

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20986/S-061

Trade Name: **NOVOLOG**

Generic Name: **Insulin Aspart [rDNA Origin] Injection**

Sponsor: **Novo Nordisk, Inc.**

Approval Date: **10/31/2013**

Indications: NOVOLOG is an insulin analog indicated to improve
glycemic control in adults and children with diabetes
mellitus

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20986/S-061

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APPLICATION NUMBER:
NDA 20986/S-061

APPROVAL LETTER



NDA 20986/S-061

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 NovoLog (insulin aspart [rDNA origin]) injection.

We acknowledge receipt of your amendments dated July 13, 2011, January 12, and March 8, 2012, February 13, March 22, May 22 and 30, August 26, and October 11, 17, and 21, 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 NovoLog 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 20986/S-061.**” 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
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APPLICATION NUMBER:
NDA 20986/S-061

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(i)(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

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/s/

MARY H PARKS
03/20/2012



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

We acknowledge receipt of your amendments dated December 15, 2009, [REDACTED] (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(I)(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 |
| (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 20986/S-061

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NovoLog safely and effectively. See full prescribing information for NovoLog.

**NovoLog® (insulin aspart [rDNA origin] injection)
solution for subcutaneous use
Initial U.S. Approval: 2000**

RECENT MAJOR CHANGES

- Warnings and Precautions, Administration (5.10) 3/2013

INDICATIONS AND USAGE

- NovoLog is an insulin analog indicated to improve glycemic control in adults and children with diabetes mellitus (1.1).

DOSAGE AND ADMINISTRATION

- The dosage of NovoLog must be individualized.
- Subcutaneous injection* NovoLog should generally be given immediately (within 5-10 minutes) prior to the start of a meal (2.2).
- Use in pumps:* Change the NovoLog in the reservoir at least every 6 days, change the infusion set, and the infusion set insertion site at least every 3 days. NovoLog should not be mixed with other insulins or with a diluent when it is used in the pump (2.3).
- Intravenous use:* NovoLog should be used at concentrations from 0.05 U/mL to 1.0 U/mL insulin aspart in infusion systems using polypropylene infusion bags. NovoLog has been shown to be stable in infusion fluids such as 0.9% sodium chloride (2.4).

DOSAGE FORMS AND STRENGTHS

Each presentation contains 100 Units of insulin aspart per mL (U-100)

- 10 mL vials (3)
- 3 mL PenFill® cartridges for the 3 mL PenFill cartridge device (3)
- 3 mL NovoLog FlexPen® (3)
- 3 mL NovoLog FlexTouch® (3)

CONTRAINDICATIONS

- Do not use during episodes of hypoglycemia (4).
- Do not use in patients with hypersensitivity to NovoLog or one of its excipients.

WARNINGS AND PRECAUTIONS

- Hypoglycemia is the most common adverse effect of insulin therapy. Glucose monitoring is recommended for all patients with diabetes. Any change of insulin dose should be made cautiously and only under medical supervision (5.1, 5.2).

- Insulin, particularly when given intravenously or in settings of poor glycemic control, can cause hypokalemia. Use caution in patients predisposed to hypokalemia (5.3).
- Like all insulins, NovoLog requirements may be reduced in patients with renal impairment or hepatic impairment (5.4, 5.5).
- Severe, life-threatening, generalized allergy, including anaphylaxis, may occur with insulin products, including NovoLog (5.6).
- Fluid retention and heart failure can occur with concomitant use of thiazolidinediones (TZDs), which are PPAR-gamma agonists, and insulin, including NovoLog (5.10)

ADVERSE REACTIONS

Adverse reactions observed with NovoLog include hypoglycemia, allergic reactions, local 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

- The following may increase the blood-glucose-lowering effect and susceptibility to hypoglycemia: oral antidiabetic products, pramlintide, ACE inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, propoxyphene, salicylates, somatostatin analogs, sulfonamide antibiotics (7).
- The following may reduce the blood-glucose-lowering effect: corticosteroids, niacin, danazol, diuretics, sympathomimetic agents (e.g., epinephrine, salbutamol, terbutaline), isoniazid, phenothiazine derivatives, somatropin, thyroid hormones, estrogens, progestogens (e.g., in oral contraceptives), atypical antipsychotics (7).
- Beta-blockers, clonidine, lithium salts, and alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin (7).
- Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia (7).
- The signs of hypoglycemia may be reduced or absent in patients taking sympatholytic products such as 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*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Treatment of Diabetes Mellitus

NovoLog is an insulin analog indicated to improve glycemic control in adults and children with diabetes mellitus.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing

NovoLog is an insulin analog with an earlier onset of action than regular human insulin. The dosage of NovoLog must be individualized. NovoLog given by subcutaneous injection should generally be used in regimens with an intermediate or long-acting insulin [*see Warnings and Precautions (5), How Supplied/Storage and Handling (16.2)*]. The total daily insulin requirement may vary and is usually between 0.5 to 1.0 units/kg/day. When used in a meal-related subcutaneous injection treatment regimen, 50 to 70% of total insulin requirements may be provided by NovoLog and the remainder provided by an intermediate-acting or long-acting insulin. Because of NovoLog's comparatively rapid onset and short duration of glucose lowering activity, some patients may require more basal insulin and more total insulin to prevent pre-meal hyperglycemia when using NovoLog than when using human regular insulin.

Do not use NovoLog that is viscous (thickened) or cloudy; use only if it is clear and colorless. NovoLog should not be used after the printed expiration date.

2.2 Subcutaneous Injection

NovoLog should be administered by subcutaneous injection in the abdominal region, buttocks, thigh, or upper arm. Because NovoLog has a more rapid onset and a shorter duration of activity than human regular insulin, it should be injected immediately (within 5-10 minutes) before a meal. Injection sites should be rotated within the same region to reduce the risk of lipodystrophy. As with all insulins, the duration of action of NovoLog will vary according to the dose, injection site, blood flow, temperature, and level of physical activity.

NovoLog may be diluted with Insulin Diluting Medium for NovoLog for subcutaneous injection. Diluting one part NovoLog to nine parts diluent will yield a concentration one-tenth that of NovoLog (equivalent to U-10). Diluting one part NovoLog to one part diluent will yield a concentration one-half that of NovoLog (equivalent to U-50).

2.3 Continuous Subcutaneous Insulin Infusion (CSII) by External Pump

NovoLog can also be infused subcutaneously by an external insulin pump [*see Warnings and Precautions (5.8, 5.9), How Supplied/Storage and Handling (16.2)*]. Diluted insulin should not be used in external insulin pumps. Because NovoLog has a more rapid onset and a shorter duration of activity than human regular insulin, pre-meal boluses of NovoLog should be infused immediately (within 5-10 minutes) before a meal. Infusion sites should be rotated within the same region to reduce the risk of lipodystrophy. The initial programming of the external insulin infusion pump should be based on the total daily insulin dose of the previous regimen. Although there is significant interpatient variability, approximately 50% of the total dose is usually given as meal-related boluses of NovoLog and the remainder is given as a basal infusion. **Change the**

NovoLog in the reservoir at least every 6 days, change the infusion sets and the infusion set insertion site at least every 3 days.

The following insulin pumps[†] have been used in NovoLog clinical or *in vitro* studies conducted by Novo Nordisk, the manufacturer of NovoLog:

- Medtronic Paradigm[®] 512 and 712
- MiniMed 508
- Disetronic[®] D-TRON[®] and H-TRON[®]

Before using a different insulin pump with NovoLog, read the pump label to make sure the pump has been evaluated with NovoLog.

2.4 Intravenous Use

NovoLog can be administered intravenously under medical supervision for glycemic control with close monitoring of blood glucose and potassium levels to avoid hypoglycemia and hypokalemia [*see Warnings and Precautions (5), How Supplied/Storage and Handling (16.2)*]. For intravenous use, NovoLog should be used at concentrations from 0.05 U/mL to 1.0 U/mL insulin aspart in infusion systems using polypropylene infusion bags. NovoLog has been shown to be stable in infusion fluids such as 0.9% sodium chloride.

Inspect NovoLog for particulate matter and discoloration prior to parenteral administration.

3 DOSAGE FORMS AND STRENGTHS

NovoLog is available in the following package sizes: each presentation contains 100 units of insulin aspart per mL (U-100).

- 10 mL vials
- 3 mL PenFill cartridges for the 3 mL PenFill cartridge delivery device (with or without the addition of a NovoPen[®] 3 PenMate[®]) with NovoFine[®] disposable needles
- 3 mL NovoLog FlexPen
- 3 mL NovoLog FlexTouch

4 CONTRAINDICATIONS

NovoLog is contraindicated

- during episodes of hypoglycemia
- in patients with hypersensitivity to NovoLog or one of its excipients.

5 WARNINGS AND PRECAUTIONS

5.1 Administration

NovoLog has a more rapid onset of action and a shorter duration of activity than regular human insulin. An injection of NovoLog should immediately be followed by a meal within 5-10 minutes. Because of NovoLog's short duration of action, a longer acting insulin should also be used in patients with type 1 diabetes and may also be needed in patients with type 2 diabetes. Glucose monitoring is recommended for all patients with diabetes and is particularly important for patients using external pump infusion therapy.

Any change of insulin dose should be made cautiously and only under medical supervision. Changing from one insulin product to another or changing the insulin strength may result in the need for a change in dosage. As with all insulin preparations, the time course of NovoLog action may vary in different individuals or at different times in the same individual and is dependent on many conditions, including the site of injection, local blood supply, temperature, and physical activity. Patients who change their level of physical activity or meal plan may require adjustment of insulin dosages. Insulin requirements may be altered during illness, emotional disturbances, or other stresses.

Patients using continuous subcutaneous insulin infusion pump therapy must be trained to administer insulin by injection and have alternate insulin therapy available in case of pump failure.

5.2 Hypoglycemia

Hypoglycemia is the most common adverse effect of all insulin therapies, including NovoLog. Severe hypoglycemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or death. Severe hypoglycemia requiring the assistance of another person and/or parenteral glucose infusion or glucagon administration has been observed in clinical trials with insulin, including trials with NovoLog.

The timing of hypoglycemia usually reflects the time-action profile of the administered insulin formulations [*see Clinical Pharmacology (12)*]. Other factors such as changes in food intake (e.g., amount of food or timing of meals), injection site, exercise, and concomitant medications may also alter the risk of hypoglycemia [*see Drug Interactions (7)*]. As with all insulins, use caution in patients with hypoglycemia unawareness and in patients who may be predisposed to hypoglycemia (e.g., patients who are fasting 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.

Rapid changes in serum glucose levels may induce symptoms of hypoglycemia in persons with diabetes, regardless of the glucose value. Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as longstanding diabetes, diabetic nerve disease, use of medications such as beta-blockers, or intensified diabetes 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. Intravenously administered insulin has a more rapid onset of action than subcutaneously administered insulin, requiring more close monitoring for hypoglycemia.

5.3 Hypokalemia

All insulin products, including NovoLog, cause a shift in potassium from the extracellular to intracellular space, possibly leading to hypokalemia that, if left untreated, may cause respiratory paralysis, ventricular arrhythmia, and death. Use caution in patients who may be at risk for hypokalemia (e.g., patients using potassium-lowering medications, patients taking medications sensitive to serum potassium concentrations, and patients receiving intravenously administered insulin).

5.4 Renal Impairment

As with other insulins, the dose requirements for NovoLog may be reduced in patients with renal impairment [*see Clinical Pharmacology (12.3)*].

5.5 Hepatic Impairment

As with other insulins, the dose requirements for NovoLog may be reduced in patients with hepatic impairment [*see Clinical Pharmacology (12.3)*].

5.6 Hypersensitivity and Allergic Reactions

Local Reactions - As with other insulin therapy, patients may experience redness, swelling, or itching at the site of NovoLog injection. These reactions usually resolve in a few days to a few weeks, but in some occasions, may require discontinuation of NovoLog. 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. Localized reactions and generalized myalgias have been reported with injected metacresol, which is an excipient in NovoLog.

Systemic Reactions - Severe, life-threatening, generalized allergy, including anaphylaxis, may occur with any insulin product, including NovoLog. Anaphylactic reactions with NovoLog have been reported post-approval. Generalized allergy to insulin may also cause whole body rash (including pruritus), dyspnea, wheezing, hypotension, tachycardia, or diaphoresis. In controlled clinical trials, allergic reactions were reported in 3 of 735 patients (0.4%) treated with regular human insulin and 10 of 1394 patients (0.7%) treated with NovoLog. In controlled and uncontrolled clinical trials, 3 of 2341 (0.1%) NovoLog-treated patients discontinued due to allergic reactions.

5.7 Antibody Production

Increases in anti-insulin antibody titers that react with both human insulin and insulin aspart have been observed in patients treated with NovoLog. Increases in anti-insulin antibodies are observed more frequently with NovoLog than with regular human insulin. Data from a 12-month controlled trial in patients with type 1 diabetes suggest that the increase in these antibodies is transient, and the differences in antibody levels between the regular human insulin and insulin aspart treatment groups observed at 3 and 6 months were no longer evident at 12 months. The clinical significance of these antibodies is not known. These antibodies do not appear to cause deterioration in glycemic control or necessitate increases in insulin dose.

5.8 Mixing of Insulins

- Mixing NovoLog with NPH human insulin immediately before injection attenuates the peak concentration of NovoLog, without significantly affecting the time to peak concentration or total bioavailability of NovoLog. If NovoLog is mixed with NPH human insulin, NovoLog should be drawn into the syringe first, and the mixture should be injected immediately after mixing.
- The efficacy and safety of mixing NovoLog with insulin preparations produced by other manufacturers have not been studied.
- Insulin mixtures should not be administered intravenously.

5.9 Continuous Subcutaneous Insulin Infusion by External Pump

When used in an external subcutaneous insulin infusion pump, NovoLog should not be mixed with any other insulin or diluent. When using NovoLog in an external insulin pump, the NovoLog-specific information should be followed (e.g., in-use time, frequency of changing infusion sets) because NovoLog-specific information may differ from general pump manual instructions.

Pump or infusion set malfunctions or insulin degradation can lead to a rapid onset of hyperglycemia and ketosis because of the small subcutaneous depot of insulin. This is especially pertinent for rapid-acting insulin analogs that are more rapidly absorbed through skin and have a shorter duration of action. Prompt identification and correction of the cause of hyperglycemia or ketosis is necessary. Interim therapy with subcutaneous injection may be required [*see Dosage and Administration (2.3), Warnings and Precautions (5.8, 5.9), How Supplied/Storage and Handling (16.2), and Patient Counseling Information (17.2)*].

NovoLog should not be exposed to temperatures greater than 37°C (98.6°F). **NovoLog that will be used in a pump should not be mixed with other insulin or with a diluent** [*see Dosage and Administration (2.3), Warnings and Precautions (5.8, 5.9), How Supplied/Storage and Handling (16.2), and Patient Counseling Information (17.2)*].

5.10 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 NovoLog, 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

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.

- *Hypoglycemia*
Hypoglycemia is the most commonly observed adverse reaction in patients using insulin, including NovoLog [*see Warnings and Precautions (5)*].
- *Insulin initiation and glucose control intensification*
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 NovoLog, can cause lipodystrophy at the site of repeated insulin injections or infusion. Lipodystrophy includes lipohypertrophy (thickening of adipose tissue) and lipoatrophy (thinning of adipose tissue), and may affect insulin absorption. Rotate insulin injection or infusion sites within the same region to reduce the risk of lipodystrophy.

- Weight gain

Weight gain can occur with some insulin therapies, including NovoLog, and has been attributed to the anabolic effects of insulin and the decrease in glucosuria.

- Peripheral Edema

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

- Frequencies of adverse drug reactions

The frequencies of adverse drug reactions during NovoLog clinical trials in patients with type 1 diabetes mellitus and type 2 diabetes mellitus are listed in the tables below.

