CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

021536Orig1s031

Trade Name:	LEVEMIR
Generic or Proper Name:	insulin detemir [rDNA origin] injection
Sponsor:	Novo Nordisk Inc.
Approval Date:	February 02, 2015
Indication:	LEVEMIR is a long-acting human insulin analog indicated to improve glycemic control in adults and children with diabetes mellitus. (1) Important Limitations of Use: □ Not recommended for treating diabetic ketoacidosis. Use intravenous, rapid acting or short-acting insulin instead.

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021536/S-031 and S-051

SUPPLEMENT APPROVAL

Novo Nordisk, Inc.
Attention: Robert B. Clark
VP Regulatory Affairs
800 Scudders Mill Road, P.O. Box 846
Plainsboro, NJ 08536

Dear Mr. Clark:

Please refer to your Supplemental New Drug Applications (sNDAs) dated and received July 17, 2009 (S-031) and August 15, 2014 (S-051), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Levemir (insulin detemir [rDNA origin] injection), 100 Units/mL.

We acknowledge receipt of your amendments dated:
Supplement S-031: August 20, 2009, May 14, 2010, March 27 and April 19, 2013, and February 20, 2015
Supplement S-051: November 10 and December 22, 2014, and January 12 and February 3, 2015

The "Changes Being Effected" supplemental new drug application (S-031) proposes to revise the labeling for Levemir to include a warning against the sharing of pens between patients.

We also refer to our letter dated July 17, 2014, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for products indicated for diabetes mellitus that have multi-dose pen presentations. This information pertains to the risk of transmission of bloodborne pathogens resulting from pen devices and pen cartridges that are intended for single patient use only, being shared among numerous patients.

The "Prior Approval" supplemental new drug application (S-051) provides for revisions to the labeling for Levemir consistent with our July 17, 2014, letter.

In our July 17, 2014, letter, we also required you to submit a plan for how you would modify the pen device to include a statement warning against the sharing of pens, on the body of the pen. In your submission dated August 15, 2014, you provided a rationale for why you believe that adding the warning statement to the body of the pen is not necessary and/or feasible. We have reviewed this rationale and found it acceptable that the warning not be placed on the body of the pen at this time.

Further, in our July 17, 2014 letter, we required you to modify the labeling for the Levemir FlexPen to include the warning against the sharing of pens. However, we acknowledge that the Levemir FlexPen was discontinued as of August 1, 2014, and therefore you are no longer required to modify the labeling for it. If you re-introduce Levemir FlexPen into the market, please update the labeling to match that for your other pens.

APPROVAL & LABELING

We have completed our review of these supplemental applications, as amended. They are 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, 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).

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/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. 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.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

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}

Jennifer Rodriguez Pippins, M.D., M.P.H.
Deputy Director for Safety
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURES:
Levemir Package Insert
Levemir Patient Package Insert
Levemir FlexTouch Pen Instructions for Use
Levemir Carton and Container labels

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

/s/

JENNIFER R PIPPINS
02/25/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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LABELING

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

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

----------RECENT MAJOR CHANGES----------
- Warnings and Precautions (5.1) 02/2015

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

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

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

----------DOSAGE FORMS AND STRENGTHS----------
Solution for injection 100 Units/mL (U-100) in

- 3 ml LEVEMIR FlexTouch®
- 10 mL vial (3)

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

----------WARNINGS AND PRECAUTIONS----------
- Never Share a LEVEMIR FlexTouch between patients, even if the needle is changed (5.1).
- Dose adjustment and monitoring: Monitor blood glucose in all patients treated with insulin. Insulin regimens should be modified cautiously and only under medical supervision (5.2)
- Administration: Do not dilute or mix with any other insulin or solution. Do not administer subcutaneously via an insulin pump, intramuscularly, or intravenously because severe hypoglycemia can occur (5.3)
- Hypoglycemia is the most common adverse reaction of insulin therapy and may be life-threatening (5.4, 6.1)
- Allergic reactions: Severe, life-threatening, generalized allergy, including anaphylaxis, can occur (5.5)
- Renal or hepatic impairment: May require adjustment of the LEVEMIR dose (5.6, 5.7)
- Fluid retention and heart failure can occur with concomitant use of thiazolidinediones (TZDs), which are PPAR-gamma agonists, and insulin, including LEVEMIR (5.9)

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

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

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

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

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

Revised: 02/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

Important Limitations of Use:

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

2 DOSAGE AND ADMINISTRATION

2.1 Dosing

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

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

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

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

Patients adjusting the amount or timing of dosing with LEVEMIR should only do so under medical supervision with appropriate glucose monitoring *[see Warnings and Precautions (5.2)]*.

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

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

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

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

2.2 Initiation of LEVEMIR Therapy

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

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

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

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

2.3 Converting to LEVEMIR from other insulin therapies

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

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

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

3 DOSAGE FORMS AND STRENGTHS

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

-
- 3 mL LEVEMIR FlexTouch®
- 10 mL vial

4 CONTRAINDICATIONS

LEVEMIR is contraindicated in patients with hypersensitivity to LEVEMIR or any of its excipients. Reactions have included anaphylaxis [*see Warnings and Precautions (5.5) and Adverse Reactions (6.1)*].

5 WARNINGS AND PRECAUTIONS

5.1 Never Share a LEVEMIR FlexTouch Between Patients

LEVEMIR FlexTouch must never be shared between patients, even if the needle is changed. Sharing poses a risk for transmission of blood-borne pathogens.

5.2 Dosage adjustment and monitoring

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

Changes in insulin strength, manufacturer, type, or method of administration may result in the need for a change in the insulin dose or an adjustment of concomitant anti-diabetic treatment.
As with all insulin preparations, the time course of action for LEVEMIR may vary in different individuals or at different times in the same individual and is dependent on many conditions, including the local blood supply, local temperature, and physical activity.

5.3 Administration
LEVEMIR should only be administered subcutaneously.

Do not administer LEVEMIR intravenously or intramuscularly. The intended duration of activity of LEVEMIR is dependent on injection into subcutaneous tissue. Intravenous or intramuscular administration of the usual subcutaneous dose could result in severe hypoglycemia [*see Warnings and Precautions (5.4)*].

Do not use LEVEMIR in insulin infusion pumps.

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

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

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

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

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

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

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

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

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

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

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

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

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

6 ADVERSE REACTIONS
The following adverse reactions are discussed elsewhere:
- Hypoglycemia *[see Warnings and Precautions (5.4)]*
- Hypersensitivity and allergic reactions *[see Warnings and Precautions (5.5)]*

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Pregnancy

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

- *Hypoglycemia*

Hypoglycemia is the most commonly observed adverse reaction in patients using insulin, including LEVEMIR *[see Warnings and Precautions (5.4)]*.

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

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

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

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

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

Table 5: Hypoglycemia in Patients with Type 1 Diabetes

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

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

Table 6: Hypoglycemia in Patients with Type 2 Diabetes

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

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

- *Insulin Initiation and Intensification of Glucose Control*

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

- *Lipodystrophy*

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

- *Weight Gain*

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

- *Peripheral Edema*

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

- *Allergic Reactions*

Local Allergy

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

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

Systemic Allergy
Severe, life-threatening, generalized allergy, including anaphylaxis, generalized skin reactions, angioedema, bronchospasm, hypotension, and shock may occur with any insulin, including LEVEMIR, and may be life-threatening *[see Warnings and Precautions (5.5)]*.

