the proposed modifier, FlexTouch, acceptable.

1.2 PRODUCT INFORMATION

In the current resubmission of the proprietary name review request, dated January 26, 2012 the Applicant referred to the December 15, 2009 for the product characteristics. The following product information is provided in the December 15, 2009 proprietary name submission:

- Active Ingredient: Insulin Detemir [rDNA]
- Indication of Use: For the treatment of adult and pediatric patients with Type 1 diabetes mellitus or adult patients with Type 2 diabetes mellitus who require basal (long acting) insulin for the control of hyperglycemia.
- Route of Administration: Subcutaneously
- Dosage Form: Injection in a prefilled pen
- Strength: 100 units/mL
- Dose and Frequency: The dose for insulin varies based on the patients' needs but usual starting dose is 0.1 units/kg to 0.2 units/kg once daily in the evening or 10 units once or twice daily in insulin naïve patients.
- How Supplied: 100 units/mL (U-100) in 3 mL FlexTouch disposable pen injector.
- Storage: The pens and the cartridges are stored between 2° and 8° C (36° and 46° F). After initial use, the product may be stored at room temperature, below 30° C (86° F) for up to four weeks.
- Container and Closure Systems: The disposable pen-injector is the PDS290 device

2. RESULTS

The following sections provide the information obtained and considered in the evaluation of the proposed proprietary name.

2.1 PROMOTIONAL ASSESSMENT

The Office of Prescription Drug Promotion (OPDP) determined the proposed name is acceptable from a promotional perspective. DMEPA and the Division of Metabolism and

Endocrinology Products (DMEP) concurred with the findings of OPDP's promotional assessment of the proposed name.

2.2 SAFETY ASSESSMENT

The following aspects of the name were considered in the overall safety evaluation.

2.2.1 United States Adopted Names (USAN) SEARCH

On February 23, 2012 the United States Adopted Name (USAN) stem search, identified that a USAN stem is not present in the proposed proprietary name.

2.2.2 Components of the Proposed Proprietary Name

The Applicant, Novo Nordisk, noted that the root name, Levemir, was not derived from one particular concept and is a currently approved name of a drug. The Applicant also noted that the modifier "FlexTouch" represents the new delivery device. This modifier is a combination of "flexible" and "touch". "Flexible" represents flexible dosing available in the pen. "Touch" represents improvements upon the design of the current Levemir® FlexPen®. Therefore, the name is not trying to convey any specific meaning to the device or drug that could be misinterpreted at any point in the medication use process. Since the currently marketed device, FlexPen and the new device, FlexTouch are both prefilled pen-injectors used for the same indication of use, route of administration, concentration, quantity, and method of use, the sole purpose of the modifier FlexTouch is to differentiate this new device from the other products in the Levemir family (e.g. Levemir FlexPen, and Levemir vials).

The modifier, FlexTouch, was evaluated in conjunction with the proposed proprietary name, Levemir, as well as separately for vulnerabilities for confusion that could lead to medication errors under NDA 021536/S-033 in OSE Review #2009-2454 dated March 15, 2010. The modifier was found acceptable. As a result, the name Levemir FlexTouch was found acceptable.

2.2.3 Medication Error Data Selection of Cases

DMEPA searched AERS database for medication errors involving Levemir which would be relevant for this review. The February 23, 2012 search of the Adverse Event Reporting System (AERS) database used the following search terms: Trade name "Levemir" and verbatim term "Levem%." The reaction terms used were the MedDRA High Level Group Terms (HLGT) "Medication Errors" and "Product Quality Issues." Since DMEPA previously performed an AERS search for Levemir on January 22, 2010 to identify medication errors related to this product and described these errors in OSE Review #2009-2454, dated March 15, 2010,.we limited our AERS search from January 23, 2010 to February 23, 2012.

Each report was reviewed for relevancy and duplication. Duplicates were merged into a single case. The NCC MERP Taxonomy of Medication Errors was used to code the type and contributing factors to the error when provided by the reporter.

After individual review, 43 reports were not included in the final analysis for the following reasons: reports of a defective device or product quality issue without a medication error, reports of an intentional overdose, reports of an adverse event without a medication error,

reports related to the use of expired product, and report of products not marketed in the US and not relevant to this review.

Following exclusions, the search yielded no relevant cases.

2.2.4 FDA Name Simulation Studies

Twenty-three practitioners participated in DMEPA's prescription studies. The interpretations did not overlap with or appear or sound similar to any currently marketed products. Five out of 8 inpatient participants interpreted the proposed root name, Levemir correctly. The most common misinterpretation occurred with participants misinterpreting the letter 'v' for 'r' in 'Le*V*emir'. All 8 inpatient participants interpreted the modifier, FlexTouch correctly.

None of the 7 voice study participants interpreted the root name, Levemir, correctly. The most common misinterpretation occurred with participants misinterpreting the letter 'e' for 'a' in 'Lev*E*mir'. All 7 voice study participants interpreted the modifier, FlexTouch, correctly.

Five out of 8 outpatient participants interpreted the proposed root name, Levemir, correctly. The most common misinterpretation occurred with participants misinterpreting the letter 'm' for 'n' in 'Leve*M*ir'. All 8 outpatient participants interpreted the modifier, FlexTouch, correctly. See Appendix C for the complete listing of interpretations from the verbal and written prescription studies.

2.2.5 Comments from Other Review Disciplines

In response to the OSE, February 22, 2012 e-mail, the Division of Metabolism and Endocrinology Products (DMEP) did not forward any comments or concerns relating to the proposed name at the initial phase of the proprietary name review.

2.2.6 Failure Mode and Effects Analysis of Similar Names

Appendix B lists possible orthographic and phonetic misinterpretations of the letters appearing in the proposed proprietary name, Levemir FlexTouch. Table 1 lists the names with orthographic, phonetic, or spelling similarity to the proposed proprietary name, Levemir FlexTouch identified by the primary reviewer, the Expert Panel Discussion (EPD), and other review disciplines.

Table 1: Collective List of Potentially Similar Names (DMEPA, EPD, Other Disciplines, FDA Name Simulation Studies, and External Name Study if applicable).

Look Similar to FlexTouch					
Name	***Source***	***Name***	***Source***	***Name***	***Source***
FlexPen	FDA	Flexicort	FDA	PenFill	FDA
Flexeril	FDA			[redacted]	[redacted]
Look Similar To Levemir FlexTouch					
Levonorgestrel	FDA	[redacted]	[redacted]	[redacted]	[redacted]
Look and Sound Similar					
FlexTouch	FDA	Levemir	FDA	[redacted]	[redacted]

Since root name "Levemir" is already marketed, we evaluated the modifier "FlexTouch" through FMEA and the proposed proprietary name as one name "Levemir FlexTouch." Our analysis of the seven names contained in Table 1 considered the information obtained in the previous sections along with their product characteristics. We determined all 7 names will not pose a risk for confusion as described in Appendix D through E.

2.2.7 Communication of DMEPA's Final Decision to Other Disciplines

DMEPA communicated our findings to the Division of Metabolism and Endocrinology Products (DMEP) via e-mail on February 23, 2012. At that time we also requested additional information or concerns that could inform our review. Per e-mail correspondence from the Division of Metabolism and Endocrinology Products (DMEP) on March 7, 2012, they stated no additional concerns with the proposed proprietary name, Levemir FlexTouch.

3 DISCUSSION

The proposed Levemir FlexTouch Pen represents improvements upon the design of the current Levemir FlexPen. The improvements include a decrease in the push button displacement from 33 mm for FlexPen® down to 0 mm for FlexTouch® pen at the maximum dose setting. This change reduces the distance that the user would need to extend their finger in order to depress the push button, especially for administering larger doses. Additionally, there is also an end-of-dose click which provides feedback to the user of when the selected dose has been completely injected. This is a new feature found only in FlexTouch® pen. It is unlikely that these differences will contribute to dosing errors if these two pens are confused for one another. However, we anticipate product selection errors between the Levemir FlexTouch and Levemir FlexPen because of the similar trade dress, similar names, similar pen colors, and the co-marketing of both products. The Sponsor plans to transition from FlexPen to the FlexTouch [redacted] (b) (4) post approval. To minimize the potential confusion anticipated from the general lack of awareness to the marketing of the new Levemir FlexTouch product, the Applicant should take steps to increase practitioner's awareness of

the introduction of this new pen and increase awareness of the transition that will occur on the market over the year following product launch.

3.1 Root Name Evaluation

The proposed proprietary name, Levemir, was submitted with a modifier, FlexTouch. The root name, Levemir was reviewed by DMEPA in OSE Consult #02-0222, dated June 4, 2003 and OSE Consult #02-0222, dated February 6, 2004. In both reviews, the proprietary name was found unacceptable due to orthographic and product characteristics similarities to Love ox. However, the Division of Metabolism and Endocrinology products overturned DMEPA's recommendation and accepted the proprietary name, Levemir on June 16, 2005. Since approval, Levemir has been marketed as Levemir (vial) and Levemir PenFill.

3.2 Modifier Evaluation

The proposed modifier, FlexTouch, was reviewed by DMEPA in OSE Review #2009-2454, dated March 15, 2010, where the modifier was found acceptable from a promotional and safety perspective.

4 CONCLUSIONS

The proposed proprietary name is acceptable from both a promotional and safety perspective.

If you have further questions or need clarifications, please contact Margarita Tossa, OSE project manager, at 301-796-4053.

4.1 COMMENTS TO THE APPLICANT

We have completed our review of the proposed proprietary name, Levemir FlexTouch, and have concluded that this name is acceptable. However, if any of the proposed product characteristics as stated in your January 26, 2012 submission are altered, DMEPA rescinds this finding and the name must be resubmitted for review.

Additionally, the proposed proprietary name must be re-reviewed 90 days prior to approval of the NDA. The conclusions upon re-review are subject to change.

5 REFERENCES

1. ***Micromedex Integrated Index (http://csi.micromedex.com)***

   Micromedex contains a variety of databases covering pharmacology, therapeutics, toxicology and diagnostics.

2. ***Phonetic and Orthographic Computer Analysis (POCA)***

   POCA is a database which was created for the Division of Medication Error Prevention and Analysis, FDA. 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. Likewise, an orthographic algorithm exists which operates in a similar fashion.

3. ***Drug Facts and Comparisons, online version, St. Louis, MO (http://factsandcomparisons.com)***

   Drug Facts and Comparisons is a compendium organized by therapeutic course; it contains monographs on prescription and OTC drugs, with charts comparing similar products. This database also lists the orphan drugs.

4. ***FDA Document Archiving, Reporting & Regulatory Tracking System [DARRTS]***

   DARRTS is a government database used to organize Applicant and Sponsor submissions as well as to store and organize assignments, reviews, and communications from the review divisions.

5. ***Division of Medication Errors Prevention and Analysis proprietary name consultation requests***

   This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention and Analysis from the Access database/tracking system.

6. ***Drugs@FDA (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm)***

   Drugs@FDA contains most of the drug products approved since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA approved brand name, generic drugs, therapeutic biological products, prescription and over-the-counter human drugs and discontinued drugs and "Chemical Type 6" approvals.

7. ***U.S. Patent and Trademark Office (http://www.uspto.gov)***

   USPTO provides information regarding patent and trademarks.

8. ***Clinical Pharmacology Online (www.clinicalpharmacology-ip.com)***

   Clinical Pharmacology contains full monographs for the most common drugs in clinical use, plus mini monographs covering investigational, less common, combination, nutraceutical and nutritional products. It also provides a keyword search engine.

9. ***Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at (www.thomson-thomson.com)***

   The Pharma In-Use Search database contains over 400,000 unique pharmaceutical trademarks and trade names that are used in about 50 countries worldwide. The data is provided under license by IMS HEALTH.

10. ***Natural Medicines Comprehensive Databases (www.naturaldatabase.com)***

    Natural Medicines contains up-to-date clinical data on the natural medicines, herbal medicines, and dietary supplements used in the western world.

11. ***Access Medicine (www.accessmedicine.com)***

    Access Medicine® from McGraw-Hill contains full-text information from approximately 60 titles; it includes tables and references. Among the titles are: Harrison's Principles of Internal Medicine, Basic & Clinical Pharmacology, and Goodman and Gilman's The Pharmacologic Basis of Therapeutics.

12. ***USAN Stems (http://www.ama-assn.org/ama/pub/about-ama/our-people/coalitions-consortiums/united-states-adopted-names-council/naming-guidelines/approved-stems.shtml)***

    USAN Stems List contains all the recognized USAN stems.

13. ***Red Book (www.thomsonhc.com/home/dispatch)***

    Red Book contains prices and product information for prescription, over-the-counter drugs, medical devices, and accessories.

14. ***Lexi-Comp (www.lexi.com)***

    Lexi-Comp is a web-based searchable version of the Drug Information Handbook.

15. ***Medical Abbreviations (www.medilexicon.com)***

    Medical Abbreviations dictionary contains commonly used medical abbreviations and their definitions.

16. ***CVS/Pharmacy (www.CVS.com)***

    This database contains commonly used over the counter products not usually identified in other databases.

17. Walgreens (www.walgreens.com)

This database contains commonly used over the counter products not usually identified in other databases.

18. Rx List (www.rxlist.com)

RxList is an online medical resource dedicated to offering detailed and current pharmaceutical information on brand and generic drugs.

19. Dogpile (www.dogpile.com)

Dogpile is a Metasearch engine that searches multiple search engines including Google, Yahoo! and Bing, and returns the most relevant results to the search.

APPENDICES

Appendix A

FDA's Proprietary Name Risk Assessment considers the promotional and safety aspects of a proposed proprietary name. The promotional review of the proposed name is conducted by OPDP. OPDP evaluates proposed proprietary names to determine if they are overly fanciful, so as to misleadingly imply unique effectiveness or composition, as well as to assess whether they contribute to overstatement of product efficacy, minimization of risk, broadening of product indications, or making of unsubstantiated superiority claims. OPDP provides their opinion to DMEPA for consideration in the overall acceptability of the proposed proprietary name.

The safety assessment is conducted by DMEPA. DMEPA staff search a standard set of databases and information sources to identify names that are similar in pronunciation, spelling, and orthographically similar when scripted to the proposed proprietary name. Additionally, we consider inclusion of USAN stems or other characteristics that when incorporated into a proprietary name may cause or contribute to medication errors (i.e., dosing interval, dosage form/route of administration, medical or product name abbreviations, names that include or suggest the composition of the drug product, etc.). DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [1]

Following the preliminary screening of the proposed proprietary name, DMEPA gathers to discuss their professional opinions on the safety of the proposed proprietary name. This meeting is commonly referred to the Center for Drug Evaluation and Research (CDER) Expert Panel discussion. DMEPA also considers other aspects of the name that may be misleading from a safety perspective. DMEPA staff conducts a prescription simulation studies using FDA health care professionals. When provided, DMEPA considers external proprietary name studies conducted by or for the Applicant/Sponsor and incorporates the findings of these studies into the overall risk assessment.

The DMEPA primary reviewer assigned to evaluate the proposed proprietary name is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name. DMEPA bases the overall risk assessment on the findings of a Failure Mode and Effects Analysis (FMEA) of the proprietary name and misleading nature of the proposed proprietary name with a focus on the avoidance of medication errors.

DMEPA uses the clinical expertise of its staff to anticipate the conditions of the clinical setting where the product is likely to be used based on the characteristics of the proposed product. DMEPA considers the product characteristics associated with the proposed product throughout the risk assessment because the product characteristics of the proposed may provide a context for communication of the drug name and ultimately determine the use of the product in the *usual* clinical practice setting.

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[1] National Coordinating Council for Medication Error Reporting and Prevention. http://www.nccmerp.org/aboutMedErrors.html. Last accessed 10/11/2007.

Typical product characteristics considered when identifying drug names that could potentially be confused with the proposed proprietary name include, but are not limited to; established name of the proposed product, proposed indication of use, dosage form, route of administration, strength, unit of measure, dosage units, recommended dose, typical quantity or volume, frequency of administration, product packaging, storage conditions, patient population, and prescriber population. DMEPA considers how these product characteristics may or may not be present in communicating a product name throughout the medication use system. Because drug name confusion can occur at any point in the medication use process, DMEPA considers the potential for confusion throughout the entire U.S. medication use process, including drug procurement, prescribing and ordering, dispensing, administration, and monitoring the impact of the medication.[2]

The DMEPA considers the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. DMEPA compares the proposed proprietary name with the proprietary and established name of existing and proposed drug products and names currently under review at the FDA. DMEPA compares the pronunciation of the proposed proprietary name with the pronunciation of other drug names because verbal communication of medication names is common in clinical settings. DMEPA examines the phonetic similarity using patterns of speech. If provided, DMEPA will consider the Sponsor's intended pronunciation of the proprietary name. However, DMEPA also considers a variety of pronunciations that could occur in the English language because the Sponsor has little control over how the name will be spoken in clinical practice. The orthographic appearance of the proposed name is evaluated using a number of different handwriting samples. DMEPA applies expertise gained from root-cause analysis of postmarketing medication errors to identify sources of ambiguity within the name that could be introduced when scripting (e.g.,"T" may look like "F," lower case 'a' looks like a lower case 'u,' etc). Additionally, other orthographic attributes that determine the overall appearance of the drug name when scripted (see Table 1 below for details).

Table 1. Criteria Used to Identify Drug Names that Look- or Sound-Similar to a Proposed Proprietary Name.

Type of Similarity	**Considerations when Searching the Databases**		
	Potential Causes of Drug Name Similarity	*Attributes Examined to Identify Similar Drug Names*	*Potential Effects*

[2] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006.

Look-alike	Similar spelling	Identical prefix Identical infix Identical suffix Length of the name Overlapping product characteristics	• Names may appear similar in print or electronic media and lead to drug name confusion in printed or electronic communication • Names may look similar when scripted and lead to drug name confusion in written communication
	Orthographic similarity	Similar spelling Length of the name/Similar shape Upstrokes Down strokes Cross-strokes Dotted letters Ambiguity introduced by scripting letters Overlapping product characteristics	• Names may look similar when scripted, and lead to drug name confusion in written communication
Sound-alike	Phonetic similarity	Identical prefix Identical infix Identical suffix Number of syllables Stresses Placement of vowel sounds Placement of consonant sounds Overlapping product characteristics	• Names may sound similar when pronounced and lead to drug name confusion in verbal communication

Lastly, DMEPA considers the potential for the proposed proprietary name to inadvertently function as a source of error for reasons other than name confusion. Post-marketing experience has demonstrated that proprietary names (or components of the proprietary name) can be a source of error in a variety of ways. Consequently, DMEPA considers and evaluates these broader safety implications of the name throughout this assessment and the medication error staff provides additional comments related to the safety of the proposed proprietary name or product based on professional experience with medication errors.

1. Database and Information Sources

DMEPA searches the internet, several standard published drug product reference texts, and FDA databases to identify existing and proposed drug names that may sound-alike or look-alike to the proposed proprietary name. A standard description of the databases used in the searches is provided in the reference section of this review. To complement the process, the DMEPA uses a computerized method of identifying phonetic and orthographic similarity between medication names. The program, Phonetic and Orthographic Computer Analysis

(POCA), uses complex algorithms to select a list of names from a database that have some similarity (phonetic, orthographic, or both) to the trademark being evaluated. Lastly, DMEPA reviews the USAN stem list to determine if any USAN stems are present within the proprietary name. The individual findings of multiple safety evaluators are pooled and presented to the CDER Expert Panel. DMEPA also evaluates if there are characteristics included in the composition that may render the name unacceptable from a safety perspective (abbreviation, dosing interval, etc.).

2. Expert Panel Discussion

DMEPA gathers gather CDER professional opinions on the safety of the proposed product and discussed the proposed proprietary name (Expert Panel Discussion). The Expert Panel is composed of Division of Medication Errors Prevention (DMEPA) staff and representatives from the Office of Prescription Drug Promotion (OPDP). We also consider input from other review disciplines (OND, ONDQA/OBP). The Expert Panel also discusses potential concerns regarding drug marketing and promotion related to the proposed names.

The primary Safety Evaluator presents the pooled results of the database and information searches to the Expert Panel for consideration. Based on the clinical and professional experiences of the Expert Panel members, the Panel may recommend additional names, additional searches by the primary Safety Evaluator to supplement the pooled results, or general advice to consider when reviewing the proposed proprietary name.

3. FDA Prescription Simulation Studies

Three separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of the proposed proprietary name with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. The studies employ healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The primary Safety Evaluator uses the results to identify orthographic or phonetic vulnerability of the proposed name to be misinterpreted by healthcare practitioners.

In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, inpatient medication orders and/or outpatient prescriptions are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. These orders are optically scanned and one prescription is delivered to a random sample of participating health professionals via e-mail. In addition, a verbal prescription is recorded on voice mail. The voice mail messages are 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 record their interpretations of the orders which are recorded electronically.

4. Comments from Other Review Disciplines

DMEPA requests the Office of New Drugs (OND) and/or Office of Generic Drugs (OGD), ONDQA or OBP for their comments or concerns with the proposed proprietary name, ask for any clinical issues that may impact the DMEPA review during the initial phase of the name review. Additionally, when applicable, at the same time DMEPA requests concurrence/non-

concurrence with OPDP's decision on the name. The primary Safety Evaluator addresses any comments or concerns in the safety evaluator's assessment.

The OND/OGD Regulatory Division is contacted a second time following our analysis of the proposed proprietary name. At this point, DMEPA conveys their decision to accept or reject the name. The OND or OGD Regulatory Division is requested to provide any further information that might inform DMEPA's final decision on the proposed name.

Additionally, other review disciplines opinions such as ONDQA or OBP may be considered depending on the proposed proprietary name.

5. Safety Evaluator Risk Assessment of the Proposed Proprietary Name

The primary Safety Evaluator applies his/her individual expertise gained from evaluating medication errors reported to FDA, considers all aspects of the name that may be misleading or confusing, conducts a Failure Mode and Effects Analysis, and provides an overall decision on acceptability dependent on their risk assessment of name confusion. Failure Mode and Effects Analysis (FMEA) is a systematic tool for evaluating a process and identifying where and how it might fail.[3] When applying FMEA to assess the risk of a proposed proprietary name, DMEPA seeks to evaluate the potential for a proposed proprietary name to be confused with another drug name because of name confusion and, thereby, cause errors to occur in the medication use system. FMEA capitalizes on the predictable and preventable nature of medication errors associated with drug name confusion. FMEA allows the Agency to identify the potential for medication errors due to orthographically or phonetically similar drug names prior to approval, where actions to overcome these issues are easier and more effective than remedies available in the post-approval phase.

In order to perform an FMEA of the proposed name, the primary Safety Evaluator must analyze the use of the product at all points in the medication use system. Because the proposed product is has not been marketed, the primary Safety Evaluator anticipates the use of the product in the usual practice settings by considering the clinical and product characteristics listed in Section 1.2 of this review. The Safety Evaluator then analyzes the proposed proprietary name in the context of the usual practice setting and works to identify potential failure modes and the effects associated with the failure modes.

In the initial stage of the Risk Assessment, the Safety Evaluator compares the proposed proprietary name to all of the names gathered from the above searches, Expert Panel Discussion, and prescription studies, external studies, and identifies potential failure modes by asking:

> ***"Is the proposed proprietary name convincingly similar to another drug name, which may cause practitioners to become confused at any point in the usual practice setting? And are there any components of the name that may function as a source of error beyond sound/look-alike?"***

An affirmative answer indicates a failure mode and represents a potential for the proposed proprietary name to be confused with another proprietary or established drug name because

[3] Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

of look- or sound-alike similarity or because of some other component of the name. If the answer to the question is no, the Safety Evaluator is not convinced that the names posses similarity that would cause confusion at any point in the medication use system, thus the name is eliminated from further review.

In the second stage of the Risk Assessment, the primary Safety Evaluator evaluates all potential failure modes to determine the likely *effect* of the drug name confusion, by asking:

> ***"Could the confusion of the drug names conceivably result in medication errors in the usual practice setting?"***

The answer to this question is a central component of the Safety Evaluator's overall risk assessment of the proprietary name. If the Safety Evaluator determines through FMEA that the name similarity would not ultimately be a source of medication errors in the usual practice setting, the primary Safety Evaluator eliminates the name from further analysis. However, if the Safety Evaluator determines through FMEA that the name similarity could ultimately cause medication errors in the usual practice setting, the Safety Evaluator will then recommend the use of an alternate proprietary name.

Moreover, DMEPA will object to the use of proposed proprietary name when the primary Safety Evaluator identifies one or more of the following conditions in the Overall Risk Assessment:

a. OPDP finds the proposed proprietary name misleading from a promotional perspective, and the Review Division concurs with OPDP's findings. The Federal Food, Drug, and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made or suggested by statement, word, design, device, or any combination thereof, whether through a PROPRIETARY name or otherwise [21 U.S.C 321(n); See also 21 U.S.C. 352(a) & (n)].

b. DMEPA identifies that the proposed proprietary name is misleading because of similarity in spelling or pronunciation to another proprietary or established name of a different drug or ingredient [CFR 201.10.(C)(5)].

c. FMEA identifies the potential for confusion between the proposed proprietary name and other proprietary or established drug name(s), and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.

d. The proposed proprietary name contains an USAN (United States Adopted Names) stem.

e. DMEPA identifies a potential source of medication error within the proposed proprietary name. For example, the proprietary name may be misleading or, inadvertently, introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug and another drug product but involve a naming characteristic that when incorporated into a proprietary name may be confusing, misleading, cause or contribute to medication errors.

If DMEPA objects to a proposed proprietary name on the basis that drug name confusion could lead to medication errors, the primary Safety Evaluator uses the FMEA process to identify strategies to reduce the risk of medication errors. DMEPA generally recommends that the Sponsor select an alternative proprietary name and submit the alternate name to the

Agency for review. However, in rare instances FMEA may identify plausible strategies that could reduce the risk of medication error of the currently proposed name. In that instance, DMEPA may be able to provide the Sponsor with recommendations that reduce or eliminate the potential for error and, thereby, would render the proposed name acceptable.

In the event that DMEPA objects to the use of the proposed proprietary name, based upon the potential for confusion with another proposed (but not yet approved) proprietary name, DMEPA will provide a contingency objection based on the date of approval. Whichever product, the Agency approves first has the right to use the proprietary name, while DMEPA will recommend that the second product to reach approval seek an alternative name.