Table 1: Treatment-Emergent Adverse Events in Patients with Type 1 Diabetes Mellitus (Adverse events with frequency $\geq 5\%$ and occurring more frequently with NovoLog compared to human regular insulin are listed)

| Preferred Term | NovoLog + NPH N= 596 | | Human Regular Insulin + NPH N= 286 | |
|-------------------|-------------------------|-----|---------------------------------------|-----|
| | N | (%) | N | (%) |
| Hypoglycemia* | 448 | 75% | 205 | 72% |
| Headache | 70 | 12% | 28 | 10% |
| Injury accidental | 65 | 11% | 29 | 10% |
| Nausea | 43 | 7% | 13 | 5% |
| Diarrhea | 28 | 5% | 9 | 3% |

*Hypoglycemia is defined as an episode of blood glucose concentration <45 mg/dL, with or without symptoms. See Section 14 for the incidence of serious hypoglycemia in the individual clinical trials.

Table 2: Treatment-Emergent Adverse Events in Patients with Type 2 Diabetes Mellitus (except for hypoglycemia, adverse events with frequency $\geq 5\%$ and occurring more frequently with NovoLog compared to human regular insulin are listed)

| | NovoLog + NPH N= 91 | | Human Regular Insulin + NPH N= 91 | |
|-------------------------|------------------------|-----|--------------------------------------|-----|
| | N | (%) | N | (%) |
| Hypoglycemia* | 25 | 27% | 33 | 36% |
| Hyporeflexia | 10 | 11% | 6 | 7% |
| Onychomycosis | 9 | 10% | 5 | 5% |
| Sensory disturbance | 8 | 9% | 6 | 7% |
| Urinary tract infection | 7 | 8% | 6 | 7% |
| Chest pain | 5 | 5% | 3 | 3% |
| Headache | 5 | 5% | 3 | 3% |
| Skin disorder | 5 | 5% | 2 | 2% |
| Abdominal pain | 5 | 5% | 1 | 1% |

| | NovoLog + NPH N= 91 | | Human Regular Insulin + NPH N= 91 | |
|-----------|------------------------|-----|--------------------------------------|-----|
| | N | (%) | N | (%) |
| Sinusitis | 5 | 5% | 1 | 1% |

*Hypoglycemia is defined as an episode of blood glucose concentration <45 mg/dL, with or without symptoms. See Section 14 for the incidence of serious hypoglycemia in the individual clinical trials.

Postmarketing Data

The following additional adverse reactions have been identified during postapproval use of NovoLog. Because these adverse reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency. Medication errors in which other insulins have been accidentally substituted for NovoLog have been identified during postapproval use [*see Patient Counseling Information (17)*].

7 DRUG INTERACTIONS

A number of substances affect glucose metabolism and may require insulin dose adjustment and particularly close monitoring.

- The following are examples of substances that may increase the blood-glucose-lowering effect and susceptibility to hypoglycemia: oral antidiabetic products, pramlintide, ACE inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, propoxyphene, salicylates, somatostatin analog (e.g., octreotide), sulfonamide antibiotics.
- The following are examples of substances that may reduce the blood-glucose-lowering effect: corticosteroids, niacin, danazol, diuretics, sympathomimetic agents (e.g., epinephrine, salbutamol, terbutaline), isoniazid, phenothiazine derivatives, somatropin, thyroid hormones, estrogens, progestogens (e.g., in oral contraceptives), atypical antipsychotics.
- Beta-blockers, clonidine, lithium salts, and alcohol may either potentiate or weaken 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 sympatholytic products such as beta-blockers, clonidine, guanethidine, and reserpine.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B. All pregnancies have a background risk of birth defects, loss, or other adverse outcome regardless of drug exposure. This background risk is increased in pregnancies complicated by hyperglycemia and may be decreased with good metabolic control. It is essential for patients with diabetes or history of gestational diabetes to maintain good metabolic control before conception and throughout pregnancy. Insulin requirements may decrease during the first trimester, generally increase during the second and third trimesters, and rapidly decline after delivery. Careful monitoring of glucose control is essential in these patients. Therefore, female patients should be advised to tell their physician if they intend to become, or if they become pregnant while taking NovoLog.

An open-label, randomized study compared the safety and efficacy of NovoLog (n=157) versus regular human insulin (n=165) in 322 pregnant women with type 1 diabetes. Two-thirds of the enrolled patients were already pregnant when they entered the study. Because only one-third of the patients enrolled before conception, the study was not large enough to evaluate the risk of congenital malformations. Both groups achieved a mean HbA_{1c} of ~ 6% during pregnancy, and there was no significant difference in the incidence of maternal hypoglycemia.

Subcutaneous reproduction and teratology studies have been performed with NovoLog and regular human insulin in rats and rabbits. In these studies, NovoLog was given to female rats before mating, during mating, and throughout pregnancy, and to rabbits during organogenesis. The effects of NovoLog did not differ from those observed with subcutaneous regular human insulin. NovoLog, like human insulin, caused pre- and post-implantation losses and visceral/skeletal abnormalities in rats at a dose of 200 U/kg/day (approximately 32 times the human subcutaneous dose of 1.0 U/kg/day, based on U/body surface area) and in rabbits at a dose of 10 U/kg/day (approximately three times the human subcutaneous dose of 1.0 U/kg/day, based on U/body surface area). The effects are probably secondary to maternal hypoglycemia at high doses. No significant effects were observed in rats at a dose of 50 U/kg/day and in rabbits at a dose of 3 U/kg/day. These doses are approximately 8 times the human subcutaneous dose of 1.0 U/kg/day for rats and equal to the human subcutaneous dose of 1.0 U/kg/day for rabbits, based on U/body surface area.

8.3 Nursing Mothers

It is unknown whether insulin aspart is excreted in human milk. Use of NovoLog is compatible with breastfeeding, but women with diabetes who are lactating may require adjustments of their insulin doses.

8.4 Pediatric Use

NovoLog is approved for use in children for subcutaneous daily injections and for subcutaneous continuous infusion by external insulin pump. NovoLog has not been studied in pediatric patients younger than 2 years of age. NovoLog has not been studied in pediatric patients with type 2 diabetes. Please see *Section 14 CLINICAL STUDIES* for summaries of clinical studies.

8.5 Geriatric Use

Of the total number of patients (n= 1,375) treated with NovoLog in 3 controlled clinical studies, 2.6% (n=36) were 65 years of age or over. One-half of these patients had type 1 diabetes (18/1285) and the other half had type 2 diabetes (18/90). The HbA_{1c} response to NovoLog, as compared to human insulin, did not differ by age, particularly in patients with type 2 diabetes. Additional studies in larger populations of patients 65 years of age or over are needed to permit conclusions regarding the safety of NovoLog in elderly compared to younger patients.

Pharmacokinetic/pharmacodynamic studies to assess the effect of age on the onset of NovoLog action have not been performed.

10 OVERDOSAGE

Excess insulin administration may cause hypoglycemia and, particularly when given intravenously, hypokalemia. 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. Sustained carbohydrate intake and observation may be necessary because hypoglycemia may recur after apparent clinical recovery. Hypokalemia must be corrected appropriately.

11 DESCRIPTION

NovoLog (insulin aspart [rDNA origin] injection) is a rapid-acting human insulin analog used to lower blood glucose. NovoLog is homologous with regular human insulin with the exception of a single substitution of the amino acid proline by aspartic acid in position B28, and is produced by recombinant DNA technology utilizing *Saccharomyces cerevisiae* (baker's yeast). Insulin aspart has the empirical formula $C_{256}H_{381}N_{65}O_{79}S_6$ and a molecular weight of 5825.8.

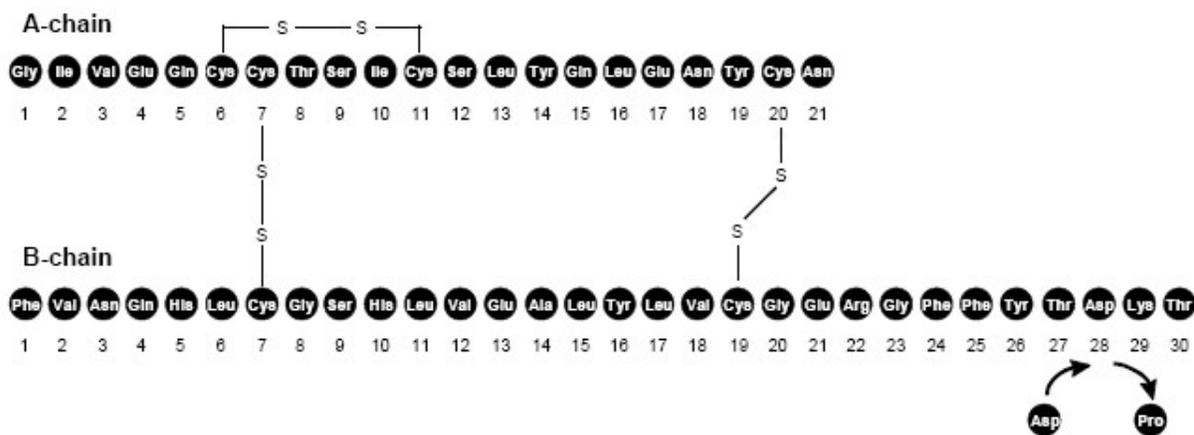


Figure 1. Structural formula of insulin aspart.

NovoLog is a sterile, aqueous, clear, and colorless solution, that contains insulin aspart 100 Units/mL, glycerin 16 mg/mL, phenol 1.50 mg/mL, metacresol 1.72 mg/mL, zinc 19.6 mcg/mL, disodium hydrogen phosphate dihydrate 1.25 mg/mL, sodium chloride 0.58 mg/mL and water for injection. NovoLog has a pH of 7.2-7.6. Hydrochloric acid 10% and/or sodium hydroxide 10% may be added to adjust pH.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The primary activity of NovoLog is the regulation of glucose metabolism. Insulins, including NovoLog, bind to the insulin receptors on muscle and fat cells and lower blood glucose by facilitating the cellular uptake of glucose and simultaneously inhibiting the output of glucose from the liver.

12.2 Pharmacodynamics

Studies in normal volunteers and patients with diabetes demonstrated that subcutaneous administration of NovoLog has a more rapid onset of action than regular human insulin.

In a study in patients with type 1 diabetes (n=22), the maximum glucose-lowering effect of NovoLog occurred between 1 and 3 hours after subcutaneous injection (see Figure 2). The duration of action for NovoLog is 3 to 5 hours. The time course of action of insulin and insulin analogs such as NovoLog may vary considerably in different individuals or within the same individual. The parameters of NovoLog activity (time of onset, peak time and duration) as designated in Figure 2 should be considered only as general guidelines. The rate of insulin absorption and onset of activity is affected by the site of injection, exercise, and other variables [see *Warnings and Precautions (5.1)*].

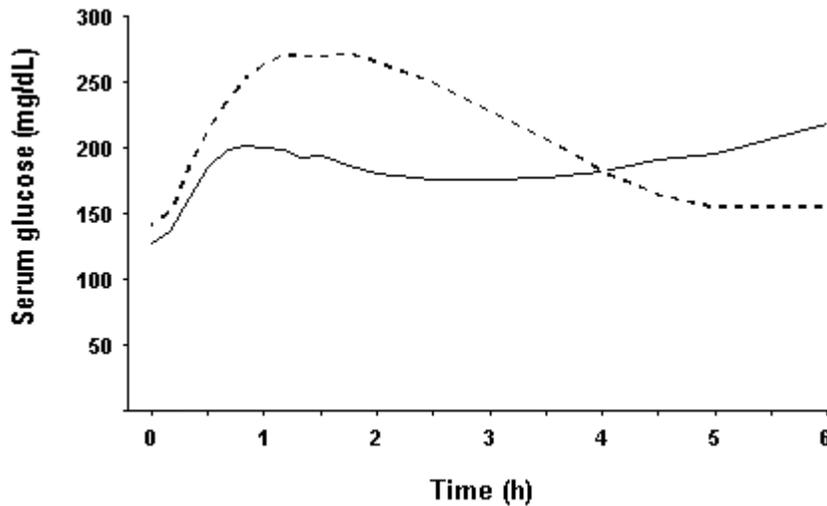
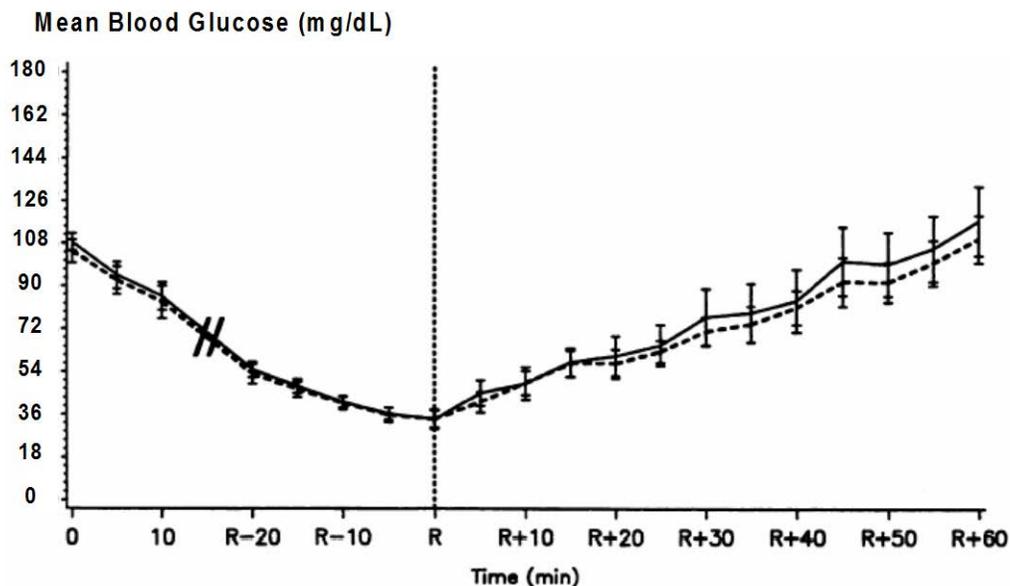


Figure 2. Serial mean serum glucose collected up to 6 hours following a single pre-meal dose of NovoLog (solid curve) or regular human insulin (hatched curve) injected immediately before a meal in 22 patients with type 1 diabetes.

A double-blind, randomized, two-way cross-over study in 16 patients with type 1 diabetes demonstrated that intravenous infusion of NovoLog resulted in a blood glucose profile that was similar to that after intravenous infusion with regular human insulin. NovoLog or human insulin was infused until the patient's blood glucose decreased to 36 mg/dL, or until the patient demonstrated signs of hypoglycemia (rise in heart rate and onset of sweating), defined as the time of autonomic reaction (R) (see Figure 3).



Note: The slashes on the mean profile indicate a jump on the time axis

Figure 3. Mean blood glucose profiles following intravenous infusion of NovoLog (hatched curve) and regular human insulin (solid curve) in 16 patients with type 1 diabetes. R represents the time of autonomic reaction.

12.3 Pharmacokinetics

The single substitution of the amino acid proline with aspartic acid at position B28 in NovoLog reduces the molecule's tendency to form hexamers as observed with regular human insulin. NovoLog is, therefore, more rapidly absorbed after subcutaneous injection compared to regular human insulin.

In a randomized, double-blind, crossover study 17 healthy Caucasian male subjects between 18 and 40 years of age received an intravenous infusion of either NovoLog or regular human insulin at 1.5 mU/kg/min for 120 minutes. The mean insulin clearance was similar for the two groups with mean values of 1.2 l/h/kg for the NovoLog group and 1.2 l/h/kg for the regular human insulin group.

Bioavailability and Absorption - NovoLog has a faster absorption, a faster onset of action, and a shorter duration of action than regular human insulin after subcutaneous injection (see Figure 2 and Figure 4). The relative bioavailability of NovoLog compared to regular human insulin indicates that the two insulins are absorbed to a similar extent.