- *Antibody Production*

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

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

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

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

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

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

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

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

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

Risk Summary

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

Clinical Considerations

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

Human Data

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

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

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

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

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

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

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

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

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

Table 8: Hypoglycemia in Pregnant Women with Type 1 Diabetes

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

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

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

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

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

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

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

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

8.5 Geriatric Use

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

10 OVERDOSAGE

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

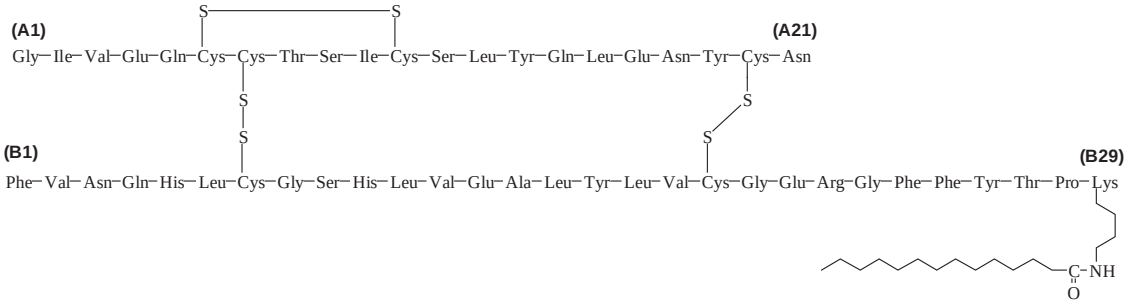
More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. After apparent clinical recovery from hypoglycemia, continued observation and additional carbohydrate intake may be necessary to avoid recurrence of hypoglycemia [*see Warnings and Precautions (5.4)*].

11 DESCRIPTION

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

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

Figure 1: Structural Formula of insulin detemir



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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

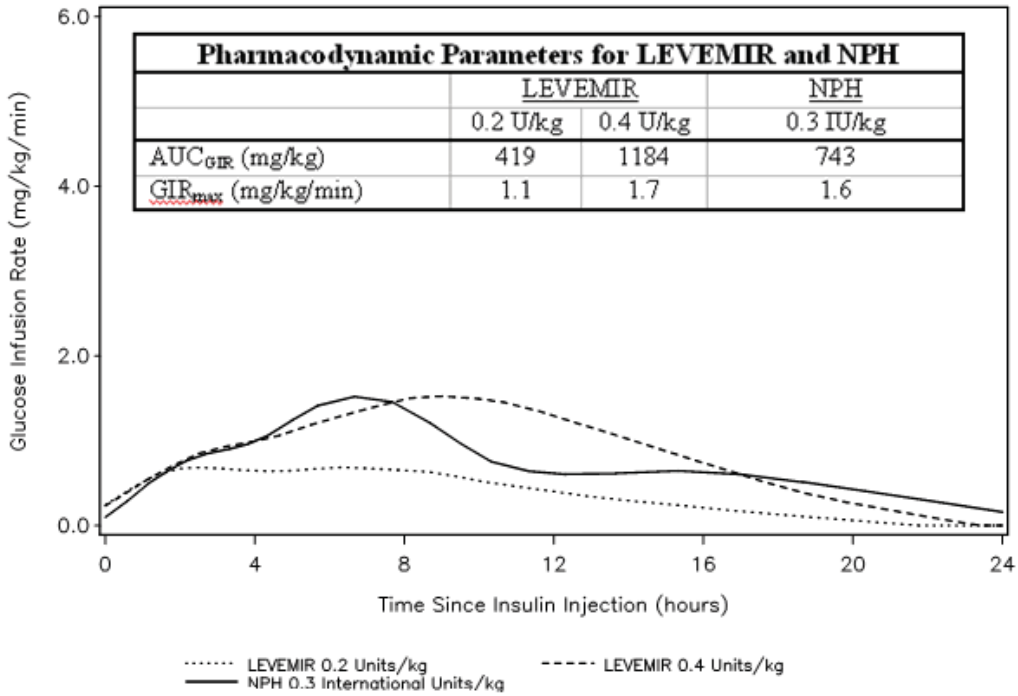
12.2 Pharmacodynamics

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

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

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

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

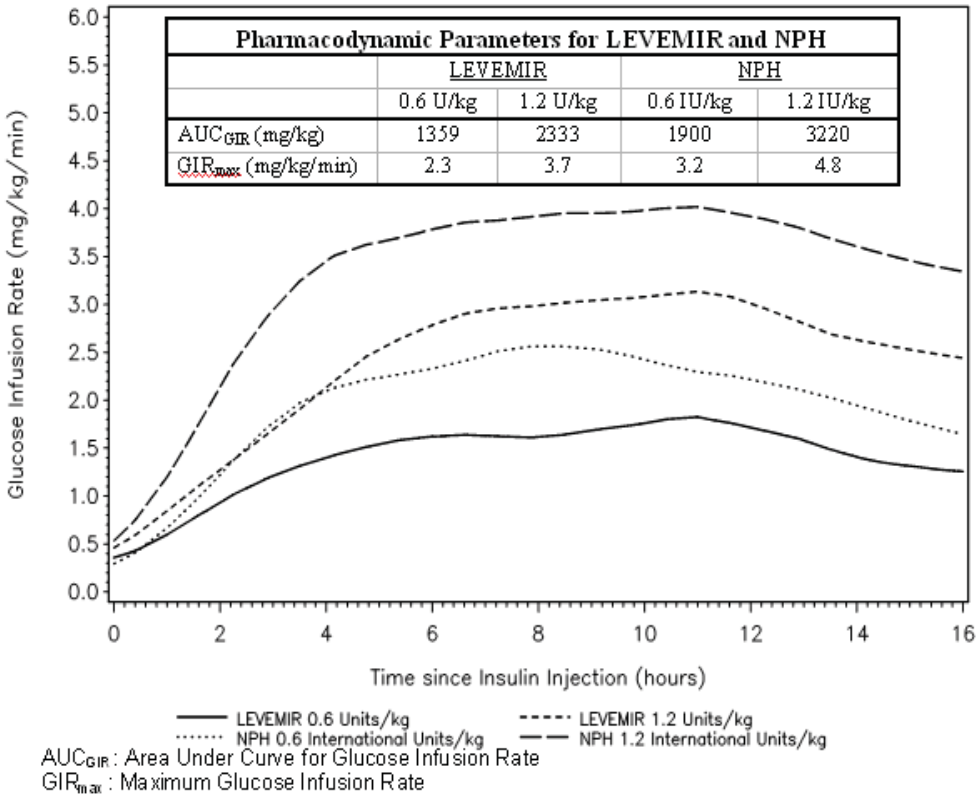


AUC_{GIR} : Area Under Curve for Glucose Infusion Rate
GIR_{max} : Maximum Glucose Infusion Rate

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

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

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



12.3 Pharmacokinetics

Absorption and Bioavailability

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

The absolute bioavailability of insulin detemir is approximately 60%.

Distribution and Elimination

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

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

Specific Populations

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

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

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

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

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

Renal impairment- A single subcutaneous dose of 0.2 Units/kg (1.2 nmol/kg) of LEVEMIR was administered to healthy subjects and those with varying degrees of renal impairment (mild, moderate, severe, and hemodialysis-dependent). In this study, there were no differences in the pharmacokinetics of LEVEMIR between healthy subjects and those with renal impairment. However, some studies with human insulin have shown increased circulating levels of insulin in patients with renal impairment. Careful glucose monitoring and dose adjustments of insulin, including LEVEMIR, may be necessary in patients with renal impairment [*see Warnings and Precautions (5.6)*].

