Indications and Usage
• Levemir® (insulin detemir [rDNA origin] injection) 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.

Important Safety Information
Contraindications
• Levemir® is contraindicated in patients with hypersensitivity to Levemir® or any of its excipients.

Warnings and Precautions
• Dosage adjustment and monitoring: Monitor blood glucose in all patients treated with insulin. Insulin regimens should be modified 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.
Levemir® FlexTouch® FAQ for Health Care Professionals (HCPs), Payers, and Institutions

About Levemir® FlexTouch®

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>What is Levemir® FlexTouch®?</td>
<td>Levemir® FlexTouch® is the latest advancement in prefilled insulin devices from Novo Nordisk. It is a prefilled insulin pen. Levemir® FlexTouch® has been designed with no push-button extension and features an end-of-dose click.</td>
</tr>
<tr>
<td>Why is Novo Nordisk introducing Levemir® FlexTouch®?</td>
<td>Novo Nordisk is committed to continuously improving the lives of people living with diabetes. Over the years, we have received input from patients, caregivers, and HCPs that has given us direction about where we need improvement. Levemir® FlexTouch® is a result of this feedback, along with dedicated research and development.</td>
</tr>
<tr>
<td>What about FlexPen®?</td>
<td>FlexPen® will continue to be available for NovoLog® and NovoLog® Mix 70/30. FlexPen® will be available for Levemir® for a limited time and is expected to be discontinued by the end of October 2014. FlexPen® may still be in stock at some pharmacies until it expires.</td>
</tr>
<tr>
<td>Will FlexTouch® be available for other Novo Nordisk diabetes products?</td>
<td>At this time, FlexTouch® will only be available for Levemir®. FlexTouch® may be available for other Novo Nordisk products in the future.</td>
</tr>
</tbody>
</table>

*Patient may or may not hear an audible click at end of dose. Dose is delivered when dial resets to 0 and the needle is held in the skin for 6 seconds. If the needle is removed earlier, patients may see a stream of insulin coming from the needle. If so, this may result in a possible underdosage by as much as 20%, and the patient should be instructed to increase the frequency of checking their blood glucose levels with possible additional insulin administration. Please see Instructions for Use (IFU) for complete instructions.

Important Safety Information (cont’d)

**Warnings and Precautions (cont’d)**

- **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. **Needles, insulin pens, or syringes should never be shared.**
- **Hypoglycemia:** Hypoglycemia is the most common adverse reaction of insulin therapy and may be life-threatening. 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.
- **Hypersensitivity and allergic reactions:** Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products, including Levemir®.
- **Renal and hepatic impairment:** Careful glucose monitoring and dose adjustments of insulin, including Levemir®, may be necessary in patients with renal or hepatic impairment.
Levemir® FlexTouch® Features

| What are the minimum and maximum doses that can be injected with Levemir® FlexTouch®? | 1 unit is the minimum dose that can be injected with Levemir® FlexTouch®. The first mark on the dose display is 1 unit (despite the line marker looking closer to 0)¹  
80 units is the maximum dose that can be injected with Levemir® FlexTouch®¹ |
| --- | --- |
| How does the new spring-loaded mechanism work? | When a user pushes the dose button, the force in the spring is released. Patient may or may not hear an audible click at end of dose. Dose is delivered when dial resets to 0 and the needle is held in the skin for 6 seconds. If the needle is removed earlier, patients may see a stream of insulin coming from the needle. If so, this may result in a possible underdosage by as much as 20%, and the patient should be instructed to increase the frequency of checking their blood glucose levels with possible additional insulin administration. Please see IFU for complete instructions¹  
Because of the spring-loaded mechanism used for dose delivery, low injection force is required to deliver insulin regardless of dose²  
The user is able to stop the injection at any time throughout dose delivery by lifting his or her finger/thumb from the button. Levemir® FlexTouch® is not an automatic insulin pen |
| What are the benefits of low injection force? Is it quantifiable? | Our research has shown that the Levemir® FlexTouch® features, including low injection force, are important to HCPs and patients. Technical tests show the injection force for Levemir® FlexTouch® is low at all doses due to the spring-loaded mechanism² |
| What needles can be used with Levemir® FlexTouch®? | All universal needles can be used with Levemir® FlexTouch®. The IFU recommends Novo Nordisk needles, such as NovoTwist® and NovoFine®, including NovoFine® Autocover®. Always use a new needle for each injection to help ensure sterility and prevent blocked needles¹ |
| Why does the Levemir® IFU include the buttocks as an injection site and the Prescribing Information (PI) does not? | The language in the IFU is consistent with the NovoLog® and NovoLog® Mix 70/30 IFU, where the buttocks are a possible injection site. The Levemir® PI does not currently include the buttocks as an injection site; therefore, patients should be instructed to inject Levemir® in the deltoid, thigh, or abdomen¹ |

Important Safety Information (cont’d)

**Warnings and Precautions (cont’d)**

- **Drug interactions:** Some medications may alter insulin requirements and subsequently increase the risk for hypoglycemia or hyperglycemia.

- **Fluid retention and heart failure with concomitant use of PPAR-gamma agonists:** Fluid retention and heart failure can occur with concomitant use of thiazolidinediones (TZDs), which are PPAR-gamma agonists, and insulin, including Levemir®. Patients should be observed for signs and symptoms of heart failure. If heart failure occurs, dosage reduction or discontinuation of the TZD must be considered.
Prescribing, Sampling, and Availability

How do I ensure Levemir® FlexTouch® appears in electronic health records (EHR) or ePrescribing (eRx) systems?