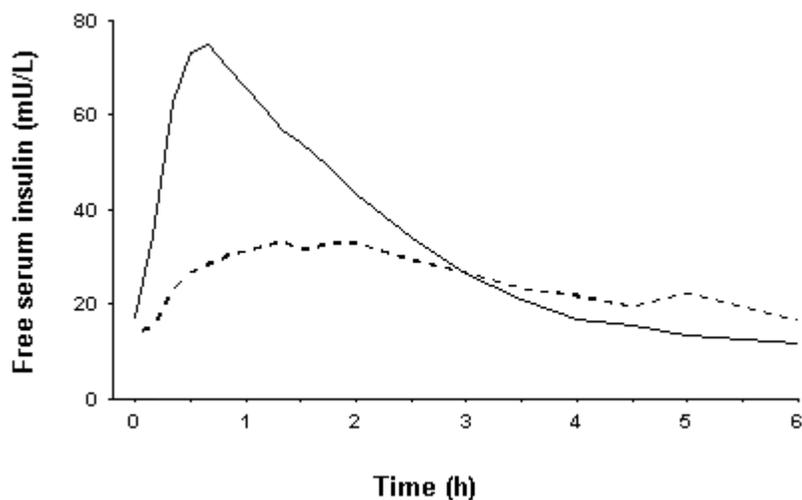


Figure 4. Serial mean serum free insulin concentration collected up to 6 hours following a single pre-meal dose of NovoLog (solid curve) or regular human insulin (hatched curve) injected immediately before a meal in 22 patients with type 1 diabetes.

In studies in healthy volunteers (total n=107) and patients with type 1 diabetes (total n=40), NovoLog consistently reached peak serum concentrations approximately twice as fast as regular human insulin. The median time to maximum concentration in these trials was 40 to 50 minutes for NovoLog versus 80 to 120 minutes for regular human insulin. In a clinical trial in patients with type 1 diabetes, NovoLog and regular human insulin, both administered subcutaneously at a dose of 0.15 U/kg body weight, reached mean maximum concentrations of 82 and 36 mU/L, respectively. Pharmacokinetic/pharmacodynamic characteristics of insulin aspart have not been established in patients with type 2 diabetes.

The intra-individual variability in time to maximum serum insulin concentration for healthy male volunteers was significantly less for NovoLog than for regular human insulin. The clinical significance of this observation has not been established.

In a clinical study in healthy non-obese subjects, the pharmacokinetic differences between NovoLog and regular human insulin described above, were observed independent of the site of injection (abdomen, thigh, or upper arm).

Distribution and Elimination - NovoLog has low binding to plasma proteins (<10%), similar to that seen with regular human insulin. After subcutaneous administration in normal male volunteers (n=24), NovoLog was more rapidly eliminated than regular human insulin with an average apparent half-life of 81 minutes compared to 141 minutes for regular human insulin.

Specific Populations

Children and Adolescents - The pharmacokinetic and pharmacodynamic properties of NovoLog and regular human insulin were evaluated in a single dose study in 18 children (6-12 years, n=9) and adolescents (13-17 years [Tanner grade ≥ 2], n=9) with type 1 diabetes. The relative differences in pharmacokinetics and pharmacodynamics in children and adolescents with

type 1 diabetes between NovoLog and regular human insulin were similar to those in healthy adult subjects and adults with type 1 diabetes.

Gender - In healthy volunteers, no difference in insulin aspart levels was seen between men and women when body weight differences were taken into account. There was no significant difference in efficacy noted (as assessed by HbA_{1c}) between genders in a trial in patients with type 1 diabetes.

Obesity - A single subcutaneous dose of 0.1 U/kg NovoLog was administered in a study of 23 patients with type 1 diabetes and a wide range of body mass index (BMI, 22-39 kg/m²). The pharmacokinetic parameters, AUC and C_{max}, of NovoLog were generally unaffected by BMI in the different groups – BMI 19-23 kg/m² (N=4); BMI 23-27 kg/m² (N=7); BMI 27-32 kg/m² (N=6) and BMI >32 kg/m² (N=6). Clearance of NovoLog was reduced by 28% in patients with BMI >32 kg/m² compared to patients with BMI <23 kg/m².

Renal Impairment - Some studies with human insulin have shown increased circulating levels of insulin in patients with renal failure. A single subcutaneous dose of 0.08 U/kg NovoLog was administered in a study to subjects with either normal (N=6) creatinine clearance (CLcr) (> 80 ml/min) or mild (N=7; CLcr = 50-80 ml/min), moderate (N=3; CLcr = 30-50 ml/min) or severe (but not requiring hemodialysis) (N=2; CLcr = <30 ml/min) renal impairment. In this small study, there was no apparent effect of creatinine clearance values on AUC and C_{max} of NovoLog. Careful glucose monitoring and dose adjustments of insulin, including NovoLog, may be necessary in patients with renal dysfunction [*see Warnings and Precautions (5.4)*].

Hepatic Impairment - Some studies with human insulin have shown increased circulating levels of insulin in patients with liver failure. A single subcutaneous dose of 0.06 U/kg NovoLog was administered in an open-label, single-dose study of 24 subjects (N=6/group) with different degree of hepatic impairment (mild, moderate and severe) having Child-Pugh Scores ranging from 0 (healthy volunteers) to 12 (severe hepatic impairment). In this small study, there was no correlation between the degree of hepatic failure and any NovoLog pharmacokinetic parameter. Careful glucose monitoring and dose adjustments of insulin, including NovoLog, may be necessary in patients with hepatic dysfunction [*see Warnings and Precautions (5.5)*].

The effect of age, ethnic origin, pregnancy and smoking on the pharmacokinetics and pharmacodynamics of NovoLog has not been studied.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Standard 2-year carcinogenicity studies in animals have not been performed to evaluate the carcinogenic potential of NovoLog. In 52-week studies, Sprague-Dawley rats were dosed subcutaneously with NovoLog at 10, 50, and 200 U/kg/day (approximately 2, 8, and 32 times the human subcutaneous dose of 1.0 U/kg/day, based on U/body surface area, respectively). At a dose of 200 U/kg/day, NovoLog increased the incidence of mammary gland tumors in females

when compared to untreated controls. The incidence of mammary tumors for NovoLog was not significantly different than for regular human insulin. The relevance of these findings to humans is not known. NovoLog was not genotoxic in the following tests: Ames test, mouse lymphoma cell forward gene mutation test, human peripheral blood lymphocyte chromosome aberration test, *in vivo* micronucleus test in mice, and in *ex vivo* UDS test in rat liver hepatocytes. In fertility studies in male and female rats, at subcutaneous doses up to 200 U/kg/day (approximately 32 times the human subcutaneous dose, based on U/body surface area), no direct adverse effects on male and female fertility, or general reproductive performance of animals was observed.

13.2 Animal Toxicology and/or Pharmacology

In standard biological assays in mice and rabbits, one unit of NovoLog has the same glucose-lowering effect as one unit of regular human insulin. In humans, the effect of NovoLog is more rapid in onset and of shorter duration, compared to regular human insulin, due to its faster absorption after subcutaneous injection (see *Section 12 CLINICAL PHARMACOLOGY* Figure 2 and Figure 4).

14 CLINICAL STUDIES

14.1 Subcutaneous Daily Injections

Two six-month, open-label, active-controlled studies were conducted to compare the safety and efficacy of NovoLog to Novolin R in adult patients with type 1 diabetes. Because the two study designs and results were similar, data are shown for only one study (see Table 3). NovoLog was administered by subcutaneous injection immediately prior to meals and regular human insulin was administered by subcutaneous injection 30 minutes before meals. NPH insulin was administered as the basal insulin in either single or divided daily doses. Changes in HbA_{1c} and the incidence rates of severe hypoglycemia (as determined from the number of events requiring intervention from a third party) were comparable for the two treatment regimens in this study (Table 3) as well as in the other clinical studies that are cited in this section. Diabetic ketoacidosis was not reported in any of the adult studies in either treatment group.

Table 3. Subcutaneous NovoLog Administration in Type 1 Diabetes (24 weeks; n=882)

| | NovoLog + NPH | Novolin R + NPH |
|--|----------------------|------------------------|
| N | 596 | 286 |
| Baseline HbA _{1c} (%)* | 7.9 ± 1.1 | 8.0 ± 1.2 |
| Change from Baseline HbA _{1c} (%) | -0.1 ± 0.8 | 0.0 ± 0.8 |
| Treatment Difference in HbA _{1c} , Mean (95% confidence interval) | -0.2 (-0.3, -0.1) | |
| Baseline insulin dose (IU/kg/24 hours)* | 0.7 ± 0.2 | 0.7 ± 0.2 |
| End-of-Study insulin dose (IU/kg/24 hours)* | 0.7 ± 0.2 | 0.7 ± 0.2 |
| Patients with severe hypoglycemia (n, %)** | 104 (17%) | 54 (19%) |
| Baseline body weight (kg)* | 75.3 ± 14.5 | 75.9 ± 13.1 |
| Weight Change from baseline (kg)* | 0.5 ± 3.3 | 0.9 ± 2.9 |

*Values are Mean ± SD

**Severe hypoglycemia refers to hypoglycemia associated with central nervous system symptoms and requiring the intervention of another person or hospitalization.

A 24-week, parallel-group study of children and adolescents with type 1 diabetes (n = 283) aged 6 to 18 years compared two subcutaneous multiple-dose treatment regimens: NovoLog (n = 187) or Novolin R (n = 96). NPH insulin was administered as the basal insulin. NovoLog achieved glycemic control comparable to Novolin R, as measured by change in HbA_{1c} (Table 4) and both treatment groups had a comparable incidence of hypoglycemia. Subcutaneous administration of NovoLog and regular human insulin have also been compared in children with type 1 diabetes (n=26) aged 2 to 6 years with similar effects on HbA_{1c} and hypoglycemia.

Table 4. Pediatric Subcutaneous Administration of NovoLog in Type 1 Diabetes (24 weeks; n=283)

| | NovoLog + NPH | Novolin R + NPH |
|--|----------------------|------------------------|
| N | 187 | 96 |
| Baseline HbA _{1c} (%)* | 8.3 ± 1.2 | 8.3 ± 1.3 |
| Change from Baseline HbA _{1c} (%) | 0.1 ± 1.0 | 0.1 ± 1.1 |
| Treatment Difference in HbA _{1c} , Mean (95% confidence interval) | 0.1 (-0.5, 0.1) | |
| Baseline insulin dose (IU/kg/24 hours)* | 0.4 ± 0.2 | 0.6 ± 0.2 |
| End-of-Study insulin dose (IU/kg/24 hours)* | 0.4 ± 0.2 | 0.7 ± 0.2 |
| Patients with severe hypoglycemia (n, %)** | 11 (6%) | 9 (9%) |
| Diabetic ketoacidosis (n, %) | 10 (5%) | 2 (2%) |
| Baseline body weight (kg)* | 50.6 ± 19.6 | 48.7 ± 15.8 |
| Weight Change from baseline (kg)* | 2.7 ± 3.5 | 2.4 ± 2.6 |

*Values are Mean ± SD

**Severe hypoglycemia refers to hypoglycemia associated with central nervous system symptoms and requiring the intervention of another person or hospitalization.

One six-month, open-label, active-controlled study was conducted to compare the safety and efficacy of NovoLog to Novolin R in patients with type 2 diabetes (Table 5). NovoLog was administered by subcutaneous injection immediately prior to meals and regular human insulin was administered by subcutaneous injection 30 minutes before meals. NPH insulin was administered as the basal insulin in either single or divided daily doses. Changes in HbA_{1c} and the rates of severe hypoglycemia (as determined from the number of events requiring intervention from a third party) were comparable for the two treatment regimens.

Table 5. Subcutaneous NovoLog Administration in Type 2 Diabetes (6 months; n=176)

| | NovoLog + NPH | Novolin R + NPH |
|--|----------------------|------------------------|
| N | 90 | 86 |
| Baseline HbA _{1c} (%)* | 8.1 ± 1.2 | 7.8 ± 1.1 |
| Change from Baseline HbA _{1c} (%) | -0.3 ± 1.0 | -0.1 ± 0.8 |
| Treatment Difference in HbA _{1c} , Mean (95% confidence interval) | - 0.1 (-0.4, -0.1) | |
| Baseline insulin dose (IU/kg/24 hours)* | 0.6 ± 0.3 | 0.6 ± 0.3 |
| End-of-Study insulin dose (IU/kg/24 hours)* | 0.7 ± 0.3 | 0.7 ± 0.3 |
| Patients with severe hypoglycemia (n, %)** | 9 (10%) | 5 (8%) |
| Baseline body weight (kg)* | 88.4 ± 13.3 | 85.8 ± 14.8 |
| Weight Change from baseline (kg)* | 1.2 ± 3.0 | 0.4 ± 3.1 |

*Values are Mean ± SD

**Severe hypoglycemia refers to hypoglycemia associated with central nervous system symptoms and requiring the intervention of another person or hospitalization.

14.2 Continuous Subcutaneous Insulin Infusion (CSII) by External Pump

Two open-label, parallel design studies (6 weeks [n=29] and 16 weeks [n=118]) compared NovoLog to buffered regular human insulin (Velosulin) in adults with type 1 diabetes receiving a subcutaneous infusion with an external insulin pump. The two treatment regimens had comparable changes in HbA_{1c} and rates of severe hypoglycemia.

Table 6. Adult Insulin Pump Study in Type 1 Diabetes (16 weeks; n=118)

| | NovoLog | Buffered human insulin |
|--|-----------------|-------------------------------|
| N | 59 | 59 |
| Baseline HbA _{1c} (%)* | 7.3 ± 0.7 | 7.5 ± 0.8 |
| Change from Baseline HbA _{1c} (%) | 0.0 ± 0.5 | 0.2 ± 0.6 |
| Treatment Difference in HbA _{1c} , Mean (95% confidence interval) | 0.3 (-0.1, 0.4) | |
| Baseline insulin dose (IU/kg/24 hours)* | 0.7 ± 0.8 | 0.6 ± 0.2 |
| End-of-Study insulin dose (IU/kg/24 hours)* | 0.7 ± 0.7 | 0.6 ± 0.2 |
| Patients with severe hypoglycemia (n, %)** | 1 (2%) | 2 (3%) |
| Baseline body weight (kg)* | 77.4 ± 16.1 | 74.8 ± 13.8 |
| Weight Change from baseline (kg)* | 0.1 ± 3.5 | -0.0 ± 1.7 |

*Values are Mean ± SD

**Severe hypoglycemia refers to hypoglycemia associated with central nervous system symptoms and requiring the intervention of another person or hospitalization.

A randomized, 16-week, open-label, parallel design study of children and adolescents with type 1 diabetes (n=298) aged 4-18 years compared two subcutaneous infusion regimens administered via an external insulin pump: NovoLog (n=198) or insulin lispro (n=100). These two treatments resulted in comparable changes from baseline in HbA_{1c} and comparable rates of hypoglycemia after 16 weeks of treatment (see Table 7).

Table 7. Pediatric Insulin Pump Study in Type 1 Diabetes (16 weeks; n=298)

| | NovoLog | Lispro |
|--|------------------|---------------|
| N | 198 | 100 |
| Baseline HbA _{1c} (%)* | 8.0 ± 0.9 | 8.2 ± 0.8 |
| Change from Baseline HbA _{1c} (%) | -0.1 ± 0.8 | -0.1 ± 0.7 |
| Treatment Difference in HbA _{1c} , Mean (95% confidence interval) | -0.1 (-0.3, 0.1) | |
| Baseline insulin dose (IU/kg/24 hours)* | 0.9 ± 0.3 | 0.9 ± 0.3 |
| End-of-Study insulin dose (IU/kg/24 hours)* | 0.9 ± 0.2 | 0.9 ± 0.2 |
| Patients with severe hypoglycemia (n, %)** | 19 (10%) | 8 (8%) |
| Diabetic ketoacidosis (n, %) | 1 (0.5%) | 0 (0) |
| Baseline body weight (kg)* | 54.1 ± 19.7 | 55.5 ± 19.0 |
| Weight Change from baseline (kg)* | 1.8 ± 2.1 | 1.6 ± 2.1 |

*Values are Mean ± SD

**Severe hypoglycemia refers to hypoglycemia associated with central nervous system symptoms and requiring the intervention of another person or hospitalization.

