Get your patients off to the right start with insulin therapy

The right start can make all the difference in helping patients with diabetes stay motivated. Use startSMART™ to help set a positive tone for initiating insulin therapy—and encourage patients to see the start of Levemir® (insulin detemir [rDNA origin] injection) as a chance to take positive steps toward improving their diabetes.

Use startSMART™ to help your patients understand

• Why it is time to add insulin to their treatment plan
• What Levemir® is and the role it plays in blood sugar control
• The importance of measuring fasting plasma glucose (FPG) and using FPG as a motivational target
• How they can adjust their Levemir® dose
• The patient support resources that are available through LevemirCare™, a free diabetes care program available to those taking Levemir®

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.

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.

Needles are sold separately and may require a prescription in some states.
Levemir®: Guide to starting doses for once-daily use in type 2 diabetes

WHEN TO DOSE: ONCE DAILY IN THE EVENING OR AT BEDTIME

HOW TO DOSE: START AT 10 UNITS OR 0.1-0.2 U/KG

Weight-based starting dose

<table>
<thead>
<tr>
<th>IF YOUR PATIENT WEIGHS...</th>
<th>START AT... (0.1 U/KG)</th>
<th>START AT... (0.2 U/KG)</th>
</tr>
</thead>
<tbody>
<tr>
<td>120-160 LB</td>
<td>6-7 U</td>
<td>11-15 U</td>
</tr>
<tr>
<td>161-200 LB</td>
<td>7-9 U</td>
<td>15-18 U</td>
</tr>
<tr>
<td>201-240 LB</td>
<td>9-11 U</td>
<td>18-22 U</td>
</tr>
<tr>
<td>241-280 LB</td>
<td>11-13 U</td>
<td>22-26 U</td>
</tr>
<tr>
<td>281-300 LB</td>
<td>13-14 U</td>
<td>26-27 U</td>
</tr>
</tbody>
</table>

Levemir® can be dosed once or twice daily.¹

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® (insulin detemir [rDNA origin] injection), 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.

¹Clinical judgment should be used to individualize starting dose and titration schedule.

²Suggested dosing based on Prescribing Information.
**Levemir®: Physician-directed patient self-titration**

Adjust dosing to reach FPG goals: 70 to 90 mg/dL or 80 to 110 mg/dL, as seen in the TITRATE™ study.²

**Titration after assessing mean 3-day FPG (mg/dL)**

<table>
<thead>
<tr>
<th>GOAL: 70-90 mg/dL</th>
<th>GOAL: 80-110 mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>If FPG is</strong></td>
<td><strong>If FPG is</strong></td>
</tr>
<tr>
<td>&gt;90 mg/dL</td>
<td>&gt;110 mg/dL</td>
</tr>
<tr>
<td>+3 UNITS</td>
<td>0 MAINTAIN CURRENT DOSE</td>
</tr>
<tr>
<td>70-90 mg/dL</td>
<td>80-110 mg/dL</td>
</tr>
<tr>
<td>&lt;70 mg/dL</td>
<td>&lt;80 mg/dL</td>
</tr>
<tr>
<td>−3 UNITS</td>
<td></td>
</tr>
</tbody>
</table>

*Clinical judgment should be used for dose adjustments and to account for hypoglycemia. The dose of Levemir® should be adjusted to achieve glycemic targets.

Dose adjustments can be made every third day based on an average of 3 consecutive FPG values.

**Example of an approximate dose (0.5 U/kg) when titrating to goal of 80 to 110 mg/dL**

<table>
<thead>
<tr>
<th>WEIGHT (LB)</th>
<th>TARGET DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>120-160</td>
<td>27-36 U</td>
</tr>
<tr>
<td>161-200</td>
<td>37-46 U</td>
</tr>
<tr>
<td>201-240</td>
<td>46-55 U</td>
</tr>
<tr>
<td>241-280</td>
<td>55-64 U</td>
</tr>
<tr>
<td>281-300</td>
<td>64-68 U</td>
</tr>
</tbody>
</table>

*Estimated based on the Blonde et al end of study dose. Levemir® dose should be adjusted based on blood glucose measurements. Dosage of Levemir® should be individualized under the supervision of a health care provider.¹,²