• **STEP 1:** Ensure you have the latest data—download the latest update from your EHR/eRx provider.
• **STEP 2:** If Levemir® FlexTouch® still is not listed, manually enter “Levemir® FlexTouch®” and please contact your local IT department and/or EHR/eRx system provider for instructions.
• **STEP 3:** Please alert your Novo Nordisk representative of the issue.

What is the NDC number?

NDC—Novo Nordisk Product
Basal Insulin Analog
00169-6438-10 Levemir® FlexTouch® 5 x 3 mL

Resources

What patient resources, including co-pay cards, will be available for Levemir® FlexTouch®?

• Novo Nordisk offers comprehensive patient resources through Cornerstones4Care®. Currently available PAL kits will work for Levemir® FlexTouch®. These kits contain co-pay cards that enable eligible patients to pay no more than $25 for the first prescription of a Novo Nordisk product and each refill for up to 2 years, and $20 for the second prescription of another Novo Nordisk medication and each refill for up to 2 years.

Cost and Coverage

Are patients going to pay more for Levemir® FlexTouch®? What is the co-pay?

• Levemir® FlexTouch® is a premium offering for patients at no additional cost—it will have the same coverage and co-pay as Levemir® FlexPen®.

References:

Important Safety Information (cont’d)

Adverse Reactions
• Adverse reactions associated with Levemir® include hypoglycemia, allergic reactions, injection site reactions, lipodystrophy, rash, pruritus, and if taken with a GLP-1 receptor agonist, diarrhea.

Use in Specific Populations
• Levemir® has not been studied in children with type 2 diabetes or in children with type 1 diabetes who are younger than 2 years of age.
• The background risk of birth defects, pregnancy loss, or other adverse events that exists for all pregnancies is increased in pregnancies complicated by hyperglycemia.
Indications and Usage
• Levemir® (insulin detemir [rDNA origin] injection) 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.

Important Safety Information
Contraindications
• Levemir® is contraindicated in patients with hypersensitivity to Levemir® or any of its excipients.

Warnings and Precautions
• Dosage adjustment and monitoring: Monitor blood glucose in all patients treated with insulin. Insulin regimens should be modified 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.
• 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. Needles, insulin pens, or syringes should never be shared.
• Hypoglycemia: Hypoglycemia is the most common adverse reaction of insulin therapy and may be life-threatening. 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.
• Hypersensitivity and allergic reactions: Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products, including Levemir®.
• Renal and hepatic impairment: Careful glucose monitoring and dose adjustments of insulin, including Levemir®, may be necessary in patients with renal or hepatic impairment.
• Drug interactions: Some medications may alter insulin requirements and subsequently increase the risk for hypoglycemia or hyperglycemia.
• Fluid retention and heart failure with concomitant use of PPAR-gamma agonists: Fluid retention and heart failure can occur with concomitant use of thiazolidinediones (TZDs), which are PPAR-gamma agonists, and insulin, including Levemir®. Patients should be observed for signs and symptoms of heart failure. If heart failure occurs, dosage reduction or discontinuation of the TZD must be considered.

Adverse Reactions
• Adverse reactions associated with Levemir® include hypoglycemia, allergic reactions, injection site reactions, lipodystrophy, rash, pruritus, and if taken with a GLP-1 receptor agonist, diarrhea.

Use in Specific Populations
• Levemir® has not been studied in children with type 2 diabetes or in children with type 1 diabetes who are younger than 2 years of age.
• The background risk of birth defects, pregnancy loss, or other adverse events that exists for all pregnancies is increased in pregnancies complicated by hyperglycemia.

Please see Important Safety Information throughout.
Please see accompanying Prescribing Information.
Needles are sold separately and may require a prescription in some states.
LEVEMIR® (insulin detemir [rDNA origin] injection)
solution for subcutaneous injection

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

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

--- WARNINGS AND PRECAUTIONS ---
Dose adjustment and monitoring: Monitor blood glucose in all patients treated with insulin. Insulin regimens should be modified cautiously and only under medical supervision (5.1)

Administration: Do not dilute or mix with any other insulin or solution. Do not administer subcutaneously via an insulin pump, intramuscularly, or intravenously because severe hypoglycemia can occur (5.2)

Hypoglycemia is the most common adverse reaction of insulin therapy and may be life-threatening (5.3, 6.1)

Hypersensitivity and Allergic Reactions: Severe, life-threatening, generalized allergy, including anaphylaxis, can occur (5.4)

Renal or hepatic impairment: May require adjustment of the LEVEMIR® dose (5.5, 5.6)

Fluid retention and heart failure can occur with concomitant use of thiazolidinediones (TZDs), which are PPAR-gamma agonists, and insulin, including LEVEMIR® (5.8)

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

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

--- DRUG INTERACTIONS ---
Certain drugs may affect glucose metabolism requiring insulin dose adjustment and close monitoring of blood glucose (7)

The signs of hypoglycemia may be reduced or absent in patients taking anti-adrenergic drugs (e.g., beta-blockers, clonidine, guanethidine, and reserpine) (7)

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

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

Revised: 10/2013
LEVEMIR® (insulin detemir [rDNA origin]) injection

5.2 Administration
LEVEMIR® should only be administered subcutaneously.
Do not administer LEVEMIR® intravenously or intramuscularly. The intended duration of activity of LEVEMIR® is dependent on injection into subcutaneous tissue. Intravenous or intramuscular administration of the same subcutaneous dose could result in severe hypoglycemia (see Warnings and Precautions (5.3)).
Do not use LEVEMIR® in insulin infusion pumps.
Do not dilute or mix LEVEMIR® with any other insulin or solution. If LEVEMIR® is diluted or mixed, the pharmacokinetic or pharmacodynamic profile (e.g., onset of action, time to peak effect) of LEVEMIR® and the mixed insulin may be altered in an unpredictable manner.