Hepatic impairment- A single subcutaneous dose of 0.2 Units/kg (1.2 nmol/kg) of LEVEMIR was administered to healthy subjects and those with varying degrees of hepatic impairment (mild, moderate and severe). LEVEMIR exposure as estimated by AUC decreased with increasing degrees of hepatic impairment with a corresponding increase in apparent clearance. However, some studies with human insulin have shown increased circulating levels of insulin in patients with liver impairment. Careful glucose monitoring and dose adjustments of insulin, including LEVEMIR, may be necessary in patients with hepatic impairment [*see Warnings and Precautions (5.7)*].

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

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

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenicity, Mutagenicity, Impairment of Fertility

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

14 CLINICAL STUDIES

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

Type 1 Diabetes – Adult

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

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

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

Table 9: Type 1 Diabetes Mellitus – Adult

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

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

Type 1 Diabetes – Pediatric

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

Table 10: Type 1 Diabetes Mellitus – Pediatric

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

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

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

Type 2 Diabetes – Adult

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

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

Table 11: Type 2 Diabetes Mellitus – Adult

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

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

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

Combination Therapy with Metformin and Liraglutide

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

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

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

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

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

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

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

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

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

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

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

16.2 Storage:

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

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

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

Vials:

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

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

The storage conditions are summarized in Table 13:

Table 13: Storage Conditions for LEVEMIR FlexTouch and Vial

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

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

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

Mixing and diluting: LEVEMIR must NOT be mixed or diluted with any other insulin or solution [See *Warnings and Precautions* (5.3)].

17 PATIENT COUNSELING INFORMATION
See FDA-Approved Patient Labeling (Patient Information and Instructions for Use)

17.1 Never Share a LEVEMIR FlexTouch Between Patients

Advise patients that they must never share a LEVEMIR FlexTouch with another person, even if the needle is changed, because doing so carries a risk for transmission of bloodborne pathogens.

17.2 Instructions for Patients

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

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

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

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

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

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

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

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

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

www.novonordisk-us.com

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

Do not share your Levemir FlexTouch with other people, even if the needle has been changed. You may give other people a serious infection, or get a serious infection from them.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Revised: 02/2015

Instructions for Use

Levemir® (LEV–uh-mere) FlexTouch® Pen

(insulin detemir [rDNA origin] injection)

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

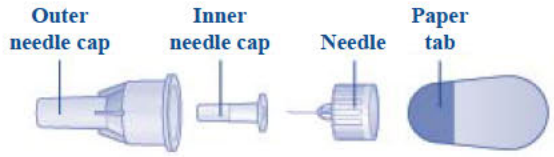
Supplies you will need to give your Levemir injection:

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

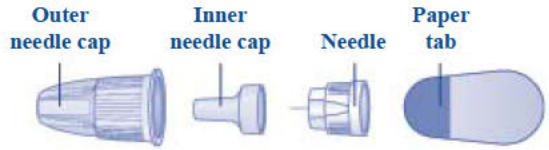
Preparing your Levemir FlexTouch Pen:

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

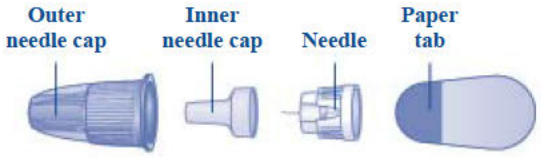
NovoFine®

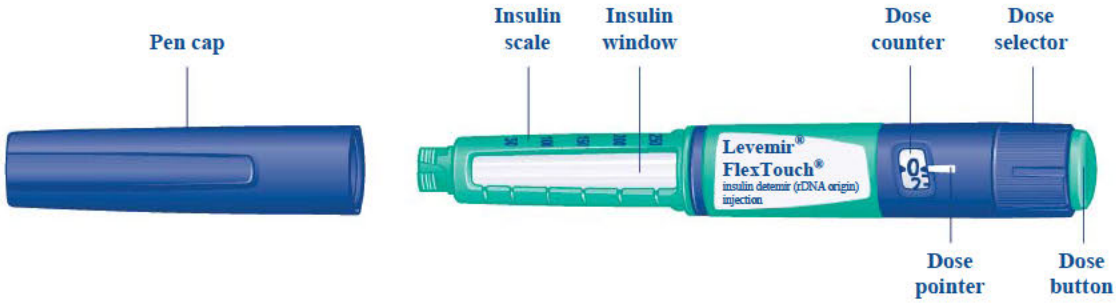


NovoFine® Plus

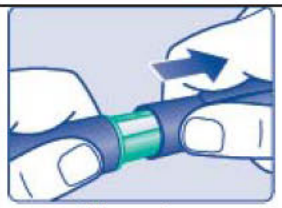


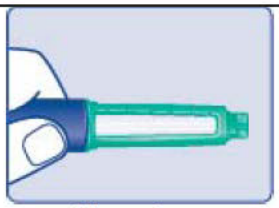
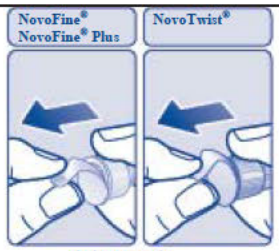
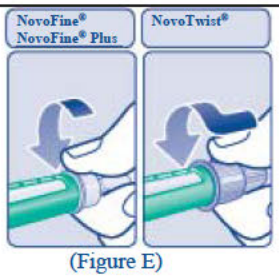
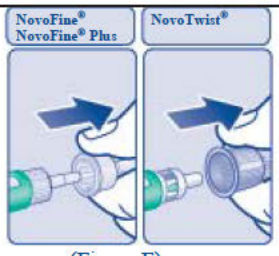
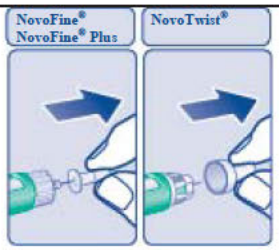
NovoTwist®



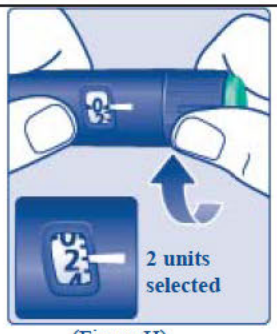
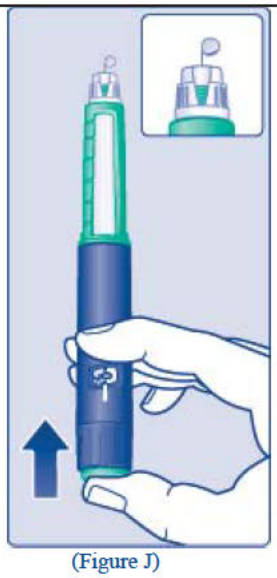


(Figure A)

Step 1: • Pull Pen cap straight off (See Figure B)	 (Figure B)
Step 2:	

• **Check the liquid in the Pen** (See Figure C). Levemir should look clear and colorless. **Do not** use it if it looks cloudy or colored.	 (Figure C)
Step 3: • **Select a new needle.** • Pull off the paper tab from the outer needle cap (See Figure D).	 (Figure D)
Step 4: • Push the capped needle straight onto the Pen and twist the needle on until it is tight (See Figure E).	 (Figure E)
Step 5: • Pull off the outer needle cap. **Do not** throw it away (See Figure F).	 (Figure F)
Step 6: • Pull off the inner needle cap and throw it away (See Figure G).	 (Figure G)

Priming your Levemir FlexTouch Pen:

Step 7: • Turn the dose selector to **select 2 units** (See Figure H).	 (Figure H)
Step 8: • Hold the Pen with the needle pointing up. Tap the top of the Pen gently a few times to let any air bubbles rise to the top (See Figure I).	 (Figure I)
Step 9: • **Hold the Pen with the needle pointing up.** Press and hold in the dose button until the dose counter shows "0". The "0" must line up with the dose pointer. • A drop of insulin should be seen at the needle tip (See Figure J). o If you **do not** see a drop of insulin, repeat steps 7 to 9, no more than 6 times. o If you **still do not** see a drop of insulin, change the needle and repeat steps 7 to 9.	 (Figure J)

Selecting your dose:

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Step 10:

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

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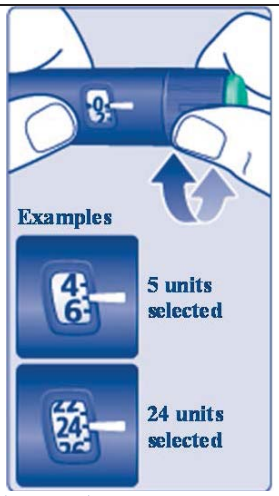

(Figure K)

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

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(Figure L)

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- **To see how much insulin is left in your Levemir FlexTouch Pen:**
  - 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.