The threshold set for objection to the proposed proprietary name may seem low to the Applicant/Sponsor. However, the safety concerns set forth in criteria a through e above are supported either by FDA regulation or by external healthcare authorities, including the Institute of Medicine (IOM), World Health Organization (WHO), the Joint Commission, and the Institute for Safe Medication Practices (ISMP). These organizations have examined medication errors resulting from look- or sound-alike drug names, confusing, or misleading names and called for regulatory authorities to address the issue prior to approval. Additionally, DMEPA contends that the threshold set for the Proprietary Name Risk Assessment is reasonable because proprietary drug name confusion is a predictable and preventable source of medication error that, in many instances, the Agency and/or Sponsor can identify and rectify prior to approval to avoid patient harm.

Furthermore, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to rectify post-approval. Educational and other post-approval efforts are low-leverage strategies that have had limited effectiveness at alleviating medication errors involving drug name confusion. Sponsors have undertaken higher-leverage strategies, such as drug name changes, in the past but at great financial cost to the Sponsor and at the expense of the public welfare, not to mention the Agency's credibility as the authority responsible for approving the error-prone proprietary name. Moreover, even after Sponsors' have changed a product's proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from practitioners' vocabulary, and as a result, the Agency has continued to receive reports of drug name confusion long after a name change in some instances. Therefore, DMEPA believes that post-approval efforts at reducing name confusion errors should be reserved for those cases in which the potential for name confusion could not be predicted prior to approval.

Appendix B: Letters with Possible Orthographic or Phonetic Misinterpretation

Letters in Name, Levemir FlexTouch	Scripted may appear as	Spoken may be interpreted as
Capital 'L'	I, S, T, or Z	w
lower case 'e'	l, p, any vowel	any vowel
lower case 'v'	n, u, r	b, f
lower case 'e'	l, p, any vowel	any vowel
lower case 'm'	rn, nn, n, v, w, vi, onc, z	'n'
lower case 'i'	any vowel	any vowel
lower case 'r'	s, n, m, e, v	
Capital 'F'	T	'P'
lower case 'l'	b, e, s, A, P, i	
lower case 'e'	l, p, any vowel	any vowel
lower case 'x'	f, k, r, t, or v	'cks'
Capital 'T'	F, I, or Z	'D' or 'B'
lower case 'o'	a, c, e, u	'Oh' or any vowel
lower case 'u'	a, e, c, i, or l	any vowel
lower case 'c'	a, e, s, or u	'k'
lower case 'h'	b, n, or k	--

Appendix C: Prescription Simulation Samples and Results

Figure 1. Levemir FlexTouch Study (Conducted on *February* 15, 2012)

Handwritten Requisition Medication Order	**Verbal Prescription**
Medication Order: Levemir Flextouch 20 units subQ at bedtime	Levemir FlexTouch Use as directed #2
Outpatient Prescription: Levemir Flextouch UAD #2	

FDA Prescription Simulation Responses (Aggregate 1 Rx Studies Report)

84 People Received Study

23 People Responded

INTERPRETATION	INPATIENT	VOICE	OUTPATIENT	TOTAL
LEREMIR FLEXTOUCH	2	0	0	2
LEVAMIR FLEX TOUCH	0	1	0	1
LEVAMIR FLEXTOUCH	0	3	0	3
LEVEMIR FLEXTOUCH	5	0	5	10
LEVEMIT FLEXTOUCH	1	0	0	1
LEVENIR FLEXTOUCH	0	0	2	2
LEVENVIR FLEXTOUCH #2	0	0	1	1
LEVIMIR FLEXTOUCH	0	1	0	1
LEVOMERE FLEX TOUCH	0	1	0	1
LIVAMIR FLEXTOUCH	0	1	0	1
TOTAL	**8**	**7**	**8**	**23**

Appendix D: Proprietary names not likely to be confused or not used in usual practice settings for the reasons described.

Proprietary Name	Active Ingredient	Similarity to modifier, FlexTouch	Failure preventions
Levemir	Insulin Detemir	Look and Sound	The subject of this review
FlexTouch	Device	Look and Sound	The subject of this review
Plan B	*Levonorgestrel*	Look	The pair have sufficient orthographic differences
PenFill	Device	Look	The pair have sufficient orthographic differences

Appendix E: Risk of medication errors due to product confusion minimized by dissimilarity of the names and/ or use in clinical practice for the reasons described.

Proposed name: **Levemir FlexTouch** **(Insulin Detemir [rDNA origin] Injection)** **Strength(s): U-100 (100 units/mL) in a 3-mL FlexTouch pen device** **Usual dose:** **0.1 to 0.2 units/kg (1 unit to 16 units) once daily in the evening or 10 units once or twice daily. Range is based on 10 kg to 80 kg weight.**	**Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion** **Causes (could be multiple)**	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
FlexPen Device; Modifier used with root name, Levemir. Product currently marketed.	**Orthographic similarity to FlexTouch:** Both begin with the letter string 'Flex' **Device characteristics:** Both represent multiple use, disposable pen and will deliver the same insulin type (i.e. Levemir)	**Orthographic differences to FlexTouch:** FlexTouch (9 letters) appears orthographically longer than FlexPen (7 letters). Although both modifiers share the same first four letters (Flex), the ending letters vary in length (5 letters vs. 3 letters) and word shape which helps to orthographically differentiate the names.
Flexicort (Hydrocortisone) Strength: Topical cream: 2.5%, 1%, 0.5% Usual dose: Apply as directed or Use as directed	**Orthographic similarity to FlexTouch:** Both begin with the letter string 'Flex'	**Orthographic similarity to FlexTouch:** Although both names share the same first four letters 'Flex' the letter string 'Touch' and 'icort' appear orthographically different when scripted. In addition, FlexTouch contains a cross stroke that is absent in Flexicort giving the names different shapes. **Dose: dose specified vs. apply sufficient amount**

Proposed name: **Levemir FlexTouch** **(Insulin Detemir [rDNA origin] Injection)** **Strength(s): U-100 (100 units/mL) in a 3-mL FlexTouch pen device** **Usual dose:** **0.1 to 0.2 units/kg (1 unit to 16 units) once daily in the evening or 10 units once or twice daily. Range is based on 10 kg to 80 kg weight.**	**Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion** **Causes (could be multiple)**	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
Flexeril (Cyclobenzaprine) Strength: Oral Tablets 5 mg, 10 mg Usual dose: Take 5 mg to 10 mg by mouth 3 times daily.	**Orthographic similarity to FlexTouch:** Both begin with the letter string 'Flex'	**Orthographic similarity to FlexTouch:** Although both names share the same first four letters 'Flex' the letter string 'Touch' and 'eril' appear orthographically different when scripted. In addition, FlexTouch contains a cross stroke that is absent in Flexeril giving the names different shapes.

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/s/

REASOL AGUSTIN
04/23/2012

YELENA L MASLOV
04/23/2012

CAROL A HOLQUIST
04/23/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	March 15, 2010
To:	Mary Parks, MD, Director Division of Metabolism and Endocrinology Products
Thru:	Carlos Mena-Grillasca, RPh, Team Leader Denise Toyer, PharmD, Deputy Director Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis (DMEPA)
From:	L. Shenee' Toombs, Pharm.D., Safety Evaluator Division of Medication Error Prevention and Analysis (DMEPA)
Subject:	Proprietary Name Review
Drug Name(s):	Levemir FlexTouch (Insulin Detemir [rDNA origin] Injection) 3 mL Prefilled pen
Application Type/Number:	NDA 021536/S-033
Sponsor:	Novo Nordisk
OSE RCM #:	2009-2454

***** Note: This review contains proprietary and confidential information that should not be released to the public.*****

CONTENTS

EXECUTIVE SUMMARY

The proposed product, Levemir FlexTouch, is a prefilled, multiple-dose, disposable pen that is planned to replace the currently marketed Levemir FlexPen. The proposal to add the modifier "FlexTouch" to the Levemir name for the proposed product to distinguish the new pen from the old pen during the (b) (4) co-marketing transition period is acceptable. The addition of the modifier is reasonable and necessary in this case to distinguish this new product from the currently marketed Levemir products. However, we anticipate medication errors between the old pen and new pen during this limited co-marketing transition period due to the similarity of the pen names, lack of awareness of the new product, similar trade dress and packaging. Although these errors will be limited to the (b) (4) co-marketing period, the Applicant should take steps to increase practitioner and patient awareness of the introduction of this new pen, explain the pen differences and ensure that patients are switched to the new pen during this transition period.

We also noted postmarketing proprietary name confusion between Levemir and Lovenox. This confusion was identified by DMEPA prior to approval of the Levemir name. However, despite our objection, DMEP approved the name. We have determined that the addition of the modifier FlexTouch should not exacerbate the name confusion with the root names. However, we will evaluate the extent of the proprietary name confusion between these two products in a separate review.

DMEPA considers this a final review; however, if approval of the supplement is delayed beyond 90 days from the date of this review, the Division of Metabolism and Endocrinology Products should notify DMEPA because the proprietary name must be re-reviewed prior to the new approval date.

Additionally, if any of the proposed product characteristics as stated in this review are altered, DMEPA rescinds this finding and the name must be resubmitted for review. The conclusions upon re-review are subject to change.

1 BACKGROUND

1.1 INTRODUCTION

This review is written in response to a request from the Novo Nordisk on December 15, 2009, to evaluate the proposed proprietary name, Levemir FlexTouch, regarding potential name confusion with other proprietary or established drug names in the usual practice setting. Novo Nordisk also submitted label and labeling for review, which will be reviewed under separate cover (RCM# 2009-2456).

1.2 PRODUCT INFORMATION

Levemir FlexTouch (Insulin Detemir [rDNA origin] Injection) is a long acting basal insulin analog indicated for once or twice daily subcutaneous administration for the treatment of adult and pediatric patients with Type 1 diabetes mellitus or adult patients with type 2 diabetes mellitus who require basal (long acting) insulin for the control of hyperglycemia. Dose should be individualized and adjusted according to the patient's blood glucose measurement.

Levemir is available in 10 mL vials, 3 mL prefilled cartridges (Levemir PenFill) which is used with Novo Nordisk 3 mL PenFill cartridge compatible insulin delivery devices (i.e. NovoPen), and in prefilled, multiple-use, disposable pens (Levemir FlexPen). Levemir is administered subcutaneously. An auto-insertion accessory is available for the Levemir product line: NovoPenMate for use with Levemir PenFill cartridges.

This supplement provides for the introduction of a new 3-mL prefilled pen, Levemir FlexTouch, in a concentration of 100 units /mL under the Levemir line.

2 METHODS AND MATERIALS

Appendix A describes the general methods and materials used by the Division of Medication Error Prevention and Analysis (DMEPA) when conducting a proprietary name risk assessment for all proprietary names. Sections 2.1, 2.2 and 2.3 identify specific information associated with the methodology for the proposed proprietary name, Levemir FlexTouch.

2.1 SEARCH CRITERIA

For this review, particular consideration was given to drug names beginning with the letters 'L' and 'F' when searching to identify potentially similar drug names, as 75% of the confused drug names reported by the USP-ISMP Medication Error Reporting Program involve pairs beginning with the same letter.[1,2]

To identify drug names that may look similar to Levemir FlexTouch, the DMEPA staff also considers the orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (16 letters, 2 words), upstrokes (5, capital letters 'L', 'F', and 'T', and lower case letters 'l', and 'h'), downstrokes (none), cross-strokes (one, lower case letter 'x'), and dotted letters (one, lower case 'i'). Additionally, several letters in Levemir FlexTouch may be vulnerable to ambiguity when scripted (see Appendix B). As such, the staff also considers these alternate appearances when identifying drug names that may look similar to Levemir FlexTouch.

When searching to identify potential names that may sound similar to Levemir FlexTouch, the DMEPA staff searches for names with similar number of syllables (five), stresses (LE-ve-mir, le-VE-mir, le-ve-MIR, FLEXtouch, flexTOUCH), and placement of vowel and consonant sounds. Additionally, the DMEPA staff considers that pronunciation of parts of the name can vary, such as the letters "le" which may be interpreted as "la"or "lo"; "ve" which may be interpreted as "va", "da", "ve", "vo", "de", or "do", and "Flex" which may be interpreted as "Bex" or "Vex" (see Appendix B). The Sponsor provided their intended pronunciation of the proprietary name (Le-ve-mir Flex-touch) in the proposed name submission and, therefore, it was taken into consideration. However, names are often mispronounced and/or spoken with regional accents and dialects, so other potential pronunciations of the name are considered.

2.2 FDA PRESCRIPTION ANALYSIS STUDIES

In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, the following inpatient medication order, outpatient and verbal prescription was communicated during the FDA prescription studies.

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1 Institute for Safe Medication Practices. Confused Drug name List (1996-2006). Available at http://www.ismp.org/Tools/confuseddrugnames.pdf

2 Kondrack, G and Dorr, B. Automatic Identification of Confusable Drug Names. Artificial Intelligence in Medicine (2005)

Figure 1. Levemir FlexTouch Study (conducted on December 31, 2009)

HANDWRITTEN REQUISITION MEDICATION ORDER	VERBAL PRESCRIPTION
Inpatient Medication Order: Levemir FlexTouch inject 12 units SC once a day	Levemir FlexTouch Inject 12 units subcutaneously once daily Dispense #2
Outpatient Prescription: Levemir FlexTouch Inject 12 units SC once a day # 2	

2.3 FDA PRESCRIPTION ADVERSE EVENT REPORTING SYSTEM (AERS) SELECTION OF CASES

Errors associated with currently marketed Levemir product names were taken into consideration when reviewing the proposed proprietary name Levemir FlexTouch. If confusion between currently marketed Levemir products already exists and leads to medication errors, introduction of the proposed proprietary name Levemir FlexTouch into the marketplace may compound that confusion and also lead to medication errors.

Thus, DMEPA searched the Adverse Event Reporting System (AERS) database on January 22, 2010 using the tradename "Levemir" and verbatim %Levem%" search criteria. The MedDRA High Level Group Term (HGLT) "Medication Errors" was used to perform the search.

The cases were manually reviewed to determine if medication errors occurred. Those cases that did not describe a medication error were excluded from further analysis. For cases describing a medication error, we reviewed the cases to identify factors that contributed to the errors and to ascertain if these risks might apply to the proposed proprietary name Levemir FlexTouch.

3 RESULTS

3.1 DATABASE AND INFORMATION SOURCES

The searches yielded a total of 10 names as having some similarity to the name Levemir FlexTouch.

Three of the ten names, Cevimeline, Vumon and Ionamine were thought to look similar to Levemir FlexTouch. The remaining seven names, were thought to look and sound similar to Levemir FlexTouch. These names include Levemir, Flex5***, Flex10***, Pulmicort Flexhaler, Flextra, Norditropin FlexPro, and FlexPen.

A search of the United States Adopted Name stem list on January 29, 2010 did not identify any United States Adopted Names (USAN) stem within the proposed name, Levemir FlexTouch.

3.2 EXPERT PANEL DISCUSSION

The Expert Panel reviewed the pool of names identified by DMEPA staff (See Section 3.1 above) and noted no additional names thought to have orthographic or phonetic similarity to Levemir FlexTouch.

DDMAC had no concerns regarding the proposed name from a promotional perspective, and did not offer any additional comments relating to the proposed name.

3.3 FDA PRESCRIPTION ANALYSIS STUDIES

A total of 60 practitioners responded. Thirty-four (n=34) respondents interpreted the name correctly as 'Levemir Flex Touch', with correct interpretations occurring in inpatient (n=10) and outpatient (n=18) written studies and in the verbal (n=6) study. The remainder of the written study responses misinterpreted the drug name, with the most common misinterpretation of the first letter of the name ('Z' vs 'L'). One response in the outpatient written study misinterpreted the modifier as 'Flexpouch' vs 'Flextouch'. In the verbal studies responses were misspelled phonetic variations of the proposed name, Levemir FlexTouch, with the most common variation occurring in the second syllable of the root name ('va'or 'va' vs. 've'). In addition, three responses omitted the modifier and one response used the modifier FlexPen. See Appendix C for the complete listing of interpretations from the verbal and written studies.

3.4 ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE SEARCH

The AERS search identified a total of 4 cases of proprietary name confusion between Levemir and Lovenox (report dates from 8/3/2007 to 7/21/2008). All of the cases took place in the hospital setting and were caused by transcription/interpretation error. Three of the cases did not reach the patient and the remaining case did not result in patient harm. Three of the cases involved the vials and one case the disposable pen (FlexPen).

In addition, we identified 7 cases of patients on both Levemir and NovoLog that inadvertently administered the wrong dose/drug (report dates from 4/23/2007 to 11/21/2008). Three of the seven cases involved the vials and the remaining four the disposable pens (FlexPen). Two cases required visits to the emergency room and one case required hospitalization. In all three cases the event resolved and the patients were discharged. Additionally, we identified one case of a dispensing error in which the patient received NovoLog FlexPen instead of Levemir FlexPen. The pharmacist believes that it was a packaging issue (wrong pen inside the box), however, no causality was established. The patient required medical intervention (i.e. visit to his physician).

3.5 COMMENTS FROM THE DIVISION OF METABOLISM AND ENDOCRINOLOGY PRODUCTS (DMEP)

3.5.1 Initial Phase of Review

In response to the OSE February 25, 2010 e-mail, the Division of Metabolism and Endocrinology Products (DMEP) did not object to the proposed proprietary name Levemir FlexTouch.

3.5.2 Midpoint of Review

On March 2, 2010 DMEPA notified the Division of Metabolism and Endocrinology Products (DMEP) via e-mail that we had no objections to the proposed proprietary name Levemir FlexTouch. Per e-mail correspondence from DMEP on March 10, 2010 they indicated they concur with our assessment of the proposed proprietary name, Levemir FlexTouch.

3.6 SAFETY EVALUATOR RISK ASSESSMENT

Independent searches by the primary Safety Evaluator identified three additional names, FlexTend, Hextend, and Lovenox thought to look or sound similar to Levemir FlexTouch and represent a potential source of confusion. One name identified by EPD, Levemir, is the root name of various insulins within the Levemir family and was therefore eliminated from further evaluation because it was considered within the FlexPen device evaluation. Thus, in total we identified twelve names as having some similarity to the proposed name, nine from EPD, one from the AERS search, and two identified by the Safety Evaluator.

4 DISCUSSION

4.1 PROMOTIONAL REVIEW

DDMAC did not find the name Levemir FlexTouch promotional. DMEPA and the Division of Metabolism and Endocrinology Products (DMEP) concurred with this assessment.

4.2 SAFETY REVIEW

4.2.1 Modifier Evaluation

The proposed product, Levemir FlexTouch, will be a replacement for the currently marketed Levemir FlexPen. The Applicant proposes to use the modifier FlexTouch to distinguish this product from the currently marketed FlexPen. Both products are prefilled pen-injectors used for the same indication of use, route of administration, concentration, quantity, and method of use. Novo Nordisk plans to announce the discontinuation of Levemir FlexPen (b) (4) post-launch of Levemir FlexTouch, (b) (4) Additionally, the proposed Levemir FlexTouch and Levemir FlexPen pens are very similar in design. Doses from each device are selected or dialed the same way. The NovoLog FlexTouch device offers patients and caregivers a shorter finger reach at higher doses and a terminal audible 'click' to provide feedback to the user that the dose has been administered.

The primary safety evaluator considered the following to determine whether or not the proposed modifier 'FlexTouch' is a potential source for medication errors.

- FlexTouch® is a modifier representing the new delivery device. This modifier is a combination of "flexible" and "touch". "Flexible" represents flexible dosing available in the pen. Levemir® FlexTouch® is a multi-dose pen where the user can select the dose to be injected by turning the dose selector. "Touch" represents improvements upon the design of the current Levemir® FlexPen®. Therefore, the name is not trying to convey any specific meaning to the device or drug that could be misinterpreted at any point in the medication use process.
- The sole purpose of the modifier FlexTouch is to differentiate this new device from the other products in the Levemir family (e.g. Levemir FlexPen, and Levemir vials).
- There are no medical abbreviations or dosing instructions associated with the modifier FlexTouch.
- FlexTouch does not appear on the error-prone abbreviation list maintained by the Institute for Safe Medication Practices (ISMP).

The use of a different modifier is an acceptable method for differentiating these two pen devices during the (b) (4) co-marketing transition period. However, we anticipate product selection errors due to a general lack of awareness of the new product to the market, similar tradedress of the labels, similar appearance of the pens, overlapping product characteristics, and similar names. To minimize the potential confusion anticipated upon product launch, the Applicant should take steps to increase practitioner and patient awareness of the new pen and educate about the required switch that will need to occur during the (b) (4) transition period.

4.2.2 Look-alike /Sound-alike Evaluation

DMEPA sought input from the review team (Clinical, CMC, DDMAC) on the safety aspects of the name. No issues were identified from these stakeholders. We evaluated twelve names for look-alike and sound-alike similarities and the use of the modifier as a potential source of medication errors using Failure Mode and Effects Analysis (FMEA) to determine if the proposed proprietary name, Levemir FlexTouch, could potentially be confused with any of the names and lead to medication errors. This analysis determined that the name similarity between Levemir FlexTouch was unlikely to result in medication errors with eleven of the twelve products for the reasons presented in Appendices D through H. However, there is a potential for confusion between Lovenox and Levemir FlexTouch.

The Lovenox and Levemir name confusion was confirmed with postmarketing data in which four cases of name confusion have been reported. One of these cases involved the currently marketed Levemir FlexPen. DMEPA originally objected to the Levemir proprietary name in ODS Consult # 02-0222, dated June 4, 2003, because of orthographic similarities with Lovenox in addition to the overlapping product characteristics. Subsequently, NovoNordisk requested a re-consideration of the proprietary name Levemir. However, DMEPA maintained the objection to the proprietary name Levemir in ODS Consult # 02-0222-1, dated February 6, 2004. Nevertheless, the Division of Metabolism and Endocrinology Product overturned DMEPA's recommendation and approved the proprietary name Levemir. The following justification was provided in the Division Director's memo dated June 16, 2005.

"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."

Since the Lovenox name confusion is occurring with both the Levemir vial formulation and the FlexPen formulation currently, (b) (4) The proposed product will replace the currently marketed pen and we conclude that the addition of the proposed modifier FlexTouch will not exacerbate this confusion with the root name. However, we will need to explore further the extent of the Levemir and Lovenox proprietary name confusion in a separate review following contact with the applicant to determine the number of reports they have received concerning this confusion.

5 CONCLUSIONS AND RECOMMENDATIONS

The Proprietary Name Risk Assessment indicates that the proposed name, Levemir FlexTouch, is vulnerable to name confusion with the currently marketed Levemir FlexPen. Although this confusion is limited to the (b) (4) co-marketing transition period, we recommend the Applicant inform both healthcare practitioners and patients of the availability of the new product and the required switch from the old pen to the new pen that will need to take place within the year long transition from Levemir FlexTouch to Levemir FlexPen.

We also noted postmarketing proprietary name confusion between Levemir and Lovenox. This confusion was identified by DMEPA prior to approval of the Levemir name. However, despite our objection, DMEP approved the name. We have determined that the addition of the modifier FlexTouch should not exacerbate the name confusion with the root names. (b) (4)

If any of the proposed product characteristics as stated in this review are altered prior to approval of the product, DMEPA rescinds this Risk Assessment finding and the name must be resubmitted for review. In the event that our Risk Assessment finding is rescinded, the evaluation of the name on resubmission is independent

of the previous Risk Assessment, and as such, the conclusions on re-review of the name are subject to change. Furthermore, if the approval of this application is delayed beyond 90 days from the signature date of this review, the proposed name must be resubmitted for evaluation.

If you have further questions or need clarifications, please contact Margarita Tossa, OSE Project Manager at 301-796-4053.

5.1 COMMENTS TO THE APPLICANT

We have completed our review of the proposed proprietary name, Levemir FlexTouch, and have concluded that it is acceptable. However, we anticipate product selection errors between the Levemir FlexTouch and Levemir FlexPen because of the similar trade dress, similar names, similar pen colors, (b) (4) To minimize the potential confusion anticipated from the general lack of awareness to the marketing of the new Levemir FlexTouch product, you should take steps to increase practitioner's awareness of the introduction of this new pen and increase awareness of the transition that will occur on the market over the year following product launch.

The proposed proprietary name, Levemir FlexTouch, will be re-reviewed 90 days prior to the approval of the Supplemental NDA. If we find the name unacceptable following the re-review, we will notify you.

If any of the proposed product characteristics are altered prior to approval of this Supplemental NDA, the proprietary name should be resubmitted for review.

REFERENCES

1. ***Micromedex Integrated Index*** *(http://csi.micromedex.com)*

   Micromedex contains a variety of databases covering pharmacology, therapeutics, toxicology and diagnostics.

2. ***Phonetic and Orthographic Computer Analysis (POCA)***

   POCA is a database which was created for the Division of Medication Error Prevention and Analysis, FDA. 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. Likewise, an orthographic algorithm exists which operates in a similar fashion.

3. ***Drug Facts and Comparisons, online version, St. Louis, MO*** *(http://factsandcomparisons.com)*

   Drug Facts and Comparisons is a compendium organized by therapeutic course; it contains monographs on prescription and OTC drugs, with charts comparing similar products.

4. ***FDA Document Archiving, Reporting & Regulatory Tracking System [DARRTS]***

DARRTS is a government database used to organize Applicant and Sponsor submissions as well as to store and organize assignments, reviews, and communications from the review divisions.

5. ***Division of Medication Errors Prevention and Analysis proprietary name consultation requests***

   This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention and Analysis from the Access database/tracking system.

6. ***Drugs@FDA*** *(http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm)*

   Drugs@FDA contains most of the drug products approved since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA approved brand name, generic drugs, therapeutic biological products, prescription and over-the-counter human drugs and discontinued drugs and "Chemical Type 6" approvals.

7. ***Electronic online version of the FDA Orange Book*** *(http://www.fda.gov/cder/ob/default.htm)*

   The FDA Orange Book provides a compilation of approved drug products with therapeutic equivalence evaluations.

8. ***U.S. Patent and Trademark Office*** *(http://www.uspto.gov)*

   USPTO provides information regarding patent and trademarks.

9. ***Clinical Pharmacology Online*** *(www.clinicalpharmacology-ip.com)*

   Clinical Pharmacology contains full monographs for the most common drugs in clinical use, plus mini monographs covering investigational, less common, combination, nutraceutical and nutritional products. It also provides a keyword search engine.

10. ***Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at*** *(www.thomson-thomson.com)*

The Pharma In-Use Search database contains over 400,000 unique pharmaceutical trademarks and trade names that are used in about 50 countries worldwide. The data is provided under license by IMS HEALTH.