**In the TITRATE™ study, Levemir® once daily helped the majority of patients with type 2 diabetes achieve A1C goal of <7%**²

**Low rates of hypoglycemia**²,³

- Nearly all hypoglycemic events were minor or symptoms only
- A single major hypoglycemic event was reported in the 70 to 90 mg/dL group; no major hypoglycemic events in the 80 to 110 mg/dL group
- Minor hypoglycemia rates were 5.09 (70-90 mg/dL) and 3.16 (80-110 mg/dL) per patient-year

Adapted from Blonde et al, 2009.²

³Minor=self-measured plasma glucose (SMPG) <56 mg/dL and not requiring third-party assistance; symptoms only=SMPG ≥56 mg/dL or no measurement; major=requiring third-party assistance.
Help your patients build upon weekly achievements in the treatment of diabetes

Inside startSMART™, your patients will find:
• “Your Levemir® startSMART™ Guide”—A guide that will answer some of their questions about starting therapy with Levemir®
• “My First Weeks With Levemir®”—A place where they can track their weekly progress and share their “Weekly Wins” with you. This booklet also contains tips to help them on their way, including information about how to save on Levemir®

Important Safety Information (cont’d)

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.


*By texting TOUCH to 51212, you consent to receive a one-time text message containing a link to the requested information from Novo Nordisk. Your consent is voluntary and you are not required to consent to receive information or other benefits from Novo Nordisk. Standard text messaging rates will apply.

Please see Important Safety Information throughout. Please see accompanying Prescribing Information.
**LEVEMIR® (insulin detemir [rDNA origin] injection) solution for subcutaneous injection**

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

---

**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)

**ADMINISTRATION**

- 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 glucose especially upon converting to LEVEMIR® and during the initial weeks thereafter (2.3)

---

**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)

---

**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)

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**DESCRIPTION**

LEVEMIR® (insulin detemir [rDNA origin] injection) solution for subcutaneous injection

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**OVERDOSAGE**

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.

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**REFERENCES**

Sections or subsections omitted from the full prescribing information are not listed.
LEVEMIR® (insulin detemir [rDNA origin]) injection

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 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.

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 of insulin being administered with LEVEMIR® should only do so under medical supervision with appropriate glucose monitoring (see Warnings and Precautions (5.1)).

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

As with all insulins, injection sites should be rotated within the same region (abdomen, thigh, buttock) from one injection to the next to reduce the risk of lipohypertrophy (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 daily total 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 two daily doses.

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 during the first few weeks of therapy to individualize the dosing under the supervision of a healthcare provider.

2.3 Converting to LEVEMIR® from other insulin therapies
If converting from insulin glargine to LEVEMIR®, the change can be done on a unit-to-unit basis. If converting from NPH insulin, the change can be done on a unit-to-unit basis.

However, some patients with type 2 diabetes may require more LEVEMIR® than NPH insulin, as observed in one trial (see Clinical Studies (14)).

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

3 DOSAGE FORMS AND STRENGTHS
LEVEMIR® solution for injection 100 Unit per mL is available as:
• 3 mL LEVEMIR® FlexPen®
• 3 mL LEVEMIR® FlexTouch®
• 10 mL Vial

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

5 WARNINGS AND PRECAUTIONS

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

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

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

5.2 Administration
LEVEMIR® should only be administered subcutaneously.

Do not administer LEVEMIR® intravenously or intramuscularly. The intended duration of activity of LEVEMIR® is dependent on injection into subcutaneous tissue. Intravenous or intramuscular administration of the intended therapeutic 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 mixture 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 may be unaccompanied, or may mask the signs and symptoms of hypoglycemia (e.g., diaphoresis, palpitations), and may lead to loss of consciousness, or death. Severe hypoglycemia requiring 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 the hypoglycemia usually reflects the time-action profile of the administered insulin formulations. Other factors such as changes in diet (e.g., amount of food or timing of meals), exercise, and concomitant medications may also alter the risk of hypoglycemia (see Drug Interactions (7)).

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

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

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

5.4 Hypersensitivity and allergic reactions
Severe, lifethreatening, generalized allergy, including anaphylaxis, can occur with insulin products, including LEVEMIR®.