5.3 Hypoglycemia
Hypoglycemia is the most common adverse reaction of insulin therapy, including LEVEMIR®. The risk of hypoglycemia increases with intensive glycemic control.
When a GLP-1 receptor agonist is used in combination with LEVEMIR®, the LEVEMIR® dose may need to be lowered or more conservatively titrated to minimize the risk of hypoglycemia (see Adverse Reactions (6.1)).
All patients must be educated to recognize and manage hypoglycemia. Severe hypoglycemia can lead to unconsciousness or convulsions and may be preceded by symptoms resembling auras or a premonition of impending death. Severe hypoglycemia requiring the assistance of another person or parental glucagon 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 the timing of food intake (e.g., amount of food or timing of meals), exercise, and concurrent 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 eratic 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, diabetetic neuropathy, use of medications such as beta-blockers, or intensified treatment. In patients with renal or hepatic impairment, use caution in the administration of LEVEMIR®.

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

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

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

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

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

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

6.1 Clinical trial experience
Because clinical trials are conducted under widely varying designs, the adverse reaction rates reported in one clinical trial may not be easily compared to 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 adequate 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 26-week period, diabetes was the only adverse reaction reported in 25% 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%)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>LEVEMIR®, %</th>
<th>NPH, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory tract infection</td>
<td>21.6</td>
<td>21.6</td>
</tr>
<tr>
<td>Headache</td>
<td>21.9</td>
<td>22.3</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>7.8</td>
<td>7.8</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>6.9</td>
<td>6.9</td>
</tr>
</tbody>
</table>

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® vs insulin aspart + insulin glargine in adult patients with type 1 diabetes (adverse reactions with incidence ≥ 5%)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>LEVEMIR®, %</th>
<th>Insulin Glargine, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory tract infection</td>
<td>21.6</td>
<td>21.6</td>
</tr>
<tr>
<td>Headache</td>
<td>21.9</td>
<td>22.3</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>7.8</td>
<td>7.8</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>6.9</td>
<td>6.9</td>
</tr>
</tbody>
</table>

In two pooled trials, a total of 869 adults with type 2 diabetes were exposed to individualized doses of LEVEMIR® (n=432) or insulin glargine (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%)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>LEVEMIR®, %</th>
<th>NPH, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory tract infection</td>
<td>21.6</td>
<td>21.6</td>
</tr>
<tr>
<td>Headache</td>
<td>21.9</td>
<td>22.3</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>7.8</td>
<td>7.8</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>6.9</td>
<td>6.9</td>
</tr>
</tbody>
</table>

A total of 347 children and adolescents (6–17 years) with type 1 diabetes were exposed to individualized doses of LEVEMIR® (n=522) or NPH (n=515). 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 open-label trial of children and adolescents with type 1 diabetes (adverse reactions with incidence ≥ 5%)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>LEVEMIR®, %</th>
<th>NPH, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory tract infection</td>
<td>21.6</td>
<td>21.6</td>
</tr>
<tr>
<td>Headache</td>
<td>21.9</td>
<td>22.3</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>7.8</td>
<td>7.8</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>6.9</td>
<td>6.9</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6.5</td>
<td>10.4</td>
</tr>
</tbody>
</table>
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 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

<table>
<thead>
<tr>
<th>Study</th>
<th>Type 1 Diabetes</th>
<th>Event/patient/year</th>
<th>Percent of patients (n/total N)</th>
<th>Event/patient/year</th>
<th>Percent of patients (n/total N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Adults</td>
<td>Twice-Daily LEVEMIR®</td>
<td>8.7 (242/296)</td>
<td>0.52</td>
<td>88.0 (242/276)</td>
</tr>
<tr>
<td></td>
<td>Adults</td>
<td>Once-Daily NPH</td>
<td>10.6 (14/132)</td>
<td>0.43</td>
<td>89.4 (118/132)</td>
</tr>
<tr>
<td>B</td>
<td>Adults</td>
<td>Twice-Daily LEVEMIR®</td>
<td>5.0 (4/80)</td>
<td>0.13</td>
<td>82.0 (132/165)</td>
</tr>
<tr>
<td></td>
<td>Adults</td>
<td>Once-Daily Giargini</td>
<td>10.1 (16/159)</td>
<td>0.31</td>
<td>77.4 (123/159)</td>
</tr>
<tr>
<td>C</td>
<td>Adults</td>
<td>Once-Daily NPH</td>
<td>7.5 (37/491)</td>
<td>0.35</td>
<td>88.4 (43/491)</td>
</tr>
<tr>
<td></td>
<td>Adults</td>
<td>Twice-Daily LEVEMIR®</td>
<td>10.2 (26/256)</td>
<td>0.32</td>
<td>87.5 (225/256)</td>
</tr>
<tr>
<td>D</td>
<td>Pediatric</td>
<td>Once- or Twice Daily LEVEMIR®</td>
<td>15.9 (73/472)</td>
<td>0.91</td>
<td>93.1 (216/232)</td>
</tr>
<tr>
<td></td>
<td>Pediatrics</td>
<td>Once- or Twice Daily LEVEMIR®</td>
<td>20.0 (23/115)</td>
<td>0.99</td>
<td>95.7 (110/115)</td>
</tr>
<tr>
<td>E</td>
<td>Pediatric</td>
<td>Once- or Twice Daily LEVEMIR®</td>
<td>17.7 (3/177)</td>
<td>0.02</td>
<td>94.9 (16/177)</td>
</tr>
<tr>
<td></td>
<td>Pediatrics</td>
<td>Once- or Twice Daily LEVEMIR®</td>
<td>7.1 (12/170)</td>
<td>0.06</td>
<td>97.6 (16/170)</td>
</tr>
</tbody>
</table>