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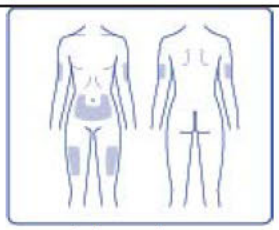
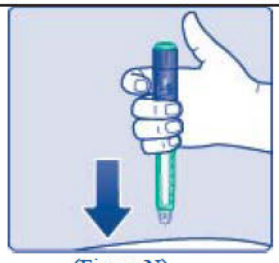
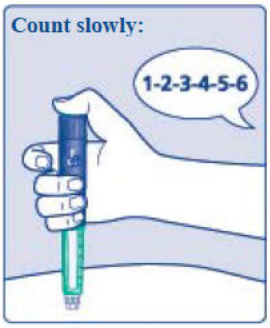
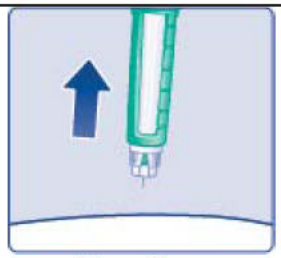
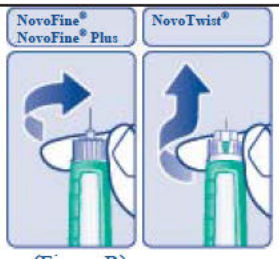
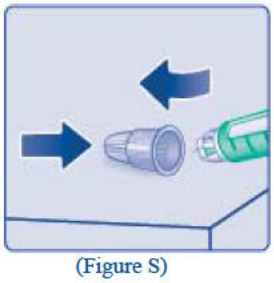
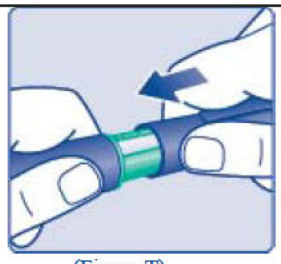
Giving your injection:

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

Step 11: • Choose your injection site and wipe the skin with an alcohol swab. Let the injection site dry before you inject your dose (See Figure M).	 (Figure M)
Step 12: • **Insert the needle into your skin** (See Figure N). o **Make sure you can see the dose counter. Do not** cover it with your fingers, this can stop your injection.	 (Figure N)
Step 13: • **Press and hold down the dose button until the dose counter shows "0"** (See Figure O). o The "0" must line up with the dose pointer. You may then hear or feel a click.	 (Figure O)
• **Keep the needle in your skin after** the dose counter has returned to "0" and **slowly count to 6** (See Figure P). o **When the dose counter returns to "0", you will not get your full dose until 6 seconds later.** o **If the needle is removed before you count to 6, you may see a stream of insulin coming from the needle tip.** o **If you see a stream of insulin coming from the needle tip**	 (Figure P)

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.	
Step 14: • **Pull the needle out of your skin** (See Figure Q). o If you see blood after you take the needle out of your skin, press the injection site lightly with a piece of gauze or an alcohol swab. **Do not** rub the area.	 (Figure Q)
Step 15: • **Carefully remove the needle from the Pen and throw it away** (See Figure R). o **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. o **Do not** store the Pen with the needle attached. Storing without the needle attached helps prevent leaking, blocking of the needle, and air from entering the Pen.	 (Figure R)  (Figure S)
Step 16: • Replace the Pen cap by pushing it straight on (See Figure T).	 (Figure T)

After your injection:

- You can put your used Levemir FlexTouch Pen and needles in a FDA-cleared sharps disposal container right away after use. Do not throw away (dispose of) loose needles and Pens in your household trash.

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

How should I store my Levemir FlexTouch Pen?

- Store unused Levemir FlexTouch Pens in the refrigerator at 36^{O}F to 46^{O}F (2^{O}C to 8^{O}C).
- Store the Pen you are currently using out of the refrigerator below 86^{O}F.
- **Do not** freeze Levemir. **Do not** use Levemir if it has been frozen.
- Keep Levemir away from heat or light.
- Unused Pens may be used until the expiration date printed on the label, if kept in the refrigerator.
- The Levemir FlexTouch Pen you are using should be thrown away after 42 days, even if it still has insulin left in it.

General Information about the safe and effective use of Levemir.

- **Keep Levemir FlexTouch Pens and needles out of the reach of children.**
- **Always** use a new needle for each injection.
- **Do not** share your Levemir FlexTouch Pen or needles with other people. You may give other people a serious infection, or get a serious infection from them.

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: 02/2015

For more information go to
www.novotraining.com/levemirflextouch/us02

Levemir®
Flextouch®

Read before first use

8-9508-31-305-X_v1-9:Layout 1 2015-01-27 9:58 AM Page 1

Code centre line Code: 100% Direction: Length: Max 29 mm (100%)

Regulatory Operations

Carton: 22-520-00-302
Current 1.0

Lacquer free area
Lacquer form (b) (4)

USA
1 pcs

Colour:
PMS (b) (4)
+ PMS (b) (4)
+ Black
+ PMS (b) (4)
+ PMS

2
8

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

Sample Kit includes:
- **(1) Levemir® FlexTouch®**
- **(7) single use NovoFine® Plus 32G needles**

For subcutaneous use.
Each mL contains 100 Units (14.20 mg/mL) of insulin detemir; glycerol 16.0 mg; phenol 1.80 mg; metacresol 2.06 mg; zinc 65.4 mcg; disodium phosphate dihydrate 0.89 mg; sodium chloride 1.17 mg and water for injection
Novo Nordisk® Levemir® FlexTouch® NovoFine® and NovoTwist® are registered trademarks of Novo Nordisk A/S
Levemir® is covered by US Patent Nos 5 750 497 5 866 538 6 011 007 6 869 930 and other patents pending
FlexTouch® pen is covered by US Patent Nos 7 686 786 6 899 699 and other patents pending

NOT TO BE USED BARCODE
USED FOR VISUAL PLACEMENT

3 00000 00000 3

40x25

www.novonordisk-us.com
1 800 727 6500
(Se habla español)
Manufactured by:
Novo Nordisk A/S
DK-2880 Bagsværd Denmark

novo nordisk®

22 520 00

Levemir® FlexTouch®
Insulin detemir (rDNA origin) injection
100 units/mL (U 100)
1×3 mL Prefilled Pen
Sample. Not for Resale

NDC 0169 6438 98 List: 643898

Levemir® FlexTouch®

Insulin detemir (rDNA origin) injection

For Single Patient Use Only

100 units/mL (U 100)
1×3 mL Prefilled Pen

For subcutaneous use only
Rx Only
Sample. Not for Resale

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

Recommended for use with NovoFine®, NovoFine® Plus or NovoTwist® disposable needles.