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

5.6 Hepatic Impairment
Non-diabetic individuals with severe hepatic impairment had lower systemic exposures to insulin detemir compared to healthy volunteers. However, some studies with human insulin have shown increased circulating insulin concentrations in patients with liver impairment.

Careful glucose monitoring and dose adjustments of insulin, including LEVEMIR®, may be necessary in patients with hepatic impairment (see Clinical Pharmacology (12.3)).

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

5.8 Fluid retention and heart failure with concomitant use of PPAR-gamma agonists
Thiazolidinediones (TZDs), which are peroxisome proliferator-activated receptor (PPAR) gamma agonists, can cause dose-related fluid retention, particularly when used in combination with insulin. Fluid retention may be associated with heart failure and can be exacerbated by concomitant use of thiazolidinediones 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)).

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

6 ADVERSE REACTIONS

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 with rates reported in another clinical trial, and may not reflect the rates actually observed in clinical practice.
Pregnancy

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

• Hypoglycemia

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

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

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

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

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</th>
<th>Diabetes</th>
<th>Adults</th>
<th>In combination with insulin aspart</th>
<th>Event/patient/year</th>
<th>Percent of patients (n/total N)</th>
<th>Percent of patients (n/total N)</th>
<th>Event/patient/year</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Type 1</td>
<td>Diabetes</td>
<td>10 weeks</td>
<td>LEVEMIR®</td>
<td>8.7 (242/276)</td>
<td>0.52</td>
<td>88.0 (242/276)</td>
<td>26.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NPH</td>
<td>10.6 (141/132)</td>
<td>0.43</td>
<td>89.4 (141/132)</td>
<td>37.5</td>
</tr>
<tr>
<td>B</td>
<td>Type 1</td>
<td>Diabetes</td>
<td>26 weeks</td>
<td>LEVEMIR®</td>
<td>5.0 (8/161)</td>
<td>0.13</td>
<td>82.0 (8/161)</td>
<td>20.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Once-Daily</td>
<td>10.1 (165/159)</td>
<td>0.31</td>
<td>77.4 (123/159)</td>
<td>21.8</td>
</tr>
<tr>
<td>C</td>
<td>Type 1</td>
<td>Diabetes</td>
<td>24 weeks</td>
<td>LEVEMIR®</td>
<td>7.5 (37/491)</td>
<td>0.35</td>
<td>88.4 (37/491)</td>
<td>31.1</td>
</tr>
<tr>
<td></td>
<td>Adults</td>
<td></td>
<td></td>
<td>Once-Daily</td>
<td>10.2 (265/256)</td>
<td>0.32</td>
<td>78.5 (255/256)</td>
<td>33.4</td>
</tr>
<tr>
<td>D</td>
<td>Type 1</td>
<td>Diabetes</td>
<td>26 weeks</td>
<td>LEVEMIR®</td>
<td>15.9 (73/459)</td>
<td>0.91</td>
<td>93.1 (73/459)</td>
<td>31.6</td>
</tr>
<tr>
<td></td>
<td>Pediatrics</td>
<td>26 weeks</td>
<td></td>
<td>Once- or Twice-Daily LEVEMIR®</td>
<td>20.0 (213/105)</td>
<td>0.99</td>
<td>95.7 (213/105)</td>
<td>37.0</td>
</tr>
<tr>
<td>E</td>
<td>Type 1</td>
<td>Diabetes</td>
<td>52 weeks</td>
<td>LEVEMIR®</td>
<td>1.7 (3/177)</td>
<td>0.02</td>
<td>94.9 (3/177)</td>
<td>56.1</td>
</tr>
<tr>
<td></td>
<td>Pediatrics</td>
<td>52 weeks</td>
<td></td>
<td>Once- or Twice-Daily LEVEMIR®</td>
<td>7.1 (12/170)</td>
<td>0.06</td>
<td>97.6 (12/170)</td>
<td>70.7</td>
</tr>
</tbody>
</table>

