LEVEMIR® (insulin detemir) injection, for subcutaneous use

Initial U.S. Approval: 2005

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

LEVEMIR® is a long-acting human insulin analog indicated to improve glycemic control in adult and pediatric patients with diabetes mellitus (1).

Limitations of Use:
Not recommended for the treatment of diabetic ketoacidosis.

DOSAGE AND ADMINISTRATION

See Full Prescribing Information for important administration instructions (2.1).

Inject subcutaneously into the thigh, upper arm, or abdomen (2.1).

Rotate injection sites to reduce risk of lipodystrophy and localized cutaneous amyloidosis (2.1).

Individualize and titrate the dose of LEVEMIR® based on the patient’s metabolic needs, blood glucose monitoring results, and glycemic control goal (2.2).

Administer subcutaneously once daily or in divided doses twice daily (2.2).

See Full Prescribing Information for recommended starting dose in insulin naïve patients and patients already on insulin therapy (2.3, 2.4).

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

• Drugs that Affect Glucose Metabolism: Adjustment of insulin dosage may be needed. (7)
• Antidrnergic Drugs (e.g., beta-blockers, clonidine, guanethidine, and reserpine): Signs and symptoms of hypoglycemia may be reduced or absent. (5.3, 7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling. Revised: 07/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Important Administration Instructions
2.2 General Dosing Instructions
2.3 Starting Dose in Insulin Naïve Patients
2.4 Switching to LEVEMIR® from Other Insulin Therapies
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Never Share a LEVEMIR® FlexTouch® Pen, Needle, or Insulin Syringe between Patients
5.2 Hyperglycemia or Hypoglycemia with Changes in Insulin Regimen
5.3 Hypoglycemia
5.4 Hypoglycemia Due to Medication Errors
5.5 Hypersensitivity Reactions
5.6 Hypokalemia
5.7 Fluid Retention and Heart Failure with Concomitant Use of PPAR-gamma Agonists
6 ADVERSE REACTIONS
6.1 Clinical Trial Experience
6.2 Postmarketing Experience
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.3 Pediatric Use
8.4 Geriatric Use
8.5 Renal Impairment
8.6 Hepatic Impairment
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
14.1 Clinical Studies in Adult Patients with Type 1 Diabetes
14.2 Clinical Studies in Pediatric Patients with Type 1 Diabetes
14.3 Clinical Studies in Adult Patients with Type 2 Diabetes
16 HOW SUPPLIED/STORAGE AND HANDLING
16.1 How Supplied
16.2 Storage
17 PATIENT COUNSELING INFORMATION

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

LEVEMIR® is indicated to improve glycemic control in adult and pediatric patients with diabetes mellitus.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

- Always check insulin labels before administration [see Warnings and Precautions (5.4)].
- Visually inspect for particulate matter and discoloration. Only use LEVEMIR® if the solution appears clear and colorless.
- Inject LEVEMIR® subcutaneously into the thigh, upper arm, or abdomen.
- Rotate injection sites within the same region from one injection to the next to reduce the risk of lipodystrophy and localized cutaneous amyloidosis. Do not inject into areas of lipodystrophy or localized cutaneous amyloidosis [see Warnings and Precautions (5.2), Adverse Reactions (6)].
- During changes to a patient’s insulin regimen, increase the frequency of blood glucose monitoring [see Warnings and Precautions (5.2)].
- Do not dilute or mix LEVEMIR® with any other insulin or solution.
- Do not administer LEVEMIR® intravenously or in an insulin infusion pump.
- LEVEMIR® FlexTouch® pen dials in 1-unit increments.
- Use LEVEMIR® FlexTouch® pens with caution in patients with visual impairment who may rely on audible clicks to dial their dose.

2.2 General Dosing Instructions

- LEVEMIR® can be administered by subcutaneous injection once or twice daily. Administer once daily doses with the evening meal or at bedtime. For twice daily dosing, administer the evening dose with the evening meal, at bedtime, or 12 hours after the morning dose.
- Individualize and titrate the dose of LEVEMIR® based on the patient’s metabolic needs, blood glucose monitoring results, and glycemic control goal.
- Dose adjustments may be needed with changes in physical activity, changes in meal patterns (i.e., macronutrient content or timing of food intake), changes in renal or hepatic function, or during acute illness to minimize the risk of hypoglycemia or hyperglycemia [see Warnings and Precautions (5.3)].
- In patients with type 1 diabetes, LEVEMIR® must be used in a regimen with rapid-acting or short-acting insulin.