Severe hypoglycemia

Percent of patients with at least 1 event (%/total N)

<table>
<thead>
<tr>
<th>Study E</th>
<th>Type 2 Diabetes</th>
<th>Event/patient/year</th>
<th>Percent of patients (n/total N)</th>
<th>Event/patient/year</th>
<th>Percent of patients (n/total N)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adults</td>
<td>Twice-Daily LEVEMIR®</td>
<td>0.4 (1/237)</td>
<td>0.01</td>
<td>0.0 (1/237)</td>
</tr>
<tr>
<td></td>
<td>Adults</td>
<td>Once-Daily NPH</td>
<td>2.5 (6/238)</td>
<td>0.08</td>
<td>2.5 (6/238)</td>
</tr>
<tr>
<td></td>
<td>Adults</td>
<td>Twice-Daily Liraglutide + Metformin</td>
<td>1.5 (9/195)</td>
<td>0.05</td>
<td>1.5 (9/195)</td>
</tr>
<tr>
<td></td>
<td>Adults</td>
<td>Once-Daily Liraglutide + Metformin</td>
<td>1.9 (15/158)</td>
<td>0.09</td>
<td>1.9 (15/158)</td>
</tr>
<tr>
<td></td>
<td>Adults</td>
<td>Once-Daily NPH</td>
<td>4.0 (8/199)</td>
<td>0.21</td>
<td>3.6 (7/199)</td>
</tr>
<tr>
<td></td>
<td>Adults</td>
<td>Once-Daily NPH</td>
<td>8.0 (15/188)</td>
<td>0.43</td>
<td>8.0 (15/188)</td>
</tr>
</tbody>
</table>

Non-severe hypoglycemia

Percent of patients (%/total N)

<table>
<thead>
<tr>
<th>Study E</th>
<th>Type 2 Diabetes</th>
<th>Event/patient/year</th>
<th>Percent of patients (n/total N)</th>
<th>Event/patient/year</th>
<th>Percent of patients (n/total N)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adults</td>
<td>Twice-Daily LEVEMIR®</td>
<td>40.5 (96/237)</td>
<td>3.5</td>
<td>40.5 (96/237)</td>
</tr>
<tr>
<td></td>
<td>Adults</td>
<td>Once-Daily NPH</td>
<td>64.3 (132/208)</td>
<td>6.9</td>
<td>64.3 (132/208)</td>
</tr>
<tr>
<td></td>
<td>Adults</td>
<td>Twice-Daily Liraglutide + Metformin</td>
<td>32.3 (65/202)</td>
<td>1.6</td>
<td>32.3 (65/202)</td>
</tr>
<tr>
<td></td>
<td>Adults</td>
<td>Once-Daily Liraglutide + Metformin</td>
<td>32.1 (64/201)</td>
<td>2.0</td>
<td>32.1 (64/201)</td>
</tr>
<tr>
<td></td>
<td>Adults</td>
<td>Once-Daily NPH</td>
<td>9.2 (15/163)</td>
<td>2.8</td>
<td>9.2 (15/163)</td>
</tr>
</tbody>
</table>

Table 6: Hypoglycemia in Patients with Type 2 Diabetes

*One subject is an outlier and was excluded due to 26 hypoglycemic episodes that the patient was able to self-treat. This patient had a history of frequent hypoglycemia prior to the study.
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 (abortion) 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%)

<table>
<thead>
<tr>
<th>LEVEMIR® %</th>
<th>NPH, %</th>
<th>n (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymmetry</td>
<td>13.2</td>
<td>10.2</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>11.8</td>
<td>5.1</td>
</tr>
<tr>
<td>Pre-eclampsia</td>
<td>10.5</td>
<td>7.0</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>9.5</td>
<td>5.7</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>8.5</td>
<td>5.1</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>5.9</td>
<td>3.8</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5.3</td>
<td>4.4</td>
</tr>
<tr>
<td>Abortion spontaneous</td>
<td>5.3</td>
<td>2.5</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>5.3</td>
<td>6.3</td>
</tr>
<tr>
<td>Orthopaedir pain</td>
<td>5.3</td>
<td>6.3</td>
</tr>
</tbody>
</table>

*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 reported in another clinical trial, and may not reflect the actual rates 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).

### Pharmacodynamic Parameters for LEVEMIR® and NPH

**AUCGIR**: Area Under Curve for Glucose Infusion Rate

**GIRmax** (mg/kg/min)

**NPH**: 0.3 Internationa l Units/kg

**LEVEMIR®**: 0.2 Units/kg

**LEVEMIR®**: 0.4 Units/kg

**Pharmacodynamic Parameters for LEVEMIR® and NPH**

**AUCGIR**: Area Under Curve for Glucose Infusion Rate

**GIRmax**: Maximum Glucose Infusion Rate

For doses in the interval of 0.2 to 0.4 Units/kg, insulin detemir exerts more than 60% of its maximum effect from 3 to 4 hours up to approximately 14 hours after dose administration.

Figure 2 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.

**Pharmacodynamic Parameters for LEVEMIR® and NPH**

**AUCGIR**: Area Under Curve for Glucose Infusion Rate

**GIRmax**: Maximum Glucose Infusion Rate

For doses in the interval of 0.2 to 0.4 Units/kg, insulin detemir exerts more than 60% 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.

### 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 throughout pregnancy at doses up to 300 mmol/kg/day (3 times a human dose of 0.5 Units/kg/day, based on plasma area under the curve (AUC)) ratios. Doses of 150 and 300 mmol/kg/day produced numbers of litters with visceral anomalies. Doses up to 900 mmol/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 gialbladder abnormalities such as small, bilobed, bifurcated, and missing gallbladders were observed at a dose of 0.65 ng/kg/day. Inhibits proteolysis, and enhances protein synthesis.