Keep in a cold place until first use.
Store at 2° 8°C (36° 46°F).
Avoid freezing.
Protect from light.

novo nordisk®

Expiry/Batch:

8 9508 31
305 X

Levemir® FlexTouch®
Insulin detemir (rDNA origin) injection
100 units/mL (U 100)
1×3 mL Prefilled Pen
Sample. Not for Resale

Levemir® FlexTouch®
Insulin detemir (rDNA origin) injection
100 units/mL (U 100)
1×3 mL Prefilled Pen
Sample. Not for Resale

Reference ID: 3706672

8-9508-31-303-X_v1-15:Layout 1 2014-11-21 10:59 AM Page 1

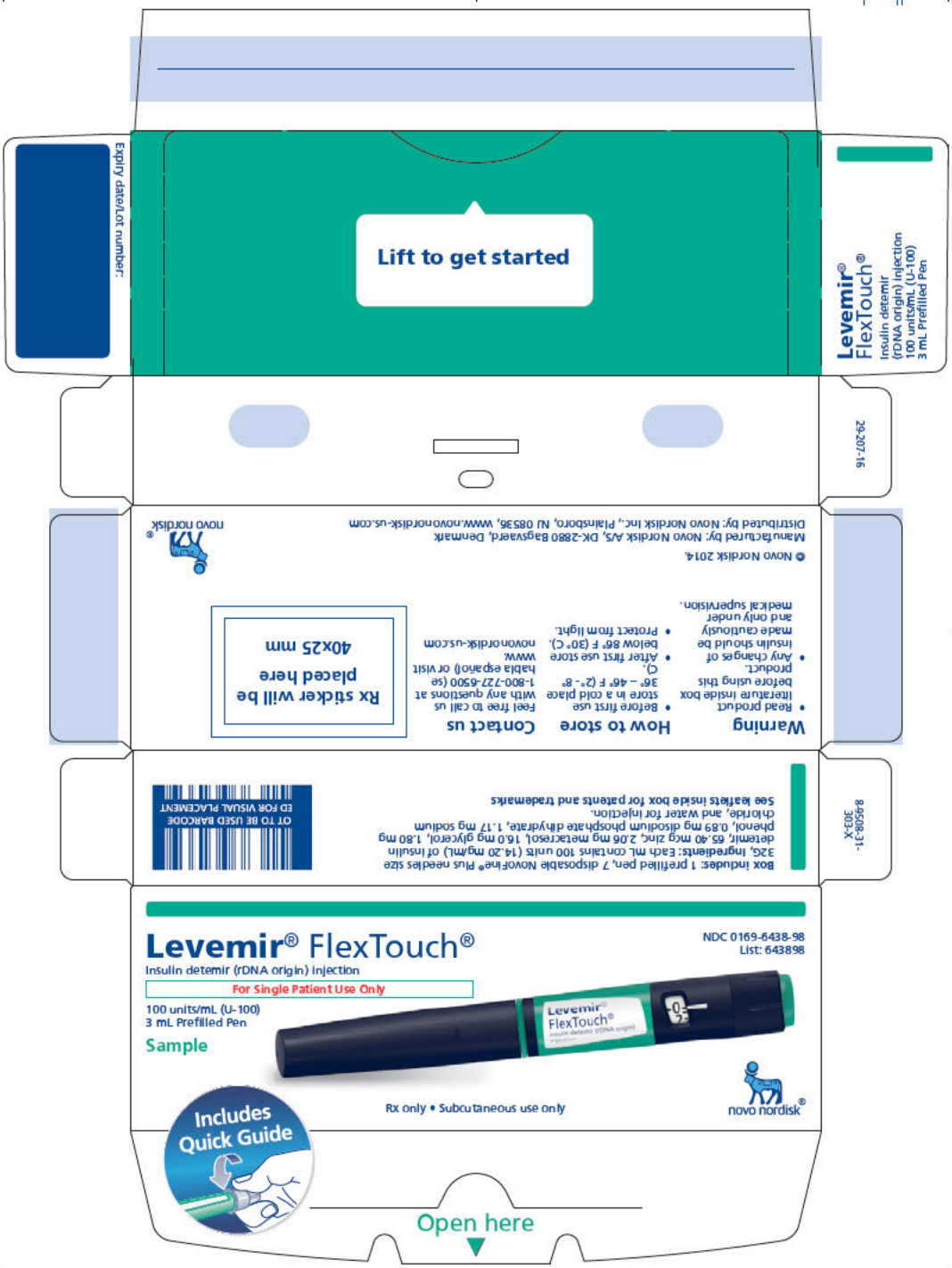
Regulatory Operations

Carton: X0_2010-29-207-16-301
Current 2.0

1 pcs with needles - Levemir
Sample - USA

Lacquer free area:
Lacquerform (b) (4)

Colour:
PMS (b) (4)
PMS
PMS
(b) (4)



Code centre line
Code: 100% Diffraction
Length: Max 29mm (100%)

Reference ID: 3706672

Regulatory Operations

Label: 2010-36,39x71,23-229
Current 1.0

Lacquer area:
Lacquerform (b) (4)

USA

Colour: PMS (b) (4)
PMS (b) (4) PMS (b) (4)

Area without lacquer

Center of Productbox

Overlap

Regulatory Operations

Label: 2010-36,39x71,23-202
Current 4.0

Lacquer area:
Lacquerform (b) (4)

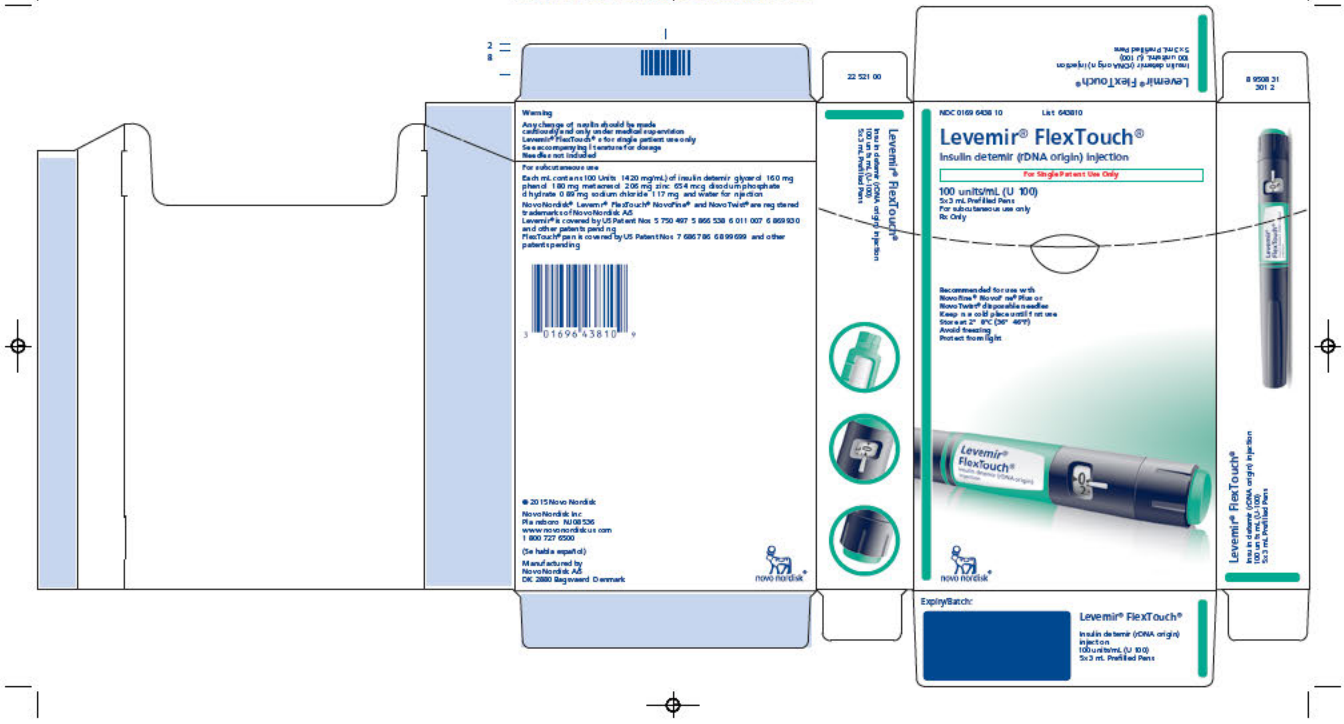
USA

Colour: PMS (b) (4)
+ PMS (b) (4)
+ PMS (b) (4)