An open-label, 16-week parallel design trial compared pre-prandial NovoLog injection in conjunction with NPH injections to NovoLog administered by continuous subcutaneous infusion in 127 adults with type 2 diabetes. The two treatment groups had similar reductions in HbA_{1c} and rates of severe hypoglycemia (Table 8) [*see Indications and Usage (1), Dosage and Administration (2), Warnings and Precautions (5) and How Supplied/Storage and Handling (16.2)*].

Table 8. Pump Therapy in Type 2 Diabetes (16 weeks; n=127)

| | NovoLog pump | NovoLog + NPH |
|--|---------------------|----------------------|
| N | 66 | 61 |
| Baseline HbA _{1c} (%)* | 8.2 ± 1.4 | 8.0 ± 1.1 |
| Change from Baseline HbA _{1c} (%) | -0.6 ± 1.1 | -0.5 ± 0.9 |
| Treatment Difference in HbA _{1c} , Mean (95% confidence interval) | 0.1 (0.4, 0.3) | |
| Baseline insulin dose (IU/kg/24 hours)* | 0.7 ± 0.3 | 0.8 ± 0.5 |
| End-of-Study insulin dose (IU/kg/24 hours)* | 0.9 ± 0.4 | 0.9 ± 0.5 |
| Baseline body weight (kg)* | 96.4 ± 17.0 | 96.9 ± 17.9 |
| Weight Change from baseline (kg)* | 1.7 ± 3.7 | 0.7 ± 4.1 |

*Values are Mean ± SD

14.3 Intravenous Administration of NovoLog

See Section 12.2 CLINICAL PHARMACOLOGY/Pharmacodynamics.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

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

| | |
|--------------------------|------------------|
| 10 mL vials | NDC 0169-7501-11 |
| 3 mL PenFill cartridges* | NDC 0169-3303-12 |
| 3 mL NovoLog FlexPen | NDC 0169-6339-10 |
| 3 mL NovoLog FlexTouch | NDC 0169-6338-10 |

*NovoLog PenFill cartridges are designed for use with Novo Nordisk 3 mL PenFill cartridge compatible insulin delivery devices (with or without the addition of a NovoPen 3 PenMate) with NovoFine disposable needles. FlexPen and FlexTouch can be used with NovoFine or NovoTwist disposable needles.

16.2 Recommended Storage

Unused NovoLog should be stored in a 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 NovoLog and do not use NovoLog if it has been frozen.** NovoLog should not be drawn into a syringe and stored for later use.

Vials: After initial use a vial may be kept at temperatures below 30°C (86°F) for up to 28 days, but should not be exposed to excessive heat or light. Opened vials may be refrigerated.

Unpunctured vials can be used until the expiration date printed on the label if they are stored in a refrigerator. Keep unused vials in the carton so they will stay clean and protected from light.

PenFill cartridges or NovoLog FlexPen and NovoLog FlexTouch:

Once a cartridge or NovoLog FlexPen or NovoLog FlexTouch is punctured, it should be kept at temperatures below 30°C (86°F) for up to 28 days, but should not be exposed to excessive heat or sunlight. A NovoLog FlexPen or NovoLog FlexTouch or cartridge in use must NOT be stored in the refrigerator. Keep the NovoLog FlexPen or NovoLog FlexTouch and all PenFill cartridges away from direct heat and sunlight. Unpunctured NovoLog FlexPen or NovoLog FlexTouch and PenFill cartridges can be used until the expiration date printed on the label if they are stored in a refrigerator. Keep unused NovoLog FlexPen or NovoLog FlexTouch and PenFill cartridges in the carton so they will stay clean and protected from light.

Always remove the needle after each injection and store the 3 mL PenFill cartridge delivery device or NovoLog FlexPen or NovoLog FlexTouch without a needle attached. This prevents contamination and/or infection, or leakage of insulin, and will ensure accurate dosing. Always use a new needle for each injection to prevent contamination.

Pump:

NovoLog in the pump reservoir should be discarded after at least every 6 days of use or after exposure to temperatures that exceed 37°C (98.6°F). The infusion set and the infusion set insertion site should be changed at least every 3 days.

Summary of Storage Conditions:

The storage conditions are summarized in the following table:

Table 9. Storage conditions for vial, PenFill cartridges, NovoLog FlexPen, and NovoLog FlexTouch

| 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) |
| 3 mL NovoLog FlexTouch | 28 days | Until expiration date | 28 days (Do not refrigerate) |

Storage of Diluted NovoLog

NovoLog diluted with Insulin Diluting Medium for NovoLog to a concentration equivalent to U-10 or equivalent to U-50 may remain in patient use at temperatures below 30°C (86°F) for 28 days.

Storage of NovoLog in Infusion Fluids

Infusion bags prepared as indicated under *Dosage and Administration (2)* are stable at room temperature for 24 hours. Some insulin will be initially adsorbed to the material of the infusion bag.

17 PATIENT COUNSELING INFORMATION

[See FDA Approved Patient Labeling (17.3)]

17.1 Physician Instructions

Maintenance of normal or near-normal glucose control is a treatment goal in diabetes mellitus and has been associated with a reduction in diabetic complications. Patients should be informed about potential risks and benefits of NovoLog therapy including the possible adverse reactions. Patients should also be offered continued education and advice on insulin therapies, injection technique, life-style management, regular glucose monitoring, periodic glycosylated hemoglobin testing, recognition and management of hypo- and hyperglycemia, adherence to meal planning, complications of insulin therapy, timing of dose, instruction in the use of injection or subcutaneous infusion devices, and proper storage of insulin. Patients should be informed that frequent, patient-performed blood glucose measurements are needed to achieve optimal glycemic control and avoid both hyper- and hypoglycemia.

Patients should receive proper training on how to use NovoLog. Instruct patients that when injecting NovoLog, 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.**

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. 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 substitutions between NovoLog and other insulin products have been reported. Patients should be instructed to always carefully check that they are administering the appropriate insulin to avoid medication errors between NovoLog and any other insulin. **The written**

prescription for NovoLog should be written clearly, to avoid confusion with other insulin products, for example, NovoLog Mix 70/30.

17.2 Patients Using Pumps

Patients using external pump infusion therapy should be trained in intensive insulin therapy with multiple injections and in the function of their pump and pump accessories.

The following insulin pumps[†] have been used in NovoLog clinical or *in vitro* studies conducted by Novo Nordisk, the manufacturer of NovoLog:

- Medtronic Paradigm[®] 512 and 712
- MiniMed 508
- Disetronic[®] D-TRON[®] and H-TRON[®]

Before using another insulin pump with NovoLog, read the pump label to make sure the pump has been evaluated with NovoLog.

NovoLog is recommended for use in any reservoir and infusion sets that are compatible with insulin and the specific pump. Please see recommended reservoir and infusion sets in the pump manual.

To avoid insulin degradation, infusion set occlusion, and loss of the preservative (metacresol), insulin in the reservoir should be replaced at least every 6 days; infusion sets and infusion set insertion sites should be changed at least every 3 days.

Insulin exposed to temperatures higher than 37°C (98.6°F) should be discarded. The temperature of the insulin may exceed ambient temperature when the pump housing, cover, tubing, or sport case is exposed to sunlight or radiant heat. Infusion sites that are erythematous, pruritic, or thickened should be reported to medical personnel, and a new site selected because continued infusion may increase the skin reaction and/or alter the absorption of NovoLog. Pump or infusion set malfunctions or insulin degradation can lead to hyperglycemia and ketosis in a short time because of the small subcutaneous depot of insulin. This is especially pertinent for rapid-acting insulin analogs that are more rapidly absorbed through skin and have shorter duration of action. These differences are particularly relevant when patients are switched from multiple injection therapy. Prompt identification and correction of the cause of hyperglycemia or ketosis is necessary. Problems include pump malfunction, infusion set occlusion, leakage, disconnection or kinking, and degraded insulin. Less commonly, hypoglycemia from pump malfunction may occur. If these problems cannot be promptly corrected, patients should resume therapy with subcutaneous insulin injection and contact their physician [*see Dosage and Administration (2), Warnings and Precautions (5) and How Supplied/Storage and Handling (16.2)*].

17.3 FDA Approved Patient Labeling

See separate leaflet.

Rx only

Date of Issue: XX-XX-20XX

Version: XX

Novo Nordisk[®], NovoLog[®], NovoPen[®] 3, PenFill[®], Novolin[®], FlexPen[®], FlexTouch[®], PenMate[®], NovoFine[®], and NovoTwist[®] are registered trademarks of Novo Nordisk A/S.

NovoLog[®] is covered by US Patent Nos. 5,618,913, 5,866,538, and other patents pending.

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

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

PenFill[®] is covered by US Patent No. 5,693,027.

†The brands listed are the registered trademarks of their respective owners and are not trademarks of Novo Nordisk A/S.

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

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

www.novonordisk-us.com

Patient Information
NovoLog® (NŌ-vŏ-log)
(insulin aspart [rDNA origin] injection)

What is NovoLog?

- NovoLog is a man-made insulin that is used to control high blood sugar in adults and children with diabetes mellitus.

Who should not take NovoLog?

Do not take NovoLog if you:

- are having an episode of low blood sugar (hypoglycemia).
- have an allergy to NovoLog or any of the ingredients in NovoLog.

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

How should I take NovoLog?

- **Read the Instructions for Use** that come with your NovoLog.
- Take NovoLog exactly as your healthcare provider tells you to.
- **NovoLog starts acting fast.** You should eat a meal within 5 to 10 minutes after you take your dose of NovoLog.
- 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 NovoLog FlexPen, FlexTouch or needles with another person.** You may give another person an infection or get an infection from them.

What should I avoid while taking NovoLog?

While taking NovoLog do not:

- Drive or operate heavy machinery, until you know how NovoLog affects you.
- Drink alcohol or use prescription or over-the-counter medicines that contain alcohol.

What are the possible side effects of NovoLog?

NovoLog 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
- blurred vision
- anxiety, irritability, or mood changes
- sweating
- slurred speech
- hunger
- confusion
- shakiness
- headache
- fast heart beat

Your insulin dose may need to change because of:

- change in level of physical activity or exercise
- increased stress
- change in diet
- weight gain or loss
- illness

Other common side effects of NovoLog may include:

- low potassium in your blood (hypokalemia), 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 NovoLog. 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 NovoLog.

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 NovoLog that is written for health professionals. Do not use NovoLog for a condition for which it was not prescribed. Do not give NovoLog to other people, even if they have the same symptoms that you have. It may harm them.

What are the ingredients in NovoLog?

Active Ingredient: insulin aspart (rDNA origin)

Inactive Ingredients: glycerin, phenol, metacresol, zinc, disodium hydrogen phosphate dihydrate, sodium chloride and water for injection

Manufactured by:

Novo Nordisk A/S

DK-2800 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.novologflectouch.com

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Instructions for Use
NovoLog® (NŌ-vō-log) FlexTouch® Pen
(insulin aspart [rDNA origin] injection)

- **NovoLog FlexTouch Pen (“Pen”)** is a **prefilled disposable pen** containing 300 units of U-100 NovoLog (insulin aspart [rDNA origin] injection) insulin. You can inject from 1 to 80 units in a single injection.
- **Do not share your NovoLog 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 NovoLog injection:

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

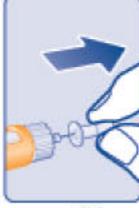
Preparing your NovoLog FlexTouch Pen:

- Wash your hands with soap and water.
- **Before you start to prepare your injection, check the NovoLog 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.**
- NovoLog should look clear and colorless. **Do not** use NovoLog if it is thick, cloudy, or is colored.
- **Do not** use NovoLog past the expiration date printed on the label or 28 days after you start using the Pen.
- **Always use a new needle for each injection to help ensure sterility and prevent blocked needles.**

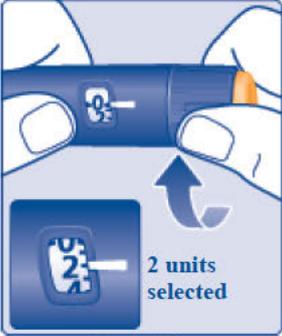


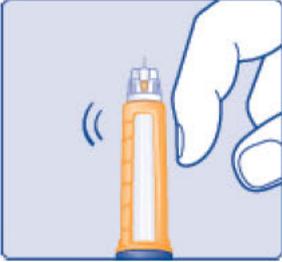
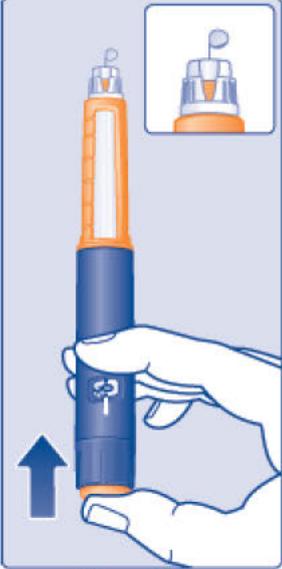
(Figure A)

| | |
|---|-------------------|
| <p>Step 1:</p> <ul style="list-style-type: none"> • Pull Pen cap straight off (See Figure B). | <p>(Figure B)</p> |
| <p>Step 2:</p> <ul style="list-style-type: none"> • Check the liquid in the Pen (See Figure C). NovoLog should look clear and colorless. Do not use it if it looks cloudy or colored. | <p>(Figure C)</p> |
| <p>Step 3:</p> <ul style="list-style-type: none"> • Select a new needle. • Pull off the paper tab from the outer needle cap (See Figure D). | <p>(Figure D)</p> |

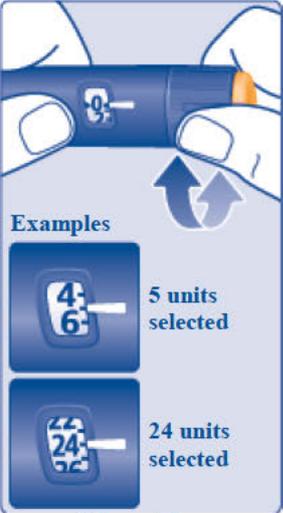
| | |
|--|--|
| <p>Step 4:</p> <ul style="list-style-type: none"> • Push the capped needle straight onto the Pen and twist the needle on until it is tight (See Figure E). | <div style="display: flex; justify-content: space-around;"> <div style="text-align: center;"> <p>NovoFine®</p>  </div> <div style="text-align: center;"> <p>NovoTwist®</p>  </div> </div> <p style="text-align: center;">(Figure E)</p> |
| <p>Step 5:</p> <ul style="list-style-type: none"> • Pull off the outer needle cap. Do not throw it away (See Figure F). | <div style="display: flex; justify-content: space-around;"> <div style="text-align: center;"> <p>NovoFine®</p>  </div> <div style="text-align: center;"> <p>NovoTwist®</p>  </div> </div> <p style="text-align: center;">(Figure F)</p> |
| <p>Step 6:</p> <ul style="list-style-type: none"> • Pull off the inner needle cap and throw it away (See Figure G). | <div style="display: flex; justify-content: space-around;"> <div style="text-align: center;"> <p>NovoFine®</p>  </div> <div style="text-align: center;"> <p>NovoTwist®</p>  </div> </div> <p style="text-align: center;">(Figure G)</p> |

Priming your NovoLog FlexTouch Pen:

| | |
|---|---|
| <p>Step 7:</p> <ul style="list-style-type: none"> • Turn the dose selector to select 2 units (See Figure H). | <div style="text-align: center;">  <p>2 units selected</p> </div> <p style="text-align: center;">(Figure H)</p> |
|---|---|

| | |
|--|---|
| <p>Step 8:</p> <ul style="list-style-type: none"> 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). |  <p>(Figure I)</p> |
| <p>Step 9:</p> <ul style="list-style-type: none"> 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). <ul style="list-style-type: none"> 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. |  <p>(Figure J)</p> |

Selecting your dose:

| | |
|--|--|
| <p>Step 10:</p> <ul style="list-style-type: none"> 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). <ul style="list-style-type: none"> 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. |  <p>(Figure K)</p> |
|--|--|