11. ***Natural Medicines Comprehensive Databases*** *(www.naturaldatabase.com)*

Natural Medicines contains up-to-date clinical data on the natural medicines, herbal medicines, and dietary supplements used in the western world.

12. ***Stat!Ref*** *(www.statref.com)*

Stat!Ref contains full-text information from approximately 30 texts; it includes tables and references. Among the database titles are: Handbook of Adverse Drug Interactions, Rudolphs Pediatrics, Basic Clinical Pharmacology, and Dictionary of Medical Acronyms Abbreviations.

13. ***USAN Stems*** *(http://www.ama-assn.org/ama/pub/category/4782.html)*

USAN Stems List contains all the recognized USAN stems.

14. ***Red Book Pharmacy's Fundamental Reference***

Red Book contains prices and product information for prescription, over-the-counter drugs, medical devices, and accessories.

15. ***Lexi-Comp*** *(www.lexi.com)*

Lexi-Comp is a web-based searchable version of the Drug Information Handbook.

16. ***Medical Abbreviations Book***

Medical Abbreviations Book contains commonly used medical abbreviations and their definitions

APPENDICES

Appendix A:

FDA's Proprietary Name Risk Assessment considers the potential for confusion between the proposed proprietary name and the proprietary and established names of drug products existing in the marketplace and those pending IND, NDA, BLA, and ANDA products currently under review by the Center. DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. 3

For the proposed proprietary name, DMEPA staff search a standard set of databases and information sources to identify names with orthographic and phonetic similarity and hold a Center for Drug Evaluation and Research (CDER) Expert Panel discussion to gather professional opinions on the safety of the proposed proprietary name. DMEPA staff also conducts internal CDER prescription analysis studies. When provided, DMEPA considers external prescription analysis study results and incorporate into the overall risk assessment.

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3 National Coordinating Council for Medication Error Reporting and Prevention. http://www.nccmerp.org/aboutMedErrors.html. Last accessed 10/11/2007.

The Safety Evaluator assigned to the Proprietary Name Risk Assessment is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name. DMEPA bases the overall risk assessment on the findings of a Failure Mode and Effects Analysis (FMEA) of the proprietary name, and focuses on the avoidance of medication errors.

FMEA is a systematic tool for evaluating a process and identifying where and how it might fail. 4 DMEPA uses FMEA to analyze whether the drug names identified with orthographic or phonetic similarity to the proposed proprietary name could cause confusion that subsequently leads to medication errors in the clinical setting. DMEPA uses the clinical expertise of its staff to anticipate the conditions of the clinical setting where the product is likely to be used based on the characteristics of the proposed product.

In addition, the product characteristics provide the context for the verbal and written communication of the drug names and can interact with the orthographic and phonetic attributes of the names to increase the risk of confusion when there is overlap or, in some instances, decrease the risk of confusion by helping to differentiate the products through dissimilarity. Accordingly, the DMEPA staff considers the product characteristics associated with the proposed drug throughout the risk assessment because the product characteristics of the proposed may provide a context for communication of the drug name and ultimately determine the use of the product in the *usual* clinical practice setting.

Typical product characteristics considered when identifying drug names that could potentially be confused with the proposed proprietary name include, but are not limited to; established name of the proposed product, proposed indication of use, dosage form, route of administration, strength, unit of measure, dosage units, recommended dose, typical quantity or volume, frequency of administration, product packaging, storage conditions, patient population, and prescriber population. Because drug name confusion can occur at any point in the medication use process, DMEPA staff considers the potential for confusion throughout the entire U.S. medication use process, including drug procurement, prescribing and ordering, dispensing, administration, and monitoring the impact of the medication.[5] DMEPA provides the product characteristics considered for this review in section one.

The Division of Medication Error Prevention and Analysis considers the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. DMEPA also compares the spelling of the proposed proprietary name with the proprietary and established name of existing and proposed drug products because similarly in spelled names may have greater likelihood to sound similar to one another when spoken or look similar to one another when scripted. DMEPA staff also examines the orthographic appearance of the proposed name using a number of different handwriting samples. Handwritten communication of drug names has a long-standing association with drug name confusion. Handwriting can cause similarly and even dissimilarly spelled drug name pairs to appear very similar to one another. The similar appearance of drug names when scripted has led to medication errors. The DMEPA staff applies expertise gained from root-cause analysis of such medication errors to identify sources of ambiguity within the name that could be introduced when scripting (e.g.,"T" may look like "F," lower case 'a' looks like a lower case 'u,' etc). Additionally, other orthographic attributes that determine the overall appearance of the drug name when scripted (see Table 1 below for details). In addition, the DMEPA staff compares the pronunciation of the proposed proprietary name with the pronunciation of other drug names because verbal communication of medication names is common in clinical settings. If provided, DMEPA will consider the Applicant's intended pronunciation of the proprietary name. However, DMEPA also considers a variety of pronunciations that could occur in the English language because the Applicant has little control over how the name will be spoken in clinical practice.

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4 Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

5 Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006.

Table 1. Criteria used to identify drug names that look- or sound-similar to a proposed proprietary name.

Type of similarity	**Considerations when searching the databases**		
	Potential causes of drug name similarity	*Attributes examined to identify similar drug names*	*Potential Effects*
Look-alike	Similar spelling	Identical prefix Identical infix Identical suffix Length of the name Overlapping product characteristics	• Names may appear similar in print or electronic media and lead to drug name confusion in printed or electronic communication • Names may look similar when scripted and lead to drug name confusion in written communication
	Orthographic similarity	Similar spelling Length of the name Upstrokes Down strokes Cross-stokes Dotted letters Ambiguity introduced by scripting letters Overlapping product characteristics	• Names may look similar when scripted, and lead to drug name confusion in written communication
Sound-alike	Phonetic similarity	Identical prefix Identical infix Identical suffix Number of syllables Stresses Placement of vowel sounds Placement of consonant sounds Overlapping product characteristics	• Names may sound similar when pronounced and lead to drug name confusion in verbal communication

Lastly, the DMEPA staff also considers the potential for the proposed proprietary name to inadvertently function as a source of error for reasons other than name confusion. Post-marketing experience has demonstrated that proprietary names (or components of the proprietary name) can be a source of error in a variety of ways. Consequently, DMEPA considers and evaluates these broader safety implications of the name throughout this assessment and the medication error staff provides additional comments related to the safety of the proposed proprietary name or product based on professional experience with medication errors.

1. Database and Information Sources

DMEPA staff conducts searches of the internet, several standard published drug product reference texts, and FDA databases to identify existing and proposed drug names that may sound-alike or look-alike to the proposed proprietary name using the criteria outlined in Section 2.1. Section 6 provides a standard description of the databases used in the searches. To complement the process, the DMEPA staff use a computerized method of identifying phonetic and orthographic similarity between medication names. The program, Phonetic and Orthographic Computer Analysis (POCA), uses complex algorithms to select a list of names from a database that have some similarity (phonetic, orthographic, or both) to the trademark being evaluated. Lastly, the DMEPA staff review the USAN stem list to determine if any USAN stems are present within the proprietary name. The individual findings of multiple safety evaluators are pooled and presented to the CDER Expert Panel.

2. CDER Expert Panel Discussion

DMEPA conducts an Expert Panel Discussion to gather CDER professional opinions on the safety of the proposed product and the proposed proprietary name. The Expert Panel is composed of Division of Medication Errors Prevention (DMEPA) staff and representatives from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The Expert Panel also discusses potential concerns regarding drug marketing and promotion related to the proposed names.

The primary Safety Evaluator presents the pooled results of the DMEPA staff to the Expert Panel for consideration. Based on the clinical and professional experiences of the Expert Panel members, the Panel may recommend the addition of names, additional searches by the primary Safety Evaluator to supplement the pooled results, or general advice to consider when reviewing the proposed proprietary name.

3. FDA Prescription Analysis Studies

Three separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of the proposed proprietary name with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. The studies employ healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The primary Safety Evaluator uses the results to identify orthographic or phonetic vulnerability of the proposed name to be misinterpreted by healthcare practitioners.

In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, inpatient medication orders and/or outpatient prescriptions are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. These orders are optically scanned and one prescription is delivered to a random sample of the 123 participating health professionals via e-mail. In addition, a verbal prescription is recorded on voice mail. The voice mail messages are 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 send their interpretations of the orders via e-mail to DMEPA.

4. Safety Evaluator Risk Assessment of the Proposed Proprietary Name

The primary Safety Evaluator applies his/her individual expertise gained from evaluating medication errors reported to FDA, conducts a Failure Mode and Effects Analysis, and provides an overall risk assessment of name confusion. Failure Mode and Effects Analysis (FMEA) is a systematic tool for evaluating a process and identifying where and how it might fail.[6] When applying FMEA to assess the risk of a proposed proprietary name, DMEPA seeks to evaluate the potential for a proposed proprietary name to be confused with another drug name because of name confusion and, thereby, cause errors to occur in the medication use system. FMEA capitalizes on the predictable and preventable nature of medication errors associated with drug name confusion. FMEA allows the Agency to identify the potential for medication errors due to orthographically or phonetically similar drug names prior to approval, where actions to overcome these issues are easier and more effective than remedies available in the post-approval phase.

In order to perform an FMEA of the proposed name, the primary Safety Evaluator must analyze the use of the product at all points in the medication use system. Because the proposed product is has not been marketed, the primary Safety Evaluator anticipates the use of the product in the usual practice settings by considering the clinical and product characteristics listed in Section one. The Safety Evaluator then analyzes the proposed proprietary name in the context of the usual practice setting and works to identify potential failure modes and the effects associated with the failure modes.

In the initial stage of the Risk Assessment, the Safety Evaluator compares the proposed proprietary name to all of the names gathered from the above searches, Expert Panel Discussion, and prescription studies, external studies, and identifies potential failure modes by asking:

> ***"Is the proposed proprietary name convincingly similar to another drug name, which may cause practitioners to become confused at any point in the usual practice setting?"***

An affirmative answer indicates a failure mode and represents a potential for the proposed proprietary name to be confused with another proprietary or established drug name because of look- or sound-alike similarity. If the answer to the question is no, the Safety Evaluator is not convinced that the names posses similarity that would cause confusion at any point in the medication use system, thus the name is eliminated from further review.

In the second stage of the Risk Assessment, the primary Safety Evaluator evaluates all potential failure modes to determine the likely *effect* of the drug name confusion, by asking:

> ***"Could the confusion of the drug names conceivably result in medication errors in the usual practice setting?"***

The answer to this question is a central component of the Safety Evaluator's overall risk assessment of the proprietary name. If the Safety Evaluator determines through FMEA that the name similarity would not ultimately be a source of medication errors in the usual practice setting, the primary Safety Evaluator eliminates the name from further analysis. However, if the Safety Evaluator determines through FMEA that the name similarity could ultimately cause medication errors in the usual practice setting, the Safety Evaluator will then recommend the use of an alternate proprietary name.

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6 Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

DMEPA will object to the use of proposed proprietary name when the primary Safety Evaluator identifies one or more of the following conditions in the Risk Assessment:

a. DDMAC finds the proposed proprietary name misleading from a promotional perspective, and the Review Division concurs with DDMAC's findings. The Federal Food, Drug, and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made or suggested by statement, word, design, device, or any combination thereof, whether through a PROPRIETARY name or otherwise [21 U.S.C 321(n); See also 21 U.S.C. 352(a) & (n)].
b. DMEPA identifies that the proposed proprietary name is misleading because of similarity in spelling or pronunciation to another proprietary or established name of a different drug or ingredient [CFR 201.10.(C)(5)].
c. FMEA identifies the potential for confusion between the proposed proprietary name and other proprietary or established drug name(s), and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.
d. The proposed proprietary name contains an USAN (United States Adopted Names) stem.
e. DMEPA identifies a potential source of medication error within the proposed proprietary name. For example, the proprietary name may be misleading or, inadvertently, introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug and another drug product.

If DMEPA objects to a proposed proprietary name on the basis that drug name confusion could lead to medication errors, the primary Safety Evaluator uses the FMEA process to identify strategies to reduce the risk of medication errors. DMEPA is likely to recommend that the Applicant select an alternative proprietary name and submit the alternate name to the Agency for DMEPA to review. However, in rare instances FMEA may identify plausible strategies that could reduce the risk of medication error of the currently proposed name. In that instance, DMEPA may be able to provide the Applicant with recommendations that reduce or eliminate the potential for error and, thereby, would render the proposed name acceptable.

In the event that DMEPA objects to the use of the proposed proprietary name, based upon the potential for confusion with another proposed (but not yet approved) proprietary name, DMEPA will provide a contingency objection based on the date of approval. Whichever product, the Agency approves first has the right to use the proprietary name, while DMEPA will recommend that the second product to reach approval seek an alternative name.

The threshold set for objection to the proposed proprietary name may seem low to the Applicant. However, the safety concerns set forth in criteria a through e are supported either by FDA regulation or by external healthcare authorities, including the Institute of Medicine (IOM), World Health Organization (WHO), Joint Commission on Accreditation of Hospitals (JCOAH), and the Institute for Safe Medication Practices (ISMP). These organizations have examined medication errors resulting from look- or sound-alike drug names and called for regulatory authorities to address the issue prior to approval. Additionally, DMEPA contends that the threshold set for the Proprietary Name Risk Assessment is reasonable because proprietary drug name confusion is a predictable and a preventable source of medication error that, in many instances, the Agency and/or Applicant can identify and rectify prior to approval to avoid patient harm.

Furthermore, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to rectify post-approval. Educational and other post-approval efforts are low-leverage strategies that have had limited effectiveness at alleviating medication errors involving drug name confusion. Applicants have undertaken higher-leverage strategies, such as drug name changes, in the past but at great financial cost to the Applicant and at the expense of the public welfare, not to mention the Agency's credibility as the authority responsible for approving the error-prone proprietary name. Moreover, even after Applicants' have changed a product's proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from practitioners' vocabulary, and as a result, the Agency has continued to receive reports of drug name confusion long after a name change in some instances. Therefore, DMEPA believes that post-approval efforts at reducing name confusion errors should be reserved for those cases in which the potential for name confusion could not be predicted prior to approval. (See Section 4 for limitations of the process).

Appendix B: Letters with possible orthographic or phonetic misinterpretation

Letters in Name NovoLog FlexTouch	Scripted may appear as	Spoken may be interpreted as
Capital 'L'	I, P, T, or Z	'N'
lower case 'e'	any vowel	any vowel
lower case 'v'	n or r	'b'
lower case 'm'	n, z, or ss	'n'
lower case 'i'	any vowel	any vowel
lower case 'r'	n, m, or v	'b'
Capital 'F'	E, J, K, P, or T	'P'
lower case 'x'	f, k, r, t, or v	'cks'
Capital 'T'	F, I, or Z	'D' or 'B'
lower case 'u'	a, e, c, i, or l	any vowel
lower case 'c'	a, e, s, or u	'k'
lower case 'h'	b, n, or k	--

Appendix C: FDA Prescription Study Responses

Inpatient Medication Order	Outpatient Prescription	Voice Prescription
Levemir Flex Touch	Levemir Flextouch	Levimeer Flextouch
Zivemir Flex Touch	Levemir Flextouch	Levemir Flex Touch
Levemir Flextouch	Levemir Flextouch	Levamir flex touch
Levemir Flex Touch	Levemir Flextouch	Levimir Flex Touch
Levemin flex touch	Levemir Flextouch	Levemir Flex Touch
Zivemir Flip touch	Levemir Flextouch	Levamir Flextouch
Livamin	Levemir Flextouch	Levemir Flextouch
Levemir	Levemir Flextouch	Levemir Flex Touch
Zevemin Flex Touch	Levemir Flextouch	Levemir Flex touch
Zevemir Flex Touch	Levemir Flextouch	Levamere Flex Touch
Levemir	Levemir Flextouch	Levamer FlexTouch
Zivimir flex Touch	Levemir Flex Pen	Levomere flextouch
Zevemir Flex Touch	Levemir Flex	Levemir Flex Touch
Levemir Flex Touch	Levemir Flextouch	Levamer Flex Touch
Levemir Flex Touch	Levemir Flextouch	Levamer flextouch
Levemir Flex Touch	Levemir Flextouch	Levamure flex touch
Levemir Flex Touch	Levemir flextouch	
Zevemin Flex Touch	Levemir Flexpouch	
Levemir Flex Touch	Levemir Flextouch	
Levemir FlexTouch	Levemir Flextouch	
Levemir FlexTouch	Levemir Flextouch	
Zevamin Flex Touch		
Zevemir Flex Touch		

Appendix D: Proprietary names that lack convincing orthographic and/or phonetic similarities

Proprietary Name	Similarity to Levemir FlexTouch
Cevimeline	Look
Vumon	Look
Ionamin	Look

Appendix E: Proposed proprietary names that were approved under a different proprietary name

Proprietary Name	Similarity to Levemir FlexTouch	Reason for Discard
Flex5*** Flex10***	Look and Sound	DMEPA objected in review #02-0175. Approved under the name Flexeril

Appendix F: Discontinued products with no generic equivalent available

Proprietary Name	Similarity to Levemir Flex Touch	Established Name
FlexTend	Look and Sound	Iron, Glucosamine Sulfate, Vitamin E, Ascorbic Acid

*** **This document contains proprietary and confidential information that should not be released to the public**

Appendix G: Product names with similarity to Levemir FlexTouch but with multiple differentiating product characteristics

Product name with potential for confusion[7]	**Similarity to Novolog FlexTouch**	**Strength/Dosage form**	**Usual dose (if applicable)**	**Differentiating Product Characteristics**
Levemir FlexTouch ***(Insulin aspart [rDNA origin] injection)***	**N/A**	**Strength:** **100 units/mL** **Dosage Form:** **-FlexTouch: multiple use, disposable pens (3 mL)** **-vials** **-Innolet (3 mL)**	Individualized dose adjusted according to blood glucose measurements once or twice daily	**N/A**
Pulmicort Flexhaler (budesonide inhalation powder)	Look and Sound	Inhaler: 90 mcg, 180 mcg,	180 mcg to 360 mcg twice daily (maximum 720 mcg twice daily)	*Dosage Form:* Injection vs. Inhaler *Route of Administration:* Subcutaneous vs. Oral Inhalation *Strength:* 100 units/mL vs. 90 mcg and 180 mcg *Units of measure:* Units vs. mcg
Flextra (Acetaminophen/Caffeine/ Phenyltoloxamine)	Look and Sound	Capsule: 425 mg/35 mg/ 45 mg	One or two capsules every two to six hours as needed for pain.	*Dosage Form:* Injection vs. Capsule *Route of Administration:* Subcutaneous vs. Oral *Units of measure:* Units vs. mg
Hextend (Hetastarch in Lactated Electrolyte Injection)	Look	6% (500 mL)	500 mL to 1000 mL per day	*Route of Administration:* Subcutaneous vs. Intravenous *Strength:* 100 units/mL vs. 6% *Units of measure:* Units vs. %

Appendix H: Potentially confusing names with multiple differentiating product characteristics

Failure Mode: Name confusion[1]	**Causes** **(could be multiple)**	**Rationale**
Levemir FlexTouch *(insulin detemir [rDNA origin] injection)*	**Strength:** **100 units/mL** **Dosage Form:** **-FlexTouch: multiple use, disposable pens (3 mL)** **-vial** **-Innolet (3 mL)**	**Usual dose:** Individualized dose adjusted according to blood glucose measurements once or twice daily
Norditropin FlexPro *(Somatropin[rDNA origin] injection)* Strength: 5 mg/ 1.5 mL 10 mg/ 1.5 mL 15 mg/1.5 mL (prefilled, multiple use, disposable pens) Usual dose: Individualized dose (weight based/indication based) subcutaneously daily	Orthographic Similarity: Similarity of the modifier 'FlexTouch' to the modifier 'FlexPro'. Both modifiers are similar in length (9 letters vs. 7 letters). Both represent multidose drug delivery pen devices.	Medication errors unlikely to occur in the usual practice setting for the following reasons: The two names (Levemir vs Norditropin) are orthographically different. In addition, the length of the root names (7 letters for Levemir vs. 11 letters for Norditropin) help differentiate them. Although both modifiers share the same first four letters (Flex), the ending letters vary in length (five letters vs. three letters) and word shape which helps to orthographically differentiate the names. FLEXTOUCH FLEXPRO 'FlexTouch' is a device used with several different products which include Levemir, Novolog, (b) (4) Physicians therefore would not write an order for 'FlexTouch' by itself but rather would need to include the drug product on each prescription, otherwise pharmacists would need to call for clarification. Additionally, Norditropin FlexPro orders will be dosed in milligrams vs the products used with the FlexTouch which would be dosed in units. Growth hormone replacement products, such as Norditropin FlexPro are generally distributed through specialty pharmacies and require a statement of medical necessity.

Appendix H (cont'd) : Potentially confusing names with multiple differentiating product characteristics

Failure Mode: Name confusion[1]	Causes (could be multiple)	Rationale
Levemir FlexTouch *(insulin detemir [rDNA origin] injection)*	**Strength:** **100 units/mL** **Dosage Form:** **-FlexTouch: multiple use, disposable pens (3 mL)** **-vials** **-Innolet (3 mL)**	**Usual dose:** Individualized dose adjusted according to blood glucose measurements once or twice daily
FlexPen Device/modifier used with the rootname: **Levemir**	Both modifiers share the name 'Flex' Similarity in the length of the names (9 letters vs. 7 letters) Both represent multiple use, disposable pen devices. Both devices will deliver the same insulin type (i.e. Levemir)	DMEPA acknowledges that selection errors will possibly occur since both names are orthographically similar, but also share overlapping product characteristics. Both products are prefilled pen-injectors that possess the same indication, route of administration, concentration, quantity, and method of use. *Rationale*: Although both modifiers share the same first four letters (Flex), the ending letters which vary in length (five letters vs. three letters) and word shape which helps to orthographically differentiate the names. FLEXTOUCH FLEXPEN If FlexTouch is approved, (b) (4) [redacted] Additionally, product selection errors occur because of similar names in combination with the similar trade dress and packaging. To minimize the potential confusion anticipated from a general lack of awareness of the new Levemir FlexTouch product, the Applicant should take steps to increase practitioner's awareness of the introduction of this new pen.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21536	SUPPL-33	NOVO NORDISK INC	LEVEMIR

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

/s/

DENISE P TOYER
03/15/2010

CAROL A HOLQUIST
03/15/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21536/S-033

OTHER REVIEW(S)

Division of Metabolism and Endocrinology Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application Number:
NDA 021536/S-033

Name of Drug:
Levemir (insulin detemir [rDNA origin]) injection, 100 Units/mL

Applicant: Novo Nordisk Inc.

Material Reviewed:

Submission Date	Receipt Date	Document Type
March 22, 2013	**March 22, 2013**	**Carton and Container**
October 11, 2013	**October 11, 2013**	**IFU, PI**
October 17, 2013	**October 21, 2013**	**PPI**

Background and Summary

Levemir (insulin detemir [rDNA origin]), injection was approved on June 16, 2005, under NDA 021536, for once or twice-daily subcutaneous administration in the treatment of adult patients with Type 1 or Type 2 diabetes mellitus who require basal (long-acting) insulin for the control of hyperglycemia.

On March 22, 2013, Novo Nordisk resubmitted this "Prior Approval" labeling supplement (S-033) in order to market Levemir in the FlexTouch pen device.

On August 21, 2013, a teleconference was held between Novo Nordisk and FDA to discuss our concerns regarding the risks caused by needle blockage in the pen. It was decided that the risk associated with needle blockage could be mitigated by improving the labeling. On August 26, 2013, Novo Nordisk sent in an amendment to this supplement in order to respond to our request. On October 8, 2013, comments on the PI, PPI, and IFU were sent to the sponsor. They responded on October 11, 2013. Our final comments were sent on October 16, 2013 to which the sponsor responded on October 17, 2013.

Review

The PI submitted on October 11, 2013, was compared to the currently approved PI, approved on March 9, 2013 (S-067). The following significant changes were noted:

- Under the section, HIGHLIGHTS- DOSAGE FORMS AND STRENGTHS, the following bullet was added:

  3mL LEVEMIR FlexTouch

- Under the section, FULL PRESCRIBING INFORMATION CONTENTS- PATIENT COUNSELING INFROMATION, the following statement was changed from:

  Never Share a LEVEMIR FlexPen Between Patients

  To:

  Never Share a LEVEMIR FlexPen or LEVEMIR FlexTouch Between Patients

- Under the section, DOSAGE FORMS AND STRENGTHS, the following bullet was added:

  3mL LEVEMIR FlexTouch

- Under the section, HOW SUPPLIED/STORAGE AND HANDLING, the following statement was added:

  3mL LEVEMIR FlexTouch NDC 0169-6438-10

- Also under the section, HOW SUPPLIED/STORAGE AND HANDLING, the following statement was changed from:

  FlexPen is for use with NovoFine® disposable needles. Each FlexPen is for use by a single patient. LEVEMIR FlexPen should never be shared between patients, even if the needle is changed.

  To:

  FlexPen and FlexTouch can be used with NovoFine® or NovoTwist® disposable needles. Each FlexPen or FlexTouch is for use by a single patient. LEVEMIR FlexPen and LEVEMIR FlexTouch should never be shared between patients, even if the needle is changed.

- Also under the section, HOW SUPPLIED/STORAGE AND HANDLING, the following statement was changed from:

Unrefrigerated LEVEMIR should be discarded 42 days after it is first kept out of the refrigerator, even if the FlexPen or vial still contains insulin.

To:

Unrefrigerated LEVEMIR should be discarded 42 days after it is first kept out of the refrigerator, even if the FlexPen, FlexTouch or vial still contains insulin.

- Also under the section, HOW SUPPLIED/STORAGE AND HANDLING, the following paragraph was changed from:

LEVEMIR FlexPen:
After initial use, the LEVEMIR FlexPen must NOT be stored in a refrigerator and must NOT be stored with the needle in place. Keep the opened (in use) LEVEMIR FlexPen away from direct heat and light at room temperature, below 30°C (86°F). Unrefrigerated LEVEMIR FlexPens should be discarded 42 days after they are first kept out of the refrigerator.

To:

LEVEMIR FlexPen or LEVEMIR FlexTouch:
After initial use, the LEVEMIR FlexPen or LEVEMIR FlexTouch must NOT be stored in a refrigerator and must NOT be stored with the needle in place. Keep the opened (in use) LEVEMIR FlexPen or LEVEMIR FlexTouch away from direct heat and light at room temperature, below 30°C (86°F). Unrefrigerated LEVEMIR FlexPen or LEVEMIR FlexTouch should be discarded 42 days after they are first kept out of the refrigerator.