Area without lacquer

Center of Productbox

Overlap



Regulatory Operations

Label: 2010-36,39x71,23-229
Current 1.0

Lacquer area:
Lacquerform (b) (4)

USA

Colour: PMS (b) (4)
PMS (b) (4) PMS (b) (4)

Area without lacquer

Center of Productbox

Overlap

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021536Orig1s031

OTHER REVIEW(S)

REGULATORY PROJECT MANAGER LABELING REVIEW
Division of Metabolism and Endocrinology Products

Application Number: NDA 021536/S-051
Product Name: Levemir (insulin detemir [rDNA origin] injection), 100 Units/mL
Applicant: Novo Nordisk, Inc.

Background and Summary

On July 17, 2014, Safety Labeling Change (SLC) notification letters were issued for all diabetes products that have approved pen presentations (see list below). The SLC letters required the applicants of these products to add a warning against the sharing of pens between patients, due to the serious risk of transmission of blood borne pathogens (see DMEPA review in DARRTS dated August 22, 2013). The warning was required to be added to all the labeling pertaining to the pens for these products, including the content of labeling and the carton and container labels. The applicants were also required to propose a plan for adding the warning to the body of the pen.

The applicants submitted supplements in response to this SLC notification on August 15, 2014, and included all the required labeling with the pen-sharing warning. They also provided a rationale for why they believe that adding the warning statement to the body of the pen is not necessary or warranted. DMEPA reviewed this rationale and found it acceptable that the warning not be placed on the body of the pen at this time (see DMEPA review in DARRTS dated October 7, 2014).

DMEPA also reviewed the carton and container labels submitted with these supplements, and asked the applicants to revise the labels (DMEPA review in DARRTS dated October 7, 2014). They reviewed the revised labels and found them acceptable and ready for approval (DMEPA review in DARRTS dated January 12, 2015). CMC was also informed about the changes being requested to the carton and container labels. Dr. Su Tran confirmed in an email dated August 21, 2014 (checked into DARRTS on February 17, 2015) that since these labeling changes do not affect the approved technical CMC information, no CMC review is necessary, and that CMC will defer to DMEPA's evaluation of the new safety language.

DMEP reviewed the package inserts submitted for these supplements, and asked the applicants to make revisions. The revised labels were found acceptable.

DMPP and DMEP reviewed the patient labeling submitted for these supplements, and asked the applicants to make revisions (DMPP review in DARRTS dated November 13, 2014). A second round of revisions was requested for some products. The revised labels were found acceptable.

The following is the list of supplements that were submitted in response to the SLC notification:

sanofi-aventis U.S. LLC

- NDA 021081/S-062 Lantus (insulin glargine [rDNA origin]), injection, 100 Units/mL
- NDA 021629/S-030 Apidra (insulin glulisine [rDNA origin] injection), 100 Units/mL

AstraZeneca AB

- NDA 021332/S-023 Symlin (pramlintide acetate) injection, 600 mcg/ml and 1000 mcg/ml
- NDA 021773/S-040 Byetta (exenatide) injection

Novo Nordisk, Inc.

- NDA 019959/S-075 Novolin N (NPH, human insulin isophane suspension [rDNA origin]), injection, 100 Units/mL
- NDA 020986/S-081 NovoLog (insulin aspart [rDNA origin] injection), 100 Units/ml
- NDA 021172/S-063 NovoLog Mix 70/30 (70% insulin aspart protamine suspension and 30% insulin aspart [rDNA origin] injection), 100 Units/ml
- NDA 021810/S-010 NovoLog Mix 50/50 (50% insulin aspart protamine suspension and 50% insulin aspart [rDNA origin] injection), 100 Units/mL
- NDA 021536/S-051 Levemir (insulin detemir [rDNA origin] injection), 100 Units/mL
- NDA 022341/S-022 Victoza (liraglutide [rDNA origin]) injection

Eli Lilly and Company

- NDA 018780/S-150 Humulin R (insulin human injection, USP [rDNA origin])
- NDA 018781/S-154 Humulin N NPH (human insulin isophane suspension [rNDA origin])
- NDA 019717/S-133 Humulin 70/30 (70% human insulin isophane suspension/30% insulin human injection, rDNA origin)
- NDA 020563/S-157 Humalog (insulin lispro [rDNA origin] injection), 100 Units/mL
- NDA 021017/S-108 Humalog Mix 75/25 (75% insulin lispro protamine suspension /25% insulin lispro [rDNA origin] injection), 100 Units/mL
- NDA 021018/S-100 Humalog Mix 50/50 (50% insulin lispro protamine suspension /50% insulin lispro [rDNA origin] injection), 100 Units/mL

In addition to the supplements listed above, the following three CBE-0 supplements were submitted by Novo Nordisk in 2009, also proposing to add a warning against the sharing of pens to the package insert, the pen Instructions for Use and the associated pen carton and container labels:

- NDA 020986/S-059 NovoLog (insulin aspart [rDNA origin] injection), 100 Units/ml: submitted and received October 16, 2009
- NDA 021172/S-046 NovoLog Mix 70/30 (70% insulin aspart protamine suspension and 30% insulin aspart [rDNA origin] injection), 100 Units/ml: submitted and received July 17, 2009
- NDA 021536/S-031 Levemir (insulin detemir [rDNA origin] injection), 100 Units/mL: submitted and received July 17, 2009

The agreed-upon labeling for the SLC supplements for NovoLog (S-081), NovoLog Mix 70-30 (S-063) and Levemir (S-051) was also submitted (on February 20, 2015) to the older 2009 supplements for NovoLog (S-059), NovoLog Mix 70-30 (S-046) and Levemir (S-031), such that action can be taken concurrently on both sets of supplements for these three products.

This labeling review is for NDA 021536/S-051 for Levemir (insulin detemir [rDNA origin] injection), 100 Units/mL. Levemir (approved June 16, 2005) is a long-acting human insulin analog indicated to improve glycemic control in adults and children with diabetes mellitus.

Materials Reviewed:

Labeling Reviewed	**Submission Date**	**Currently approved (date and supplement)**
Package Insert	12/22/14	10/31/13 (S-033)
Patient Package Insert	2/3/15	10/31/13 (S-033)
IFU- Levemir FlexTouch Pen	2/3/15	1/23/15 (S-050)

Review

Each piece of proposed labeling was compared to the currently approved version, using either the Microsoft Word or the Adobe Acrobat electronic comparison functions. The comparison documents are attached below.

Recommendations

The labeling was reviewed and found acceptable by Clinical (Dr. Jennifer Pippins), DMPP (Robin Duer, Shawna Hutchins and Aman Sarai) and DMEPA (Sarah Vee and Yelena Maslov). This supplement is ready for approval.