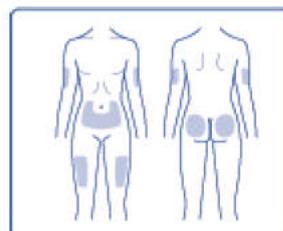
| | |
|--|--|
| <ul style="list-style-type: none"> The NovoLog FlexTouch Pen insulin scale will show you how much insulin is left in your Pen (See Figure L). |  <p>(Figure L)</p> |
| <ul style="list-style-type: none"> To see how much insulin is left in your NovoLog FlexTouch Pen: <ul style="list-style-type: none"> 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. If the dose counter shows less than 80, the number shown in the dose counter is the number of units left in your Pen. | |

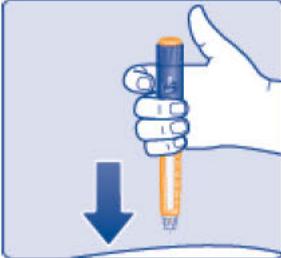
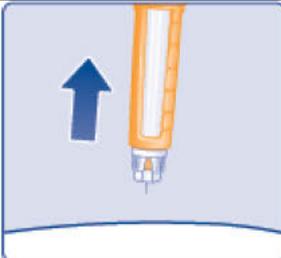
Giving your injection:

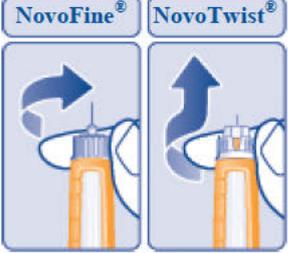
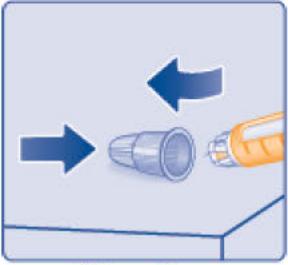
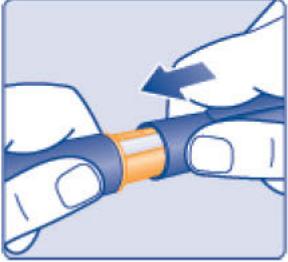
- Inject your NovoLog exactly as your healthcare provider has shown you. Your healthcare provider should tell you if you need to pinch the skin before injecting.
- NovoLog can be injected under the skin (subcutaneously) of your stomach area (abdomen), buttocks, upper legs (thighs) or upper arms.
- Change (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) |
| <p>Step 12:</p> <ul style="list-style-type: none"> • Insert the needle into your skin (See Figure N). <ul style="list-style-type: none"> ○ Make sure you can see the dose counter. Do not cover it with your fingers, this can stop your injection. |  <p>(Figure N)</p> |
| <p>Step 13:</p> <ul style="list-style-type: none"> • Press and hold down the dose button until the dose counter shows "0" (See Figure O). <ul style="list-style-type: none"> ○ The "0" must line up with the dose pointer. You may then hear or feel a click. • Keep the needle in your skin after the dose counter has returned to "0" and slowly count to 6 (See Figure P). <ul style="list-style-type: none"> ○ 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. |  <p>(Figure O)</p>  <p>(Figure P)</p> |
| <p>Step 14:</p> <ul style="list-style-type: none"> • Pull the needle out of your skin (See Figure Q). <ul style="list-style-type: none"> ○ 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 |  <p>(Figure Q)</p> |

| | |
|--|--|
| <p>alcohol swab. Do not rub the area.</p> | |
| <p>Step 15:</p> <ul style="list-style-type: none"> • Carefully remove the needle from the Pen and throw it away (See Figure R). <ul style="list-style-type: none"> ○ 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 into the outer needle cap (See Figure S). Safely remove the needle and throw it away as soon as you can. <ul style="list-style-type: none"> ○ 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. | <div style="display: flex; justify-content: space-around;"> <div style="text-align: center;">  <p>(Figure R)</p> </div> <div style="text-align: center;">  <p>(Figure S)</p> </div> </div> |
| <p>Step 16:</p> <ul style="list-style-type: none"> • Replace the Pen cap by pushing it straight on (See Figure T). | <div style="text-align: center;">  <p>(Figure T)</p> </div> |

After your injection:

- Put your used NovoLog 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 NovoLog FlexTouch Pen?

- Store unused NovoLog 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°F.
- **Do not** freeze NovoLog. **Do not** use NovoLog if it has been frozen.
- Keep NovoLog away from heat or light.
- Unused Pens may be used until the expiration date printed on the label, if kept in the refrigerator.
- The NovoLog FlexTouch Pen you are using should be thrown away after 28 days, even if it still has insulin left in it.

General Information about the safe and effective use of NovoLog.

- **Keep NovoLog 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

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 20986/S-061

CHEMISTRY REVIEW(S)

| | | |
|--|---|---|
| CHEMISTRY REVIEW #2 | 1. ORGANIZATION ONDQA/DNDQA III/Branch IX | 2. NDA NUMBER Bundled supplement- see below |
| 3. NAME AND ADDRESS OF APPLICANT Novo Nordisk Inc. 100 College Road West Princeton, NJ 08540 | | 4. SUPPLEMENT NUMBER, DATE 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® | Insulin aspart (rDNA Origin) injection | N020986/S-061, 22-Mar-2013 N021536/S-033, 22-Mar-2013 |
| Levemir® | Insulin detemir (rDNA Origin) injection | |
| 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 | | |
| <p>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®.</p> <p>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.</p> <p>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.</p> | | |
| 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 | | |

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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 | | |
| <p>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)</p> <p>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.</p> | | |
| 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 | | |

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

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/s/

PALLAIAH THAMMANA
05/14/2010

JAMES D VIDRA
05/14/2010

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 20986/S-061

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: NovoLog FlexTouch (Insulin Aspart),
100 units/mL (U-100)

Application Type/Number: NDA 020986/S-061

Applicant/Sponsor: Novo Nordisk

OSE RCM #: 2013-1619

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

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1 INTRODUCTION

This review evaluates the proposed proprietary name, NovoLog 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 NovoLog FlexTouch, under NDA 020986/S-061 in OSE Review #2009-2457, dated March 15, 2010 and #2012-279, dated April 23, 2012. DMEPA found the root name, NovoLog, 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 Aspart [rDNA]
- Indication of Use: To improve glycemic control in adults and children with diabetes mellitus.
- 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 0.5 to 1 units/kg/day.
- 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). Do not freeze. After initial use, the product in either configuration 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 30, 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, NovoLog, 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 NovoLog® 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 NovoLog family (e.g. NovoLog FlexPen, and NovoLog vials).

The modifier, FlexTouch, was evaluated in conjunction with the proposed proprietary name, NovoLog, as well as separately for vulnerabilities for confusion that could lead to medication errors under NDA 020986/S-061 in OSE Review #2009-2457, dated March 15, 2010 and #2012-279, dated April 23, 2012. The modifier was found acceptable. As a result, the name NovoLog 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-eight of the 30 outpatient participants responded correctly and the most common misinterpretation occurred with 2 participants omitting the letter ‘o’ in the root name (i.e., ‘Novolog’ as ‘Nov_log and ‘Novol_g’). Eighteen of the 22 inpatient participants responded correctly and the most common misinterpretation occurred with 2 participants misinterpreting the letter ‘o’ for ‘a’ (i.e., Novolog misinterpreted as Novalog). Sixteen of the 21 voice participants responded correctly and a common misinterpretation occurred with 4 participants misinterpreting the letter ‘o’ for ‘a’ (i.e., Novolog misinterpreted as Novalog). 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) 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 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 (#2009-2457 and #2012-279) and product characteristics remained the same, we determined that none of the previously identified names raises concerns related to orthographic or phonetic similarity to Novolog 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, NovoLog 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, NovoLog 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.

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 | | |
|---------------------------|--|---|--------------------------|
| | <i>Potential Causes of Drug Name Similarity</i> | <i>Attributes Examined to Identify Similar Drug Names</i> | <i>Potential Effects</i> |

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 | <ul style="list-style-type: none"> 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 | <ul style="list-style-type: none"> 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 | <ul style="list-style-type: none"> 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 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 possess 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.

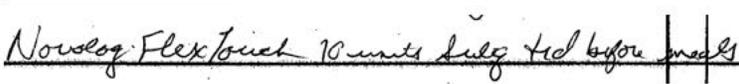
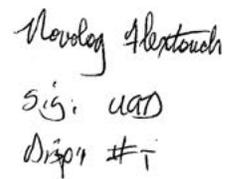
Furthermore, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to rectify post-approval. Educational and other post-approval efforts are low-leverage strategies that have had limited effectiveness at alleviating medication errors 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, NovoLog FlexTouch | Scripted may appear as | Spoken may be interpreted as |
|------------------------------------|------------------------|------------------------------|
| Capital 'N' | A, V, or W | 'M' |
| lower case 'o' | a, c, e, u | 'Oh' or any vowel |
| lower case 'v' | n or r | 'b' |
| lower case 'o' | a, c, e, u | 'Oh' or any vowel |
| lower case 'l' | b, e, s, A, P, i | |
| lower case 'o' | a, c, e, u | 'Oh' or any vowel |
| lower case 'g' | j, p, or q | 'k' |
| 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. NovoLog FlexTouch Study (Conducted on June 14, 2013)

| Handwritten Requisition Medication Order | Verbal Prescription |
|--|---|
| <p><u>Medication Order:</u></p>  | <p>Novolog FlexTouch Use as directed #2</p> |
| <p><u>Outpatient Prescription:</u></p>  | |

FDA Prescription Simulation Responses (Aggregate 1 Rx Studies Report)

191 People Received Study

73 People Responded

Study Name: Novolog FlexTouch

| Total | 30 | 21 | 22 | |
|-----------------------|-------------------|--------------|------------------|--------------|
| INTERPRETATION | OUTPATIENT | VOICE | INPATIENT | TOTAL |
| NOUSLOG FLEXTOUCH | 0 | 0 | 1 | 1 |
| NOVALOG | 0 | 1 | 0 | 1 |
| NOVALOG FLEX TOUCH | 0 | 1 | 0 | 1 |
| NOVALOG FLEXTOUCH | 0 | 2 | 2 | 4 |
| NOVLOG FLEXTOUCH | 1 | 0 | 0 | 1 |
| NOVOLG FLEXTOUCH | 1 | 0 | 0 | 1 |
| NOVOLOG | 0 | 1 | 0 | 1 |
| NOVOLOG FEXTOUCH | 0 | 0 | 1 | 1 |
| NOVOLOG FLEX TOUCH | 0 | 8 | 3 | 11 |
| NOVOLOG FLEXTOUCH | 28 | 8 | 15 | 51 |

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(s): 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): NovoLog (Insulin Aspart), 100 units/mL (U-100)
FlexTouch Pen

Application Type/Number: NDA 020986/S-061

Applicant/Sponsor: Novo Nordisk

OSE RCM #: 2012-279

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

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1 INTRODUCTION

This review evaluates the proposed proprietary name, NovoLog 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 NovoLog FlexTouch, under NDA 020986/S-061 in OSE Review #2009-2457, dated March 15, 2010. DMEPA found the root name, NovoLog 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 Aspart [rDNA]
- Indication of Use: To improve glycemic control in adults and children with diabetes mellitus.
- 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 0.5 to 1 units/kg/day.
- 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). Do not freeze. After initial use, the product in either configuration 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 24, 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, NovoLog, 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 NovoLog® 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 NovoLog family (e.g. NovoLog FlexPen, and NovoLog vials).

The modifier, FlexTouch, was evaluated in conjunction with the proposed proprietary name, NovoLog, as well as separately for vulnerabilities for confusion that could lead to medication errors under NDA 020986/S-061 in OSE Review #2009-2457, dated March 15, 2010. The modifier was found acceptable. As a result, the name NovoLog FlexTouch was found acceptable.

2.2.3 Medication Error Data Selection of Cases

DMEPA searched AERS database for medication errors involving NovoLog which would be relevant for this review. The February 24, 2012 search of the Adverse Event Reporting System (AERS) database used the following search terms: Trade name “NovoLog” and verbatim term “Novolo%.” 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 NovoLog on January 22, 2010 to determine medication errors related to this product and have been reported in OSE review #2009-2457, dated March 15, 2010. Therefore, for this review, we limited our search of the database 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, 70 reports were not included in the final analysis for the following reasons: reports of a defective device, report of a product quality issue with no medication error, report of an intentional overdose, report of an adverse event without a medication error, the insulin in the PenFill cartridge in the report was a concomitant medication not involved in the medication error, report of an omission due to patient compliance or as the insulin was held during the treatment of a co morbid condition, report of an insulin product

not in a PenFill presentation, a report of the use of an expired product, and a report of a product not marketed in the US.

Following exclusions, the search yielded no relevant cases.

2.2.4 FDA Name Simulation Studies

Twenty-five 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 name, NovoLog correctly. The most common misinterpretation occurred with participants misinterpreting the letter ‘v’ for ‘r’ in ‘NoVaLog.’ All 8 inpatient participants interpreted the modifier, FlexTouch correctly. Four out of 9 voice participants interpreted the proposed name, NovoLog, correctly. The most common misinterpretation occurred with participants misinterpreting the letter ‘o’ for ‘a’ and ‘NovoLog’. All 9 inpatient participants interpreted the modifier, FlexTouch correctly. All 8 outpatient participants interpreted the proposed name, NovoLog, and 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, NovoLog FlexTouch. Table 1 lists the names with orthographic, phonetic, or spelling similarity to the proposed proprietary name, NovoLog 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 | | | | | |
|------------------------|--------|-----------|--------|---------|--------|
| Name | Source | Name | Source | Name | Source |
| FlexPen | FDA | Flexicort | FDA | Penfill | FDA |
| Flexeril | FDA | | | | |
| Look and Sound Similar | | | | | |
| FlexTouch | FDA | NovoLog | FDA | | |

Since root name “Novolog” is already marketed, we evaluated the modifier “FlexTouch” through FMEA and the proposed proprietary name as one name “NovoLog FlexTouch.” Our analysis of the six names contained in Table 1 considered the information obtained in the

previous sections along with their product characteristics. We determined all six 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, NovoLog FlexTouch.

3 DISCUSSION

The proposed NovoLog FlexTouch Pen represents improvements upon the design of the current NovoLog 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 Novolog FlexTouch and Novolog 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 (b) (4) post approval. To minimize the potential confusion anticipated from the general lack of awareness to the marketing of the new NovoLog 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 Modifier Evaluation

The proposed modifier, FlexTouch, was reviewed by DMEPA in OSE Review #2009-2457, 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, NovoLog 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.

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 | | |
|---------------------------|--|---|--------------------------|
| | <i>Potential Causes of Drug Name Similarity</i> | <i>Attributes Examined to Identify Similar Drug Names</i> | <i>Potential Effects</i> |

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 | <ul style="list-style-type: none"> 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 | <ul style="list-style-type: none"> 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 | <ul style="list-style-type: none"> 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 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 possess 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.