- Also under the section, HOW SUPPLIED/STORAGE AND HANDLING, the title of Table 13 was changed from:

Storage Conditions for LEVEMIR FlexPen and vial

To:

Storage Conditions for LEVEMIR FlexPen, LEVEMIR FlexTouch, and vial

- Also under the section, HOW SUPPLIED/STORAGE AND HANDLING, the following line was added to Table 13:

	Not in-use (unopened) Refridgerated	Not in-use (unopened) Room Temperature (below 30C)	In-use (opened)
3mL LEVEMIR FlexTouch	Until expiration date	42 days	42 days Room Temperature (below 30C) **(Do not refridgerate)**

- Under the section, PATIENT COUNSELING INFORMATION, the following paragraph was added:

  Patients should receive proper training on how to use Levemir. Instruct patients that when injecting Levemir, they must press and hold down the dose button until the dose counter shows 0 and then keep the needle in the skin and count slowly to 6. When the dose counter returns to 0, the prescribed dose is not completely delivered until 6 seconds later. If the needle is removed earlier, they may see a stream of insulin coming from the needle tip. If so, the full dose will not be delivered (a possible under-dose may occur by as much as 20%), and they should increase the frequency of checking their blood glucose levels and possible additional insulin administration may be necessary.

  • If 0 does not appear in the dose counter after continuously pressing the dose button, the patient may have used a blocked needle. In this case they would **not** have received **any** insulin – even though the dose counter has moved from the original dose that was set.

  • If the patient did have a blocked needle, instruct them to change the needle as described in Section 5 of the Instructions for Use and repeat all steps in the IFU starting with Section 1: Prepare your pen with a new needle. **Make sure the patient selects the full dose needed.**

- Also under the section, PATIENT COUSNELING INFROAMTION, the following paragraph was changed from:

  17.2 Never Share a LEVEMIR FlexPen Between Patients
  Counsel patients that they should never share a LEVEMIR FlexPen with another person, even if the needle is changed. Sharing of the FlexPen between patients may pose a risk of transmission of infection.

  To:

17.2 Never Share a LEVEMIR FlexPen or LEVEMIR FlexTouch Between Patients
Counsel patients that they should never share a LEVEMIR FlexPen or LEVEMIR FlexTouch with another person, even if the needle is changed. Sharing of the FlexPen or FlexTouch between patients may pose a risk of transmission of infection.

- Also under the section, PATIENT COUSNELING INFROAMTION, the following statment was changed from:

  Novo Nordisk®, Levemir®, NovoLog®, FlexPen®, and NovoFine® are registered trademarks of NovoNordisk A/S.

  To:

  Novo Nordisk®, Levemir®, NovoLog®, FlexPen®, FlexTouch®, NovoFine®, and NovoTwist® are registered trademarks of Novo Nordisk A/S.

- Also under the section, PATIENT COUSNELING INFROAMTION, the following statment was changed from:

  FlexPen® is covered by US Patent Nos. 6,582,404, 6,004,297, 6,235,400 and other patents pending.

  To:

  FlexPen® is covered by US Patent Nos. RE 41,956, 6,004,297, RE 43,834 and other patents pending.

- Also under the section, PATIENT COUSNELING INFROAMTION, the following statment was added:

  FlexTouch® is covered by US patent Nos. 7,686,786, 6,899,699, and other patents pending.

- Also under the section, PATIENT COUSNELING INFROAMTION, the following statment was changed from:

  For information about LEVEMIR contact:
  Novo Nordisk Inc.
  100 College Road West
  Princeton, NJ 08540
  1-800-727-6500

  To:

For information about LEVEMIR contact:
Novo Nordisk Inc.
800 Scudders Mill Road
Plainsboro, New Jersey 08536
1-800-727-6500

The PPI submitted on October 11, 2013, will be attached to the approval letter. During review the PPI was reformatted by the Division of Medical Policy Programs to a one page PPI. The following reviewers have cleared this document:

Clinical- Ali Mohamadi
Division of Medication Error Prevention and Analysis- Yelena Maslov
Division of Medical Policy Programs – Shawna Hutching and Melissa Hullet
Office of Prescription Drug Promotion – Ankur Kalola

The IFU submitted on October 11, 2013, will be attached to the approval letter.

Substantial changes were made to the formatting of the IFU. The following reviewers have cleared this document:

Clinical- Ali Mohamadi
Division of Medication Error Prevention and Analysis- Yelena Maslov
Division of Medical Policy Programs – Shawna Hutchins and Melissa Hullet
Office of Prescription Drug Promotion – Ankur Kalola

The new carton and container labels for the FlexTouch, submitted on March 22, 2013, will be attached to the approval letter.

The following reviewers have cleared the carton and container labels:

Chemistry Manufacturing and Controls - Pallaiah Thammana
Office of Prescription Drug Promotion - Ankur Kalola

Conclusion

The changes to this were either requested by FDA or provide for addition of the FlexTouch trade name. An approval letter for these supplements should be issued.

Callie Cappel-Lynch	October 28, 2013
Regulatory Project Manager	Date
Julie Van der Waag	October 25, 2013
Chief, Project Management Staff	Date

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

/s/

CALLIE C CAPPEL-LYNCH
10/28/2013

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

******Pre-decisional Agency Information******

Memorandum

Date: **September 09, 2013**

To: Callie Cappel-Lynch, Regulatory Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

From: Ankur Kalola, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP Labeling Consult Request

NDA 20986/S-061 Novolog® (insulin aspart [rDNA origin] injection) solution for subcutaneous injection

NDA 21536/S-033 Levemir® (insulin detemir [rDNA origin] injection) solution for subcutaneous injection

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On May 23, 2013 OPDP received a consult request from DMEP to review the proposed draft Prescribing Information (PI), Patient Information (PPI), Instructions for Use (IFU) of each Novolog and Levemir. OPDP's comments on the proposed draft PIs are based on the versions available from the following locations sent via email by Callie Cappel-Lynch on August 26, 2013:

- Novolog EDR Location: \\CDSESUB1\evsprod\NDA020986\020986.enx
- Levemir EDR Location: \\CDSESUB1\evsprod\NDA021536\021536.enx

OPDP's comments on the PIs are provided directly on the marked versions below.

Additionally, OPDP will work collaboratively with DMPP to provide comments on the PPIs and IFUs under separate cover.

Thank you for the opportunity to comment on these materials. If you have any questions, please contact Ankur Kalola at 301-796-4530 or Ankur.Kalola@fda.hhs.gov.

46 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

ANKUR S KALOLA
09/09/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	September 06, 2013
To:	Mary Parks, MD Director **Division of Metabolism and Endocrinology Products (DMEP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Melissa Hulett, MSBA, BSN, RN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Shawna Hutchins, MPH, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Ankur Kalola, Pharm.D. Consumer Safety Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Inserts (PPI's) and Instructions for Use (IFU's)
Drug Name (established name):	• NovoLog (insulin aspart [rDNA origin] injection) • Levemir (insulin detemir [rDNA origin] injection)
Dosage Form and Route:	Solution for Subcutaneous Use
Application Type/Number:	• NDA 20986/S-061 • NDA 21536/S-033
Tracked Safety Issue Number:	• TSI 00651
Applicant:	Novo Nordisk Inc.

1 INTRODUCTION

On March 22, 2013, Novo Nordisk Inc., re-submitted for the Agency's review Prior Approval Supplements (S-061 and S-033) to the New Drug Applications (NDA 20986 and 21536) for NovoLog (insulin aspart [rDNA origin] injection) and Levemir (insulin detemir [rDNA origin] injection) solution for subcutaneous use. Prior Approval Supplements (S-061 and S-033) were originally submitted on December 15, 2009, received a Complete Response Letter on August 20, 2010, were re-submitted on July 13, 2011, and received a second Complete Response Letter on March 20, 2012. The March 22, 2013 re-submission constituted a complete response to the Agency's Complete Response Letter issued on March 20, 2012.

On August 26, 2013, Novo Nordisk Inc., submitted an amendment to the March 22, 2013 submission for the purpose of providing a response to deficiencies noted in a General Advice Letter issued by the Agency on August 12, 2013.

NovoLog (insulin aspart [rDNA origin] injection) and Levemir (insulin detemir [rDNA origin] injection) were originally approved on June 07, 2000, and June 16, 2005, respectively, and are indicated to improve glycemic control in adults and children with diabetes mellitus.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Metabolism and Endocrinology Products (DMEP) on March 27, 2013 and May 23, 2013, respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Inserts (PPI's) and Instructions for Use (IFU's) for NovoLog (insulin aspart [rDNA origin] injection) and Levemir (insulin detemir [rDNA origin] injection) solution for subcutaneous use.

2 MATERIAL REVIEWED

- Draft NovoLog (insulin aspart [rDNA origin] injection) PPI and IFU received on August 26, 2013 and received by DMPP on August 28, 2013.
- Draft Levemir (insulin detemir [rDNA origin] injection) PPI and IFU received on August 26, 2013 and received by DMPP on August 28, 2013.
- Draft NovoLog (insulin aspart [rDNA origin] injection) PPI and IFU received on August 26, 2013 and received by OPDP on August 28, 2013.
- Draft Levemir (insulin detemir [rDNA origin] injection) PPI and IFU received on August 26, 2013 and received by OPDP on August 28, 2013.
- Draft NovoLog (insulin aspart [rDNA origin] injection) Prescribing Information (PI) received on August 26, 2013, revised by the Review Division throughout the review cycle, and received by DMPP on August 28, 2013.
- Draft Levemir (insulin detemir [rDNA origin] injection) Prescribing Information (PI) received on August 26, 2013, revised by the Review Division throughout the review cycle, and received by DMPP on August 28, 2013.

- Draft NovoLog (insulin aspart [rDNA origin] injection) Prescribing Information (PI) received on August 26, 2013, revised by the Review Division throughout the review cycle, and received by OPDP on August 28, 2013.
- Draft Levemir (insulin detemir [rDNA origin] injection) Prescribing Information (PI) received on August 26, 2013, revised by the Review Division throughout the review cycle, and received by OPDP on August 28, 2013.

3 REVIEW METHODS

The Patient Labeling Team (PLT) is continuously working to reduce redundancy and to make patient information more consistent, concise, and to include the information necessary for patients to take their medications.

In 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI and IFU documents using the Verdana font, size 11.

In our collaborative review of the PPI's and IFU's we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI's and IFU's are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI's and IFU's meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI's and IFU's are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI's and IFU's are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI's and IFU's.

Please let us know if you have any questions.

63 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

SHAWNA L HUTCHINS
09/06/2013

ANKUR S KALOLA
09/06/2013

LASHAWN M GRIFFITHS
09/06/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES MEMORANDUM

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
White Oak Building 66
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: July 22, 2013
From: Lana Shiu, M.D.
General Hospital Devices Branch, DAGID, ODE, CDRH
To: Callie Cappel-Lynch
Project Manager, DMEP, OND, CDER
Via: Jacqueline Ryan, M.D.
Combination Products Team Leader, GHDB, DAGID, CDRH

Subject: Novolog NDA 020986/S061, Levemir NDA 021536/S033, (b) (4)
(b) (4)
CDRH Tracking: ICC1300134

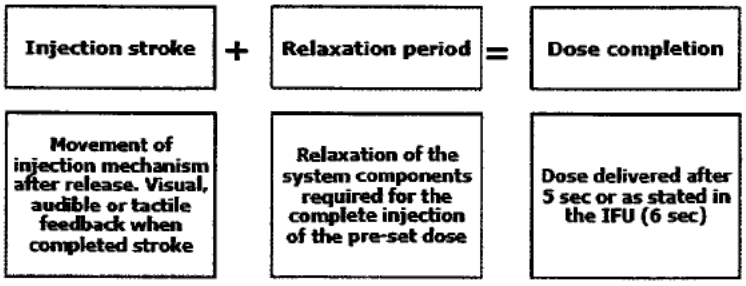
1. Issue

CDRH 3/6/2012 consult memo stated the following to the Sponsor:

"The dose accuracy testing submitted does not comply with ISO 111608-1, Pen-Injectors for medical use-Part 1: *Pen-injectors- Requirements and test methods.* This standard requires that the "Pen injector shall indicate, by visual, audible or tactile means or any combination of these, that the injection stroke has been completed." The scale drum on the PDS290 pen injector does not indicate that the injection stroke has been completed. An additional one second or more is needed to complete the injection. If the needle is removed from the skin when the scale drum has reached zero, the patient may be under-dosed by as much as 20.4% of the dialed dose. CDRH does not believe that this dosing accuracy failure can be or should be mitigated by labeling. You should provide a drug delivery device which is ISO 11608-1 compliant."

Novo Nordisk 3/23/2012 responded to the above question in (b) (4).

Figure 1: Description of a Complete Injection per ISO 11608-1



"According to the definition in ISO 11608-1, the time it takes to inject a full dose is the duration of the injection stroke plus the relaxation time. The duration of the injection stroke alone is not equivalent to the time it takes to deliver the full insulin dose. Some of the dose has been delivered during the injection stroke and the remainder during the relaxation of the system. This is the case for the PDS290 pen-injector as well as for all other marketed pre-filled insulin pen-injectors in the US, including the FlexPen, SoloStar, and KwikPen. In order to account for the relaxation of the system, which is compliant with ISO 11608-1, the Instructions For Use (IFU) state that the needle must be held under the skin for a specified amount of time."

Device Description
The PDS290 Pen injector is a prefilled disposable pen injector which, according to the sponsor is based on the FlexPen. Improvements were made for readability of the dose counter, larger inspection window, no protrusion of dose button, less dose force, more ergonomic grip, improved dose delivery and easier needle handling.

Documents Reviewed
CDRH Review Memo of Usability Test Protocol for (b) (4)
CDRH Consult Review (b) (4)
(b) (4)
(b) (4)
ISO 11608-1: 2000 - **Pen-injectors for medical use —** Part 1: **Pen-injectors — Requirements and test methods**

Review and Comments

Page 12/38 of ISO 11608-1:2000 states the following:

3.6
injection stroke
that portion of a parenteral injection involving movement of the injection mechanism following initiation by the release mechanism

NOTE It does not include the subsequent relaxation of the system components required for the complete injection of the pre-set dose.

Page 14/38 of ISO 11608-1: 2000 states the following under Section 5 – General requirements

The pen-injector shall indicate, by visual, audible or tactile means or any combination of these, that the injection stroke has been completed.

Page 28/38 of ISO 11608-1: 2000 states the following under Section 15.3 – Instructions for Use

h) time to wait before removing the needle from the injection site;

The sponsor, Novo Nordisk, is technically correct in their response stating that their device complies with ISO 11608-1. Their device does show a visual cue when the injection stroke volume is complete by setting the counter to zero. However, ISO 11608-1 also recognized that injection stroke is not equivalent to complete injection of the pre-set dose in that in order to complete injection, there is also subsequent relaxation of the system components following injection stroke. Thus, ISO 11608-1 under section 15.3 (Instructions for Use) also stipulated that IFU should be clear regarding the time to wait before removing the needle from the injection site in order for the patient to receive the full dose of medication.

PDS290 IFU specifies to hold the needle under the skin for 6 seconds, but the common mistake among patients is to pull out the needle as soon as the counter is re-set to zero. The larger the volume of medication to deliver, the longer time it would take for the whole dose of medication to travel through the pen-injector system to the tip of the needle and thus it is very important for those insulin-resistant patients (receiving large amounts of insulin per injection) to hold the needle under the skin for the specified period of time in order to receive the full prescribed dose of insulin.

Novo Nordisk has demonstrated that early needle removal can lead to under-dosing by as much as 20.4% in their testing and thus should prominently highlight this warning in their written labeling as well as their education of the diabetic educators so these educators can hammer this point home with their patients along with the possible hyperglycemic consequences if they disregard this warning.

Recommendation

1. **Novo Nordisk should clearly highlight in their labeling that when the counter is reset to zero, the prescribed dose is not completely delivered until 6 seconds later.**
2. **Prominent warning to the patients in the labeling that if the needle is removed before counting to 6 seconds after the counter is reset to zero, then under-dosing will occur by as much as 20% and patient may have hyperglycemic consequences and require additional insulin administration.**
3. **Novo Nordisk should target the diabetic educators/prescribing clinicians to emphasize this under-dosing problem so that these educators can re-enforce these points with their patients regarding the clinical adverse consequences as well as the economic burden of increased medication cost (clinicians often increase the insulin dose assuming that previously prescribed insulin did not have the desired effect).**

Lana Shiu, M.D.

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/s/

CALLIE C CAPPEL-LYNCH
08/09/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES **MEMORANDUM**

Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993

DATE: July 26, 2013

FROM: QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGID

THROUGH: Ron Kaye, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGID

TO: Callie Cappel-Lynch, Regulatory Project Manager, CDER/OND/ODEII/DMEP
Please see letter-ready comments in blue text on page 2 of this memo

SUBJECT: NDAs 29086/S61 and NDA 211536/S33
Applicant: Novo Nordisk
Drug: Novolog and Levemir
Device: Peninjector
Intended Use: for treatment of diabetes
CDRH CTS Tracking: ICC1300172/CON138404

QuynhNhu Nguyen, Combination Products Human Factors Specialist

Ron Kaye, Human Factors and Device Use-Safety Team Leader

Overview and Recommendations

The Division of Metabolism and Endocrinology Products, Office of Drug Evaluation II, Office of New Drugs, Center for Drug Evaluation and Research, requested a Human Factors consultative review of the resubmission of the NDAs 20986 S61 and 21536 S33 by Novo Nordisk. The Applicant seeks FDA's approval for the PDS290 pen injector used for management of diabetes. This review provides CDRH's review and recommendations on the Human Factors related information contained in the sNDA.

In this submission, the Sponsor conducted a focused HFE/usability validation test, UT103 on the handling of the PDS290 (b) (4) 200 U/mL pen-injector to supplement the primary usability test, UT54, and a supplemental usability test, UT86. UT103 is designed to revalidate the peninjector after modifications made to the instructions for use (IFU) and the ancillary instructional video. There were multiple use errors were seen in the untrained group, mostly with the blocked needle condition i.e. blocked needle not detected, and user misinterprets the dose delivered after detecting blocked needle. As previously evaluated, for blocked needle conditions, the device dose counter may show a displacement of to a maximum of 7 units, which the user can misinterpret that the 7 units have been delivered, and if the user detects the blocked needle and attempt to fix it, they may not realize that they need to redial the full dose, which can result in underdosing. This reviewer discussed the issue with an endocrinologist and device reviewer. This issue appears to be unique to this device platform. The mechanism for which the dose dial operates should not impacted by the block needle condition i.e. the dose counter should not change when there is no insulin delivered. In addition, the clinical impact of 7 units being underdosed can be clinically significant depending on the patient's sensitivity to insulin. Therefore, CDRH HF recommends that these issues be addressed so that these use errors are effectively minimized. Please transmit the following deficiency to the Sponsor:

We reviewed your study results for UT103. We noted that the modifications to the IFU and training showed improvement in use performance in the training group e.g. there were no patterns of use errors. However, the use errors seen in the untrained group indicated user continue to experience use errors especially with the blocked needle situation, which you previously reported in UT86. Even with the modifications to the IFU and training video, we believe that the dose counter is not optimally designed in the case of a blocked needle as it can mislead users to interpret that some insulin has been delivered when in actuality, no insulin has been delivered. We also believe that the clinical impact of up to 7 units being underdosed due to blocked needle situation can be clinically significant depending on the patient's sensitivity to insulin, and if the user does not realize the problem, this can result in repeated underdosing. We recommend that you further address this problem by modifying the product design so that the dose counter does not change the number of units displayed on the window when no insulin has been delivered. Additionally, further review of the most recent version of the IFU indicated that it does not describe the hazard in detail nor provide instructions for the proper user response to address the hazard and to resolve a blocked needle situation. Please revise the IFU to notify the user of blocked needle situation, and provide instructions for proper user response.

CDRH Human Factors Review

Combination Product Device Information

NDAs 29086/S61 and NDA 211536/S33
Applicant: Novo Nordisk
Drug: Novolog and Levemir
Device: Peninjector
Intended Use: for treatment of diabetes
Review Materials:
Links to the cover letter and EDR location for each NDA:
Cover Letter: \\CDSESUB1\EVSPROD\NDA020986\0113\m1\us\102-cover-letters\cover.pdf
EDR Location: \\CDSESUB1\EVSPROD\NDA020986\020986.enx
EDR Location: \\CDSESUB1\EVSPROD\NDA021536\021536.enx

CDRH Human Factors Involvement History

Date	Involvements
7/26/2013	CDRH HF provided a review of the human factors report for Levemir® and NovoLog® PDS290 Pen-Injector (UT 103)
3/7/2012	CDRH HF provided a review of the human factors reports for Levemir® and NovoLog® PDS290 Pen-Injector (UT 86)

Summary of Review Materials and Reviewer Discussion

In this supplement, the Sponsor conducted a focused HFE/usability validation test, PDS290-UT103-2012 (UT103) on the handling of the PDS290 (b) (4) 200 U/mL pen-injector in addition to the primary usability test, UT54, and a supplemental usability test, UT86. UT103 was designed to assess the additional mitigations implemented for the instructions for use (IFU) and the ancillary instructional video to address the following specific concerns received in the FDA's Discipline Review letter of July 09, 2012:

- Not setting the dose correctly for the (b) (4) 200 U/mL due to dose conversion
- Misinterpreted the dose delivered after detecting blocked needle
- Needle not held in skin for appropriate amount of time
- Validation of the PDS290 pen-injector by inpatient nurses

This study included 98 participants of the intended user population (adults/elderly/inpatient nurses) for the (b) (4) 200 U/mL pen-injector that were discussed and agreed to with the FDA during the Type C meeting teleconference held on October 03, 2012. The test included a normal injection and an artificially blocked needle task. The participants were divided into two groups where one received training prior to participating in the usability test session and one group did not. The study results are summarized in the following tables:

Table 6-2 Overview of task failure occurrences for trained participants

Task failure description	No. of task failures	Clinical evaluation of task failures
Pen is not primed before first injection	1	In the worst case, a single underdose, resulting in a transient, mild increase in blood glucose level (no or mild symptoms) with no medical consequences
Needle stick injury	1	Minor pain

Table 6-3 Overview of task failure occurrences for untrained participants

Task failure description	No. of task failures	Clinical evaluation of task failures
Blocked needle is not detected	3	In the worst case, a single underdose, resulting in a transient, mild increase in blood glucose level (no or mild symptoms) with no medical consequences
Needle is not fully inserted prior to injection start	1	
Needle is not removed after injection	1	
Misinterprets the dose delivered after detecting blocked needle	9	
Pen is not primed before first injection	18	
Dose not set correctly	1	No relevant or measurable effect in a real life setting
Pen-injector cap is not mounted after use	1	
Needle stick injury	1	Minor pain

While CDRH HF review is focused on the results of the training portion of the study, there appears to be a significant number of use errors observed in the untrained group. These use errors were seen mostly with the blocked needle condition i.e. blocked needle not detected, and user misinterprets the dose delivered after detecting blocked needle. These errors were also observed in the previous study. As a result, CDRH HF recommends that these issues be addressed so that these use errors are effectively minimized.

Appendix 1: Previous CDRH Review

DATE: 3/7/2012

FROM: QuynhNhu Nguyen, Biomedical Engineer, CDRH/ODE/DAGID
THROUGH: Ron Kaye, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGID
CC: Molly Story, Human Factors and Accessible Medical Technology Specialist, CDRH/ODE/DAGID
TO: Rachel Hartford, CDER/OND/ODEII/DMEP
SUBJECT: **sNDA 20986 and 21536, Novo Nordisk, PDS290 FlexTouch**
Project Manager: Rachel Hartford
CTS Tracking: GEN1200172/CON124052, Human Factors/Usability Review

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Review Summary

The Division of Metabolism and Endocrinology Products, Office of Drug Evaluation II, Office of New Drugs, Center for Drug Evaluation and Research, requested a Human Factors consultative review of the resubmission of the NDAs 20986 and 21536 by Novo Nordisk. The Applicant seeks FDA's approval for the PDS290 pen injector used for management of diabetes. This review provides CDRH's review and recommendations on the Human Factors related information contained in the sNDA.

Please note that the device platform used in this combination product is identical the device under [redacted] (b) (4). The Human Factors testing for those two NDAs illustrated major concerns regarding human factors/use-safety for which we issued an Information Request letter. For both sets of NDAs, the Human Factors testing showed use errors/failures continue to occur and therefore, findings regarding human factors/use safety concerns have not fully addressed. The reviewer is concerned that after two rounds of Human Factors validation testing performed on the PDS290 device (for multiple NDA submissions), users continue to experience failures that can impact safe and effective use of the device. These results indicated that failures and use errors that the device and its user interface including instructions and labeling as designed does not effective minimize hazards associated with use. The reviewer recommends that Novo Nordisk take the results of these evaluations and use them to further optimize the training, IFU and/or device user interface so that use errors are effectively minimized. Novo Nordisk should be asked to provide a proposal on how these use errors and failures can be addressed, and they should note any further mitigation/improvements should be demonstrated through focused HF/usability validation. Please see the recommendation section (page 6) for questions to be transmitted to Novo Nordisk.

CDRH Human Factors Review

Review Materials

sNDA Submission

Links to submissions:

Novolog NDA 020986/S-061 EDR Location: \\CDSESUB1\EVSPROD\NDA020986\0086

Levemir NDA 021536/S-033 EDR Location: \\CDSESUB1\EVSPROD\NDA021536\0063

- Module 3.2.P.7 Risk management analysis input to usability test
- Module 3.2.P.7 Summative usability test plan PDS290-UT64-2011
- Module 3.2.P.7 Validation of Device Use Levemir® and NovoLog® PDS290 Pen-Injector. Risk Management Conclusions, Final Report, with Appendix Summative Usability Test of PDS290 Pen Injector, Differentiation and Handling Tasks

CDRH HF Review

Combination Product Device Information

Submission Number: NDA 20986 - NovoLog® insulin aspart (rDNA origin) injection
NDA 21536 - Levemir® insulin detemir (rDNA origin) injection

Applicant: Novo Nordisk

Drug Constituent: PDS-290 Pen-Injector

Intended Use: Treatment of Diabetes (type 1 and 2)

CDRH Human Factors Involvement History

- 23-JUN-2010: CDRH Human Factors provided a review on Human Factors information for the device constituent of the NDA. The Human Factors review and recommendation were included in Nikhil Thakur's device review memo.
- 24-JAN-2012: CDRH Human Factors was requested to provide a consultative review on the resubmission of the NDA.