Kati Johnson	2/19/2015
Regulatory Project Manager	Date
Mehreen Hai	2/20/15
Safety Regulatory Project Manager	Date

Drafted: Mehreen Hai/2.10.15
Reviewed: Julie Van der Waag/2.10.15
Completed: Kati Johnson/2.19.15
Finalized: Mehreen Hai/2.20.15

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/s/

MEHREEN HAI
02/25/2015

MEDICAL OFFICER REVIEW

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

APPLICATION #:	**21-536**	**APPLICATION TYPE:**	**sNDA……**
SPONSOR:	**Novo Nordisk**	**PROPRIETARY NAME:**	**Levemir…….**
CATEGORY OF DRUG:	**Antidiabetic**	**USAN / Established Name:**	**insulin detemir …**
		ROUTE:	**Injection……..**
MEDICAL REVIEWER:	**Robert I Misbin..**	**REVIEW DATE:**	**January 12, 2010……..**

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
July 17, 2009			
Labeling change to prevent needle sharing			

Signed: **Medical Reviewer: Robert I Misbin MD** **Date: January 12, 2010**

Medical Team Leader: _____ **Date: _____**

On July 17, 2009, Novo Nordisk submitted a Changes Being Effected Supplement for NDA 21-536 as summarized below.

Change:

- Revision of the FlexPen trade and sample cartons, instructions for use section of the patient package insert, and physician insert to include warning against the sharing of insulin pens

Location in label	Changes made in this submission
FlexPen sample and trade cartons *Front panel:* For use with NovoFine® disposable needles or other products specifically recommended by Novo Nordisk.	*Changed to:* (b) (4) (b) (4). *Added:* Single patient use only

Location in label	Changes made in this submission
FlexPen Instructions for Use *Warning bullet*: Use (Trade name) FlexPen as directed to treat your diabetes. Do not share it with anyone else even if they also have diabetes.	*Changed to*: (b) (4)
FlexPen Physician Insert *In Warnings section in Levemir*	*Added:* (b) (4)

The purpose of this labeling change was to prevent spread of infectious disease through shared use of equipment used for injecting insulin.

Recommendation:

1 The "How supplied" section of the label should contain the statement:

A Levemir pen should never be shared between patients, even if the needle is changed.

2 Under "Patients counseling" should be stated:

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

3 The Instruction for Use Section should state:

Never share a Levemir pen with another person, even if the needle is changed. Sharing of the pen between patients may pose a risk of transmission of infection.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21536	SUPPL-31	NOVO NORDISK INC	LEVEMIR

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/s/

ROBERT I MISBIN
01/12/2010

ILAN IRONY
01/12/2010

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:	November 12, 2009
To:	Mary Parks, MD, Director Division of Metabolism and Endocrinology Products
Thru:	Carlos M. Mena-Grillasca, R.Ph., Team Leader Denise Toyer, PharmD, Deputy Director Division of Medication Error Prevention and Analysis (DMEPA)
From:	Walter Fava, R.Ph., Safety Evaluator Division of Medication Error Prevention and Analysis (DMEPA)
Subject:	Label and Labeling Review
Drug Name(s):	Novolog Mix 70/30 (70% insulin aspart protamine suspension and 30% insulin aspart [rDNA origin]) Injection 100 units/mL (U-100) 3 mL Prefilled pen Levemir (insulin detemir [rDNA origin]) Injection 100 units/mL (U-100) 3 mL Prefilled Pen
Application Type/Number:	NDA 021172/S-046 NDA 021536/S-029
Applicant/Applicant:	Novo Nordisk Inc.
OSE RCM #:	2009-1532

CONTENTS

1 INTRODUCTION

This review is written in response to a request from the Division of Metabolism and Endocrinology Products to evaluate the revised text in the labels and labeling for Novolog Mix 70/30 FlexPen and Levemir FlexPen instructing patients not to share needles or pens. Considering that his issue is well known to FDA and that this supplement is solely focused on addressing this issue we did not conduct an AERS search. In addition, the known causes have been established and documented in the literature.[1,2]

2 MATERIALS REVIEWED

The Division of Medication Error Prevention and Analysis (DMEPA) used Failure Mode and Effects Analysis (FMEA)[3] in our evaluation of the labels and labeling submitted for review. We reviewed the labels and labeling submitted by the Applicant on July 17, 2009 and August 20, 2009 along with the currently approved labels and labeling submitted by the Applicant for Novolog Mix 70/30 FlexPen (10/14/08) and Levemir FlexPen (8/14/09) (see Appendices A through D for images):

- **Novolog Mix 70/30**
    - Retail and physician sample carton labeling
    - Prescribing information (no image)
    - Patient instructions for use (no image)
    - Patient information (no image)
- **Levemir**
    - Retail and physician sample carton labeling
    - Prescribing information (no image)
    - Patient instructions for use (no image)
    - Patient information (no image)

3 RECOMMENDATIONS

Our evaluation of the proposed labels and labeling noted areas of needed improvement in order to minimize the potential for medication errors. Section 3.1 *Comments to the Applicant* contains our recommendations for the container label and carton labeling. We request the recommendations in Section 3.1 be communicated to the Applicant prior to approval.

3.1 COMMENTS TO THE APPLICANT

A. Novolog Mix 70/30 FlexPen Container Labels (Retail and physician sample)

If space permits, include the statement 'Single Patient Use Only', to minimize the risk of patients sharing the FlexPen after they have removed the pen from the carton.

---

[1] ISMP Medication Safety Alert! Acute Care, Institute for Safe Medication Practices (ISMP). February 12, 2009, Vol. 14, Issue 3.

[2] Risk of Transmission of Blood-borne Pathogens from Shared Use of Insulin Pens, Information for Healthcare Professionals, FDA Alert, March 19, 2009
<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm133352.htm>

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

B. Novolog Mix 70/30 FlexPen Carton Labels (Retail and physician sample)

Revise the statement on the side panel, [redacted] (b) (4)' to read, 'Single patient use only' to be consistent with the presentation on the principle display panel.

C. Levemir FlexPen Container Label (Retail and physician sample)

If space permits, include the statement 'Single Patient Use Only', to minimize the risk of patients sharing the FlexPen after they have removed the pen from the carton.

D. Levemir Carton Labeling (Retail and Physician Sample)

Revise the statement on the side panel, [redacted] (b) (4) to read, 'Single patient use only' to be consistent with the presentation on the principle display panel.

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21172	SUPPL-46	NOVO NORDISK INC	NOVOLOG MIX 70/30
NDA-21536	SUPPL-31	NOVO NORDISK INC	LEVEMIR

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/s/

CARLOS M MENA-GRILLASCA
11/12/2009

DENISE P TOYER
11/17/2009

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:	September 11, 2009
To:	Mary Parks, M.D., Director **Division of Metabolic and Endocrinology Products (DMEP)**
Through:	Claudia Karwoski, Pharm.D., Director **Division of Risk Management (DRISK)** LaShawn Griffiths, MSHS-PH, BSN, RN Acting Team Leader **Division of Risk Management**
From:	Robin Duer, MBA, BSN, RN Patient Product Information Reviewer **Division of Risk Management**
Subject:	DRISK Review of Patient Labeling, Patient Instructions for Use
Drug Names:	Novolog Mix 70/30 (70% insulin aspart protamine suspension and 30% insulin aspart injection [rDNA origin]) Levemir (insulin detemir [rDNA origin]) injection)
Application Type/Numbers:	NDA 021172/S-046 NDA 021536/S-031
Applicant/sponsor:	Novo Nordisk, Inc.
OSE RCM #:	2009-1532

On July 17, 2009 the Agency received a Changes Being Effected (CBE-0) labeling supplement from the Applicant which provided for labeling changes to the carton labeling, Package Insert (PI) and Patient Instructions for Use (IFU) for the Novolog Mix and Levemir FlexPen products. The proposed labeling included the addition of a warning against sharing insulin pens. On August 24, 2009 the Division of Metabolic and Endocrinology Products (DMEP) requested that the Division of Risk Management review the proposed labeling change submitted for the IFU.