### 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 to a nursing women. 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 310 of 1032 patients (29.6%) 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 this 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 insulin hypoglycemia 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 prolonged fasting, 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 continuous glucagon infusion by hypoglycemia, continued observation and additional carbohydrate intake may be necessary to avoid recurrence of hypoglycemia (see Warnings and Precautions (5.3)).

### 11 DESCRIPTION

LEVEMIR® (insulin detemir [rDNA origin]) 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 B30 glycine 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 C267H402O76N64S6 and a molecular weight of 9016.9. 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 mg 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 the long terminal phase 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**

**Figure 3: Activity Profiles in Patients with Type 2 Diabetes in a 16-hour Glucose Clamp Study**
after subcutaneous administration to the thigh where AUC(0-8) was 30-40% lower and AUC(0-16) 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 1.0 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) vs. elderly (≥68 years) healthy subjects, the insulin detemir AUC was up to 35% higher in 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 racial groups.

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, and severe, and hemodialysis-dependent). In this study, there were no differences in the pharmacokinetics of LEVEMIR® between healthy subjects and those with renal impairment. However, some studies with human insulin have shown increased circulating levels of insulin in patients with renal impairment. Careful glucose monitoring and dose adjustments of insulin, including LEVEMIR®, may be necessary in patients with renal impairment (see Warnings and Precautions (5.5)).

Hepatic Impairment - A single subcutaneous dose of 0.2 Units/kg (1.2 nmol/kg) of LEVEMIR® was administered to healthy subjects and those with varying degrees of hepatic impairment (mild, moderate and severe). LEVEMIR® exposure as estimated by AUC decreased with increasing degrees of hepatic impairment with a corresponding increase in apparent clearance. However, some studies with human insulin have shown increased circulating levels of insulin in patients with liver impairment. Careful glucose monitoring and dose adjustments of insulin, including LEVEMIR®, may be necessary in patients with hepatic impairment (see Warnings and Precautions (5.5)).

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 test 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. AUC-0-8, AUC-0-16, and AUC-0-8/2 gave no adverse effect 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) 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 the pre-dinner 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 glycated hemoglobin (HbA1c) with LEVEMIR® was similar to that with NPH insulin or insulin glargine.

Table 9: Type 1 Diabetes Mellitus – Adult

<table>
<thead>
<tr>
<th>Study A</th>
<th>Study B</th>
<th>Study C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment duration</td>
<td>16 weeks</td>
<td>26 weeks</td>
</tr>
<tr>
<td>Treatment in combination with</td>
<td>Twice-daily LEVEMIR®</td>
<td>Twice-daily NPH</td>
</tr>
<tr>
<td>Number of subjects treated</td>
<td>276</td>
<td>133</td>
</tr>
<tr>
<td>Baseline HbA1c (%)</td>
<td>8.6</td>
<td>8.9</td>
</tr>
<tr>
<td>Adj. mean change from baseline</td>
<td>-0.8*</td>
<td>-0.5**</td>
</tr>
<tr>
<td>95% CI for Treatment difference</td>
<td>(0.3, 0.0)</td>
<td>(0.4, 0.0)</td>
</tr>
<tr>
<td>Baseline mean</td>
<td>209</td>
<td>213</td>
</tr>
<tr>
<td>Adj. mean change from baseline</td>
<td>-44*</td>
<td>-39**</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>74.6</td>
<td>77.5</td>
</tr>
<tr>
<td>Adj. mean change from baseline</td>
<td>0.2*</td>
<td>0.8*</td>
</tr>
<tr>
<td>95% CI for Treatment difference</td>
<td>(-0.3, 0.3)</td>
<td>(-0.3, 0.3)</td>
</tr>
</tbody>
</table>

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

Table 10: Type 1 Diabetes Mellitus – Pediatric

<table>
<thead>
<tr>
<th>Study D</th>
<th>Study E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment duration</td>
<td>26 weeks</td>
</tr>
<tr>
<td>Treatment in combination with</td>
<td>Once- or Twice Daily LEVEMIR®</td>
</tr>
<tr>
<td>Number of subjects treated</td>
<td>232</td>
</tr>
<tr>
<td>Baseline HbA1c (%)</td>
<td>8.8</td>
</tr>
<tr>
<td>Adj. mean change from baseline</td>
<td>-0.7**</td>
</tr>
<tr>
<td>LEVEMIR® – NPH 95% CI for Treatment difference</td>
<td>-0.1, -0.3</td>
</tr>
<tr>
<td>Baseline mean</td>
<td>48</td>
</tr>
<tr>
<td>Adj. mean change from baseline</td>
<td>9</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>46.3</td>
</tr>
<tr>
<td>Adj. mean change from baseline</td>
<td>1.6*</td>
</tr>
</tbody>
</table>

*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 metformin. All patients had two or more of the following oral antidiabetic medications: metformin, an insulin secretagogue, or a gluco- glucosidase inhibitor. All patients were insulin-naïve at the time of randomization, LEVEMIR® and NPH insulin similarly lowered HbA1c from baseline (Table 11). In a 22-week, open-label, randomized clinical study (Study F, n=120), patients 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 HbA1c or FPG, LEVEMIR® had efficacy similar to that of NPH insulin.