Review of Human Factors Related Information - Human Factors Report (Dated June 29, 2011)

Device Description

PDS290 is a pen-shaped, disposable injector that are prefilled with 300 unites insulin in total. The maximum dose per injection is 80 unites and the dose increment is 1 unit. The device is intended to function with a standard needle thread type A1 or a needle with a bayonet coupling. The PDS290-pen injector is currently approved by FDA for use with growth hormone (Norditropin FlePro).

It is estimated that more than half of all patients with type 2 diabetes are prescribed only on insulin product, either a basal insulin like Levemir or a combination product like Novolog Mix 70/30. Most other users are prescribed both basal and bolus insulin products.

(b) (4)

[redacted]

Figure 1: Levemir® FlexTouch® pen-injector (top) and Novolog® FlexTouch® pen-injector (bottom).
Pens are shown without caps.

Figure 2: Graphical depiction of PDS290 pen-injector with the trade name 'Levemir®FlexTouch®'

Summary of Human Factors Information

The sponsor submitted two main documents for Human Factors review:

- Risk Management Analysis Input to Usability Test (Doc ID:001054853, Dated 11-APR-2011)
- Validation of Device Use (UT64 Report, Dated 07-JUL-2011)

The device will be used in the home environment and hospital setting. Training is required for use with the product including identifying insulin variant(s). Once prescribed, the users can inject themselves or are injected by a caregiver/parent or a healthcare professional. However, different levels of training can be expected in real life. Therefore, as in real life situations, participants have been subject to different levels of training in the test environment. The participants were divided into different groups of 57 trained and 34 untrained participants (including the 4 pharmacists only performing the carton differentiation)

To prepare the pen-injector, a new needle is mounted by the user and the pen-injector is primed, thereafter the intended dose is set by rotating the dose selector clockwise (when looking directly at the PDS290 pen-injectors' dose button) until the required dose is visible in the display. The dose button does not protrude from the PDS290 pen-injector when dialling the dose selector. Dose delivery is accomplished by inserting the needle subcutaneously and pressing the dose button. During dose delivery, the PDS290 pen-injector produces a series of clicks to confirm that the injection is occurring. A distinct end-of-dose-click indicates when the display has returned to "0" (The clicks are only a supportive feedback). The full dose is delivered when the needle has been kept inserted into the skin at least 6 seconds after the display has returned to "0". The "6 second" duration is a conservative approach, and that exact duration is not safety critical, from a medical perspective provided that the timing is kept below 6 seconds, as the PDS290 pen-injector is within the dosage requirements, in accordance with ISO 11608-1 before the "6 second" duration.

Critical task categories have been identified by analysis (Use Error Risk Analysis) and during evaluation of post-market surveillance:

- Differentiation design: Dispensing errors at the pharmacy and selection of the wrong pen-injector in the home environment are the main reasons for mixing-up treatment. These types of use errors may have serious consequences for the user.
- Dose administration: This critical task category addresses a series of specific PDS290 pen-injector features, which have been made throughout development process based upon user input including readability improvements, improvements to Instructions for Use, testing of dose reversal process.
- Device handling: This critical task category addresses the remaining safety features as well as improvements to test methodology, which are not covered in differentiation design and dose administration.

When performing an injection with the PDS290 pen-injector, the following user steps/primary operation functions must be carried out.
Step 1: Pick the correct PDS290 carton/pen-injector with the intended insulin product
Step 2: Cap removal
Step 3: Verification via label and cartridge holder that it is the correct pen
Step 4: Check that the insulin in the pen-injector is clear and colourless
Step 5: Needle mounting
Step 6: Checking the insulin flow (priming)
Step 7: Setting intended dose (reversing the dose setting, if necessary)
Step 8: Understand the End-of-content indication (feature ensuring that no larger dose can be dialled than is left in the cartridge)
o This step only applies if the user is going to inject a dose larger than the remaining left in cartridge
Step 9: Subcutaneous needle insert
Step 10: Injecting the dose, including checking that scale drum returns to "0", and 6 seconds waiting time with needle in the skin, that is, full dose has been delivered
Step 11: Needle removal and disposal of used needle
Step 12: Cap mounting

The intended users of the pen-injector include patients, caregivers and healthcare professionals. There are five distinct user groups:
- Children (age 10 to 17) who self inject without a parent's involvement.
- Adults (age 18 to 64) who self-inject.
- Elderly (age 65 and older) who self-inject.
- Caregivers (age 18 to 64) who perform injections on others, such as young children, spouses and elderly.
- Healthcare professionals who provide injection pen prescriptions and teach others how to perform injections.

Known postmarket problems associated with a use error related event includewrong drug administered (0.12 events per million pens sold); drug dispensing error (0.05 events per million pens sold); incorrect storage of drug (0.04 events per million pens sold); wrong technique in drug usage process (0.03 events per million pens sold); incorrect dose administered (0.03 events per

million pens sold). In the early Concept Development Phase, the FlexPen® Life Cycle Management Plan, 2003, Ethnographic end-user video studies, 2003, expert panels, and market research were used to generate the basic design concepts for the PDS290 pen-injector. In addition, more than 2,800 users – children, adults, elderly, caregivers, and HCPs - participated in over 40 human factor testing studies performed in testing facilities, clinical setting or in the home.

The following table provides a summary of the objective/observational test results:

Risk identifier	Total opportunities to commit the use error	Number of participants committing error (no of participants in total)	Number of errors	Overall error rate	Success rate	Root causes assessed by Wiklund R&D to be common to many pen-injectors	Root causes assessed by Wiklund R&D as pen-injector specific
User chooses a carton with the wrong product and does not correct the error	281	4 (n=91)	9	3.20%	96.80%	9	0
User chooses a pen with the wrong product and does not correct the error	277	6 (n=87)	11	3.97%	96.03%	11	0
Needle is not screwed on all the way and error is not detected during priming	720	3 (n=87)	9	1.25%	98.75%	9	0
Pen is not primed before first injection	857	13 (n=87)	23	2.68%	97.32%	23	0
Pen is not primed between injections	857	24 (n=87)	66	7.70%	92.30%	66	0
Blocked needle is not detected	96	6 (n=87)	6	6.25%	93.75%	5	1[a)]
Dose not set correctly	660	12 (n=87)	12	1.82%	98.18%	7	5[a)]
Miscalculates second dose amount when splitting dose between nearly empty pen and new pen	57	8 (n=87)	8	14.04%	85.96%	8	0
Needle is not fully inserted prior to injection start	619	2 (n=87)	2	0.32%	99.68%	2	0
Dose button is not held down until dose counter is back to "0"	619	2 (n=87)	4	0.65%	99.35%	4	0
Needle is not removed after injection	720	10 (n=87)	23	3.19%	96.81%	23	0
Pen-injector cap is not mounted after use	619	3 (n=87)	5	0.81%	99.19%	5	0
Needle cap is not removed before insertion	619	4 (n=87)	24	3.88%	96.12%	24	0
Needle is not held in skin for 6 seconds after the scale is back to "0"	619	36 (n=87)	120	19.39%	80.61%	120	0

Despite many observed use errors, there were no additional mitigations implemented, and Novo Nordisk believes that the residual risks are minimal.

Review Comments

The reviewer notes that the device platform used in this combination product is identical the device under [redacted](b) (4) which is also from Novo

Nordisk. The Human Factors testing conducted with the product under those two NDAs illustrated major concerns regarding human factors/use-safety for which CDER issued an Information Request letter. The Human Factors testing for the subject NDAs also showed similar human factors/use safety concerns, where the test results did not provide the necessary evidence those representative users can use the device safely and effectively. Use errors and failures were observed across all user tasks, and some critical tasks showed a high proportion of use errors.

The reviewer is concerned that even with two rounds of Human Factors validation testing performed on the same device (for multiple NDA submissions), users continue to experience use errors/failures that can impact safe and effective use of the device. These results indicated that the device and its user interface including labeling/instructions for use as designed does not effective minimize hazards associated with use for which additional mitigations are necessary. These additional mitigations must be validated to demonstrate that the device can be used safely and effectively by the intended users.

The following deficiencies were communicated to CDER.

1. Provide additional information/clarification for the Validation of Device Use (UT64 NN Report, Dated 07-JUL-2011). This study reported high proportion of participants committing use errors across tasks associated with delivering an injection and some of the errors resulted in needle-prick injuries. Most of the use errors can result in underdosing, or when users not able to set the correct dose, can result in overdosing. Other use errors can result in needle-prick injuries, contamination, and infection. In the report, you provided some root cause analysis along with the position that the current mitigations are effective and that the residual risks are minimal, and stated that the root causes were associated with the users (i.e. user forgetfulness, habit, and misunderstanding) and that the root causes were not unique to the proposed pen-injector, or that the participants did not receive the necessary training. Please note that the Agency remains concerned with the study results showing significant safety related issues and critical hazards where you believe that no additional mitigations are necessary, and that potential failures might continue to occur in actual use. As a result, at this time, the Agency does not have adequate evidence to reasonable determine that the device can be used safely and effectively. The Agency requests that you take the results of these evaluations and use them to further optimize the device user interface including labeling/IFU so that use errors are effectively minimized. Please note that improvements should be demonstrated through focused HF/usability validation.

   Please address the following concerns:

   a. The Agency is most concerned with the following errors which could result in incorrect therapy/treatment. Of the 87 participants, you reported that
      - 12 participants did not set the dose correctly for their injection resulting in 12 use errors.

- 8 participants miscalculated second dose when using two pens resulting in 9 use errors.
- 2 participants did not hold the dose button down until it scales back to 0 position resulting in 4 use errors
- 36 participants did not hold the needle in the skin for an appropriate amount of time resulting in 120 use errors
- 4 participants experienced needle prick injuries resulting in 5 use errors
- 3 participants did not put the cab back on after use resulting in 5 use errors
- 3 participants did not detect blocked needle resulting in 3 use errors

additional clarification is necessary for the following items:

i. For the use errors associated with participants who did not set the dose correctly for their injection, the narrative provided in the root cause analysis section was not clear on how the use error occurred among the sequence of use interaction steps, and what "visual feedback" the users received or did not receive from the device. It was also not clear if any of the users recognize that a full dose has not been delivered, and what aspect of the device designed allowed them to do so. Address the above concerns and provide a side by side comparison of the correct injection sequence versus the sequence for which all of the use errors occurred. Also, clearly describe how the user errors occurred along with screen shots of the device status at each of the steps. Indicate which of these participants ultimately delivered/did not deliver a correct dose. Also provide a clarification on the "visual feedback" and clarification on the clinical significance of the one participant who injected both a priming dose and a prescribed dose. Also, provide subjective feedback from users on the root cause of the use errors in your analysis of the errors.

ii. For the use errors associated with participants miscalculating second dose when using two pens. The use errors analysis did not include the necessary subjective data that are focused on identifying the root cause of the failures and potential design improvements recommendations from the perspective of representative users. The report remained unclear in terms of which of these participants ultimately delivered/did not deliver a correct dose. Provide additional information that addresses the above concerns.

iii. For the use errors associated with participants did not hold the dose button down until it scales back to 0 position resulting in 4 use errors, the Agency notes that this is a critical task in ensuring that the patients receive a full dose of intended insulin. It appears that the user interface including instructions for use and labeling do not provide sufficient feedback to the users and to prevent underdosing. Provide a proposal on how these errors can be addressed, and note any further mitigation will need to be evaluated for effectiveness.

iv. For the use errors associated with participants who did not hold the needle in the skin for an appropriate amount of time, it is unclear why you specified that the needle should be held in the skin for 6 seconds, but

stated that dose accuracy testing demonstrated that a full dose can be delivered 1 second after the dose counter returns to "0." The report did not include the necessary subjective data that are focused on identifying the root cause of the failures and potential design improvements recommendations from the perspective of representative users. Furthermore, stating that the root causes were associated with user forgetfulness, habit, and misunderstanding, etc. or that the root causes were not unique to the proposed pen-injector did not provide adequate evidence demonstrating that the device can be used safely and effective. It appears that the user interface including instructions for use and labeling do not provide sufficient feedback to the users and to prevent underdosing. Please provide a proposal on how these errors can be addressed, and note any further mitigation will need to be evaluated for effectiveness.

v. For the use errors associated with participants experienced needle prick injuries, the Agency is concerned with needle prick injuries associated with the use of this product and requests that you optimize the design and/or IFU and training to minimize the rate of occurrence of needle prick injuries.

vi. For the use errors associated with participants who did not put the cab back on after use resulting in 4 use errors, the sponsor stated these errors can result in underdosing. It is not clear how degradation caused by exposure to sunlight due to cap not mounted after use can result in underdosing. Furthermore, it is not clear what is the clinical impact of patients injecting insulin that has been degraded, and how would the patient detect that the insulin has been degraded. The Agency believes the device user interface can be further optimized to improve use performance.

vii. For the use errors associated with participants who did not detect blocked needle, you stated that the resulting harm is that patient may miss a dose. It is not clear if the pen-injector provides any feedback to user in this situation, and whether or not the users recognize that they did not receive any insulin. Indicate what aspects of the device design were or were not effective in mitigating use-related risks, and why potential improvement the to device design will not fully mitigate those use related risks.

viii. You also reported deviations and close calls. While these are "deviations" and "close-calls" that did no result in medical consequences, you did not provide a discussion of how users were able to recognize the potential failures and what steps they took correct themselves. Please provide in your discussion how the design of the device and its labeling influenced the patient's behavior for self-correction.

b. Please note that the Agency expects to review a report of the human factors/usability evaluation and validation testing without any pattern of use errors, and a conclusion that the device is reasonably safe and effective for the

intended users, uses and use conditions can be determined based on the test results. At this time, the Agency is concerned with that your testing did not provide the level of evidence necessary to support a conclusion that the device can be used safely and effectively by representative users. In addition, the Agency notes that the device platform used in this combination product is identical the device under [redacted] (b) (4) The Human Factors testing for those two NDAs illustrated major concerns regarding human factors/use-safety for which we issued an Information Request letter. For both sets of NDAs, the Human Factors testing showed use errors/failures continue to occur and therefore, findings regarding human factors/use safety concerns have not fully addressed. The Agency is concerned that after two rounds of Human Factors validation testing performed on the PDS290 device (for multiple NDA submissions), users continue to experience failures that can impact safe and effective use of the device. These results indicated that failures and use errors that the device and its user interface including instructions and labeling as designed does not effective minimize hazards associated with use. The Agency recommends that you take the results of these evaluations and use them to further optimize the training, IFU and/or device user interface so that use errors are effectively minimized. Provide a proposal on how these use errors and failures can be addressed, and note any further mitigation/improvements should be demonstrated through focused HF/usability validation.

Guidance on human factors procedures to follow can be found in *Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management,* available online at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm.

Note that we recently published a draft guidance document that, while not yet in effect, might also be useful in understanding our current thinking and our approach to human factors. It is titled, *Applying Human Factors and Usability Engineering to Optimize Medical Device Design* and can be found online at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm.

In responding to these deficiencies, the Sponsor provided additional clarifications and analyses. However, the review of the Sponsor's response generated the following deficiencies:

The UT86 report, while demonstrating that through improving IFU and training materials, the use errors can be reduced, we are concerned with the results of the study continue to show use errors that can result in incorrect dosing that require further mitigations. We are most concerned with the following findings:

1 participant did not set dose correctly and committed use error

You reported that this participant was an elderly, pen-experienced, and untrained participant. The participant was on basal bolus insulin therapy with Lantus vial and syringe as basal insulin and NovoLog FlexPen as bolus insulin. It should be noted that the Novolog FlexPen delivers 1 unit increments of insulin when dialled. When using his vial and syringe, he has to convert number of units to the correct volume. The test reslts reported that this participant dialled and administered an incorrect dose during two different tasks during normal injection and during end-of content/split dose between two pens. You also reported that one participant experienced close call with this step. Because this type of use error can result incorrect dosing in actual use and while you have taken helpful measures to reduce the potential of use errors, it appears that you do not directly address the potential of risk of users converting the number of units required based on the prescribed dose. We recommends that you implement further mitigation via modifying the IFU to inform the users that regardless of the concentration of insulin used, the PDS290 pen-injectors are designed to deliver the specified number of insulin units as prescribed, and that the users do not need to perform any dose conversion.

1 participant misinterpret the dose delivered after detecting blocked needle
You reported that this participant was an elderly, pen-experienced and untrained participant. The participant set the dose correctly (instructed dose - 36 units of 200 U/ml (b) (4) and attempted to administer the injection. However, due the block needle scenario, the participant incorrectly concluded that he had delivered 10 units, and that he needed to deliver 26 additional units to administer the full 36 unit dose. The participant replaced the needle on the pen-injector and administered 26 units, rather than 36 units. Because this type of use error can result incorrect dosing in actual use and while you have taken helpful measures to reduce the potential of use errors, it appears that you do not directly address the potential of risk of users misinterpreting that some insulin has been delivered when in actuality, no insulin has been delivered in situation where the needle is blocked. You also reported that two participants experienced close call with this step. As previously communicated in our General Advice letter dated May 3, 2012, this finding indicated that user might not be aware of the potential for dose counter malfunction associated with blocked needles i.e. the device dose counter may wrongly report that up to a maximum of 7 units have been delivered. This could result in clinically significant dosing errors after the user discovers that the needle on the device is blocked. We conclude that the dose counter, which serves as a visual feedback to the users, is not optimally designed as it can mislead users and cause confusion with regards to dosing after the device problem (i.e. blocked needle) is discovered. If there are no design alternatives to reduce this risk further, we recommend that you implement further mitigation via modifying the IFU to inform the users that in case of a blocked needle, the dose counter will display a value that is different from the original dose that the user has set. In addition, the IFU should provide specific instructions for use to resolve a blocked needle situation.

2 participants did not hold the needle at the injection site for the specified time
You reported that one participant was an elderly, pen-experienced and trained participant committed one use error during her fifth task (blocked needle). The other participant was an adult, pen-naïve and untrained participant committed one use error during the first task (normal injection). The participants both set the dose correctly and administered the injection, but held

the needle in the cushion for less than one second after the dose counter had returned to"0". You also reported that one participant experienced close call with this step. As previously communicated in our General Advice letter dated May 3, 2012, we are concerned that you instruct patients to hold the needle for 6 seconds. However, in the study, you defined that it is only a use error if the participant did not keep the needle in the skin for at least 1 second after the dose counter returns to "0." If proper injection is defined as holding the needle for 6 seconds, then the study should demonstrate that users can hold the device for 6 seconds.

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/s/

CALLIE C CAPPEL-LYNCH
08/09/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label, Labeling and Packaging Review

Date:	July 18, 2013
Reviewer:	Sarah K. Vee, PharmD Division of Medication Error Prevention and Analysis
Team Leader:	Yelena Maslov, PharmD Division of Medication Error Prevention and Analysis
Associate Director:	Scott Dallas, RPh Division of Medication Error Prevention and Analysis
Drug Names and Strengths:	Novolog and Levemir FlexTouch
Application Type/Number:	NDA 20986/S-061 and NDA 21536/S-033
Applicant/sponsor:	Novo Nordisk
OSE RCM #:	2013-827 & 828

*** This document contains proprietary and confidential information that should not be released to the public.***

Contents

1 INTRODUCTION

This review evaluates the proposed container label, carton labeling, and instructions for use (IFU) for Novolog (NDA 20986) and Levemir (NDA 21536) for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

Prior Approval Supplements for NDA 20986/S-061 and NDA 21536/S-033 were submitted on December 15, 2009. These Prior Approval Labeling Supplements provide for the addition of a new prefilled multiple-dose disposable insulin delivery device, PDS290 prefilled pen (FlexTouch).

- The Agency issued a Complete Response (CR) Letter on August 20, 2010 citing inadequate human factors testing.
- On July 13, 2011 the Applicant submitted a response to the August 20, 2010 CR letter.
- The Center for Devices and Radiologic Health (CDRH) communicated to the Division of Metabolic and Endocrine Products (DMEP) on March 5, 2012 that the PDS290 pen device is not in compliance with ISO standard 11608-1. A second CR letter was issued on March 20, 2012.
- A general advice letter dated March 16, 2012 was sent regarding their human factors study that the Applicant submitted on July 13, 2011 that provided comments and recommendations.
- On March 22, 2013 the Applicant resubmitted a response to the Mach 20, 2012 CR letter and provided a response regarding the compliance with the ISO 11608-1 standard. The Applicant stated that the ISO compliance issue is addressed by the March 23, 2012 response to (b) (4) which has the same proposed PDS290 pen injector device.
    - The Applicant also stated that the summative usability testing (UT54, UT64, UT86, UT103) for the PDS290 pen injectors validated all use-safety related aspects of the device and demonstrated that the improvements to the IFU and ancillary instructional video have proven effective in mitigating the use errors that were listed in the Agency's Information Request/General Advice letters.

1.2 PRODUCT INFORMATION – NOVOLOG

The following product information is provided in the 3/22/2013 resubmission for S-061.

- Active Ingredient: Insulin aspart [rDNA origin]
- Indication of Use: an insulin analog indicated to improve glycemic control in adults and children with diabetes mellitus
- Route of Administration: Subcutaneous injection
- Dosage Form: solution

- Strength: 100 units per mL
- Dose and Frequency: Individualized
- How Supplied: 10 mL vials, 3 mL PenFill cartridges, 3 mL Prefilled pen
- Storage:

NovoLog presentation	Not in-use (unopened) Room Temperature (below 30°C)	Not in-use (unopened) Refrigerated	In-use (opened) Room Temperature (below 30°C)
10 mL vial	28 days	Until expiration date	28 days (refrigerated/room temperature)
3 mL PenFill cartridges	28 days	Until expiration date	28 days (Do not refrigerate)
3 mL NovoLog FlexPen	28 days	Until expiration date	28 days (Do not refrigerate)

1.3 PRODUCT INFORMATION - LEVEMIR

The following product information is provided in the 3/22/13 resubmission for S-033.

- Active Ingredient: insulin detemir [rDNA origin]
- Indication of Use: long-acting human insulin analog indicated to improve glycemic control in adults and children with diabetes mellitus
- Route of Administration: subcutaneous injection
- Dosage Form: solution
- Strength: 100 units per mL
- Dose and Frequency: individualized dose once or twice daily
- How Supplied: 10 mL vial, 3 mL prefilled pen
- Storage:

	Not in-use (unopened) Refrigerated	Not in-use (unopened) Room Temperature (below 30°C)	**In-use (opened)**
3 mL FlexPen	Until expiration date	42 days*	42 days* Room Temperature (below 30°C) **(Do not refrigerate)**
3 mL FlexTouch	Until expiration date	42 days*	42 days* Room Temperature (below 30°C) **(Do not refrigerate)**
10 mL vial	Until expiration date	42 days*	42 days* Refrigerated or Room Temperature (below 30°C)

2 METHODS AND MATERIALS REVIEWED

DMEPA reviewed the Novolog and Levemir container labels, carton and package insert labeling submitted by the Applicant.

2.1 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,[1] along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Novolog Labeling submitted March 22, 2013 (Appendix A)
- Levemir Labeling submitted March 22, 2013 (Appendix B)
- Insert Labeling submitted March 22, 2013 (no image)

2.2 PREVIOUSLY COMPLETED REVIEWS

DMEPA had previously reviews the proprietary names "Levemir FlexTouch" and Novolog Flextouch" in OSE Reviews 2009-2457 and 2012-279 and found the names acceptable.

Additionally, DMEPA had previously reviewed carton (trade and sample) and IFU for Novolog and Levemir FlexPens in OSE Review #2009-1281. This review looked at the Applicant's revised color of the cartridge holder from (b) (4) to match the color of the approved labels for each product (i.e. orange for Novolog FlexPen and green for Levemir FlexPen). DMEPA concluded that there is no evidence that the changes to the NovoLog FlexPens and Levemir FlexPens cartridge holder colors that have been marketed since December 2008 and February 2009, respectively, have caused medication errors leading to significant safety issues.

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

DMEPA also reviewed Human Factors Usability Protocols UT54, UT86, and UT103 as outlined below:

- December 2011: CDRH human factors team provided comments regarding the deficiencies of the summative user handing study (UT54) which were communicated to Novo Nordisk.
- February 16, 2012: Novo Nordisk submitted a protocol for a summative usability study (UT86) which assesses the changes made to the proposed training and Instructions for Use for the FlexTouch Pen (PDS290).
- June 26, 2012: DMEPA provided review of the data reported in UT86 in OSE review # 2012-1040.
    1. The use errors and close calls were few and distributed between both the trained and untrained participants using the PDS290 with the insulin in the 100 units/mL presentation. Furthermore, many of the use errors are not specific to the PDS290 and generally managed adequately in other pen devices via labeling. Overall, DMEPA finds from a medication error perspective that the summative study adequately demonstrates patients can safety and effectively use the FlexTouch Pen to administer (b) (4) in the 100 units/mL presentations and thus are acceptable.
- December 17, 2012: Novo Nordisk submitted the results of UT103 which was reviewed in OSE review 2012-2962.
    1. The use errors and close calls related to setting the dose in UT103 were few and distributed between both the trained and untrained participants using the PDS290 with the (b) (4) 200 units/mL presentation. We conclude based on the data provided from UT103 that the labeling, product design, and 1-800 support line minimize the risk of confusion from the (b) (4) FlexTouch pen in the 200 units/mL concentration would result in medication error. Overall, DMEPA finds from a medication error perspective that the summative study adequately demonstrates patients and healthcare providers can safely use the PDS290 to administer (b) (4) FlexTouch 200 units/mL presentation at this time and thus is suitable for approval.

2.3 OPEN TSI FOR INSULIN PENS

There is an open TSI involving insulin pens. TSI 651 was opened on March 12, 2009 to address the safety issue of potential exposure to blood borne pathogens with sharing of single patient use pen injectors. The review is ongoing and is relevant to this review regarding label and labeling recommendations.

3 DISCUSSION AND CONCLUSIONS

The Applicant's proposal to replace the FlexPen prefilled pen devices with the FlexTouch (PDS290) prefilled pen devices for Novolog and Levemir is acceptable based on the results and reviews that were conducted regarding the PDS290 prefilled pen devices summarized in Section 2.2.

DMEPA concludes that the proposed carton labeling, container label, and pen color schemes are acceptable because these products are already marketed and we have not identified any reports of confusion between them.

However, DMEPA concludes that proposed package insert, carton labeling and container label can be improved to promote the safe use of the product.

4 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA supplements:

A. Highlights of Prescribing Information

1. We recommend addition of the statement "Never Share a Novolog Flextouch Pen Between Patients, even if the needle is changed" under Section 5.1 to Warnings and Precautions.