In our review of the IFU we

- simplified the wording
- ensured that the PI is consistent with the IFU for this change

We have reviewed this proposed labeling change to the IFU and recommend the following patient-friendly language.

Applicant's proposed language:

(b) (4)

Our revised patient-friendly language:

(b) (4)

We note that the Applicant has proposed that this warning be added to the Warnings section of the PI, but not to the Precautions section, Information for Patients subsection of the PI. This warning should be added to both the "Warnings and Precautions" section of the PI.

Please let us know if you have any questions.

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/s/

ROBIN E DUER
09/11/2009

CLAUDIA B KARWOSKI
09/11/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:	FROM:
Mail: OSE	Rachel Hartford, DMEP, x60331

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
24Aug09		21-172/S046 21-536/S031	CBE-0 Supplements	20Aug2009

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Novolog Mix 70/30 (21-172) Levemir (21-536)		Insulin	21Sep2009

NAME OF FIRM: Novo Nordisk

REASON FOR REQUEST

I. GENERAL

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

II. BIOMETRICS

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

III. BIOPHARMACEUTICS

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

IV. DRUG EXPERIENCE

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

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Added warning against the sharing of insulin pens to the FlexPen cartons (sample and trade). Please review the new warning in the PI , PPI., and cartons. The initial submission contained picture in pdf of the printed PI and PPI ; requested pdf documents for each. They were submitted on 20Aug09.

20Aug09 submission Links:
nda021536 EDR Location: \\CDSESUB1\EVSPROD\NDA021536\021536.enx
nda021172 EDR Location: \\CDSESUB1\EVSPROD\NDA021172\021172.enx

Initial submission links:
nda021172 EDR Location: \\CDSESUB1\EVSPROD\NDA021172\021172.enx
nda021536 EDR Location: \\CDSESUB1\EVSPROD\NDA021536\021536.enx

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Rachel Hartford	☒ e-MAIL /DARRTS ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 21172	SUPPL 46	NOVO NORDISK INC	NOVOLOG MIX 70/30
NDA 21172	SUPPL 46	NOVO NORDISK INC	NOVOLOG MIX 70/30
NDA 21536	SUPPL 31	NOVO NORDISK INC	LEVEMIR
NDA 21536	SUPPL 31	NOVO NORDISK INC	LEVEMIR

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/s/

RACHEL E HARTFORD
08/24/2009

MEDICAL OFFICER REVIEW

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

APPLICATION #:	**21-536**	**APPLICATION TYPE:**	**New NDA……**
SPONSOR:	**Novo Nordisk**	**PROPRIETARY NAME:**	**Levemir……..**
CATEGORY OF DRUG:	**Antidiabetic**	**USAN / Established Name:**	**Insulin Detemir……..**
		ROUTE:	**Injection……..**
MEDICAL REVIEWER:	**Robert I Misbin..**	**REVIEW DATE:**	**July 22, 2009……..**

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
July 17, 2009			

CBE supplement to prevent needle sharing.

Signed: **Medical Reviewer: Robert I Misbin MD** **Date: July 22, 2009**

Medical Team Leader: _____ **Date: _____**

On July 17, 2009, in accordance with 21 CFR 314.70(c)(6)(iii), Novo Nordisk submitted a Changes Being Effected Supplement for NDA 21-536 as summarized below.

Location in label	Changes made in this submission
FlexPen sample and trade cartons *Front panel:* For use with NovoFine® disposable needles or other products specifically recommended by Novo Nordisk.	*Changed to:* (b) (4) (b) (4). *Added:* Single patient use only

Location in label Changes made in this submission

FlexPen Instructions for Use *Warning bullet*: Use (Trade name) FlexPen as directed to treat your diabetes. Do not share it with anyone else even if they also have diabetes.	*Changed to*: (b) (4)
FlexPen Physician Insert *In Warnings section in Levemir and NovoLog Mix 70/30*	*Added:* (b) (4) .

Recommendation: This change in labeling will help prevent needle sharing and should be approved.

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/s/

Robert Misbin
7/22/2009 10:12:50 AM
MEDICAL OFFICER

Hylton Joffe
7/22/2009 10:19:22 AM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021536Orig1s031

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

From: Hai, Mehreen
To: "LIZD (Liz D"Amato)"; LOKO (Lois Kotkoskie)
Subject: Pending supplements for sharing of pens
Date: Thursday, December 06, 2012 3:49:00 PM

Hi Liz and Lois,

This is in reference to the pending supplements below, that provide for the warning against sharing of insulin pens

NovoLog 70/30 (NDA 021172/S-046)
Levemir (NDA 021536/S-031)
Novolog (NDA 20986/S-059)

We have the following recommendations for language for the different labeling pieces. It is acceptable to delete 'pen' if the combo device has the word in it's title (FlexPen).

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Package Insert

Instead of the language proposed under the Warning and Precautions section, please insert the following:

(b) (4) Never Share a [DRUG NAME] Pen Between Patients
(b) (4) patients that they (b) (4) never share a [DRUG NAME] pen with another person, even if the needle is changed. (b) (4)

==========

Patient Package Insert

Please add the following under “How should I take NovoLog”, after the “Change (rotate) your injection site” bullet.

Never share your [DRUG NAME] pen with (b) (4). You may give (b) (4) or get (b) (4) from them (b) (4)

==========

Instructions for Use (b) (4).

Do not share your [DRUG NAME] pen (b) (4) with (b) (4) You may give (b) (4) or get (b) (4) from them.

==========

Carton and Container labels

Container Labels (Retail and physician sample):
If space permits, include the statement ‘Single Patient Use Only’, to minimize the risk of patients sharing the FlexPen after they have removed the pen from the carton.

Carton Labels (Retail and physician sample):
Revise the statement on the side panel, (b) (4)’ to read, ‘Single patient use only’ to be

consistent with the presentation on the principle display panel.

==========

Please make the suggested changes and resubmit to the referenced supplements, and please let me know if you have any questions.
Thank you,

Mehreen Hai, Ph.D.
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
mehreen.hai@fda.hhs.gov
Ph: 301-796-5073
Fax: 301-796-9712

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/s/

MEHREEN HAI
12/06/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21-172/S-046
NDA 21-536/S-031

CBE-0 SUPPLEMENTS

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

Dear Dr. McElligott:

We have received your supplemental drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

NDA / Supplement #	Name of Drug Product	Dated and Received
21-172/S-046	NovoLog Mix 70/30 (70% insulin aspart protamine suspension and 30% insulin aspart [rDNA origin]) injection	July 17, 2009
21-536/S-031	Levemir (insulin detemir [rDNA origin] injection)	July 17, 2009

These supplemental applications, submitted as "Supplement - Changes Being Effected" propose the following to strengthen the warning against the sharing of insulin pens:

1) Addition of "…FlexPen must (b) (4) be shared" to the package inserts
2) Changing the FlexPen instructions for use leaflets from "Do not share …" to "… (b) (4) (b) (4) ."
3) Addition of "single patient use only" to the Flex Pen carton labeling

Unless we notify you within 60 days of the receipt date that the applications are not sufficiently complete to permit a substantive review, we will file the applications on **September 15, 2009** in accordance with 21 CFR 314.101(a). If the applications are filed, the user fee goal date will be **January 17, 2010**.

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have 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
08/24/2009