Table 11: Type 2 Diabetes Mellitus – Adult

<table>
<thead>
<tr>
<th>Study</th>
<th>Study F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment duration</td>
<td>24 weeks</td>
</tr>
<tr>
<td>Treatment in combination with</td>
<td>oral agents</td>
</tr>
<tr>
<td>Twice-daily LEVEMIR®</td>
<td>NPH</td>
</tr>
<tr>
<td>Number of subjects tested</td>
<td>239</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.6</td>
</tr>
<tr>
<td>Adj. mean change from baseline</td>
<td>-2.0</td>
</tr>
<tr>
<td>LEVEMIR® – NPH</td>
<td>95% CI for treatment difference</td>
</tr>
<tr>
<td>Basal insulin dose (units/day)</td>
<td></td>
</tr>
<tr>
<td>Baseline mean</td>
<td>17</td>
</tr>
<tr>
<td>Mean change from baseline</td>
<td>48</td>
</tr>
<tr>
<td>Total insulin dose* (units/day)</td>
<td>-</td>
</tr>
<tr>
<td>Basal insulin mean</td>
<td>-</td>
</tr>
<tr>
<td>Mean change from baseline</td>
<td>-</td>
</tr>
<tr>
<td>Baseline mean</td>
<td>48</td>
</tr>
<tr>
<td>Mean change from baseline</td>
<td>-</td>
</tr>
<tr>
<td>Fasting blood glucose (mg/dL)</td>
<td></td>
</tr>
<tr>
<td>Baseline mean</td>
<td>82.5</td>
</tr>
<tr>
<td>Adj. mean change from baseline</td>
<td>1.2</td>
</tr>
</tbody>
</table>

*Study E – Conducted in insulin-naïve patients
**Study F – Fasting blood glucose data not collected
***An CANCOVA model adjusted for baseline value, country and oral antidiabetic treatment category.

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

16 How Supplied/Storage and Handling

16.1 How Supplied

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

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

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

16.2 Storage:

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

Do not use LEVEMIR® if it has been frozen.

Unopened (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 LEVEMIR® can be kept refrigerated at room temperature, below 30°C (86°F) as long as it is kept as cool as possible and away from direct heat and light. Unrefrigerated LEVEMIR® should be discarded 42 days after it is first kept out of the refrigerator, even if the FlexPen®, FlexTouch®, or vial still contains insulin.

Vials:

After initial use, vials should be stored in a refrigerator, never in a freezer. If refrigeration is not possible, the in-use vial can be kept refrigerated 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® vials should be discarded 42 days after they are first kept out of the refrigerator.

The storage conditions are summarized in Table 13.

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

<table>
<thead>
<tr>
<th>Condition</th>
<th>Not in-use (unopened) Refrigerated</th>
<th>Not in-use (unopened) Room Temperature (below 30°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 mL LEVEMIR® FlexPen®</td>
<td>Until expiration date</td>
<td>42 days*</td>
</tr>
<tr>
<td>Room Temperature (below 30°C)</td>
<td>(Do not refrigerate)</td>
<td></td>
</tr>
<tr>
<td>3 mL LEVEMIR® FlexTouch®</td>
<td>Until expiration date</td>
<td>42 days*</td>
</tr>
<tr>
<td>Room Temperature (below 30°C)</td>
<td>(Do not refrigerate)</td>
<td></td>
</tr>
<tr>
<td>10 mL vial</td>
<td>Until expiration date</td>
<td>42 days*</td>
</tr>
<tr>
<td>Room Temperature (below 30°C)</td>
<td>(Do not refrigerate)</td>
<td></td>
</tr>
</tbody>
</table>

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

16.3 Preparation and handling

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

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

17 Patient Counseling Information

See FDA-Approved Patient Labeling (Patient Information and Instructions for Use).
17.2 Never Share a LEVEMIR® FlexPen® or LEVEMIR® FlexTouch® Between Patients

Counsel patients that they should never share a LEVEMIR® FlexPen® or LEVEMIR® FlexTouch® with another person, even if the needle is changed. Sharing of the FlexPen® or FlexTouch® between patients may pose a risk of transmission of infection.
**What is Levemir®?**
- Levemir® is a man-made insulin that is used to control high blood sugar in adults and children with diabetes mellitus.
- Levemir® is not meant for use to treat diabetic ketoacidosis.

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

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

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

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

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

**What are the possible side effects of Levemir®?**
Levemir® may cause serious side effects that can lead to death, including:
- Low blood sugar (hypoglycemia). Signs and symptoms that may indicate low blood sugar include:
  - dizziness or light-headedness
  - sweating
  - confusion
  - headache
  - blurred vision
  - slurred speech
  - shakiness
  - fast heart beat
- Your insulin dose may need to change because of:
  - change in level of physical activity or exercise
  - weight gain or loss
  - increased stress
  - illness
  - anxiety, irritability, or mood changes
  - hunger
  - change in diet
- Other common side effects of Levemir® may include:
  - Reactions at the injection site, itching, rash, serious allergic reactions (whole body reactions), skin thickening or pits at the injection site (lipodystrophy), weight gain, and swelling of your hands and feet.

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

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

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

**What are the ingredients in Levemir®?**
**Active Ingredient:** insulin detemir (rDNA origin)

**Inactive Ingredients:** zinc, m-cresol, glycerol, phenol, disodium phosphate dihydrate, sodium chloride and water for injection. Hydrochloric acid or sodium hydroxide may be added.

**Manufactured by:**
Novo Nordisk A/S
DK-2880 Bagsvaerd, Denmark
For more information, go to www.novonordisk-us.com or call 1-800-727-6500.

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

**Revised: 10/2013**

For more information go to www.levemirflextouch.com
How should I inject LEVEMIR® with a syringe?

1. Pinch your skin between two fingers, push the needle into the skinfold, using a dart-like motion and push the plunger to inject the insulin under your skin. The needle will be straight in.