2. Make the same revision for Levemir Flextouch pen.

B. Full Prescribing Information, Section 5, Warning and Precautions

1. We recommend adding Section 5.1 "Never Share a Novolog Flextouch Pen Between Patients" or "Never Share a Levemir Flextouch Pen Between Patients". Please put the following verbatim under this Section: "Novolog Flextouch pens should never be shared between patients, even if the needle is changed. Sharing of the pen between patients poses a risk of transmission of blood-borne pathogens".

2. Make the same revision for Levemir Flextouch pen.

C. Full Prescribing Information, Section 17.1

1. We recommend adding Section 17.1 "Never Share a Novolog Flextouch Pen Between Patients". Please put the following verbatim in that Section: "Advise patients that they should never share a Novolog Flextouch pen with another person, even if the needle is changed, because doing so carries a risk of transmission of blood-borne pathogens".

2. Make the same revision for Levemir Flextouch pen.

D. Container Label and Carton Labeling

1. We recommend that the statement "For Single Patient Use Only" remain on a separate line from other text and emphasized with color or other method of differentiation to draw attention to this statement. We recommend increasing the prominence of this statement to help mitigate the unsafe practice of insulin pen sharing.

If you have further questions or need clarifications, please contact Margarita Tossa, project manager, at 301-796-4053.

8 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

YELENA L MASLOV on behalf of SARAH K VEE
07/19/2013

YELENA L MASLOV
07/19/2013

SCOTT M DALLAS
07/19/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Human Factors Protocol Memorandum

Date:	March 12, 2012
Reviewer:	Jamie Wilkins Parker, Pharm.D. Division of Medication Error Prevention and Analysis (DMEPA)
Acting Team Leader:	Yelena Maslov, Pharm.D. Division of Medication Error Prevention and Analysis (DMEPA)
Deputy Division Director:	Kellie A. Taylor, Pharm.D., MPH Division of Medication Error Prevention and Analysis (DMEPA)
Drug Name and Strength:	Novolog (Insulin aspart) and Levemir (Insulin detemir)
Application Type/Number:	NDA 020986/S-061, NDA 021536/S-033
Applicant:	Novo Nordisk
OSE RCM #:	2012-241, 2012-365

1 INTRODUCTION

This memorandum responds to a request from the Division of Metabolic and Endocrine Products (DMEP) for DMEPA's evaluation of the Human Factors Usability study for Levemir and Novolog PDS290 pen injector.

2 BACKGROUND

The Applicant submitted a completed Human Factors and Usability report for the PDS290 pen injector on July 13, 2011. The Center for Devices and Radiologic Health (CDRH) communicated to the Division of Metabolic and Endocrine Products (DMEP) on March 5, 2012 that the PDS290 pen device is not in compliance with ISO standard 111608-1.

3 CONCLUSIONS AND RECOMMENDATIONS

The proposed pen injector, the PDS 290, is not in compliance with ISO standard 111608-1, and thus CDRH requires design changes of the device. The submitted data for the completed Human Factors Usability study for this device is therefore irrelevant at this time. However, we do have comments on the protocol, if the same or a similar protocol were to be used for any future devices. Please see our comments below:

A. Human Factors Study Protocol

1. Group Size, Composition, and Tasks:

   i. Your participant group does not include any inpatient nursing staff. Please include at least 15 nurses in any future studies, as they are a user group for one of your intended use settings for the device.

   ii. Testing should occur with not only NovoTwist® needles, but with any needle appropriate for use with your device, as a user may not solely rely on NovoTwist® needles for insulin delivery.

   iii. Although in your summative testing an analysis was completed on marketed insulin prefilled pen-injectors and cartons from two major competitors, it appears that those prefilled pen-injectors were not included in final validation testing. There continue to be ongoing selection errors not only within Novo-Nordisk's product line, but throughout multiple manufacturers' product lines. Therefore, if feasible, include other manufacturer's pens within your differentiation tasks.

   iv. We recommend submission of any new proposed Human Factors and Validation protocols for review prior to implementation of any further testing.

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/s/

JAMIE C WILKINS PARKER
03/13/2012

YELENA L MASLOV
03/13/2012

KELLIE A TAYLOR
03/14/2012

3/5/2012 GEN120172, CON124052

MANDATORY: Send a copy of the consult request form to the Office of Combination Products (OCP) as follows:
--Originating Center: When the consult request is initiated.
--Consulting Center: When the consult is completed.
Email: combination@fda.gov or FAX: 301-847-8619

For additional information: Contact OCP by email or by telephone (301-796-8930) or refer to OCP's intranet page http://inside.fda.gov:9003/ProgramsInitiatives/CombinationProducts/ReviewerTools/default.htm.

For Consulting Center Use Only:
Date Received: 1/24/2012
Assigned to: QuynhNhu Nguyen
Date Assigned:
Assigned by:
Completed date: 3/7/2012
Reviewer Initials: QNN
Supervisory Concurrence: Ron Kaye

Intercenter Request for Consultative or Collaborative Review Form

To (Consulting Center):
Center: CDRH
Division: ODE/DAGID/GHDB
Mail Code: HF
Consulting Reviewer Name:
Building/Room #:
Phone #:
Fax #:
Email Address:
RPM/CSO Name and Mail Code: Jaqueline Ryan

From (Originating Center):
Center: CDER
Division: DMEP
Mail Code: HF-510
Requesting Reviewer Name:
Building/Room #:
Phone#:
Fax #:
Email Address:
RPM/CSO Name and Mail Code: Rachel Hartford x60331
Requesting Reviewer's Concurring Supervisor's Name:

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: 24Jan12
Requested Completion Date: 5Mar12

Submission/Application Number: Novolog 020986/S-061 Levemir 021536/S-033
(Not Barcode Number)
Submission Type: sNDA resubmission
(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: 13July11
Official Submission Due Date: 5Mar12

Name of Product: Novolog FlexTouch (PDS290) Levemir FlexTouch (PDS290)
Name of Firm: Novo Nordisk

Intended Use: (375 characters max) Treatment of Diabetes

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):
(525 characters max) Resubmission.

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) Please review the resubmission. The initial CDRH review and resulting CR letter were sent via email to Jackie Ryan today.

Novolog EDR Location: \\CDSESUB1\EVSPROD\NDA020986\020986.enx
Supporting Document Number: 423 eCTD Sequence Number: 0086
Levemir EDR Location: \\CDSESUB1\EVSPROD\NDA021536\021536.enx
Supporting Document Number: 167 eCTD Sequence Number: 0063

Note: (b) (4)

DEPARTMENT OF HEALTH AND HUMAN SERVICES **MEMORANDUM**

Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

DATE: 3/7/2012
FROM: QuynhNhu Nguyen, Biomedical Engineer, CDRH/ODE/DAGID 3/7/2012
THROUGH: Ron Kaye, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGID 3/7/2012
CC: Molly Story, PhD, Human Factors and Accessible Medical Technology Specialist, CDRH/ODE/DAGID
TO: Rachel Hartford, CDER/OND/ODEII/DMEP
SUBJECT: **sNDA 20986 and 21536, Novo Nordisk, PDS290 FlexTouch**
Project Manager: Rachel Hartford
CTS Tracking: GEN1200172/CON124052, Human Factors/Usability Review

Review Summary

The Division of Metabolism and Endocrinology Products, Office of Drug Evaluation II, Office of New Drugs, Center for Drug Evaluation and Research, requested a Human Factors consultative review of the resubmission of the NDAs 20986 and 21536 by Novo Nordisk. The Applicant seeks FDA's approval for the PDS290 pen injector used for management of diabetes. This review provides CDRH's review and recommendations on the Human Factors related information contained in the sNDA.

Please note that the device platform used in this combination product is identical the device under NDAs [redacted] (b) (4) The Human Factors testing for those two NDAs illustrated major concerns regarding human factors/use-safety for which we issued an Information Request letter. For both sets of NDAs, the Human Factors testing showed use errors/failures continue to occur and therefore, findings regarding human factors/use safety concerns have not fully addressed. The reviewer is concerned that after two rounds of Human Factors validation testing performed on the PDS290 device (for multiple NDA submissions), users continue to experience failures that can impact safe and effective use of the device. These results indicated that failures and use errors that the device and its user interface including instructions and labeling as designed does not effective minimize hazards associated with use. The reviewer recommends that Novo Nordisk take the results of these evaluations and use them to further optimize the training, IFU and/or device user interface so that use errors are effectively minimized. Novo Nordisk should be asked to provide a proposal on how these use errors and failures can be addressed, and they should note any further mitigation/improvements should be demonstrated through focused HF/usability validation. Please see the recommendation section (page 6) for questions to be transmitted to Novo Nordisk.

CDRH Human Factors Review

Review Materials

sNDA Submission
Links to submissions:
Novolog NDA 020986/S-061 EDR Location: \\CDSESUB1\EVSPROD\NDA020986\0086
Levemir NDA 021536/S-033 EDR Location: \\CDSESUB1\EVSPROD\NDA021536\0063

- Module 3.2.P.7 Risk management analysis input to usability test
- Module 3.2.P.7 Summative usability test plan PDS290-UT64-2011
- Module 3.2.P.7 Validation of Device Use Levemir® and NovoLog® PDS290 Pen-Injector. Risk Management Conclusions, Final Report, with Appendix Summative Usability Test of PDS290 Pen Injector, Differentiation and Handling Tasks

CDRH HF Review

Combination Product Device Information

Submission Number: NDA 20986 - NovoLog® insulin aspart (rDNA origin) injection
NDA 21536 - Levemir® insulin detemir (rDNA origin) injection
Applicant: Novo Nordisk
Drug Constituent: PDS-290 Pen-Injector
Intended Use: Treatment of Diabetes (type 1 and 2)

CDRH Human Factors Involvement History

- 23-JUN-2010: CDRH Human Factors provided a review on Human Factors information for the device constituent of the NDA. The Human Factors review and recommendation were included in Nikhil Thakur's device review memo.
- 24-JAN-2012: CDRH Human Factors was requested to provide a consultative review on the resubmission of the NDA.

Review of Human Factors Related Information - Human Factors Report (Dated June 29, 2011)

Device Description
PDS290 is a pen-shaped, disposable injector that are prefilled with 300 unites insulin in total. The maximum dose per injection is 80 unites and the dose increment is 1 unit. The device is intended to function with a standard needle thread type A1 or a needle with a bayonet coupling. The PDS290-pen injector is currently approved by FDA for use with growth hormone (Norditropin FlePro).

It is estimated that more than half of all patients with type 2 diabetes are prescribed only on insulin product, either a basal insulin like Levemir or a combination product like Novolog Mix 70/30. Most other users are prescribed both basal and bolus insulin products.

Summary of Human Factors Information

The sponsor submitted two main documents for Human Factors review:

- Risk Management Analysis Input to Usability Test (Doc ID:001054853, Dated 11-APR-2011)
- Validation of Device Use (UT64 Report, Dated 07-JUL-2011)

The device will be used in the home environment and hospital setting. Training is required for use with the product including identifying insulin variant(s). Once prescribed, the users can inject themselves or are injected by a caregiver/parent or a healthcare professional. However, different levels of training can be expected in real life. Therefore, as in real life situations, participants have been subject to different levels of training in the test environment. The participants were divided into different groups of 57 trained and 34 untrained participants (including the 4 pharmacists only performing the carton differentiation)

To prepare the pen-injector, a new needle is mounted by the user and the pen-injector is primed, thereafter the intended dose is set by rotating the dose selector clockwise (when looking directly at the PDS290 pen-injectors' dose button) until the required dose is visible in the display. The dose button does not protrude from the PDS290 pen-injector when dialling the dose selector. Dose delivery is accomplished by inserting the needle subcutaneously and pressing the dose button. During dose delivery, the PDS290 pen-injector produces a series of clicks to confirm that the injection is occurring. A distinct end-of-dose-click indicates when the display has returned to "0" (The clicks are only a supportive feedback). The full dose is delivered when the needle has been kept inserted into the skin at least 6 seconds after the display has returned to "0". The "6 second" duration is a conservative approach, and that exact duration is not safety critical, from a medical perspective provided that the timing is kept below 6 seconds, as the PDS290 pen-injector is within the dosage requirements, in accordance with ISO 11608-1 before the "6 second" duration.

Critical task categories have been identified by analysis (Use Error Risk Analysis) and during evaluation of post-market surveillance:

• Differentiation design: Dispensing errors at the pharmacy and selection of the wrong pen-injector in the home environment are the main reasons for mixing-up treatment. These types of use errors may have serious consequences for the user.

• Dose administration: This critical task category addresses a series of specific PDS290 pen-injector features, which have been made throughout development process based upon user input including readability improvements, improvements to Instructions for Use, testing of dose reversal process.
• Device handling: This critical task category addresses the remaining safety features as well as improvements to test methodology, which are not covered in differentiation design and dose administration.

When performing an injection with the PDS290 pen-injector, the following user steps/primary operation functions must be carried out.
Step 1: Pick the correct PDS290 carton/pen-injector with the intended insulin product
Step 2: Cap removal
Step 3: Verification via label and cartridge holder that it is the correct pen
Step 4: Check that the insulin in the pen-injector is clear and colourless
Step 5: Needle mounting
Step 6: Checking the insulin flow (priming)
Step 7: Setting intended dose (reversing the dose setting, if necessary)
Step 8: Understand the End-of-content indication (feature ensuring that no larger dose can be dialled than is left in the cartridge)
o This step only applies if the user is going to inject a dose larger than the remaining left in cartridge
Step 9: Subcutaneous needle insert
Step 10: Injecting the dose, including checking that scale drum returns to "0", and 6 seconds waiting time with needle in the skin, that is, full dose has been delivered
Step 11: Needle removal and disposal of used needle
Step 12: Cap mounting

The intended users of the pen-injector include patients, caregivers and healthcare professionals. There are five distinct user groups:

- Children (age 10 to 17) who self inject without a parent's involvement.
- Adults (age 18 to 64) who self-inject.
- Elderly (age 65 and older) who self-inject.
- Caregivers (age 18 to 64) who perform injections on others, such as young children, spouses and elderly.
- Healthcare professionals who provide injection pen prescriptions and teach others how to perform injections.

Known postmarket problems associated with a use error related event includewrong drug administered (0.12 events per million pens sold); drug dispensing error (0.05 events per million pens sold); incorrect storage of drug (0.04 events per million pens sold); wrong technique in drug usage process (0.03 events per million pens sold); incorrect dose administered (0.03 events per million pens sold). In the early Concept Development Phase, the FlexPen® Life Cycle Management Plan, 2003, Ethnographic end-user video studies, 2003, expert panels, and market research were used to generate the basic design concepts for the PDS290 pen-injector. In addition, more than 2,800 users – children, adults, elderly, caregivers, and HCPs - participated in over 40 human factor testing studies performed in testing facilities, clinical setting or in the home.

The following table provides a summary of the objective/observational test results:

Risk identifier	Total opportunities to commit the use error	Number of participants committing error (no of participants in total)	Number of errors	Overall error rate	Success rate	Root causes assessed by Wiklund R&D to be common to many pen-injectors	Root causes assessed by Wiklund R&D as pen-injector specific
User chooses a carton with the wrong product and does not correct the error	281	4 (n=91)	9	3.20%	96.80%	9	0
User chooses a pen with the wrong product and does not correct the error	277	6 (n=87)	11	3.97%	96.03%	11	0
Needle is not screwed on all the way and error is not detected during priming	720	3 (n=87)	9	1.25%	98.75%	9	0
Pen is not primed before first injection	857	13 (n=87)	23	2.68%	97.32%	23	0
Pen is not primed between injections	857	24 (n=87)	66	7.70%	92.30%	66	0
Blocked needle is not detected	96	6 (n=87)	6	6.25%	93.75%	5	1[a)]
Dose not set correctly	660	12 (n=87)	12	1.82%	98.18%	7	5[a)]
Miscalculates second dose amount when splitting dose between nearly empty pen and new pen	57	8 (n=87)	8	14.04%	85.96%	8	0
Needle is not fully inserted prior to injection start	619	2 (n=87)	2	0.32%	99.68%	2	0
Dose button is not held down until dose counter is back to "0"	619	2 (n=87)	4	0.65%	99.35%	4	0
Needle is not removed after injection	720	10 (n=87)	23	3.19%	96.81%	23	0
Pen-injector cap is not mounted after use	619	3 (n=87)	5	0.81%	99.19%	5	0
Needle cap is not removed before insertion	619	4 (n=87)	24	3.88%	96.12%	24	0
Needle is not held in skin for 6 seconds after the scale is back to "0"	619	36 (n=87)	120	19.39%	80.61%	120	0

Despite many observed use errors, there were no additional mitigations implemented, and Novo Nordisk believes that the residual risks are minimal.

Review Comments

The reviewer notes that the device platform used in this combination product is identical the device under [redacted](b) (4), which is also from Novo Nordisk. The Human Factors testing conducted with the product under those two NDAs illustrated major concerns regarding human factors/use-safety for which CDER issued an Information Request letter. The Human Factors testing for the subject NDAs also showed

similar human factors/use safety concerns, where the test results did not provide the necessary evidence those representative users can use the device safely and effectively. Use errors and failures were observed across all user tasks, and some critical tasks showed a high proportion of use errors.

The reviewer is concerned that even with two rounds of Human Factors validation testing performed on the same device (for multiple NDA submissions), users continue to experience use errors/failures that can impact safe and effective use of the device. These results indicated that the device and its user interface including labeling/instructions for use as designed does not effective minimize hazards associated with use for which additional mitigations are necessary. These additional mitigations must be validated to demonstrate that the device can be used safely and effectively by the intended users.

Human Factors Recommendations

Please transmit the following deficiencies to Novo Nordisk.

1. Provide additional information/clarification for the Validation of Device Use (UT64 NN Report, Dated 07-JUL-2011). This study reported high proportion of participants committing use errors across tasks associated with delivering an injection and some of the errors resulted in needle-prick injuries. Most of the use errors can result in underdosing, or when users not able to set the correct dose, can result in overdosing. Other use errors can result in needle-prick injuries, contamination, and infection. In the report, you provided some root cause analysis along with the position that the current mitigations are effective and that the residual risks are minimal, and stated that the root causes were associated with the users (i.e. user forgetfulness, habit, and misunderstanding) and that the root causes were not unique to the proposed pen-injector, or that the participants did not receive the necessary training. Please note that the Agency remains concerned with the study results showing significant safety related issues and critical hazards where you believe that no additional mitigations are necessary, and that potential failures might continue to occur in actual use. As a result, at this time, the Agency does not have adequate evidence to reasonable determine that the device can be used safely and effectively. The Agency requests that you take the results of these evaluations and use them to further optimize the device user interface including labeling/IFU so that use errors are effectively minimized. Please note that improvements should be demonstrated through focused HF/usability validation.

   Please address the following concerns:

   a. The Agency is most concerned with the following errors which could result in incorrect therapy/treatment. Of the 87 participants, you reported that
      - 12 participants did not set the dose correctly for their injection resulting in 12 use errors.
      - 8 participants miscalculated second dose when using two pens resulting in 9 use errors.
      - 2 participants did not hold the dose button down until it scales back to 0 position resulting in 4 use errors

- 36 participants did not hold the needle in the skin for an appropriate amount of time resulting in 120 use errors
- 4 participants experienced needle prick injuries resulting in 5 use errors
- 3 participants did not put the cab back on after use resulting in 5 use errors
- 3 participants did not detect blocked needle resulting in 3 use errors

additional clarification is necessary for the following items:

i. For the use errors associated with participants who did not set the dose correctly for their injection, the narrative provided in the root cause analysis section was not clear on how the use error occurred among the sequence of use interaction steps, and what "visual feedback" the users received or did not receive from the device. It was also not clear if any of the users recognize that a full dose has not been delivered, and what aspect of the device designed allowed them to do so. Address the above concerns and provide a side by side comparison of the correct injection sequence versus the sequence for which all of the use errors occurred. Also, clearly describe how the user errors occurred along with screen shots of the device status at each of the steps. Indicate which of these participants ultimately delivered/did not deliver a correct dose. Also provide a clarification on the "visual feedback" and clarification on the clinical significance of the one participant who injected both a priming dose and a prescribed dose. Also, provide subjective feedback from users on the root cause of the use errors in your analysis of the errors.

ii. For the use errors associated with participants miscalculating second dose when using two pens. The use errors analysis did not include the necessary subjective data that are focused on identifying the root cause of the failures and potential design improvements recommendations from the perspective of representative users. The report remained unclear in terms of which of these participants ultimately delivered/did not deliver a correct dose. Provide additional information that addresses the above concerns.

iii. For the use errors associated with participants did not hold the dose button down until it scales back to 0 position resulting in 4 use errors, the Agency notes that this is a critical task in ensuring that the patients receive a full dose of intended insulin. It appears that the user interface including instructions for use and labeling do not provide sufficient feedback to the users and to prevent underdosing. Provide a proposal on how these errors can be addressed, and note any further mitigation will need to be evaluated for effectiveness.

iv. For the use errors associated with participants who did not hold the needle in the skin for an appropriate amount of time, it is unclear why you specified that the needle should be held in the skin for 6 seconds, but stated that dose accuracy testing demonstrated that a full dose can be delivered 1 second after the dose counter returns to "0." The report did not include the necessary subjective data that are focused on identifying the root cause of the failures and potential design improvements recommendations from the perspective of representative users. Furthermore, stating that the root causes were associated with user

forgetfulness, habit, and misunderstanding, etc. or that the root causes were not unique to the proposed pen-injector did not provide adequate evidence demonstrating that the device can be used safely and effective. It appears that the user interface including instructions for use and labeling do not provide sufficient feedback to the users and to prevent underdosing. Please provide a proposal on how these errors can be addressed, and note any further mitigation will need to be evaluated for effectiveness.

v. For the use errors associated with participants experienced needle prick injuries, the Agency is concerned with needle prick injuries associated with the use of this product and requests that you optimize the design and/or IFU and training to minimize the rate of occurrence of needle prick injuries.

vi. For the use errors associated with participants who did not put the cab back on after use resulting in 4 use errors, the sponsor stated these errors can result in underdosing. It is not clear how degradation caused by exposure to sunlight due to cap not mounted after use can result in underdosing. Furthermore, it is not clear what is the clinical impact of patients injecting insulin that has been degraded, and how would the patient detect that the insulin has been degraded. The Agency believes the device user interface can be further optimized to improve use performance.

vii. For the use errors associated with participants who did not detect blocked needle, you stated that the resulting harm is that patient may miss a dose. It is not clear if the pen-injector provides any feedback to user in this situation, and whether or not the users recognize that they did not receive any insulin. Indicate what aspects of the device design were or were not effective in mitigating use-related risks, and why potential improvement the to device design will not fully mitigate those use related risks.

viii. You also reported deviations and close calls. While these are "deviations" and "close-calls" that did no result in medical consequences, you did not provide a discussion of how users were able to recognize the potential failures and what steps they took correct themselves. Please provide in your discussion how the design of the device and its labeling influenced the patient's behavior for self-correction.

b. Please note that the Agency expects to review a report of the human factors/usability evaluation and validation testing without any pattern of use errors, and a conclusion that the device is reasonably safe and effective for the intended users, uses and use conditions can be determined based on the test results. At this time, the Agency is concerned with that your testing did not provide the level of evidence necessary to support a conclusion that the device can be used safely and effectively by representative users. In addition, the Agency notes that the device platform used in this combination product is identical the device under [redacted] (b) (4). The Human Factors testing for those two NDAs illustrated major concerns regarding human factors/use-safety for which we issued an Information Request letter. For both

sets of NDAs, the Human Factors testing showed use errors/failures continue to occur and therefore, findings regarding human factors/use safety concerns have not fully addressed. The Agency is concerned that after two rounds of Human Factors validation testing performed on the PDS290 device (for multiple NDA submissions), users continue to experience failures that can impact safe and effective use of the device. These results indicated that failures and use errors that the device and its user interface including instructions and labeling as designed does not effective minimize hazards associated with use. The Agency recommends that you take the results of these evaluations and use them to further optimize the training, IFU and/or device user interface so that use errors are effectively minimized. Provide a proposal on how these use errors and failures can be addressed, and note any further mitigation/improvements should be demonstrated through focused HF/usability validation.

Guidance on human factors procedures to follow can be found in *Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management,* available online at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm.

Note that we recently published a draft guidance document that, while not yet in effect, might also be useful in understanding our current thinking and our approach to human factors. It is titled, *Applying Human Factors and Usability Engineering to Optimize Medical Device Design* and can be found online at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm.

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/s/

RACHEL E HARTFORD
03/12/2012
On behalf of QuynhNhu Nguyen, Biomedical Engineer, CDRH/ODE/DAGID

DEPARTMENT OF HEALTH AND HUMAN SERVICES **MEMORANDUM**

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
White Oak Building 66
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: March 5, 2012
From: Jacqueline Ryan, Combination Products Team Leader, WO66, RM 1257
General Hospital Devices Branch, DAGID, ODE, CDRH

To: Rachel Hartford, Regulatory Project Manager, CDER/ DMEP
Subject: CDRH Consult, CTS GEN 1200197, NDA 021536 PDS290Pen injector to deliver Levemir (insulin detemir)

1. Issue

The Center for Drug Evaluation and Research (CDER) has requested a consult from the Center for Devices and Radiological Health (CDRH), regarding NDA 021536. The device constituent of this combination product consists of the PDS290 Pen injector to deliver Levemir (insulin detemir).

2. Device Description

The PDS290 pen-injector is a prefilled multi dose device which cannot be reloaded and is intended to be registered as a drug or a drug and device. (b) (4)

3. Documents Reviewed

NDA 021536\0063

4. CDRH Review and Comments

The sponsor states:
In the Complete Response letter, the Agency requested clarification on the dose accuracy testing, specifically regarding the statement that "the push buttons were blocked" and on the functionality of the (b) (4) *in the original device.*

The push button blockage occurred during qualification testing of the original device. The blockage was due to the (b) (4) *in the original device. In early development stages of the pen injector,* (b) (4) (b) (4)

The final device design addressed the potential issue of the (b) (4) (b) (4)

Dose accuracy tests at the standard temperature (18 – 28°C), hot atmosphere (40°C), and cold atmosphere (5°C) have been performed on the final released Levemir and NovoLog PDS290 pen injectors in accordance with ISO 11680-1

All results from the dose accuracy testing were within the dose accuracy specification limits. Therefore, NovoLog and Levemir PDS290 pen injectors, as final devices, met the requirements as defined in ISO 11608-1, and passed the performance testing that they were subjected to.