Table 6: Hypoglycemia in Patients with Type 2 Diabetes

<table>
<thead>
<tr>
<th>Study</th>
<th>Type 2 Diabetes</th>
<th>Adults</th>
<th>In combination with oral agents</th>
<th>Event/patient/year</th>
<th>Percent of patients (n/total N)</th>
<th>Percent of patients (n/total N)</th>
<th>Event/patient/year</th>
</tr>
</thead>
<tbody>
<tr>
<td>E</td>
<td>Type 2 Diabetes</td>
<td>Adults</td>
<td>Twice-Daily LEVEMIR®</td>
<td>0.4 (123/287)</td>
<td>0.01</td>
<td>0.08</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>Type 2 Diabetes</td>
<td>Adults</td>
<td>Twice-Daily NPH</td>
<td>0.25 (6/238)</td>
<td>0.25</td>
<td>1.5 (1/195)</td>
<td>0.40</td>
</tr>
<tr>
<td></td>
<td>Type 2 Diabetes</td>
<td>Adults</td>
<td>Once-Daily LEVEMIR®</td>
<td>0.08 (3/37)</td>
<td>0.09</td>
<td>0.08</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>Type 2 Diabetes</td>
<td>Adults</td>
<td>Once-Daily NPH</td>
<td>0.05 (7/143)</td>
<td>0.01</td>
<td>0.09</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>Type 2 Diabetes</td>
<td>Adults</td>
<td>Once-Daily Metformin</td>
<td>0.05 (3/60)</td>
<td>0.07</td>
<td>0.09</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>Type 2 Diabetes</td>
<td>Adults</td>
<td>Once-Daily Metformin</td>
<td>0.05 (3/60)</td>
<td>0.07</td>
<td>0.09</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

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 become pregnant or plan to become pregnant while using LEVEMIR®. A randomized controlled clinical trial of pregnant women with type 1 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 insulin have not indicated that insulin detemir and human insulin had similar effects regarding embryotoxicity and teratogenicity that were attributed to maternal hyperglycemia.

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 156 women in the NPH arm were enrolled in the study (from which seven women were excluded because NPH insulin was used). In the intent-to-treat population, the adjusted mean HbA1C (standard error) at gestational week 36 was 6.27% (0.053) in LEVEMIR®-treated patients (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. Of the cases of pre-eclampsia observed in the study, many drugs, including human insulin, are excreted in human milk, 10.5% nasopharyngitis and headache. These are consistent with ≥5% in normal animals. The duration of action of LEVEMIR® is mediated by slowed systemic absorption of insulin detemir molecules from the injection site due to the distribution 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. 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

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 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®, % | NPH, % (N=158) |
| Headache | 14.4 | 10.6 |
| Lower back pain | 11.8 | 10.6 |
| Abdominal pain, upper | 10.5 | 7.0 |
| Urinary tract infection | 9.5 | 5.7 |
| Constipation | 8.6 | 5.1 |
| Abdominal pain lower | 8.6 | 3.8 |
| Vomiting | 8.4 | 4.4 |
| Abdominal pain, lower | 6.3 | 3.8 |
| Constipation | 5.3 | 2.5 |
| Diarrhea | 5.3 | 2.5 |
| Abdominal pain, upper | 5.3 | 2.5 |
| Flatulence | 5.3 | 2.5 |
| Oropharyngeal pain | 5.3 | 2.5 |

*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 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

| Table 8: Hypoglycemia in Pregnant Women with Type 1 Diabetes |
|---|---|---|---|
| | LEVEMIR®, % | NPH, % (N=158) |
| Severe hypoglycemia* | 16.4 | 20.9 |
| Patients at least 1 event (N=20) | 16.4 (25/152) | 20.9 (33/158) |
| Event/patient/year | 1.1 | 1.2 |
| Non-severe hypoglycemia* | 94.7 | 82.4 |
| Patients at least 1 event (N=140) | 94.7 (145/152) | 82.4 (146/158) |
| Event/patient/year | 114.2 | 108.4 |

*For definition regarding severe and non-severe hypoglycemia see section 6.5. 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.

At or before 36 to 37 weeks of gestation, 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 35 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 in rabbits. Embryotoxicity and embryolethal developmental 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 in the data 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 310 of 11822 patients (26.6%) 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 incidence of hypoglycemia and the duration of the action of insulin detemir, 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 necessary. More severe episodes with coma, seizure, or neurolologic impairment may be treated with intramuscular/subcutaneous glucagon or intravenous glucose. In cases of serious hypoglycemia, hypoglycemia may be difficult to recognize in the elderly.