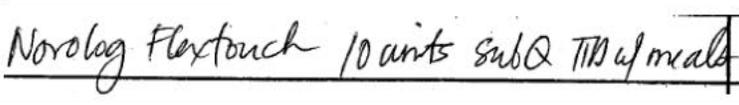
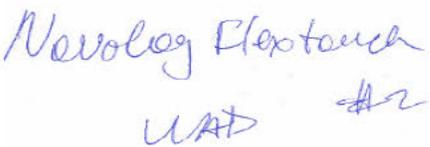
Furthermore, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to rectify post-approval. Educational and other post-approval efforts are low-leverage strategies that have had limited effectiveness at alleviating medication errors 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, NovoLog FlexTouch | Scripted may appear as | Spoken may be interpreted as |
|------------------------------------|------------------------|------------------------------|
| Capital 'N' | A, V, or W | 'M' |
| lower case 'o' | a, c, e, u | 'Oh' or any vowel |
| lower case 'v' | n or r | 'b' |
| lower case 'o' | a, c, e, u | 'Oh' or any vowel |
| lower case 'l' | b, e, s, A, P, i | |
| lower case 'o' | a, c, e, u | 'Oh' or any vowel |
| lower case 'g' | j, p, or q | 'k' |
| 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. NovoLog FlexTouch Study (Conducted on February 15, 2012)

| Handwritten Requisition Medication Order | Verbal Prescription |
|--|---|
| <p><u>Medication Order:</u></p>  | <p>Novolog FlexTouch Use as directed #2</p> |
| <p><u>Outpatient Prescription:</u></p>  | |

FDA Prescription Simulation Responses (Aggregate 1 Rx Studies Report)

84 People Received Study

25 People Responded

Study Name: NovoLog FlexTouch

| INTERPRETATION | INPATIENT | VOICE | OUTPATIENT | TOTAL |
|-----------------------|------------------|--------------|-------------------|--------------|
| NOROLOG FLEXTOUCH | 2 | 0 | 0 | 2 |
| NOVALOG FLEX TOUCH | 0 | 2 | 0 | 2 |
| NOVALOG FLEXTOUCH | 1 | 3 | 0 | 4 |
| NOVOLOG FLEX TOUCH | 0 | 2 | 0 | 2 |
| NOVOLOG FLEXTOUCH | 5 | 2 | 7 | 14 |
| NOVOLOG FLEXTOUCH #2 | 0 | 0 | 1 | 1 |
| TOTAL | 8 | 9 | 8 | 25 |

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 | Failure preventions |
|-------------------------|--------------------------|-------------------|---|
| NovoLog | Insulin Aspart | Look and Sound | The subject of this review |
| FlexTouch | Device | Look and Sound | The subject of this review |
| 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.

| <p>Proposed name: NovoLog FlexTouch (Insulin Aspart [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.</p> | <p>Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion Causes (could be multiple)</p> | <p>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</p> |
|--|--|--|
| <p>FlexPen Device; Modifier used with root name, NovoLog. Product currently marketed.</p> | <p>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. NovoLog)</p> | <p>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.</p> |
| <p>Flexicort (Hydrocortisone) Strength: Topical cream: 2.5%, 1%, 0.5% Usual dose: Apply as directed or Use as directed</p> | <p>Orthographic similarity to FlexTouch: Both begin with the letter string ‘Flex’</p> | <p>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. Regulatory History: Withdrawn FR effective September 5, 1995</p> |

| <p>Proposed name: NovoLog FlexTouch (Insulin Aspart [rDNA origin] Injection)</p> <p>Strength(s): U-100 (100 units/mL) in a 3-mL FlexTouch pen device</p> <p>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.</p> | <p>Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion</p> <p>Causes (could be multiple)</p> | <p>Prevention of Failure Mode</p> <p>In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names</p> |
|--|--|---|
| <p>Flexeril (Cyclobenzaprine)</p> <p>Strength: Oral Tablets 5 mg, 10 mg</p> <p>Usual dose: Take 5 mg to 10 mg by mouth 3 times daily.</p> | <p>Orthographic similarity to FlexTouch: Both begin with the letter string ‘Flex’</p> | <p>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.</p> |

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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): NovoLog FlexTouch (Insulin Aspart [rDNA origin] Injection)
3 mL Prefilled pen

Application Type/Number: NDA 020986/S-061

Sponsor: Novo Nordisk

OSE RCM #: 2009-2457

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

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EXECUTIVE SUMMARY

The proposed product, NovoLog FlexTouch, is a prefilled, multiple-dose, disposable pen in the NovoLog product line. NovoLog is currently marketed in vials, PenFill cartridges for use with NovoPen and in prefilled, multiple-use, disposable NovoLog FlexPens. The Applicant is proposing to add the modifier “FlexTouch” to the NovoLog name for the proposed product. The addition of the modifier is reasonable and necessary in this case to distinguish this new product from the currently marketed NovoLog products. Even with the addition of the modifier the greatest risk of proprietary name confusion will occur within the NovoLog product line.

The Applicant will discontinue the NovoLog FlexPen within (b) (4) of marketing the NovoLog FlexTouch and anticipates co-marketing of both pens for approximately (b) (4). However, because there is some marketing overlap, the introduction of this new pen may result in name confusion with the currently marketed product line for several reasons. The most common cause of such confusion is lack of awareness of the new product and prescribing errors in which the modifier (i.e. FlexTouch) is omitted from the prescription. Additionally, product selection errors may occur because of the similarity in names (i.e. NovoLog FlexTouch vs NovoLog FlexPen) in combination with the similar trade dress and packaging. To minimize the potential confusion anticipated from prescribing failures and general lack of awareness to the marketing of the new NovoLog 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.

Since the nomenclature follows how typical product lines are developed we find the proposed proprietary name NovoLog FlexTouch conditionally acceptable for this product. 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 Novo Nordisk on December 15, 2009, to evaluate the proposed proprietary name, NovoLog 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# 2009-2458).

1.2 PRODUCT INFORMATION

NovoLog FlexTouch (Insulin Aspart [rDNA origin] Injection) is an insulin analog indicated to improve glycemic control in adults and children with diabetes mellitus. The dose is individualized; however, total daily insulin requirements may vary and is usually between 0.5 to 1 units/kg/day.

NovoLog is available in 10 mL vials, 3 mL prefilled cartridges (NovoLog 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 (NovoLog FlexPen). NovoLog is administered subcutaneously. An auto-insertion accessory is available for the NovoLog product line: NovoPenMate for use with NovoLog PenFill cartridges.

This supplement provides for the introduction of a new 3-mL prefilled pen, NovoLog FlexTouch, in a concentration of 100 units /mL under the NovoLog line. The Applicant plans to announce the discontinuation of NovoLog FlexPen six months post-launch of NovoLog FlexTouch, and anticipates the market to be clear of NovoLog FlexPen within approximately (b) (4) of NovoLog FlexTouch market availability.

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, NovoLog FlexTouch.

2.1 SEARCH CRITERIA

For this review, particular consideration was given to drug names beginning with the letters ‘N’ 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 NovoLog 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 (6, capital letters ‘N’, ‘L’, ‘F’, and ‘T’, and lower case letters ‘l’, and ‘h’), downstrokes (1, lower case letter ‘g’), cross-strokes (three, upper case letter ‘F’ and ‘T’ and lower case letter ‘x’), and dotted letters (none). Additionally, several letters in NovoLog 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 NovoLog FlexTouch.

When searching to identify potential names that may sound similar to NovoLog FlexTouch, the DMEPA staff searches for names with similar number of syllables (five), stresses (NO-vo-log, no-VO-log, no-vo-LOG, 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 “No” which may be interpreted as “kno” or “know”; “Flex” which may be interpreted as “Flex”, “Bex” or “Vex” (See Appendix B). The Sponsor provided their intended pronunciation of the proprietary name (No-vo-log 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.

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. NovoLog FlexTouch Study (conducted on January 10, 2010)

| HANDWRITTEN REQUISITION MEDICATION ORDER | VERBAL PRESCRIPTION |
|---|---|
| <p><u>Inpatient Medication Order:</u></p> <p><i>Novolog flex touch inject</i> <i>7 units SC BID AC</i></p> | <p>NovoLog FlexTouch Inject 7 units subQ bid before meals</p> |
| <p><u>Outpatient Prescription:</u></p> <p><i>Novo Log Flex Touch</i> <i>Inject 7 units sc</i> <i>twice a day before meals</i></p> | |

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

Errors associated with currently marketed NovoLog product names were taken into consideration when reviewing the proposed proprietary name NovoLog FlexTouch. If confusion between currently marketed NovoLog products already exists and leads to medication errors, introduction of the proposed proprietary name NovoLog 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 “NovoLog” and verbatim %NovoLog% 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 NovoLog FlexTouch.

3 RESULTS

3.1 DATABASE AND INFORMATION SOURCES

The searches yielded a total of 16 names as having some similarity to the name NovoLog FlexTouch.

One of the sixteen names, Navstel, was thought to look like NovoLog FlexTouch. The remaining fifteen names, NovoLog, NovoLog Mix 70/30, Flex5***, Flex10***, Novolin R Flex***, Novolin N Flex***, Novolin 70/30 Flex***, NovoLog Mix 50/50, Pulmicort Flexhaler, Flextra, Norditropin FlexPro, Novolin 70/30, Novolin N, Novolin R, FlexPen were thought to look and sound similar to NovoLog FlexTouch.

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, NovoLog 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 NovoLog 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 64 practitioners responded. Forty-two (n=42) respondents interpreted the name correctly as 'NovoLog Flex Touch', with correct interpretations occurring in inpatient (n=19) and outpatient (n=10) written studies and in the verbal (n=13) study. The remainder of the written study responses misinterpreted the drug name, with the most common misinterpretation occurring in the last syllable of the name. ('lg' vs. 'log'). In the verbal studies responses were misspelled phonetic variations of the proposed name, NovoLog FlexTouch, with the most common variation occurring in the second syllable of the root name ('va' vs. 'vo'). Three responses interpreted the root name "NovoLog" correctly, but omitted the modifier. 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 did not identify any cases of proprietary name confusion with the pen device. The cases describe known errors between the Humalog, NovoLog, NovoLog Mix 70/30, Humalog 75/25, Humulin 70/30, Novolin 70/30, and Novolin N products. These errors involve established root names within the insulin family of products and will not be exacerbated with the addition of a modifier to the NovoLog root name.

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 NovoLog FlexTouch at the initial phase of the review.

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 NovoLog FlexTouch. Per e-mail correspondence from DMEP on March 10, 2010 they indicated they concur with our assessment of the proposed proprietary name, NovoLog FlexTouch.

3.6 SAFETY EVALUATOR RISK ASSESSMENT

Independent searches by the primary Safety Evaluator identified two additional names, FlexTend and Hextend thought to look or sound similar to NovoLog FlexTouch and represent a potential source of confusion. Two names identified by the EPD, NovoLog and NovoLog Mix 70/30, are the root names of various insulins within the NovoLog family and were therefore eliminated from further evaluation because they were considered within the FlexPen device evaluation. Thus, in total we identified sixteen names as having some similarity to the proposed name, fourteen from EPD, and two identified by the Safety Evaluator.

4 DISCUSSION

4.1 PROMOTIONAL REVIEW

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

4.2 SAFETY REVIEW

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 sixteen names for look-alike and sound-alike similarities and the use of the modifier as a potential source of medication errors.

4.2.1 Look-alike / Sound-alike Evaluation

DMEPA evaluated the sixteen names identified using Failure Mode and Effects Analysis (FMEA) to determine if the proposed proprietary name, NovoLog FlexTouch, could potentially be confused with any of the names and lead to medication errors. This analysis determined that the name similarity between NovoLog FlexTouch was unlikely to result in medication errors with any of the sixteen products for the reasons presented in Appendices D through H.

4.2.2 Modifier Evaluation

The proposed product, NovoLog FlexTouch, will be a replacement for the currently marketed NovoLog FlexPen product line. Both products are prefilled pen-injectors that possess the same indication, route of administration, concentration, quantity, and method of use. If NovoLog FlexTouch is approved, Novo Nordisk plans to announce the discontinuation of NovoLog FlexPen (b) (4) post-launch of NovoLog FlexTouch, and anticipates the market to be clear of NovoLog FlexPen within approximately (b) (4) of NovoLog FlexTouch market availability. The Applicant proposes to use the modifier FlexTouch to distinguish this product from the currently marketed FlexPen. Our analysis indicated that a modifier is an acceptable method for differentiating these two devices. We anticipate confusion may occur due to a general lack of awareness of the new product introduced to the market, overlapping product characteristics, similarity in modifiers, and prescribers often omit modifiers.

The primary safety evaluator also 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. NovoLog® 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 NovoLog® 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 Novolog family (e.g. Novolog FlexPen, and Novolog Mix 70/30 FlexPen).
- 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).

Additionally, the proposed NovoLog FlexTouch and NovoLog 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. 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 NovoLog FlexTouch and NovoLog FlexPen because of the similar trade dress, similar names, similar pen colors, and the co-marketing for [REDACTED] (b) (4). To minimize the potential confusion anticipated from the general lack of awareness to the marketing of the new NovoLog 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.

5 CONCLUSIONS AND RECOMMENDATIONS

The Proprietary Name Risk Assessment findings indicate that the proposed name, NovoLog FlexTouch, is vulnerable to name confusion with the currently marketed NovoLog products that could lead to medication errors. A modifier is needed to differentiate the product within the NovoLog product line (i.e. NovoLog FlexPen, vials and prefilled cartridges) because Novolog FlexTouch and Novolog FlexPen will be co-marketed for [REDACTED] (b) (4). Since the co-marketing is limited we have no objection to the proprietary name, NovoLog FlexTouch, for this product at this time.

However, 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, NovoLog FlexTouch, and have concluded that it is acceptable. However, we anticipate product selection errors between the NovoLog FlexTouch and NovoLog FlexPen because of the similar trade dress, similar names, similar pen colors, and the co-marketing for approximately [REDACTED] (b) (4). To minimize the potential confusion anticipated from the general lack of awareness to the marketing of the new NovoLog 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, NovoLog 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.

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 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.

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 | | |
|--------------------|---|---|---|
| | <i>Potential causes of drug name similarity</i> | <i>Attributes examined to identify similar drug names</i> | <i>Potential Effects</i> |
| Look-alike | Similar spelling | Identical prefix Identical infix Identical suffix Length of the name Overlapping product characteristics | <ul style="list-style-type: none"> 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-strokes Dotted letters Ambiguity introduced by scripting letters Overlapping product characteristics | <ul style="list-style-type: none"> 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 | <ul style="list-style-type: none"> 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 possess 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.

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 ‘N’ | A, V, or W | ‘M’ |
| lower case ‘o’ | a, e, c, or u | any vowel |
| lower case ‘v’ | n or r | ‘b’ |
| Capital ‘L’ | P, F, Z, C, h, or e | ‘w’ |
| lower case ‘g’ | j, p, or q | ‘k’ |
| Capital ‘F’ | E, J, K, P, or T | ‘P’ |
| lower case ‘e’ | 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 ‘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 |
|-----------------------------------|--------------------------------|---------------------------|
| Novolog Flex Touch | Now Lg Flex touch | novolog flextouch |
| novolog flex touch | Novolog Flex Touch | Novalog Flextouch |
| Novolog flex touch | Now Inj. Flex Touch | Novolog Flextouch |
| Novolog flex touch | Nova Log Flex Touch | Novolog Flex Touch |
| novolog flex touch | Novolog FlexTouch | Novolog |
| novolog flex touch | NovoLog Flex Touch | Novolog Flextouch |
| Novolog Flex Touch | New LG Flex Touch | Novolog |
| Novolog flex touch | Novolog LG, Flex Touch | Novolog Flex Touch |
| Novolog FlexTouch | Now Lez Flex Touch | Novolog Flex Touch |
| Novolog Flex Touch | Now Lg Flex Touch | Novolog flextouch |
| Novalog Flex Touch | Novo Lg Flex Touch | Novolog Flextouch |
| Novolog glex touch | Now Lg Flex Touch | Novolog Flex Touch |
| novolog flex touch | Novalog flextouch | Novolog FlexTouch |
| novolog flex touch | novolog flex touch | Novalog Flex touch |
| novolog flux touch | Novolog Flex Touch | Novolog Flextouch |
| Novolog flex touch | Novolog | Novolog Flextouch |
| Novolog flex touch | Novolog Flex Touch | Novolog Flex Touch |
| Novolog Flex Touch | Novolog Flex Touch | |
| Novolog flex touch | Novolog Flex Touch | |
| Novolog flex touch | Novolog Flex Touch | |
| Novolog flex touch | Novo Lg Flex Touch | |
| Novolog flex touch | Now Lg Flex Touch | |
| | Novolog flex touch | |
| | Nav Lg. Flex Touch | |
| | Novo Lg flex touch | |

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

| Proprietary Name | Similarity to NovoLog FlexTouch |
|------------------|---------------------------------|
| Navstel | Look |