The reviewer notes that the test summary states that "6 seconds after the scale drum has returned to "0", the weight of the dose is measured and registered by the PC." The dose accuracy testing submitted does not comply with ISO 111608-1, Pen-Injectors for medical use-Part 1: *Pen-injectors- Requirements and test methods.* This standard requires that the "Pen injector shall indicate, by visual, audible or tactile means or any combination of these, that the injection stroke has been completed." Dose accuracy testing must be measured. using the volume that has been expelled from the device when the scale drum reaches zero.

CDRH has reviewed the PDS 290 pen injector for (b) (4) We have noted that the scale drum on the PDS290 pen injector does not indicate that the injection stroke has been completed. An additional one second or more is needed to complete the injection. If the needle is removed from the skin when the scale drum has reached zero, the patient may be under-dosed by as much as 20.4% of the dialed dose. CDRH does not believe that this dosing accuracy failure can be or should be mitigated by labeling. CDRH recommends that the sponsor provide a drug delivery device which is ISO 11608-1 compliant.

5. CDRH Recommendation

The dose accuracy testing submitted does not comply with ISO 111608-1, Pen-Injectors for medical use-Part 1: *Pen-injectors- Requirements and test methods.* This standard requires that the "Pen injector shall indicate, by visual, audible or tactile means or any combination of these, that the injection stroke has been completed." Dose accuracy testing must be measured using the volume that has been expelled from the device when the scale drum reaches zero. You have measured dose accuracy 6 seconds after the scale drum has returned to zero. CDRH recommends that you provide a drug delivery device which is ISO 11608-1 compliant.

If you have any questions, please contact Jacqueline Ryan at 301-796-9599.

Sincerely,

Jacqueline Ryan
Combination Products Team Leader, GHDB

Concurred By:

Richard Chapman
Branch Chief, GHDB

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/s/

RACHEL E HARTFORD
03/05/2012
On behalf of Jackie Ryan, CDRH

DEPARTMENT OF HEALTH AND HUMAN SERVICES **MEMORANDUM**

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
White Oak Building 66
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: June 23, 2010

From: Nikhil Thakur, Combination Products Team Leader WO66, RM2562
General Hospital Devices Branch, DAGID, ODE, CDRH

To: Pallaiah Thammana, Ph. D, Requesting Reviewer, WO21, Room 2655
Division Of Metabolism And Endocrinology Products, ODE II, OND, CDER

Subject: CON105102 Regarding Bundled NDA Submission:
NDA 20986 - NovoLog® insulin aspart (rDNA origin) injection
NDA 21536 - Levemir® insulin detemir (rDNA origin) injection
[redacted] (b) (4)

1. **Issue**

Center for Drug Evaluation and Research has requested a consult from the Center for Devices and Radiological Health, regarding NovoNordisk's NDA's 20986, 21536 [redacted] (b) (4) All of these products are delivered through a common auto-injector device (NovoNordisk's PDS-290 Pen-Injector).

The consult requested CDRH to evaluate the device constituent of this combination product.

2. **Documents Reviewed**

NDA 20986 - NovoLog® insulin aspart (rDNA origin) injection
NDA 21536 - Levemir® insulin detemir (rDNA origin) injection
[redacted] (b) (4)

3. **CDRH Review and Comments**

Device Description:

PDS290 is a pen-shaped, prefilled device containing a 3 ml cartridges with insulin. Therefore the drug is not in contact with the device. The device is intended to function with a standard needle thread type A1 or a needle with a bayonet coupling.

[redacted] (b) (4)

(b) (4)

PDS290 was developed to fulfill the international standard for drug injectors, ISO 11608-1 (Pen injectors for medical use - Part1: Requirements and test methods). It is noteworthy that FDA recognizes this standard and its amendments in its entirety.

To deliver a dose, the user simply sets the dose on the dial mechanism on the device, and then presses the Push Button to activate the delivery mechanism. The pen will deliver the requested dose. The user receives visual feedback (sees the dose in the dosing window return to zero) and audible/tactile feedback (hears and feels 1 click from the device for each unit of drug that is delivered) to demonstrate that the dose is being delivered. At the end of the dose, the dosing dial will stop moving, and the user will hear a distinct click indicating that the dose has been delivered.

The device consists of several features to enhance the operability and safety of the device.

Figure 1. Assembled PDS-290 Pen Injector

(b) (4)

(b) (4)

Review of Bench Testing Performed:

The Sponsor challenged the performance characteristics of the device constituent for this combination product in terms of dose accuracy, free fall, and human factors. The Sponsor states

that these tests were performed per ISO 11608, which is one of the standards that FDA recognizes.

Regarding the Dose Accuracy Test, the Sponsor tested the accuracy of the device to deliver a requested dose after preconditioning the device in a standard (18°C - 28°C, 25 %RH – 75 %RH), cold (5°C ± 3°C) and hot (40°C ± 2°C, 50 %RH ± 10 %RH) environment. The dose accuracy test also assessed the ability of the device to deliver an accurate dose (+/- 5%) while in the standard, cold and hot environments.

Regarding the drop test, the device was dropped using the 1-meter drop test protocol from ISO 11608. 10 units were dropped in the horizontal position, 10 units were dropped in the vertical position with the cap facing down, and 10 units were dropped in the vertical position with the push button facing down.

There was one failure regarding the dose accuracy tests associated with the blockage of the push button for one unit during the dose accuracy test after the device was exposed to the cold environment. A similar blockage occurred on one unit after exposure to the hot environment.

The Sponsor states that the blockage was [redacted] (b) (4) The Sponsor's corrective action consisted of removing the [redacted] (b) (4) for future use. The following question should be conveyed to the Sponsor:

While conducting the dose accuracy tests on the PDS-290 Pen Injector, you stated that two devices' push buttons were blocked. You clarified that one of these devices' push button failed after exposure to the cold environment, and the second failed after exposure to the hot environment. You also stated that the blockage of the push buttons was caused by [redacted] (b) (4) *Please address the following questions:*

a. *Review of your test summary indicates that the blockage did not hinder the delivery of the insulin dose. Please further clarify the terminology that the "push buttons were blocked." Specifically, if the push button was blocked, then how was the dose delivered.*
b. *Please identify the function of* [redacted] (b) (4) *. Also, identify the impact on the functionality of the device if the* [redacted] (b) (4) *were removed. For example, does the device lose some tactile or audible feedback when the user* [redacted] (b) (4) *into the PDS-290 Pen injector?*
c. *Please provide performance data to demonstrate that the revised device met the requirements of ISO 11608, and passed the performance testing that it was subjected to.*
d. *Please identify whether human factors / usability testing was performed using the original device, or the revised device. If the original device was utilized in the human factors testing, but the revised device was not, please explain your rationale for not testing the usability of the revised device.*

Review of Human Factors Testing Performed:

I consulted Mr. Ron Kaye, CDRH's Human Factors Expert regarding the usability testing that was performed for this device. Mr. Kaye's consult is attached at the end of this memorandum, but in summary, it appears that the Sponsor has not satisfied the requirements for human factors testing.

4. CDRH Recommendation

CDRH recommends that the following questions and concerns be addressed by the Sponsor:

Bench Testing:

1. *While conducting the dose accuracy tests on the PDS-290 Pen Injector, you stated that two devices' push buttons were blocked. You clarified that one of these devices' push button*

failed after exposure to the cold environment, and the second failed after exposure to the hot environment. You also stated that the blockage of the push buttons was caused by (b) (4) *Please address the following questions:*

a. *Review of your test summary indicates that the blockage did not hinder the delivery of the insulin dose. Please further clarify the terminology that the "push buttons were blocked." Specifically, if the push button was blocked, then how was the dose delivered.*
b. *Please identify the function of the* (b) (4) *. Also, identify the impact on the functionality of the device if the* (b) (4) *were removed. For example, does the device lose some tactile or audible feedback when the user* (b) (4) (b) (4) *into the PDS-290 Pen injector?*
c. *Please provide performance data to demonstrate that the revised device met the requirements of ISO 11608, and passed the performance testing that it was subjected to.*
d. *Please identify whether human factors / usability testing was performed using the original device, or the revised device. If the original device was utilized in the human factors testing, but the revised device was not, please explain your rationale for not testing the usability of the revised device.*

Human Factors Testing:

Your final usability reports do not provide sufficient information to support the Agency's determination that your injectors and accessories have been designed such that they are safe and effective for their intended users. Of most concern is a lack of priority on risk associated with use, and lack of meaningful performance and subjective measures that pertain to critical aspects of device use. Note that study results consisting of general subjective measures of "ease of use," "acceptability," and the like, do not provide the Agency with necessary and sufficient information for successful review of your application.

The intent of the a human factors validation study is to demonstrate that the device can be used by representative users under simulated conditions without patterns of failures or difficulties that could result in clinical impact to patients or, in some cases, to users themselves. To the extent that failures with use do occur, the study should collect sufficient and appropriate data such that these failures can be described in terms of their cause from the perspective of the representative users. The test report should present a summary of these results within a discussion of whether or not and the extent to which failures found are due to aspects of the design of the device, its labeling, the content or proximity of training and whether modifications are necessary. If so, such modifications should be reevaluated to demonstrate that device use has been optimized with respect to safety and effectiveness. Note that the Agency may agree or disagree with this determination, and plans to modify design problems in future device versions for problems that impact safety are generally unacceptable.

2. *Please review the Center Guidance on Human Factors and Risk Management available at: http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094461.pdf*

3. *Relative priority of tasks. The Agency needs to understand the relative priority of the tasks you selected for testing in terms of the potential results of inadequate performance on these tasks. Indeed, the tasks selected for testing should be selected on this basis. You have not provided a rationale for selecting the tasks you tested. Please provide this information, or if sufficient HF/Usability evaluation has not been performed, perform the evaluations necessary to do so.*

4. *Comprehensiveness of task set. The Agency needs to understand that the tasks you chose to test represent the extent of the tasks that could lead to use-related problems (as defined).*

5. *Realism of simulated use. Your reports did not discuss how the device system was used during the evaluations. Please describe how the device was used by study participants and particularly the use scenarios involving critically important tasks.*

6. *Performance criteria. Your testing was based on rating scales and objectives. The Agency expects users to perform critical tasks correctly 100% of the time. If errors occur on critical tasks, they should be counted as "failures." Each "failure" should be described with respect to its nature, its cause and what the result of the failure means with respect to inappropriate dosing or inadvertent injury with the injector.*

7. *Data analysis. Your analysis of performance and subjective data should be directed toward understanding user performance and particularly task failures. The analysis should determine the nature of failures based on subjective and objective evaluation data. Please provide this information, or if sufficient HF/Usability evaluation has not been performed, perform the evaluations necessary to do so.*

8. *Training. You do not describe how training was involved in your evaluation or the extent to which it is necessary for professional or home users. Please provide this information, or if sufficient HF/Usability evaluation has not been performed, perform the evaluations necessary to do so.*

9. *Users. The Agency expects simulated use validation testing (Human Factors Validation) to be performed under simulated use conditions and involve a minimum of 15 representative device users for each distinct population of users. You have separated pediatric as well as elderly users in your initial studies, therefore your study would involve 15 for each of those groups as well as another group of 15 "typical" users.*

Please contact me at (301) 796 – 5536 if you have any questions or concerns.

Nikhil Thakur
Senior Regulatory Review Officer
LCDR, USPHS

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20986	SUPPL-61	NOVO NORDISK INC	Aspart (NOVOLOG)
[redacted] (b) (4)			
NDA-21536	SUPPL-33	NOVO NORDISK INC	LEVEMIR

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/s/

RACHEL E HARTFORD
08/19/2010
On behalf of Nikhil Thakur, CDRH

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21536/S-033

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

******Pre-decisional Agency Information******

Memorandum

Date: **October 23, 2013**

To: Callie Cappel-Lynch, Regulatory Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

From: Ankur Kalola, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP Labeling Consult Request

NDA 20986/S-061 Novolog® (insulin aspart [rDNA origin] injection) solution for subcutaneous injection

NDA 21536/S-033 Levemir® (insulin detemir [rDNA origin] injection) solution for subcutaneous injection

---

On October 23, 2013 OPDP received a consult request from DMEP to review the proposed Carton and Container labeling for each Novolog and Levemir. OPDP's comments on the proposed Carton and Container are based on the versions available from the following locations:

- Novolog EDR Location: \\CDSESUB1\EVSPROD\NDA020986\020986.enx
- Levemir EDR Location: \\CDSESUB1\EVSPROD\NDA021536\021536.enx

OPDP does not have any comments on the carton/container labels at this time.

Thank you for the opportunity to comment on these materials. If you have any questions, please contact Ankur Kalola at 301-796-4530 or Ankur.Kalola@fda.hhs.gov.

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/s/

ANKUR S KALOLA
10/23/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO:	FROM: (Name/Title, Office/Division/Phone number of requestor)
CDER-DDMAC-RPM **Attn: Ankur Kalola**	Callie Cappel-Lynch Project Manager DMEP 301 796 8436

REQUEST DATE	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
10/23/13		21536/S33 20986/S61	

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
Levemir Novolog	Standard	Insulin	10/30/13

NAME OF FIRM:	
Novo Nordisk	PDUFA Date: 9/22/13

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
- ☐ PACKAGE INSERT (PI)
- ☐ PATIENT PACKAGE INSERT (PPI)
- ☒ CARTON/CONTAINER LABELING
- ☐ MEDICATION GUIDE
- ☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
- ☐ ORIGINAL NDA/BLA
- ☐ IND
- ☐ EFFICACY SUPPLEMENT
- ☐ SAFETY SUPPLEMENT
- ☒ LABELING SUPPLEMENT
- ☐ PLR CONVERSION

REASON FOR LABELING CONSULT
- ☐ INITIAL PROPOSED LABELING
- ☒ LABELING REVISION

EDR link to submission:
EDR Location: \\CDSESUB1\EVSPROD\NDA020986\020986.enx
EDR Location: \\CDSESUB1\EVSPROD\NDA021536\021536.enx

Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

COMMENTS/SPECIAL INSTRUCTIONS: Novo Nordisk has resubmitted a labeling supplement for Levemir and Novolog Flextouch Pens. Goal date is September 22, 2013. Please review the carton and container labels submitted 3/22/13. Thank you!

SIGNATURE OF REQUESTER
Callie Cappel-Lynch

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) ☐ eMAIL ☐ HAND

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/s/

CALLIE C CAPPEL-LYNCH
10/23/2013

From:	CappelLynch, Callie
To:	"RSPR (Rick Spring)"
Subject:	RE: NDA 020986/S-061/NDA 021536/S-033: NovoLog/Levemir PDS290 prefilled pen (FlexTouch) - Submitted our response
Date:	Wednesday, October 16, 2013 10:36:00 AM
Attachments:	proposed-patient-tracked.doc proposed-physician-flextouch-tracked.doc

Hi Rick,

Please see the attached comments. We have no further comment on the submitted Novolog IFU or PPI or on the Levemir PI or IFU. If you have any questions, feel free to contact me.

Thank you,
Callie

From: RSPR (Rick Spring) [mailto:rspr@novonordisk.com]
Sent: Thursday, October 10, 2013 9:26 PM
To: CappelLynch, Callie
Subject: RE: NDA 020986/S-061/NDA 021536/S-033: NovoLog/Levemir PDS290 prefilled pen (FlexTouch) - Submitted our response

Callie,

Just a note to let you know that we submitted our response to the comments below today. A quick summary is the following:

- We accepted all of the Agency's comments received for the PI (included a 'clean' version of the document in the submission).
- We accepted all comments for the PPI and IFU ('clean' and 'track changes'. Tracked changes represent either typographical/format corrections or changes to keep language consistent between NovoLog and Levemir).

Have a great weekend!

Rick

From: CappelLynch, Callie [mailto:Callie.CappelLynch@fda.hhs.gov]
Sent: Tuesday, October 08, 2013 4:45 PM
To: RSPR (Rick Spring)
Cc: CappelLynch, Callie
Subject: RE: NDA 020986/S-061/NDA 021536/S-033: NovoLog/Levemir PDS290 prefilled pen (FlexTouch) - Follow up

Hi Rick,

Please see the attached labeling with comments (PI, PPI, IFUs) for the NovoLog and Levemir FlexTouch supplements (12 documents total). To answer your question below, as of right now, we are still on working status. I don't have many details on the situation beyond that. If you have any questions please contact me.

Thank you,
Callie

From: RSPR (Rick Spring) [mailto:rspr@novonordisk.com]
Sent: Tuesday, October 08, 2013 11:33 AM
To: CappelLynch, Callie
Subject: RE: NDA 020986/S-061/NDA 021536/S-033: NovoLog/Levemir PDS290 prefilled pen (FlexTouch) - Follow up

Callie,

Hi! Since we last communicated, things have changed at your end with the government shutdown. I was wondering if you could give me an idea how things might go from here? Thank you.

Rick

From: CappelLynch, Callie [mailto:Callie.CappelLynch@fda.hhs.gov]
Sent: Monday, September 30, 2013 12:32 PM
To: RSPR (Rick Spring)
Subject: RE: NDA 020986/S-061/NDA 021536/S-033: NovoLog/Levemir PDS290 prefilled pen (FlexTouch) - Follow up

Hi Rick,

The discipline reviews have been completed. The team is reviewing all comments and we hope to have them to you this week.

Callie

From: RSPR (Rick Spring) [mailto:rspr@novonordisk.com]
Sent: Monday, September 30, 2013 12:22 PM
To: CappelLynch, Callie
Subject: RE: NDA 020986/S-061/NDA 021536/S-033: NovoLog/Levemir PDS290 prefilled pen (FlexTouch) - Follow up

Callie,

Hi! How are things looking at this point? Thank you.

Rick

From: CappelLynch, Callie [mailto:Callie.CappelLynch@fda.hhs.gov]
Sent: Thursday, September 19, 2013 3:29 PM
To: RSPR (Rick Spring)
Subject: RE: NDA 020986/S-061/NDA 021536/S-033: NovoLog/Levemir PDS290 prefilled pen (FlexTouch) - Follow up

Hi Rick,

Due to the amount of disciplines reviewing the labeling, it looks like we may need to go beyond the goal date for these supplements. At this time I am hoping to get comments to you by the end of next week. If this changes I will let you know promptly. I apologize for the inconvenience. If you have any questions feel free to contact me.

Thank you,
Callie

From: RSPR (Rick Spring) [mailto:rspr@novonordisk.com]
Sent: Friday, September 13, 2013 12:01 PM
To: CappelLynch, Callie
Subject: RE: NDA 020986/S-061/NDA 021536/S-033: NovoLog/Levemir PDS290 prefilled pen (FlexTouch) - Follow up

Callie,
Hi! Do you think you'll have comments by EOB today? I'd like to have the team ready to promptly respond. Thank you.

Rick

From: CappelLynch, Callie [mailto:Callie.CappelLynch@fda.hhs.gov]
Sent: Monday, September 09, 2013 12:22 PM
To: RSPR (Rick Spring)
Subject: RE: NDA 020986/S-061/NDA 021536/S-033: NovoLog/Levemir PDS290 prefilled pen (FlexTouch) - Follow up

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Callie,
Hi! I just wanted to follow up on our amendment sent on Monday, August 26th to see if you had any comments or questions. Are we still on track for meeting the goal date of September 22nd for the supplements? Thank you.

Rick

Rick Spring
Associate Director, Regulatory Affairs
Novo Nordisk Inc.
800 Scudders Mill Road
Plainsboro, New Jersey 08536
USA
609-987-5046 (direct)
rspr@novonordisk.com

29 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

CALLIE C CAPPEL-LYNCH
10/16/2013

From:	CappelLynch, Callie
To:	RSPR (Rick Spring)
Cc:	CappelLynch, Callie
Subject:	RE: NDA 020986/S-061/NDA 021536/S-033: NovoLog/Levemir PDS290 prefilled pen (FlexTouch) - Follow up
Date:	Tuesday, October 08, 2013 4:45:06 PM
Attachments:	(NovoLog FlexTouch) 20986 S-061 IFU clean.doc (NovoLog FlexTouch) 20986 S-061 IFU track changes.doc (NovoLog) 20986 S-061 PPI clean.doc (NovoLog) 20986 S-061 PPI track changes.doc proposed-physician-flextouch clean.doc proposed-physician-flextouch track changes.doc (Levemir FlexTouch) 21536 S-033 IFU clean.doc (Levemir FlexTouch) 21536 S-033 IFU tracked changes.doc (Levemir) 21536 S-033 PPI clean.doc (Levemir) 21536 S-033 PPI tracked changes.doc proposed-physician-flextouch clean.doc proposed-physician-flextouch tracked changes.doc

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Rick

Rick Spring
Associate Director, Regulatory Affairs
Novo Nordisk Inc.
800 Scudders Mill Road
Plainsboro, New Jersey 08536
USA
609-987-5046 (direct)
rspr@novonordisk.com

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/s/

CALLIE C CAPPEL-LYNCH
10/08/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 021536/S033

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Novo Nordisk Inc.
P.O. Box 846
Plainsboro, NJ 08536

Attention: Robert B. Clark
Vice President, Regulatory Affairs

Dear Mr. Clark:

Please refer to your December 15, 2009, supplemental New Drug Application (sNDA) submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Levemir® (insulin detemir [rDNA origin] injection), 100 units/mL. Please also refer to your complete resubmission to this sNDA, dated and received March 22, 2013.

We also refer to:

- Your initial proprietary name submission, dated December 15, 2009, for the proposed proprietary name Levemir® FlexTouch®;
- Our initial correspondence dated March 15, 2010, finding this proposed proprietary name conditionally acceptable;
- Your May 22, 2013, correspondence requesting re-review of your proposed proprietary name, Levemir® FlexTouch®, and to your May 30, 2013, amendment to the initial request.

We have completed our review of the proposed proprietary name, Levemir® FlexTouch® and have concluded that it is acceptable.

The proposed proprietary name, Levemir® FlexTouch®, will be re-reviewed 90 days prior to the approval of the sNDA. If we find name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your May 22, 2013, submission are altered prior to approval of the supplemental application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Margarita Tossa, Safety Regulatory Project Manger in the Office of Surveillance and Epidemiology, at (301) 796-4053. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Callie Cappel-Lunch at (301) 796-8436.

Sincerely,

{See appended electronic signature page}

Kellie Taylor, PharmD, MPH
Deputy Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

KELLIE A TAYLOR
08/19/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020986/S-061
NDA 21536/S-033

GENERAL ADVICE

Novo Nordisk, Inc.
Attention: Robert B. Clark
Vice President, Regulatory Affairs
100 College Road West
Princeton, NJ 08540

Dear Mr. Clark:

Please refer to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for NovoLog (insulin aspart [rDNA origin]) injection and Levemir (insulin determir [rDNA origin]) injection.

We also refer to your March 22, 2013, submission, containing a complete response to our action letter dated March 20, 2012.

We have reviewed the referenced material and have the following recommendations.

1. Clearly state in the labeling for the PDS290 Pen injector that when the counter is reset to zero, the prescribed dose is not completely delivered until 6 seconds later.

2. Include a warning in the labeling to patients that if the needle is removed before the patient counts to 6 seconds after the counter is reset to zero, then under-dosing may occur by as much as 20%, possibly resulting in the need for additional insulin administration.

3. Propose a plan to target diabetic educators/ prescribing clinicians to emphasize the under-dosing problem so that these educators can re-enforce this point with patients.

4. In our review of study UT103, we note that the modifications to the instructions for use (IFU) and training showed improvement in use performance in the training group, e.g. there were no patterns of use errors. However, the use errors seen in the untrained group indicate that un-trained users continue to experience use errors, especially with the blocked needle situation, consistent with results for study UT86. Therefore, we believe that the dose counter is not optimally designed, in particular for the situation of a blocked needle, because the current design can mislead users to interpret that some insulin has been delivered when in actuality, no insulin has been delivered. We believe that the clinical impact of up to 7 units being under-dosed due to a blocked needle situation has the potential to be significant. We recommend that if feasible, you modify the product

design so that the dose counter does not change the number of units displayed on the window when no insulin has been delivered.

5. We recommend that you revise the IFU to notify the user of blocked needle situation, and provide instructions for proper user response to address the hazard and to resolve a blocked needle situation.

If you have questions, call Callie Cappel-Lynch, Regulatory Project Manager, at (301) 796 8436.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of New Drugs
Center for Drug Evaluation and ResearchCenter for Drug Evaluation and Research

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/s/

MARY H PARKS
08/12/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO:	FROM: (Name/Title, Office/Division/Phone number of requestor)
CDER-DDMAC-RPM	Callie Cappel-Lynch Project Manager DMEP 301 796 8436

REQUEST DATE	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
5/23/13		21536/S33 20986/S61	

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
Levemir Novolog	Standard	Insulin	8/22/13

NAME OF FIRM:	
Novonordisk	PDUFA Date: 9/22/13

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
- ☐ PACKAGE INSERT (PI)
- ☐ PATIENT PACKAGE INSERT (PPI)
- ☐ CARTON/CONTAINER LABELING
- ☐ MEDICATION GUIDE
- ☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
- ☐ ORIGINAL NDA/BLA
- ☐ IND
- ☐ EFFICACY SUPPLEMENT
- ☐ SAFETY SUPPLEMENT
- ☒ LABELING SUPPLEMENT
- ☐ PLR CONVERSION

REASON FOR LABELING CONSULT
- ☐ INITIAL PROPOSED LABELING
- ☐ LABELING REVISION

EDR link to submission:
EDR Location: \\CDSESUB1\EVSPROD\NDA020986\020986.enx
EDR Location: \\CDSESUB1\EVSPROD\NDA021536\021536.enx

Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

COMMENTS/SPECIAL INSTRUCTIONS: Nove Nordisk has resubmitted a labeling supplement for Levemir and Novolog Flextouch Pens. Goal date is September 22, 2013. Emails will be sent out regarding interim meeting dates. Please send me reviewer assignments for review of the labeling so I can add them to the meeting invites. Thank you!