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 distribution 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. 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
after subcutaneous administration to the thigh where AUC0-α was 30-40% lower and AUC0-∞ 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 Cmax 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 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 populations.

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

Hepatic Impairment - A single subcutaneous dose of 0.2 Units/kg (1.2 nmol/kg) of LEVEMIR® was administered to healthy subjects and those with varying degrees of hepatic impairment in 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 study in bacteria, human peripheral blood lymphocyte chromosomal 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 treatment recommendations 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 (HbA1c) 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 HbA1c and fasting plasma glucose (FPG) reductions compared to the NPH-treated patients (Table 9). Differences in timing of LEVEMIR® administration had no effect on HbA1c, 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 HbA1c 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 HbA1c.

Table 9: Type 1 Diabetes Mellitus – Adult

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment Duration</th>
<th>Treatment in Combination</th>
<th>Insulin Type</th>
<th>HbA1c (%)*</th>
<th>Adj. Mean Change from Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>16 weeks</td>
<td>Twice-daily LEVEMIR®</td>
<td>Once-daily NPH</td>
<td>6.9</td>
<td>-0.6*</td>
</tr>
<tr>
<td>B</td>
<td>26 weeks</td>
<td>Twice-daily LEVEMIR®</td>
<td>Once-daily NPH</td>
<td>7.0</td>
<td>-0.7*</td>
</tr>
<tr>
<td>C</td>
<td>24 weeks</td>
<td>Twice-daily LEVEMIR®</td>
<td>Once-daily NPH</td>
<td>6.9</td>
<td>-0.7*</td>
</tr>
</tbody>
</table>

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

**From an ANCOVA model adjusted for baseline value, geographical region, gender and age (covariate).

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

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

Table 10: Type 1 Diabetes Mellitus – Pediatric

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment Duration</th>
<th>Treatment in combination with</th>
<th>Insulin Type</th>
<th>Baseline HbA1c (%)</th>
<th>Adj. Mean Change from Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>D</td>
<td>26 weeks</td>
<td>Once- or Twice Daily LEVEMIR®</td>
<td>Once-daily NPH</td>
<td>7.4</td>
<td>-0.3*</td>
</tr>
<tr>
<td>I</td>
<td>52 weeks</td>
<td>Once- or Twice Daily LEVEMIR®</td>
<td>Once-daily NPH</td>
<td>7.6</td>
<td>-0.3*</td>
</tr>
</tbody>
</table>

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

**From an ANCOVA model adjusted for baseline value and study site.
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 or without two of the following oral antidiabetic medications: metformin, an insulin secretagogue, or a glucagon–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=714), subjects 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 E</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>24-hour twice-daily LEVEMIR®</td>
<td>15/15</td>
</tr>
<tr>
<td>24-hour once-daily LEVEMIR®</td>
<td>15/15</td>
</tr>
<tr>
<td>Total number of subjects</td>
<td>233</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>8.6</td>
</tr>
<tr>
<td>Adj. mean from baseline</td>
<td>2.0</td>
</tr>
<tr>
<td>Difference</td>
<td>-0.6**</td>
</tr>
<tr>
<td>95% CI</td>
<td>(-0.9, -0.3)</td>
</tr>
<tr>
<td>Fasting Plasma Glucose (mg/dL) (Mean)</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>220</td>
</tr>
<tr>
<td>Adj. mean from baseline</td>
<td>16</td>
</tr>
<tr>
<td>Difference</td>
<td>20</td>
</tr>
<tr>
<td>95% CI</td>
<td>(-20, -10)</td>
</tr>
<tr>
<td>Pregnancy</td>
<td></td>
</tr>
<tr>
<td>A randomized, open-label, controlled clinical trial has been conducted in pregnant women with type 1 diabetes. (See Use in Specific Populations (8.1))</td>
<td></td>
</tr>
</tbody>
</table>

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

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

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

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

16.2 Storage:

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

Do not use LEVEMIR® if it has been frozen.