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

| Proprietary Name | Similarity to NovoLog FlexTouch | Reason for Discard |
|---|---------------------------------|--|
| Flex5*** Flex10*** | Look and Sound | DMEPA objected in review #02-0175. Approved under the name Flexeril |
| Novolin R Flex*** Novolin N Flex*** Novolin 70/30 Flex*** | Look and Sound | DMEPA objected in review #00-0056. No product currently marketed under these names |

Appendix F: Discontinued products with no generic equivalent available

| Proprietary Name | Similarity to NovoLog Flex Touch | Established Name |
|-------------------|----------------------------------|--|
| FlexTend | Look and Sound | Iron, Glucosamine Sulfate, Vitamin E, Ascorbic Acid |
| NovoLog Mix 50/50 | Look and Sound | insulin aspart protamine recombinant; insulin aspart recombinant |

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

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

| Product name with potential for confusion⁷ | Similarity to NovoLog FlexTouch | Strength/Dosage form | Usual dose (if applicable) | Differentiating Product Characteristics |
|---|--|--|--|---|
| Novolog FlexTouch <i>(Insulin aspart [rdNA origin] injection)</i> | N/A | Strength: 100 units/mL Dosage Form: -FlexTouch: multiple use, disposable pens (3 mL) | Individualized dose (usually 0.5 to 1 unit/kg/day) in divided doses | 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) | <i>Dosage Form:</i> Injection vs. Inhaler <i>Route of Administration:</i> Subcutaneous vs. Oral Inhalation <i>Strength:</i> 100 units/mL vs. 90 mcg and 180 mcg <i>Units of measure:</i> 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. | <i>Dosage Form:</i> Injection vs. Capsule <i>Route of Administration:</i> Subcutaneous vs. Oral <i>Units of measure:</i> Units vs. mg |
| Hextend (Hetastarch in Lactated Electrolyte Injection) | Look | 6% (500 mL) | 500 mL to 1000 mL per day | <i>Route of Administration:</i> Subcutaneous vs. Intravenous <i>Strength:</i> 100 units/mL vs. 6% <i>Units of measure:</i> Units vs. % |

Appendix H: Potentially confusing names with multiple differentiating product characteristics

| Failure Mode: Name confusion ¹ | Causes (could be multiple) | Rationale |
|---|---|--|
| <p>Novolog FlexTouch (<i>Insulin aspart [rDNA origin] injection</i>)</p> | <p>Strength: 100 units/mL</p> <p>Dosage Form: -FlexTouch: multiple use, disposable pens (3 mL)</p> | <p>Usual dose: Individualized dose (usually 0.5 to 1 unit/kg/day) in divided doses</p> |
| <p>Norditropin FlexPro (<i>Somatropin[rDNA origin] injection</i>)</p> <p>Strength: 5 mg/1.5 mL 10 mg/1.5 mL 15 mg/1.5 mL (prefilled, multiple use, disposable pens)</p> <p>Usual dose: Individualized dose (weight based/indication based) subcutaneously daily</p> | <p>Orthographic Similarity: Both root names begin with the letter 'N'. 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.</p> | <p>Medication errors unlikely to occur in the usual practice setting for the following reasons:</p> <p>The two names (Novolog vs Norditropin) are orthographically different. In addition, the lengths of the root names (7 letters for NovoLog vs 11 letters Norditropin) help differentiate them.</p> <p>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.</p> <p style="text-align: center;"> FLEX TOUCH FLEX PRO </p> <p>'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.</p> <p>Additionally, Norditropin FlexPro orders will be dosed in milligrams vs the products used with the FlexTouch which would be dosed in units.</p> <p>Growth hormone replacement products, such as Norditropin FlexPro are generally distributed through specialty pharmacies and require a statement of medical necessity.</p> |

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

| Failure Mode: Name confusion ¹ | Causes (could be multiple) | Rationale |
|--|--|---|
| <p>Novolog FlexTouch (<i>Insulin aspart [rDNA origin] injection</i>)</p> | <p>Strength: 100 units/mL</p> <p>Dosage Form: -FlexTouch: multiple use, disposable pens (3 mL)</p> | <p>Usual dose: Individualized dose (usually 0.5 to 1 unit/kg/day) in divided doses</p> |
| <p>Novolin 70/30 (70% NPH, Human Insulin Isophane Suspension and 30% Regular, Human Insulin Injection [rDNA origin])</p> <p>Novolin N (NPH, Human Insulin Isophane Suspension [rDNA origin])</p> <p>Novolin R (Regular Human Insulin Injection[rDNA origin])</p> <p>Product Characteristics</p> <p>Indication: Blood glucose lowering</p> <p>Dosage form: solution/suspension for subcutaneous use</p> <p>Strengths: 100 units/mL</p> <p>Frequency of adm.: Novolin R - within 15 to 30 minutes of eating a meal Novolin N and Novolin 70/30 - within 30 to 60 minutes of a meal</p> <p>Usual dose: individualized by body weight</p> <p>Route: subcutaneous</p> <p>Class: OTC</p> | <p>Orthographic similarity of the family names ‘NovoLog’ and ‘Novolin’.</p> | <p>Medication errors unlikely to occur in the usual practice setting with the addition of the modifier FlexTouch</p> <p><i>Rationale:</i></p> <p>Novolin is the Family name for a group of insulins including Novolin R, Novolin N, and Novolin 70/30. We recognize the similarity of the root names of these two products (Novolog vs Novolin) is a current source of medication errors.</p> <p>DMEPA considers the addition of the modifier ‘FlexTouch’ to the Novolog line of insulin products will differentiate these two product lines.</p> |

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

| Failure Mode: Name confusion ¹ | Causes (could be multiple) | Rationale |
|--|--|---|
| <p>Novolog FlexTouch (<i>Insulin aspart [rDNA origin] injection</i>)</p> | <p>Strength: 100 units/mL</p> <p>Dosage Form: -FlexTouch: multiple use, disposable pens (3 mL)</p> | <p>Usual dose: Individualized dose (usually 0.5 to 1 unit/kg/day) in divided doses</p> |
| <p>FlexPen Device/modifier used with the rootnames: NovoLog NovoLog Mix 70/30</p> | <p>Both modifiers share the name 'Flex'</p> <p>Similarity in the length of the names (9 letters vs 7 letters)</p> <p>Both represent multiple use, disposable pen devices.</p> <p>Both devices will deliver the same insulin types (i.e. NovoLog)</p> | <p>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.</p> <p><i>Rationale:</i></p> <p>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.</p> <p style="text-align: center;"> FLEXTOUCH FLEXPEN </p> <p>If FlexTouch is approved, (b) (4)</p> <div style="background-color: gray; width: 100%; height: 20px; margin-top: 5px;"></div> <p>Product selection errors may occur because of similar names in combination with similar trade dress and packaging. To minimize the potential confusion anticipated from a general lack of awareness of the new NovoLog FlexTouch product, the Applicant should take steps to increase practitioner's awareness of the introduction of this new pen.</p> |

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|-------------------------|------------------------|---------------------|--------------|
| NDA-20986 | SUPPL-61 | NOVO NORDISK INC | NOVOLOG |

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/s/

CARLOS M MENA-GRILLASCA
03/15/2010

DENISE P TOYER
03/15/2010

CAROL A HOLQUIST
03/15/2010

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 20986/S-061

OTHER REVIEW(S)

Division of Metabolism and Endocrinology Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application Number:

NDA 020986/S-61

Name of Drug:

Novolog (insulin aspart [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, PPI |
| October 21, 2013 | October 21, 2013 | PI |

Background and Summary

Novolog (insulin aspart [rDNA origin]), injection was approved on June 7, 2000, under NDA 020986, for treatment of diabetes mellitus.

On March 22, 2013, Novo Nordisk resubmitted this “Prior Approval” labeling supplement (S-061) in order to market Novolog 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 21, 2013.

Review

The PI submitted on October 21, 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 OF PRESCRIBING INFORMATION- DOSAGE FORMS AND STRENGTHS, the following bullet was added:

3mL NovoLog FlexTouch

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

3mL NovoLog FlexTouch

- Under the section, HOW SUPPLIED, the following bullet was added:

3mL NovoLog FlexTouch NDC 0169-6338-10

- Also under the section, HOW SUPPLIED, the following statement was added:

FlexPen and FlexTouch can be used with NovoFine or NovoTwist disposable needles.

- Under the section, RECOMMENDED STORAGE, the following paragraph was changed from:

PenFill cartridges or NovoLog FlexPen:

Once a cartridge or a NovoLog FlexPen is punctured, it should be kept at temperatures below 30°C (86°F) for up to 28 days, but should not be exposed to excessive heat or sunlight. A NovoLog FlexPen or cartridge in use must NOT be stored in the refrigerator. Keep the NovoLog FlexPen and all PenFill cartridges away from direct heat and sunlight. Unpunctured NovoLog FlexPen and PenFill cartridges can be used until the expiration date printed on the label if they are stored in a refrigerator. Keep unused NovoLog FlexPen and PenFill cartridges in the carton so they will stay clean and protected from light.

Always remove the needle after each injection and store the 3 mL PenFill cartridge delivery device or NovoLog FlexPen without a needle attached. This prevents contamination and/or infection, or leakage of insulin, and will ensure accurate dosing.

Always use a new needle for each injection to prevent contamination.

To:

PenFill cartridges or NovoLog FlexPen and NovoLog FlexTouch:

Once a cartridge or NovoLog FlexPen or NovoLog FlexTouch is punctured, it should be kept at temperatures below 30°C (86°F) for up to 28 days, but should not be exposed to excessive heat or sunlight. A NovoLog FlexPen or NovoLog FlexTouch or cartridge in use must NOT be stored in the refrigerator. Keep the NovoLog FlexPen or NovoLog FlexTouch and all PenFill cartridges away from direct heat and sunlight. Unpunctured NovoLog FlexPen or NovoLog FlexTouch and PenFill cartridges can be used until the expiration date printed on the label if they are stored in a refrigerator. Keep unused NovoLog FlexPen or NovoLog FlexTouch and PenFill cartridges in the carton so they will stay clean and protected from light.

Always remove the needle after each injection and store the 3 mL PenFill cartridge delivery device or NovoLog FlexPen or NovoLog FlexTouch without a needle attached. This prevents contamination and/or infection, or leakage of insulin, and will ensure accurate dosing. Always use a new needle for each injection to prevent contamination.

- Also under the section RECOMMENDED STORAGE, the title of Table 9 was changed from:

Storage conditions for vial, PenFill cartridges and NovoLog FlexPen

To:

Storage conditions for vial, PenFill cartridges, NovoLog FlexPen, and NovoLog FlexTouch

- Also under the section RECOMMENDED STORAGE, the following information was also added to Table 9:

| NovoLog Presentation | Not in-use (unopened) Room Temperature (below 30C) | Not in-use (unopened) Refrigerated | In-use (opened) Room Temperature (below 30C) |
|-----------------------|--|------------------------------------|--|
| 3mL NovoLog FlexTouch | 28 day | Until expiration date | 28 days (Do not refrigerate) |

- Under the section PHYSICIAN INSTRUCTIONS, the following paragraph was added:

Patients should receive proper training on how to use NovoLog. Instruct patients that when injecting NovoLog, 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.**

- Under the section FDA APPROVED PATIENT LABELING, the following statement was changed from:

Novo Nordisk®, *NovoLog®*, *NovoPen® 3*, *PenFill®*, *Novolin®*, *FlexPen®*, *PenMate®* and *NovoFine®* are registered trademarks of Novo Nordisk A/S.

To:

Novo Nordisk®, *NovoLog®*, *NovoPen® 3*, *PenFill®*, *Novolin®*, *FlexPen®*, *FlexTouch®*, *PenMate®* *NovoFine®*, and *NovoTwist®* are registered trademarks of Novo Nordisk A/S.

- Also under the section FDA APPROVED PATIENT LABELING, the following statement was changed from:

FlexPen® is covered by US Patent Nos. 6,582,404, 6,004,297, 6,235,004, 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 FDA APPROVED PATIENT LABELING, the following statement was added:

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

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 Hutching 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 |

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/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

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

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/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 APFont 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.

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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)

CDRH Tracking: ICC1300134

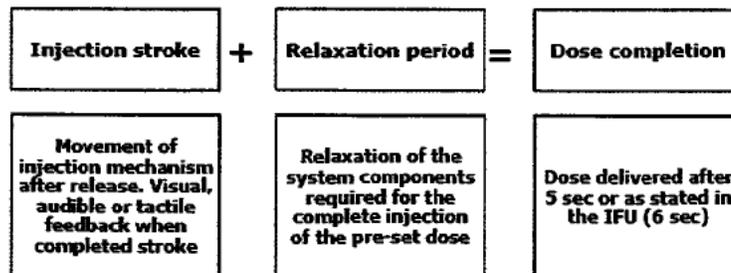
1. Issue

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 [REDACTED] (b) (4)

CDRH Consult Review [REDACTED] (b) (4)

[REDACTED] (b) (4)

[REDACTED] (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

NDA 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

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 effectively 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)

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 include wrong 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 ^{b)} |
| 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 ^{(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 effectively 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 effectively. 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 cap 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 effectively 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 results 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 in 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 recommend 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 misinterpreted 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 to the blocked 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 in 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 a 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 users 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.

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
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.***

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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 March 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 handling 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 safely 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 GEN 1200172, CON 124052

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: Quynh Nhu Nguyen
 Date Assigned: _____
 Assigned by: _____
 Completed date: 3/7/2012
 Reviewer Initials: QNN
 Supervisory Concurrence: Pam 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 020986/5-061 Levemir 021536/5-033
(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

Note: _____ (b) (4)



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

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

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 (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 effectively 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.

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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 include wrong 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 (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 effectively 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 cap 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 effectively. 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 cap 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 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 not 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 to 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 to the device under (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 effectively 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



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 12001979, NDA 020986 PDS290 Pen injector to deliver
Novolog (insulin aspart [rDNA origin]).

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 020986. The device constituent of this combination product consists of the PDS290 Pen injector to deliver Novolog (insulin aspart [rDNA origin]).

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 020986\0086

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)

The final device design addressed the potential issue of the short moulded ratchet click arm (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 11608-1, 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 [REDACTED] (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 11608-1, 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

(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 (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

(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.

(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.