SIGNATURE OF REQUESTER
Callie Cappel-Lynch

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) ☐ eMAIL ☐ HAND

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/s/

CALLIE C CAPPEL-LYNCH
05/23/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR PATIENT LABELING REVIEW CONSULTATION

TO:

CDER-DMPP-PatientLabelingTeam

FROM: (Name/Title, Office/Division/Phone number of requestor)

Callie Cappel-Lynch
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Callie.cappellynch@fda.hhs.gov
(301) 796-8436

REQUEST DATE:	NDA/BLA NO.:	TYPE OF DOCUMENTS: (PLEASE CHECK OFF BELOW)
3/27/13	NDA 20986/S61 NDA 21536/S33	

NAME OF DRUG:	PRIORITY CONSIDERATION:	CLASSIFICATION OF DRUG:	DESIRED COMPLETION DATE (Generally 2 Weeks after receiving substantially complete labeling)
Novolog Levemir	Standard	Insulin	

SPONSOR:
Novo Nordisk

PDUFA Date: 9/22/13

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
- ☒ PATIENT PACKAGE INSERT (PPI)
- ☐ MEDICATION GUIDE
- ☒ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
- ☐ ORIGINAL NDA/BLA
- ☐ EFFICACY SUPPLEMENT
- ☐ SAFETY SUPPLEMENT
- ☒ LABELING SUPPLEMENT
- ☐ MANUFACTURING (CMC) SUPPLEMENT
- ☐ PLR CONVERSION

REASON FOR LABELING CONSULT
- ☐ INITIAL PROPOSED LABELING
- ☒ LABELING REVISION

EDR link to submission:

Cover Letter: \\CDSESUB1\EVSPROD\NDA020986\0113\m1\us\102-cover-letters\cover.pdf
EDR Location: \\CDSESUB1\EVSPROD\NDA020986\020986.enx
EDR Location: \\CDSESUB1\EVSPROD\NDA021536\021536.enx

Please Note: DMPP uses substantially complete labeling, which has already been marked up by the CDER Review Team, when reviewing MedGuides, IFUs, and PPIs. Once the substantially complete labeling is received, DMPP will complete its review within 14 calendar days. Please provide a copy of the sponsor's proposed patient labeling in Word format.

COMMENTS/SPECIAL INSTRUCTIONS:

Novo has resubmitted labeling supplements for Flex touch pens for NDA 20986/S-061 (Novolog) and 21536/S-033 (Levemir). This supplement was submitted as a Prior Approval Supplement on December 15, 2009. We issued a CR letter August 20, 2010. The company resubmitted on July 13, 2011 and again received a CR letter on March 20, 2012. They requested an extension of time for resubmission on February 13, 2013 and it was granted February 21, 2013. They are now resubmitting this supplement in response to the March 20th CR letter. Included in the response are:

1) Labeling documents (carton/container, PI, PPI, IFU)
2) ISO Compliance Response
3) Validation of Device Use Final Report

We will send you the SCPI as soon as it is ready.

SIGNATURE OF REQUESTER
Callie Cappel-Lynch

Reference ID: 3285947

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) ☐ eMAIL (BLAs Only) ☒ DARRTS

Version: 12/9/2011

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/s/

CALLIE C CAPPEL LYNCH
04/01/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Mail: OSE

FROM: Callie Cappel-Lynch
Division of Metabolism and Endocrinology Products
(301) 796-8436
Callie.cappellynch@fda.hhs.gov

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
3/27/13		20986/S-061 21536/S-033	Response to CR	3/22/13

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Novolog and Levemir	Standard	Insulin	7/22/13

NAME OF FIRM: Novo Nordisk

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:

Novo has resubmitted labeling supplements for Flex touch pens for NDA 20986/S-061 (Novolog) and 21536/S-033 (Levemir). This supplement was submitted as a Prior Approval Supplement on December 15, 2009. We issued a CR letter August 20, 2010. The company resubmitted on July 13, 2011 and again received a CR letter on March 20, 2012. They requested an extension of time for resubmission on February 13, 2013 and it was granted February 21, 2013. They are now resubmitting this supplement in response to the March 20th CR letter.

1) Labeling documents (carton/container, PI, PPI, IFU)
2) ISO Compliance Response
3) Validation of Device Use Final Report

Word documents will be emailed once a reviewer has been assigned.

We request you complete your review by July 22, 2013.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Callie Cappel-Lynch	☐ MAIL ☐ HAND

SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

CALLIE C CAPPEL LYNCH
04/01/2013

MANDATORY: Send a copy of the consult request form to the Office of Combination Products (OCP) as follows:
--Originating Center: When the consult request is initiated.
--Consulting Center: When the consult is completed.
Email: combination@fda.gov or FAX: 301-847-8619

For additional information: Contact OCP by email or by telephone (301-796-8930) or refer to OCP's intranet page http://inside.fda.gov:9003/ProgramsInitiatives/CombinationProducts/ReviewerTools/default.htm.

For Consulting Center Use Only:

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

Completed date: _____
Reviewer Initials: _____
Supervisory Concurrence: _____

Intercenter Request for Consultative or Collaborative Review Form

To (Consulting Center):
Center: CDRH
Division: ODE/DAGID/GHDB
Mail Code: HF
Consulting Reviewer Name:
Building/Room #:
Phone #:
Fax #:
Email Address:
RPM/CSO Name and Mail Code: Jaqueline Ryan

From (Originating Center):
Center: CDER
Division: DMEP
Mail Code: HF-510
Requesting Reviewer Name:
Building/Room #:
Phone#:
Fax #:
Email Address:
RPM/CSO Name and Mail Code: Rachel Hartford x60331
Requesting Reviewer's Concurring Supervisor's Name:

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: 24Jan12
Requested Completion Date: 5Mar12

Submission/Application Number: Novolog 020986/S-061 Levemir 021536/S-033
(Not Barcode Number)
Submission Type: sNDA resubmission
(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: 13July11
Official Submission Due Date: 5Mar12

Name of Product: Novolog FlexTouch (PDS290) Levemir FlexTouch (PDS290)
Name of Firm: Novo Nordisk

Intended Use: (375 characters max) Treatment of Diabetes

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):
(525 characters max) Resubmission.

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) Please review the resubmission. The initial CDRH review and resulting CR letter were sent via email to Jackie Ryan today.

Novolog EDR Location: \\CDSESUB1\EVSPROD\NDA020986\020986.enx
Supporting Document Number: 423 eCTD Sequence Number: 0086
Levemir EDR Location: \\CDSESUB1\EVSPROD\NDA021536\021536.enx
Supporting Document Number: 167 eCTD Sequence Number: 0063

Reference ID: 3285931
Note: (b) (4)

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/s/

CALLIE C CAPPEL LYNCH
04/01/2013

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Email: combination@fda.gov or FAX: 301-847-8619

For additional information: Contact OCP by email or by telephone (301-796-8930) or refer to OCP's intranet page http://inside.fda.gov:9003/ProgramsInitiatives/CombinationProducts/ReviewerTools/default.htm.

For Consulting Center Use Only:

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

Completed date: _____
Reviewer Initials: _____
Supervisory Concurrence: _____

Intercenter Request for Consultative or Collaborative Review Form

To (Consulting Center):
Center: CDRH
Division: ODE/DAGID/GHDB
Mail Code: HF
Consulting Reviewer Name:
Building/Room #:
Phone #:
Fax #:
Email Address:
RPM/CSO Name and Mail Code: Jaqueline Ryan

From (Originating Center):
Center: CDER
Division: DMEP
Mail Code: HF-510
Requesting Reviewer Name:
Building/Room #:
Phone#:
Fax #:
Email Address:
RPM/CSO Name and Mail Code: Rachel Hartford x60331
Requesting Reviewer's Concurring Supervisor's Name:

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Date of Request: 24Jan12
Requested Completion Date: 5Mar12

Submission/Application Number: Novolog 020986/S-061 Levemir 021536/S-033
(Not Barcode Number)
Submission Type: sNDA resubmission
(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: 13July11
Official Submission Due Date: 5Mar12

Name of Product: Novolog FlexTouch (PDS290) Levemir FlexTouch (PDS290)
Name of Firm: Novo Nordisk

Intended Use: (375 characters max) Treatment of Diabetes

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):
(525 characters max) Resubmission.

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) **Please review the resubmission. The initial CDRH review and resulting CR letter were sent via email to Jackie Ryan today.**

Novolog EDR Location: \\CDSESUB1\EVSPROD\NDA020986\020986.enx
Supporting Document Number: 423 eCTD Sequence Number: 0086
Levemir EDR Location: \\CDSESUB1\EVSPROD\NDA021536\021536.enx
Supporting Document Number: 167 eCTD Sequence Number: 0063

Note: (b) (4)

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/s/

CALLIE C CAPPEL LYNCH
04/01/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020986/S-061
NDA 021536/S-033

COMPLETE RESPONSE –LABELING

Novo Nordisk Inc.
Attention: Robert B. Clark
Vice President, Regulatory Affairs
P.O. Box 846
Plainsboro, NJ 08536

Dear Mr. Clark:

We acknowledge receipt on March 22, 2013, of your resubmissions dated March 22, 2013, to your supplemental new drug applications for NovoLog (insulin aspart [rDNA origin]) injection and Levemir (insulin determir [rDNA origin]) injection.

These amendments constitute a complete response to our action letter dated March 20, 2012.

If you have any questions, call me at (301) 796 - 8436.

Sincerely,

{See appended electronic signature page}

Callie Cappel-Lynch, Pharm.D.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

CALLIE C CAPPEL LYNCH
03/28/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021536/S-033

GENERAL ADVICE

Novo Nordisk Inc.
Attention: Robert B. Clark
Vice President, Regulatory Affairs
P.O. Box 846
Plainsboro, NJ 08536

Dear Mr. Clark:

Please refer to your supplemental new drug application) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Levemir (insuling detemir [rDNA origin] injection).

We also refer to your submission dated February 13, 2013, containing a request for an extension of one year in which to resubmit the application, in the form of a response to our complete response letter dated March 20, 2012.

We grant your request for the extension of one year to resubmit this application. We remind you that per 21 CFR 314.110(c), an applicant's failure to resubmit the application within the extended time period or to request an additional extension may be considered a request by the applicant to withdraw the application.

If you have any questions, call Callie Cappel-Lynch, Pharm.D., Regulatory Project Manager, at (301) 796-8436.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

MARY H PARKS
02/21/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 021536/S-033

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

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

Attention: Anne Phillips, MD
Corporate Vice President
Clinical, Medical and Regulatory Affairs

Dear Dr. Phillips:

Please refer to your December 15, 2009, supplemental New Drug Application (sNDA) submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Levemir® (insulin detemir [rDNA origin] injection). Please also refer to your complete resubmission to this sNDA, dated and received July 13, 2011.

We also refer to:

- Your initial proprietary name submission, dated December 15, 2009, for the proposed proprietary name Levemir® FlexTouch®;
- Our initial correspondence dated March 15, 2010, finding this proposed proprietary name conditionally acceptable;
- Your January 26, 2012, correspondence requesting re-review of your proposed proprietary name, Levemir® FlexTouch®;

We have completed our review of the proposed proprietary name, Levemir® FlexTouch® and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your January 26, 2012, submission are altered prior to approval of the supplemental application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Margarita Tossa, Safety Regulatory Project Manger in the Office of Surveillance and Epidemiology, at (301) 796-4053. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Rachel Hartford at (301) 796-0331.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
04/24/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020986/S-061
NDA 021536/S-033

GENERAL ADVICE

Novo Nordisk Inc.
Attention: Anne Phillips, M.D.
Corporate Vice President, Clinical, Medical and Regulatory Affairs
100 College Road West
Princeton, NJ 08540

Dear Dr. Phillips:

Please refer to your Supplemental New Drug Applications (sNDAs) dated and received December 15, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for: Novolog (insulin aspart [rDNA origin] injection) and Levemir (insulin detemir [rDNA origin] injection).

We have reviewed the Human Factors Studies in your July 13, 2011, submission and have the following comments and recommendations.

DEVICE

Human Factors:

1. Provide additional information/clarification for the Validation of Device Use (UT64 NN Report, Dated 07-JUL-2011). This study reported high proportion of participants committing use errors across tasks associated with delivering an injection and some of the errors resulted in needle-prick injuries. Most of the use errors can result in underdosing, or when users not able to set the correct dose, can result in overdosing. Other use errors can result in needle-prick injuries, contamination, and infection. In the report, you provided some root cause analysis along with the position that the current mitigations are effective and that the residual risks are minimal, and stated that the root causes were associated with the users (i.e. user forgetfulness, habit, and misunderstanding) and that the root causes were not unique to the proposed pen-injector, or that the participants did not receive the necessary training. We remain concerned with the study results showing significant safety related issues and critical hazards where you believe that no additional mitigations are necessary, and that potential failures might continue to occur in actual use. As a result, we do not have adequate evidence to reasonably determine that the device can be used safely and effectively. Take the results of these evaluations and use them to further optimize the device user interface including labeling/Instructions For Use (IFU) so that use errors are effectively minimized.

Improvements should be demonstrated through focused Human Factors (HF)/usability validation.

Address the following concerns:

a. We are most concerned with the following errors which could result in incorrect therapy/treatment. Of the 87 participants, you reported that
   - 12 participants did not set the dose correctly for their injection resulting in 12 use errors.
   - 8 participants miscalculated second dose when using two pens resulting in 9 use errors.
   - 2 participants did not hold the dose button down until it scales back to 0 position resulting in 4 use errors
   - 36 participants did not hold the needle in the skin for an appropriate amount of time resulting in 120 use errors
   - 4 participants experienced needle prick injuries resulting in 5 use errors
   - 3 participants did not put the cap back on after use resulting in 5 use errors
   - 3 participants did not detect blocked needles resulting in 3 use errors

   additional clarification is necessary for the following items:

   i. For the use errors associated with participants who did not set the dose correctly for their injection, the narrative provided in the root cause analysis section was not clear on how the use error occurred among the sequence of use interaction steps, and what "visual feedback" the users received or did not receive from the device. It was also not clear if any of the users recognize that a full dose had not been delivered, and what aspect of the device design allowed them to do so. Address the above concerns and provide a side by side comparison of the correct injection sequence versus the sequence for which all of the use errors occurred. Clearly describe how the user errors occurred along with screen shots of the device status at each of the steps. Indicate which of these participants ultimately delivered/did not deliver a correct dose. Provide a clarification on the "visual feedback" and clarification on the clinical significance of the one participant who injected both a priming dose and a prescribed dose. Provide subjective feedback from users on the root cause of the use errors in your analysis of the errors.

   ii. For the use errors associated with participants miscalculating second dose when using two pens. The use errors analysis did not include the necessary subjective data that are focused on identifying the root cause of the failures and potential design improvements recommendations from the perspective of representative users. The report remained unclear in terms of which of these participants ultimately delivered/did not deliver a correct dose. Provide additional information that addresses the above concerns.

   iii. For the use errors associated with participants did not hold the dose button down until it scales back to 0 position resulting in 4 use errors, this is a critical task in ensuring that the patients receive a full dose of intended insulin. It appears that the user interface including instructions for use and

labeling do not provide sufficient feedback to the users and to prevent underdosing. Provide a proposal on how these errors can be addressed, and note any further mitigation will need to be evaluated for effectiveness.

iv. For the use errors associated with participants who did not hold the needle in the skin for an appropriate amount of time, it is unclear why you specified that the needle should be held in the skin for 6 seconds, but stated that dose accuracy testing demonstrated that a full dose can be delivered 1 second after the dose counter returns to "0." The report did not include the necessary subjective data that are focused on identifying the root cause of the failures and potential design improvements recommendations from the perspective of representative users. Furthermore, stating that the root causes were associated with user forgetfulness, habit, and misunderstanding, etc. or that the root causes were not unique to the proposed pen-injector did not provide adequate evidence demonstrating that the device can be used safely and effective. It appears that the user interface including instructions for use and labeling do not provide sufficient feedback to the users to prevent underdosing. Provide a proposal on how these errors can be addressed, and note any further mitigation will need to be evaluated for effectiveness.

v. For the use errors associated with participants who experienced needle prick injuries; we are concerned with needle prick injuries associated with the use of this product and requests that you optimize the design and/or IFU and training to minimize the rate of occurrence of needle prick injuries.

vi. For the use errors associated with participants who did not put the cap back on after use resulting in 4 use errors, you stated these errors can result in underdosing. It is not clear how degradation caused by exposure to sunlight due to cap not mounted after use can result in underdosing. Furthermore, it is not clear what is the clinical impact of patients injecting insulin that has been degraded, and how would the patient detect that the insulin has been degraded. The device user interface can be further optimized to improve use performance.

vii. For the use errors associated with participants who did not detect a blocked needle, you stated that the resulting harm is that patient may miss a dose. It is not clear if the pen-injector provides any feedback to user in this situation, and whether or not the users recognize that they did not receive any insulin. Indicate what aspects of the device design were or were not effective in mitigating use-related risks, and why potential improvement to the device design will not fully mitigate those use related risks.

viii. You also reported deviations and close calls. While these are "deviations" and "close-calls" that did no result in medical consequences, you did not provide a discussion of how users were able to recognize the potential failures and what steps they took correct themselves. Provide in your

discussion how the design of the device and its labeling influenced the patient's behavior for self-correction.

b. We expect to review a report of the human factors/usability evaluation and validation testing without any pattern of use errors, and a conclusion that the device is reasonably safe and effective for the intended users, uses and use conditions can be determined based on the test results. Your testing did not provide the level of evidence necessary to support a conclusion that the device can be used safely and effectively by representative users. The PDS290 was submitted to multiple NDAs; the Human Factors testing showed use errors/failures continue to occur and therefore, findings regarding human factors/use safety concerns have not been fully addressed. We are concerned that after two rounds of Human Factors validation testing performed on the PDS290 device, users continue to experience failures that can impact safe and effective use of the device. These results indicated that failures and use errors that the device and its user interface including instructions and labeling as designed does not effective minimize hazards associated with use. Take the results of these evaluations and use them to further optimize the training, IFU and/or device user interface so that use errors are effectively minimized. Provide a proposal on how these use errors and failures can be addressed, and note any further mitigation/improvements should be demonstrated through focused HF/usability validation.

2. Guidance on human factors procedures to follow can be found in *Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management* (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm).

3. The recently published draft guidance *Applying Human Factors and Usability Engineering to Optimize Medical Device Design* (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm) is useful in understanding our current thinking and approach to human factors.

Group Size, Composition, and Tasks:

4. Your participant group does not include any inpatient nursing staff. Include at least 15 nurses in any future studies, as they are a user group for one of your intended use settings for the device.

5. Testing should occur with not only NovoTwist® needles, but with any needle appropriate for use with your device, as a user may not solely rely on NovoTwist® needles for insulin delivery.

6. Although in your summative testing an analysis was completed on marketed insulin prefilled pen-injectors and cartons from two major competitors, it appears that those prefilled pen-injectors were not included in final validation testing. There continue to be ongoing selection errors not only within Novo Nordisk's product line, but throughout multiple manufacturers' product lines. Therefore, if feasible, include other manufacturer's pens within your differentiation tasks.

7. We recommend submission of any new proposed Human Factors and Validation protocols for review prior to implementation of any further testing.

If you have any questions, call Rachel Hartford, Regulatory Project Manager, at (301) 796-0331.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

MARY H PARKS
03/16/2012

Hartford, Rachel

From: Hartford, Rachel
Sent: Wednesday, February 29, 2012 12:55 PM
To: 'CDCA (Cindy Cao)'
Subject: Information Request for PDS290 Novolog NDA 020986/S-061 & Levemir NDA 021536/S-033

Good Afternoon,

We note that your December 15, 2009, submissions included a transition plan from the FlexPen to the FlexTouch six months after approval. Please update us on your plans.

Thanks,

Rachel

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

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/s/

RACHEL E HARTFORD
02/29/2012

MANDATORY: Send a copy of the consult request form to the Office of Combination Products (OCP) as follows:
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Email: combination@fda.gov or FAX: 301-847-8619

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For Consulting Center Use Only:

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

Completed date: _____
Reviewer Initials: _____
Supervisory Concurrence: _____

Intercenter Request for Consultative or Collaborative Review Form

To (Consulting Center):
Center: CDRH
Division: ODE/DAGID/GHDB
Mail Code: HF
Consulting Reviewer Name:
Building/Room #:
Phone #:
Fax #:
Email Address:
RPM/CSO Name and Mail Code: Jaqueline Ryan

From (Originating Center):
Center: CDER
Division: DMEP
Mail Code: HF-510
Requesting Reviewer Name:
Building/Room #:
Phone#:
Fax #:
Email Address:
RPM/CSO Name and Mail Code: Rachel Hartford x60331
Requesting Reviewer's Concurring Supervisor's Name:

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Date of Request: 24Jan12
Requested Completion Date: 5Mar12

Submission/Application Number: Novolog 020986/S-061 Levemir 021536/S-033
(Not Barcode Number)
Submission Type: sNDA resubmission
(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: 13July11
Official Submission Due Date: 5Mar12

Name of Product: Novolog FlexTouch (PDS290) Levemir FlexTouch (PDS290)
Name of Firm: Novo Nordisk

Intended Use: (375 characters max) Treatment of Diabetes

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):
(525 characters max) Resubmission.

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) Please review the resubmission. The initial CDRH review and resulting CR letter were sent via email to Jackie Ryan today.

Novolog EDR Location: \\CDSESUB1\EVSPROD\NDA020986\020986.enx
Supporting Document Number: 423 eCTD Sequence Number: 0086
Levemir EDR Location: \\CDSESUB1\EVSPROD\NDA021536\021536.enx
Supporting Document Number: 167 eCTD Sequence Number: 0063

Reference ID: 3076188

(b) (4)

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/s/

RACHEL E HARTFORD
01/24/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:			FROM:	
Mail: OSE			Rachel Hartford/ DMEP/ x60331	
DATE 24Jan12	IND NO.	NDA NO. Novolog 020986/S061 Levemir 021536/S-033	TYPE OF DOCUMENT resubmission	DATE OF DOCUMENT 13July11
NAME OF DRUG Novolog & Levemir	PRIORITY CONSIDERATION Routine		CLASSIFICATION OF DRUG Insulin	DESIRED COMPLETION DATE 23Mar12

NAME OF FIRM: Novo Nordisk

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: Please review the resubmission to include: IFUs, cartons, containers, accuracy testing reports, and summative usability plan. Thanks!

Novolog **EDR Location:** \\CDSESUB1\EVSPROD\NDA020986\020986.enx
Supporting Document Number: 423
eCTD Sequence Number: 0086

Levemir EDR Location: \\CDSESUB1\EVSPROD\NDA021536\021536.enx
Supporting Document Number: 167
eCTD Sequence Number: 0063

Note: [redacted] (b) (4)

SIGNATURE OF REQUESTER Rachel Hartford	METHOD OF DELIVERY (Check one) ☒ DARRTS ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

RACHEL E HARTFORD
01/24/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020986/S-061
NDA 021536/S-033

COMPLETE RESPONSE –LABELING

Novo Nordisk Inc.
Attention: Anne Phillips, M.D.
CVP, Clinical, Medical and Regulatory Affairs
100 College Road West
Princeton, NJ 08540

Dear Dr. Phillips:

We acknowledge receipt of the resubmission dated and received July 13, 2011, to your supplemental new drug applications for Novolog (insulin aspart [rDNA origin] injection) and Levemir (insulin detemir [rDNA origin] injection).

This amendment constitutes a complete response to our August 20, 2010, action letter. The user fee goal date is January 13, 2012.

If you have any questions, call me at (301) 796-0331.

Sincerely,

{See appended electronic signature page}

Rachel Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

RACHEL E HARTFORD
08/03/2011

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Silver Spring, MD 20993

NDA 021536/S-033

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

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

Attention: Mary Ann McElligott, Ph.D.
Associate Vice President, Regulatory Affairs

Dear Dr. McElligott:

Please refer to your December 15, 2009, supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Levemir (insulin detemir [rDNA origin] injection).

We also refer to your December 15, 2009 correspondence, received December 15, 2009, requesting review of your proposed proprietary name, Levemir FlexTouch.

We have completed our review of the proposed proprietary name, Levemir FlexTouch and have concluded that it is acceptable. However, we anticipate product selection errors between the Levemir FlexTouch and Levemir FlexPen during the (b) (4) co-marketing transition period from the old to the new pen device due to the similar trade dress, similar names, and similar pen colors. To address this potential and limited confusion, we request you take steps to increase practitioner and patient awareness to the introduction of this new pen, the differences in the pens and required product switch that will need to occur over the (b) (4) transition period.

The proposed proprietary name, Levemir FlexTouch, will be re-reviewed 90 days prior to the approval of the sNDA. If we find name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your December 15, 2009, submission are altered prior to approval of the supplemental application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Margarita Tossa, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4053. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager Rachel Hartford at (301) 796-0331.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21536	SUPPL-33	NOVO NORDISK INC	LEVEMIR

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/s/

CAROL A HOLQUIST
03/15/2010

For Consulting Center Use Only:

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

Completed date: _____
Reviewer Initials: _____
Supervisory Concurrence: _____

Intercenter Request for Consultative or Collaborative Review Form

To (Consulting Center):
Center: CDRH
Division: ODE/DAGID/GHDB
Mail Code: HF_- Z-480
Consulting Reviewer Name:
Building/Room #:
Phone #:
Fax #:
Email Address:
RPM/CSO Name and Mail Code: Alan Stevens x66294

From (Originating Center):
Center: CDER
Division: Division of Metabolic and Endocrine Products
Mail Code: HFD-510
Requesting Reviewer Name: Pallaiah Thammana
Building/Room #: WO 21/2655
Phone#: 301-796-3884
Fax #:
Email Address:
RPM/CSO Name and Mail Code: Rachel Hartford
Requesting Reviewer's Concurring Supervisor's Name:
PAL - Janice Brown

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: 11Mar10
Submission/Application Number: NDA 020986/S061, NDA 021536/S033, and (b) (4)
Requested Completion Date: **12Apr2010**
Submission Type: NDA

Type of Product: ☒ Drug-device combination ☐ Drug-biologic combination ☐ Device-biologic combination ☐ Drug-device-biologic combination ☐ Not a combination product
Submission Receipt Date: 15Dec2009
Official Submission Due Date:
Name of Product: Novolog NDA 020986/S061, Levemir NDA 021536/S033, and (b) (4)
Name of Firm: Novo Nordisk

Intended Use: treatment of type 1 and type 2 diabetes mellitus.

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):
CMC Prior Approval Supplement for addition of the PDS 290 prefilled pen (FlexTouch). Please review the new device.
nda020986 EDR Location: \\CDSESUB1\EVSPROD\NDA020986\020986.enx
(b) (4)
nda021536 EDR Location: \\CDSESUB1\EVSPROD\NDA021536\021536.enx

Documents to be returned to Requesting Reviewer? π Yes ☐ π 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 ☒ π Collaborative Review ☐

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20986	SUPPL-61	NOVO NORDISK INC	NOVOLOG
[redacted] (b) (4)			
NDA-21536	SUPPL-33	NOVO NORDISK INC	LEVEMIR

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/s/

RACHEL E HARTFORD
03/11/2010