2. Keep the needle under your skin for at least 6 seconds to make sure you have injected all the insulin. After you pull the needle from your skin you may see a drop of Levemir® at the needle tip. This is normal and has no effect on the dose you just received.

3. If blood appears after you pull the needle from your skin, press the injection site lightly with an alcohol swab. Do not rub the area.

4. After each injection, remove the needle without recapping and dispose of it in a puncture-resistant container. Used syringes, needles, and lancets should be placed in sharps containers (such as red biohazard containers), hard plastic containers (such as detergent bottles), or metal containers (such as an empty coffee can). Such containers should be sealed and disposed of properly.

How should I use the LEVEMIR® 10 mL vial?

1. Check to make sure that you have the correct type of insulin. This is especially important if you use different types of insulin.

2. Look at the vial and the insulin. The LEVEMIR® insulin should be clear and colorless. The tamper-resistant cap should be in place before the first use. If the cap has been removed before your first use of the vial, or if the insulin is cloudy or colored, do not use the insulin and return it to your pharmacy.

3. Wash your hands with soap and water.

4. If you are using a new vial, pull off the tamper-resistant cap.

5. Do not roll or shake the vial. Shaking the vial right before the dose is drawn into the syringe may cause bubbles or foam. This can cause you to draw up the wrong dose of insulin. The insulin should be used only if it is clear and colorless.

6. Pull back the plunger on your syringe until the black tip reaches the marking for the number of units you will inject.

7. Push the needle through the rubber stopper into the vial.

8. Push the plunger all the way in. This inserts air into the vial.

9. Turn the vial and syringe upside down and slowly pull the plunger back to a few units beyond the correct dose that you need.

10. If there are air bubbles, tap the syringe gently with your finger to raise the air bubbles to the top of the needle. Then slowly push the plunger to the correct unit marking for your dose.

11. Check to make sure you have the right dose of LEVEMIR® in the syringe.

12. Pull the syringe out of the vial.

13. Inject your LEVEMIR® right away as instructed by your healthcare provider.
Instructions For Use LEVEMIR® FlexPen®

Please carefully read the following instructions for use before using your LEVEMIR® FlexPen® and each time you get a refill. You should read the instructions in this manual even if you have used a LEVEMIR® FlexPen® before.

LEVEMIR® FlexPen® is a disposable dial-a-dose insulin pen. You can select doses from 1 to 60 units in increments of 1 unit. LEVEMIR® FlexPen® is designed to be used with NovoFine® needles.

LEVEMIR® FlexPen® should not be used by people who are blind or have severe eyesight problems without the help of a person who has good eyesight and who is trained to use the LEVEMIR® FlexPen® the right way.

Getting ready

Make sure you have the following items:

- LEVEMIR® FlexPen®
- NovoFine® disposable needles
- Alcohol swab

PREPARING YOUR LEVEMIR® FLEXPEN®

Wash your hands with soap and water. Before you start to prepare your injection, check the label to make sure that 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.

A. Pull off the pen cap (see diagram A).

Wipe the rubber stopper with an alcohol swab.

B. Attaching the needle

Remove the protective tab from a new disposable needle.

Attach the needle tightly onto your FlexPen®. It is important that the needle is put on straight (see diagram B).

Never place a disposable needle on your LEVEMIR® FlexPen® until you are ready to give your injection.

C. Pull off the big outer needle cap (see diagram C).

D. Pull off the inner needle cap and throw it away (see diagram D).

Always use a new needle for each injection to cut down the chance of infection and to prevent blocked needles.

E. Be careful not to bend or damage the needle before use.

F. To reduce the risk of needle sticks, never put the inner needle cap back on the needle.

Giving the airshot before each injection

Before each injection, small amounts of air may collect in the cartridge

Before each injection, small amounts of air may collect in the cartridge. Giving the airshot before each injection can help prevent leakage of insulin.

Inject the dose by pressing the push-button all the way in until the 0 lines up with the pointer (see diagram I). Be careful only to push the button after the needle is in the skin.

Turning the dose selector will not inject insulin.

J. Keep the needle in the skin for at least 6 seconds, and keep the push-button pressed all the way in until the needle has been pulled out from the skin (see diagram J). This will make sure that the full dose has been given.

You may see a drop of LEVEMIR® at the needle tip. This is normal and has no effect on the dose you just received. If blood appears after you take the needle out of your skin, press the injection site lightly with an alcohol swab. Do not rub the area.

After the injection

Carefully remove the needle from the pen after each injection.

This helps to prevent infection and leakage of insulin. You can carefully recap the needle with the bigger outer cap to help make it easier to remove the needle.

Do not recap the needle with the small inner cap. Recapping with this small part can increase your chances of having a needle stick injury.

Put the needle in a sharps container or some type of hard plastic or metal container with a screw top such as a detergent bottle or empty coffee can. These containers should be sealed and thrown away the right way. Check with your healthcare provider about the right way to throw away used syringes and needles. There may be local or state laws about how to throw away used needles and syringes. Do not throw away used needles and syringes in household trash or recycling bins.

K. Put the pen cap on the LEVEMIR® FlexPen® and store the LEVEMIR® FlexPen® without the needle attached (see diagram K).

The LEVEMIR® FlexPen® prevents the cartridge from being completely emptied. It can deliver 300 units then you should throw it away in a sharps container or some type of hard plastic or metal container with a screw top, such as a detergent bottle or empty coffee can.

FUNCTION CHECK

If your LEVEMIR® FlexPen® is not working the right way, follow the steps below:

- Attach a new NovoFine® needle.
- Remove the big outer needle cap and the inner needle cap.
- Do an airshot as described in “Giving the airshot before each injection” (see diagram E through G).
- Put the big outer needle cap onto the needle. Do not put on the inner needle cap.
- Turn the dose selector so the dose indicator window shows 20 units.
- Hold the LEVEMIR® FlexPen® so the needle is pointing down.
- Press the push-button all the way in.