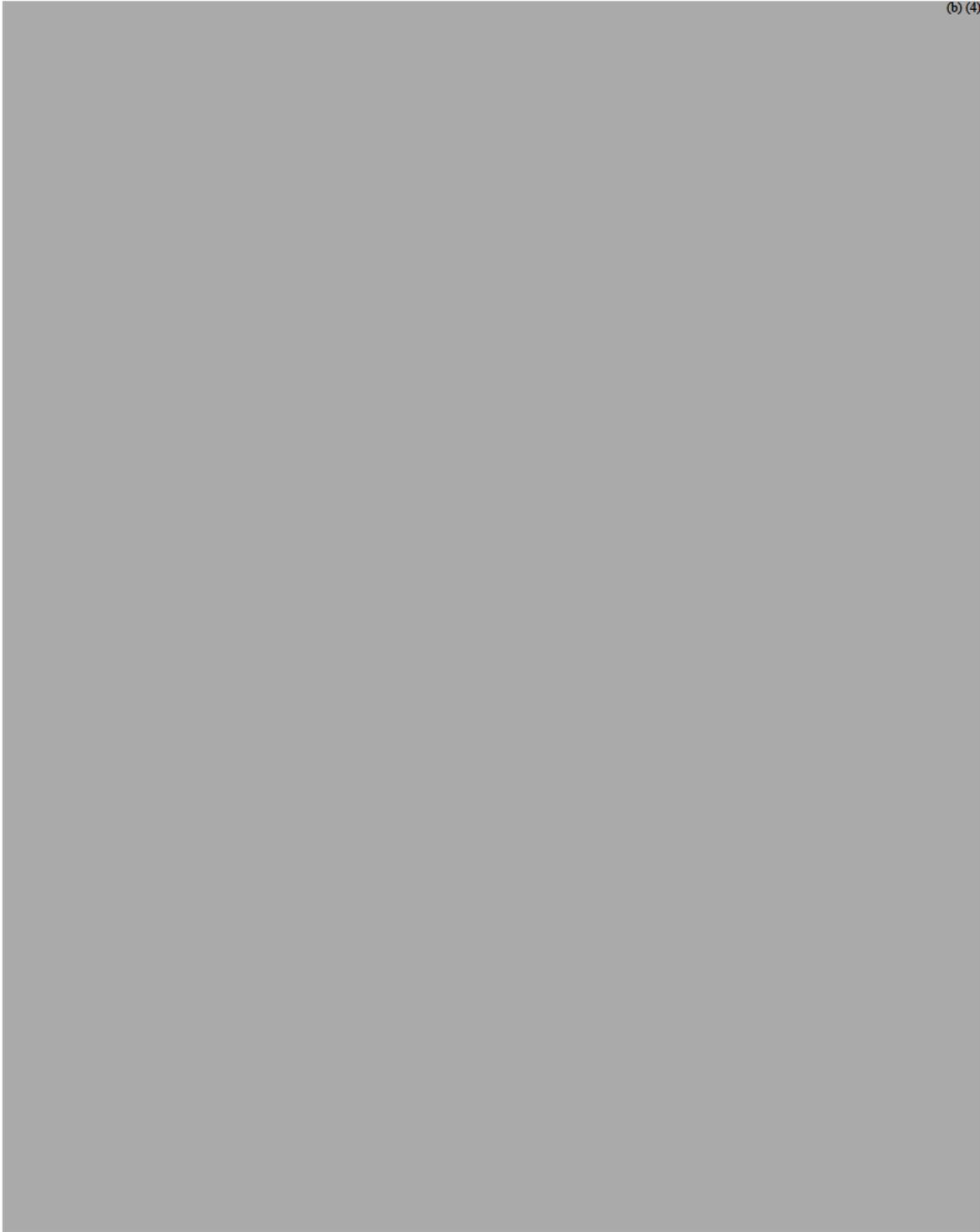
(b) (4)



Figure 1. Assembled PDS-290 Pen Injector

(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 (b) (4). The Sponsor's corrective action consisted of removing the (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 (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 (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) 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) 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.

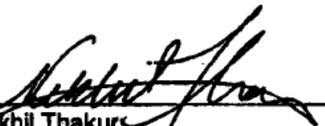
The intent of the a human factors validation study is to demonstrate that the device can be used by representative users under simulated conditions without patterns of failures or difficulties that could result in clinical impact to patients or, in some cases, to users themselves. To the extent that 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) |
| (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 20986/S-061

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 ADMINISTRATION | | REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW CONSULTATION **Please send immediately following the Filing/Planning meeting** | | |
| TO: CDER-DDMAC-RPM Attn: Ankur Kalola | | FROM: (Name/Title, Office/Division/Phone number of requestor) Callie Cappel-Lynch Project Manager DMEP 301 796 8436 | | |
| REQUEST DATE 10/23/13 | IND NO. | NDA/BLA NO. 21536/S33 20986/S61 | TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW) | |
| NAME OF DRUG Levemir Novolog | PRIORITY CONSIDERATION Standard | CLASSIFICATION OF DRUG Insulin | DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting) 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) <input type="checkbox"/> PACKAGE INSERT (PI) <input type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input checked="" type="checkbox"/> CARTON/CONTAINER LABELING <input type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE(IFU) | | TYPE OF APPLICATION/SUBMISSION <input type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> IND <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input checked="" type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> PLR CONVERSION | | REASON FOR LABELING CONSULT <input type="checkbox"/> INITIAL PROPOSED LABELING <input checked="" type="checkbox"/> 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 Fixtouch 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) <input type="checkbox"/> eMAIL <input type="checkbox"/> 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-flexitouch-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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From: RSPR (Rick Spring) [<mailto:rspr@novonordisk.com>]
Sent: Monday, September 09, 2013 12:01 PM
To: CappelLynch, Callie
Subject: NDA 020986/S-061/NDA 021536/S-033: NovoLog/Levemir PDS290 prefilled pen (FlexTouch) - Follow up

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

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

From: [Cappell Lynch, Callie](#)
To: [RSPR \(Rick Spring\)](#)
Cc: [Cappell Lynch, 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](#)

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: Cappell Lynch, Callie
Subject: RE: NDA 020986/S-061/NDA 021536/S-033: NovoLog/Levemir PDS290 prefilled pen (FlexTouch) - Follow up

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Thank you,
Callie

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Sent: Monday, September 09, 2013 12:01 PM
To: CappellLynch, Callie
Subject: NDA 020986/S-061/NDA 021536/S-033: NovoLog/Levemir PDS290 prefilled pen (FlexTouch) - Follow up

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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

This e-mail (including any attachments) is intended for the addressee(s) stated above only and may contain confidential information protected by law. You are hereby notified that any unauthorized reading, disclosure, copying or distribution of this e-mail or use of information contained herein is strictly prohibited and may violate rights to proprietary information. If you are not an intended recipient, please return this e-mail to the sender and delete it immediately hereafter. Thank you.

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/s/

CALLIE C CAPPEL-LYNCH
10/08/2013



NDA 020986/S061

**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 NovoLog® (insulin aspart [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 NovoLog® 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, NovoLog® FlexTouch®, and to your May 30, 2013, amendment to the initial request.

We have completed our review of the proposed proprietary name, NovoLog® FlexTouch® and have concluded that it is acceptable.

The proposed proprietary name, NovoLog® 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



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 detemir [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 Research
Center 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 ADMINISTRATION | | REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW CONSULTATION **Please send immediately following the Filing/Planning meeting** | | |
| TO: CDER-DDMAC-RPM | | FROM: (Name/Title, Office/Division/Phone number of requestor) Callie Cappel-Lynch Project Manager DMEP 301 796 8436 | | |
| REQUEST DATE 5/23/13 | IND NO. | NDA/BLA NO. 21536/S33 20986/S61 | TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW) | |
| NAME OF DRUG Levemir Novolog | PRIORITY CONSIDERATION Standard | CLASSIFICATION OF DRUG Insulin | DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting) 8/22/13 | |
| NAME OF FIRM: Novonordisk | | PDUFA Date: 9/22/13 | | |
| TYPE OF LABEL TO REVIEW | | | | |
| TYPE OF LABELING: (Check all that apply) | | TYPE OF APPLICATION/SUBMISSION | | REASON FOR LABELING CONSULT |
| <input type="checkbox"/> PACKAGE INSERT (PI) <input type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input type="checkbox"/> CARTON/CONTAINER LABELING <input type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE(IFU) | | <input type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> IND <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input checked="" type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> PLR CONVERSION | | <input type="checkbox"/> INITIAL PROPOSED LABELING <input type="checkbox"/> 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: Novonordisk 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) <input type="checkbox"/> eMAIL <input type="checkbox"/> HAND | | |

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/s/

CALLIE C CAPPEL-LYNCH
05/23/2013

REQUEST FOR PATIENT LABELING REVIEW CONSULTATION

| | |
|--|---|
| <p>TO:</p> <p>CDER-DMPP-PatientLabelingTeam</p> | <p>FROM: (Name/Title, Office/Division/Phone number of requestor)</p> <p>Callie Cappel-Lynch Regulatory Project Manager Division of Metabolism and Endocrinology Products Callie.cappellynch@fda.hhs.gov (301) 796-8436</p> |
|--|---|

| | | |
|--|--|---|
| <p>REQUEST DATE:</p> <p>3/27/13</p> | <p>NDA/BLA NO.:</p> <p>NDA 20986/S61 NDA 21536/S33</p> | <p>TYPE OF DOCUMENTS:</p> <p>(PLEASE CHECK OFF BELOW)</p> |
|--|--|---|

| | | | |
|---|--|---|---|
| <p>NAME OF DRUG:</p> <p>Novolog Levemir</p> | <p>PRIORITY CONSIDERATION:</p> <p>Standard</p> | <p>CLASSIFICATION OF DRUG:</p> <p>Insulin</p> | <p>DESIRED COMPLETION DATE</p> <p>(Generally 2 Weeks after receiving substantially complete labeling)</p> |
|---|--|---|---|

| | |
|--|----------------------------|
| <p>SPONSOR:</p> <p>Novo Nordisk</p> | <p>PDUFA Date: 9/22/13</p> |
|--|----------------------------|

TYPE OF LABEL TO REVIEW

| | | |
|--|--|--|
| <p>TYPE OF LABELING: (Check all that apply)</p> <p><input checked="" type="checkbox"/> PATIENT PACKAGE INSERT (PPI)</p> <p><input type="checkbox"/> MEDICATION GUIDE</p> <p><input checked="" type="checkbox"/> INSTRUCTIONS FOR USE(IFU)</p> | <p>TYPE OF APPLICATION/SUBMISSION</p> <p><input type="checkbox"/> ORIGINAL NDA/BLA</p> <p><input type="checkbox"/> EFFICACY SUPPLEMENT</p> <p><input type="checkbox"/> SAFETY SUPPLEMENT</p> <p><input checked="" type="checkbox"/> LABELING SUPPLEMENT</p> <p><input type="checkbox"/> MANUFACTURING (CMC) SUPPLEMENT</p> <p><input type="checkbox"/> PLR CONVERSION</p> | <p>REASON FOR LABELING CONSULT</p> <p><input type="checkbox"/> INITIAL PROPOSED LABELING</p> <p><input checked="" type="checkbox"/> LABELING REVISION</p> |
|--|--|--|

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

| | |
|-----------------------|---|
| SIGNATURE OF RECEIVER | METHOD OF DELIVERY (Check one) <input type="checkbox"/> eMAIL (BLAs Only) <input checked="" type="checkbox"/> 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 ADMINISTRATION | | 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 3/27/13 | IND NO. | NDA NO. 20986/S-061 21536/S-033 | TYPE OF DOCUMENT Response to CR | DATE OF DOCUMENT 3/22/13 | |
| NAME OF DRUG Novolog and Levemir | | PRIORITY CONSIDERATION Standard | CLASSIFICATION OF DRUG Insulin | DESIRED COMPLETION DATE 7/22/13 | |
| NAME OF FIRM: Novo Nordisk | | | | | |
| REASON FOR REQUEST | | | | | |
| I. GENERAL | | | | | |
| <input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY | | <input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input checked="" type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT | | <input checked="" type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW): | |
| II. BIOMETRICS | | | | | |
| STATISTICAL EVALUATION BRANCH | | | STATISTICAL APPLICATION BRANCH | | |
| <input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW): | | | <input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW): | | |
| III. BIOPHARMACEUTICS | | | | | |
| <input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES | | | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST | | |
| IV. DRUG EXPERIENCE | | | | | |
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | | | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS | | |
| V. SCIENTIFIC INVESTIGATIONS | | | | | |
| <input type="checkbox"/> CLINICAL | | | <input type="checkbox"/> PRECLINICAL | | |
| COMMENTS/SPECIAL INSTRUCTIONS: | | | | | |
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| SIGNATURE OF REQUESTER Callie Cappel-Lynch | | | METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND | | |

Reference ID: 3285938

| | |
|-----------------------|------------------------|
| 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:
Division: Combination Products
Mail Code: HF
Consulting Reviewer Name: Jacqueline Ryan
Building/Room #: 66/2256
Phone #: 301 796 9599
Fax #:
Email Address: jaqueline.ryan@fda.hhs.gov
RPM/CSO Name and Mail Code:

From (Originating Center):

Center: CDER
Division: Metabolism and Endocrinology
Mail Code: HF
Requesting Reviewer Name:
Building/Room #: 22/3362
Phone #: 301 796 8436
Fax #:
Email Address: callie.cappellynch@fda.hhs.gov
RPM/CSO Name and Mail Code:
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: 3/27/2013

Requested Completion Date: 7/22/2013

Submission/Application Number: NDA 29086/S61 and NDA 21536/S33
(Not Barcode Number)

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

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

Submission Receipt Date: 3/22/2013

Official Submission Due Date: 9/22/2013

Name of Product:

Name of Firm:

Intended Use:

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):

- 1) Labeling documents (carton/container, PI, PPI, IFU)
- 2) ISO Compliance Response
- 3) Validation of Device Use Final Report

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

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 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.

Cover Letter: \\CDSESUB1\EVSPROD\NDA020986\0113\m1\us\102-cover-letters\cover.pdf

Reference ID: 3205034 EDR ID: CDSESUB1\EVSPROD\NDA020986\020986.enx

EDR Location: \\CDSESUB1\EVSPROD\NDA021536\021536.enx

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
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:

Division: Combination Products

Mail Code: HF

Consulting Reviewer Name: Jacqueline Ryan

Building/Room #: 66/2256

Phone #: 301 796 9599

Fax #:

Email Address: jaqueline.ryan@fda.hhs.gov

RPM/CSO Name and Mail Code:

From (Originating Center):

Center: CDER

Division: Metabolism and Endocrinology

Mail Code: HF

Requesting Reviewer Name:

Building/Room #: 22/3362

Phone #: 301 796 8436

Fax #:

Email Address: callie.cappellynch@fda.hhs.gov

RPM/CSO Name and Mail Code:

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: 3/27/2013

Requested Completion Date: 7/22/2013

Submission/Application Number: NDA 29086/S61 and NDA 21536/S33
(Not Barcode Number)

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

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

Submission Receipt Date: 3/22/2013

Official Submission Due Date: 9/22/2013

Name of Product:

Name of Firm:

Intended Use:

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):

- 1) Labeling documents (carton/container, PI, PPI, IFU)
- 2) ISO Compliance Response
- 3) Validation of Device Use Final Report

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

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 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.

Cover Letter: \\CDSESUB1\EVSPROD\NDA020986\0113\m1\us\102-cover-letters\cover.pdf

Reference ID: 3285924 CDSESUB1\EVSPROD\NDA020986\020986.enx

EDR Location: \\CDSESUB1\EVSPROD\NDA021536\021536.enx

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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 detemir [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



NDA 020986/S-061

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 NovoLog (insulin aspart [rDNA origin] injection), 100 Units/ml.

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



NDA 020986/S-061

**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 NovoLog® (insulin aspart [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 NovoLog® 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, NovoLog® FlexTouch®;

We have completed our review of the proposed proprietary name, NovoLog® 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 errorsadditional 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 effectively. 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 not 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 effectively 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:

--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: 3076188

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/s/

RACHEL E HARTFORD
01/24/2012

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|--|---------|---|-----------------------------------|------------------------------------|
| DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION | | REQUEST FOR CONSULTATION | | |
| TO (Division/Office): Mail: OSE | | FROM: 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 | | | | |
| <input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): | | | | |
| II. BIOMETRICS | | | | |
| STATISTICAL EVALUATION BRANCH | | STATISTICAL APPLICATION BRANCH | | |
| <input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW): | | <input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW): | | |
| III. BIOPHARMACEUTICS | | | | |
| <input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES | | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST | | |
| IV. DRUG EXPERIENCE | | | | |
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS | | |
| V. SCIENTIFIC INVESTIGATIONS | | | | |
| <input type="checkbox"/> CLINICAL | | <input type="checkbox"/> 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: (b) (4) | | | | |
| SIGNATURE OF REQUESTER Rachel Hartford | | METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DARRTS <input type="checkbox"/> 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



NDA 020986/S-061

**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 NovoLog (insulin aspart [rDNA origin] injection).

We also refer to your December 15, 2009 correspondence, received December 15, 2009, requesting review of your proposed proprietary name, NovoLog FlexTouch.

We have completed our review of the proposed proprietary name, NovoLog FlexTouch and have concluded that it is acceptable. However, we anticipate product selection errors between the NovoLog Mix 70/30 FlexTouch and NovoLog Mix 70/30 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, NovoLog FlexTouch, will be re-reviewed 90 days prior to the approval of the sNDA. If we find the 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-20986 | ----- SUPPL-61 | ----- NOVO NORDISK INC | ----- NOVOLOG |

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/s/

CAROL A HOLQUIST
03/15/2010

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

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/s/

RACHEL E HARTFORD
03/11/2010