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

If refrigeration is not possible, unused (unopened) LEVEMIR® can be kept out of the refrigerator, even if the FlexPen®, FlexTouch®, or vial is not refrigerated, as long as it is kept as cool as possible and away from direct heat and light. If the room temperature exceeds 30°C (86°F), the vial should be discarded if it becomes warm. If the vial is kept out of the refrigerator, the patient should continue 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 should be instructed on how 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 intermittent conditions (illness, stress, or emotional disturbances), an insulin allergy, and possible additional insulin administration.

Patients should receive proper training on how to use LEVEMIR®, instruct patients that when injecting LEVEMIR®, the patient should press and hold down the dose button until the dose counter shows the correct dose. The patient should 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 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 should 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.

LEVEMIR® (insulin detemir [rDNA origin] injection)
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.
**Patient Information**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

For more information, go to www.novonordisk-us.com or call 1-800-727-6500.

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

Revised: 10/2013

For more information go to www.levemirflextouch.com
Patient Instructions For Use
LEVEMIR® 10 mL vial

Please read the following Instructions for use carefully before using your LEVEMIR® 10 mL vial and each time you get a refill. You should read the instructions in this manual even if you have used an insulin 10 mL vial before.

How should I use the LEVEMIR® 10 mL vial?
Using the 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.

Before each use, wipe the rubber stopper with an alcohol wipe.

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.

How should I inject LEVEMIR® with a syringe?
If you clean your injection site with an alcohol swab, let the injection site dry before you inject. Talk with your healthcare provider about how to rotate injection sites and how to give an injection.

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.
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).

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 during normal use. To avoid injecting air and to ensure you take the right dose of insulin:
E. Turn the dose selector to select 2 units (see diagram E).
F. Hold your LEVEMIR® FlexPen® with the needle pointing up. Tap the cartridge gently with your finger a few times to make any air bubbles collect at the top of the cartridge (see diagram F).
G. While you keep the needle pointing upwards, press the push-button all the way in (see diagram G). The dose selector returns to 0.
H. A drop of insulin should appear at the needle tip. If not, change the needle and repeat the procedure no more than 6 times.
If you do not see a drop of insulin after 6 times, do not use the LEVEMIR® FlexPen® and contact Novo Nordisk at 1-800-727-6500.

A small air bubble may remain at the needle tip, but it will not be injected.

SELECTING YOUR DOSE
Check and make sure that the dose selector is set at 0.

H. Turn the dose selector to the number of units you need to inject. The pointer should line up with your dose.
The dose can be corrected either up or down by turning the dose selector in either direction until the correct dose lines up with the pointer (see diagram H). When turning the dose selector, be careful not to press the push-button as insulin will come out.
You cannot select a dose larger than the number of units left in the cartridge.
You will hear a click for every single unit dialed. Do not set 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.

I. Insert the needle into your skin.

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.

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
L. 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 be 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®. Soaking 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.

K. 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 No. 6,004,297, RE 43,834, RE 41,956 and other patents pending.
Manufactured by:
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For information about LEVEMIR® contact:
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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® FlexTouch® Pen
- a new NovoFine® or NovoTwist® needle
- alcohol swab
- 1 sharps container for throwing away used Pens and needles.

See “Disposing of used Levemir® FlexTouch® Pens and needles” at the end of these instructions.

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

NovoFine®
- Outer needle cap
- Inner needle cap
- Needle
- Paper tab

NovoTwist®
- Outer needle cap
- Inner needle cap
- Needle
- Paper tab
- Pen cap

Insulin scale
Insulin window
Dose counter
Dose selector
Dose pointer
Dose button

(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)

Step 7:
- Turn the dose selector to select 2 units (See Figure H).

(Figure H)

Step 8:
- Hold the Pen with the needle pointing up. Tap the top of the Pen gently a few times to let any air bubbles rise to the top (See Figure I).

(Figure I)

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

(Figure J)

Step 10:
- Turn the dose selector to select the number of units you need to inject. The dose pointer should line up with your dose (See Figure K).
  - If you select the wrong dose, you can turn the dose selector forwards or backwards to the correct dose.
  - The even numbers are printed on the dial.
  - The odd numbers are shown as lines.

(Figure K)

Examples
- 0
  - 5 units selected
  - 24 units selected
  - Approx. 200 units left

(Figure L)

Selecting your dose:

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