The insulin should fill the lower part of the big outer needle cap to the marker (see diagram L). If LEVEMIR® FlexPen® has released too much or too little insulin, do the function check again. If the same problem happens again, do not use your LEVEMIR® FlexPen® and contact Novo Nordisk at 1-800-727-6500.

Maintenance

Your FlexPen® is designed to work accurately and safely. It must be handled with care. If you drop your FlexPen® it could get damaged. If you are concerned that your FlexPen® is damaged, use a new one. You can clean the outside of your FlexPen® by wiping it with a damp cloth. Do not soak or wash your FlexPen®. Sealing or washing the FlexPen® could damage it. Do not refill your FlexPen®.

Remove the needle from the LEVEMIR® FlexPen® after each injection. This helps to cut down your chance of infection, prevent leakage of insulin. Be careful when handling used needles to avoid needle sticks and transfer of infections.

Keep your LEVEMIR® FlexPen® and needles out of the reach of children.

Use LEVEMIR® FlexPen® as directed to treat your diabetes. Needles and LEVEMIR® FlexPen® must not be shared.

Always use a new needle for each injection.

Novo Nordisk is not responsible for harm due to using this insulin pen with products not recommended by Novo Nordisk.

As a safety measure, always carry a spare insulin delivery device in case your LEVEMIR® FlexPen® is lost or damaged.

Remember to keep the disposable LEVEMIR® FlexPen® with you. Do not leave it in a car or other location where it can get too hot or too cold.

Revised: May 2013

Novo Nordisk®, LEVEMIR®, FlexPen®, and NovoFine® 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.

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

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
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Instructions for Use

Levemir® (LEV–uh–mere) FlexTouch® Pen
(insulin detemir [rDNA origin] injection)

• Levemir® FlexTouch® Pen (“Pen”) is a prefilled disposable pen containing 300 units of U-100 Levemir® (insulin detemir [rDNA origin] injection) insulin. You can inject from 1 to 80 units in a single injection.

• Do not share your Levemir® FlexTouch® Pen with another person. You may give an infection to them or get an infection from them.

• This Pen is not recommended for use by the blind or visually impaired without the assistance of a person trained in the proper use of the product.

Supplies you will need to give your Levemir® injection:

- Levemir® (LEV–uh–mere) FlexTouch® Pen
- needle cap
- needle cap
- alcohol swab
- NovoFine® needle
- 1 sharps container for throwing away used Pens and needles.
- Levemir® 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.

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.

Step 2:

- Pull Pen cap straight off (See Figure B).

Step 3:

- Select a new needle.
- Pull off the paper tab from the outer needle cap (See Figure D).

Step 4:

- Push the capped needle straight onto the Pen and twist the needle on until it is tight (See Figure E).

Step 5:

- Pull off the outer needle cap. Do not throw it away (See Figure F).

Step 6:

- Pull off the inner needle cap and throw it away (See Figure G).

Step 7:

- Turn the dose selector to select 2 units (See 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).

Step 9:

- Hold the Pen with the needle pointing up. Press and hold in the dose button until the dose counter shows “0”. The “0” must line up with the dose pointer.

- A drop of insulin should be seen at the needle tip (See Figure J).

- If you do not see a drop of insulin, repeat steps 7 to 9, no more than 6 times.

- If you still do not see a drop of insulin, change the needle and repeat steps 7 to 9.

Selecting your dose:

- 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.

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

Example:

- Approx. 200 units left

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

Step 11:
Choose your injection site and wipe the skin with an alcohol swab. Let the injection site dry before you inject your dose (See Figure M).

Step 12:
Insert the needle into your skin (See Figure N).
- Make sure you can see the dose counter. Do not cover it with your fingers, this can stop your injection.
- Keep the needle in your skin after the dose counter has returned to “0” (See Figure O).
  - When the dose counter returns to “0”, you will not get your full dose until 6 seconds later.
  - If the needle is removed before you count to 6, you may see a stream of insulin coming from the needle tip.
  - If you see a stream of insulin coming from the needle tip you will not get your full dose. If this happens you should check your blood sugar levels more often because you may need more insulin.

Step 13:
Press and hold down the dose button until the dose counter shows “0” (See Figure Q).
  - The “0” must line up with the dose pointer. You may then hear or feel a click.
- Keep the needle in your skin after the dose counter has returned to “0” and slowly count to 6 (See Figure P).
  - When the dose counter returns to “0”, you will not get your full dose until 6 seconds later.
  - If the needle is removed before you count to 6, you may see a stream of insulin coming from the needle tip.
  - If you see a stream of insulin coming from the needle tip you will not get your full dose. If this happens you should check your blood sugar levels more often because you may need more insulin.

Step 14:
Pull the needle out of your skin (See Figure Q).
  - If you see blood after you take the needle out of your skin, press the injection site lightly with a piece of gauze or an alcohol swab. Do not rub the area.

Step 15:
Carefully remove the needle from the Pen and throw it away (See Figure R).
- Do not recap the needle. Recapping the needle can lead to needle stick injury.
- If you do not have a sharps container, carefully slip the needle into the outer needle cap (See Figure S). Safely remove the needle and throw it away as soon as you can.
- 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.

Step 16:
Replace the Pen cap by pushing it straight on (See Figure T).

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

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

General Information about the safe and effective use of Levemir®:
- Keep Levemir® FlexTouch® Pens and needles out of the reach of children.
- Always use a new needle for each injection.
- Do not share Pens or needles.

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