2.3 Starting Dose in Insulin Naïve Patients

Recommended Starting Dosage in Patients with Type 1 Diabetes

The recommended starting dose of LEVEMIR® in patients with type 1 diabetes mellitus is approximately one-third to one-half of the total daily insulin dose. The remainder of the total daily insulin dose should be administered as short-acting pre-meal insulin. As a general rule, 0.2 to 0.4 units of insulin per kilogram of body weight can be used to calculate the initial total daily insulin dose in insulin naïve patients with type 1 diabetes.

Recommended Starting Dosage in Patients with Type 2 Diabetes

The recommended starting dose of LEVEMIR® in patients with type 2 diabetes mellitus inadequately controlled on oral antidiabetic medications or a GLP-1 receptor agonist is 10 units (or 0.1 units/kg to 0.2 units/kg) given once daily in the evening or divided into a twice daily regimen.

2.4 Switching to LEVEMIR® from Other Insulin Therapies

Dosage adjustments are recommended to lower the risk of hypoglycemia when switching patients to LEVEMIR® from another insulin therapy [see Warnings and Precautions (5.3)].

- 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 mellitus may require more LEVEMIR® than NPH insulin, as observed in one trial [see Clinical Studies (14)].

3 DOSAGE FORMS AND STRENGTHS

Injection: 100 units/mL (U-100), is a clear, colorless, solution available as:
- 3 mL single-patient-use FlexTouch® prefilled pen
- 10 mL multiple-dose vial

4 CONTRAINDICATIONS

LEVEMIR® is contraindicated:
- During episodes of hypoglycemia [see Warnings and Precautions (5.6)].
- In patients with hypersensitivity to insulin detemir or any of the excipients in LEVEMIR®. Reactions have included anaphylaxis [see Warnings and Precautions (5.5) and Adverse Reactions (6.1)].

5 WARNINGS AND PRECAUTIONS

5.1 Never Share a LEVEMIR® FlexTouch® Pen, Needle, or Insulin Syringe Between Patients

LEVEMIR® FlexTouch® prefilled pens must never be shared between patients. Even when the needle or injection site is changed. Patients using LEVEMIR® vials should never share needles or syringes with another person.

Sharing poses a risk for transmission of blood-borne pathogens.

5.2 Limitations of Use

All insulins, including LEVEMIR®, cause a shift in potassium from the extracellular to intracellular space, possibly leading to hypokalemia. Untreated hypokalemia may cause respiratory paralysis, ventricular arrhythmia, and death. Monitor potassium levels in patients at risk for hypokalemia if indicated (e.g., patients using potassium-lowering medications, patients taking medications sensitive to serum potassium concentrations).

5.3 Fluid Retention and Heart Failure with Concomitant Use of PPAR-gamma Agonists

Triazolinediones (TZDs), which are peroxisome proliferator-activator receptor gamma (PPAR-gamma) agonists, can cause dose-related fluid retention, when used in combination with insulin. Fluid retention may lead to or exacerbate heart failure. Patients treated with insulin, including LEVEMIR®, and a PPAR-gamma agonist should be observed for signs and symptoms of heart failure. If heart failure is observed, the PPAR-gamma agonist should be considered.

6 ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere:
- Hypoglycemia [see Warnings and Precautions (5.3)]
- Hypoglycemia Due to Medication errors [see Warnings and Precautions (5.4)]
- Hypersensitivity Reactions [see Warnings and Precautions (5.5)]
- Hypokalemia [see Warnings and Precautions (5.6)]

6.1 Clinical Trial Experience

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

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

In two pooled trials, adults with type 1 diabetes were exposed to individualized doses of LEVEMIR® (n=761) or NPH (n=388). The mean duration of exposure to LEVEMIR® was 153 days, and the total exposure to LEVEMIR® at 317 patient-years. The most common adverse reactions are summarized in Table 1.

Table 1: Adverse Reactions occurring in ≥5% of LEVEMIR®-Treated Adult Patients with Type 1 Diabetes Mellitus in Two Trials of 16 Weeks and 24 Weeks Duration

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>LEVEMIR®, % (n=761)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory tract infection</td>
<td>26.1</td>
</tr>
<tr>
<td>Headache</td>
<td>22.6</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>9.5</td>
</tr>
<tr>
<td>Influenza-like illness</td>
<td>7.8</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>6.0</td>
</tr>
</tbody>
</table>
| Adults with type 1 diabetes were exposed to 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 occurring in ≥5% of LEVEMIR®-Treated Adult Patients with Type 1 Diabetes Mellitus in a 26-week Trial

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>LEVEMIR®, % (n=161)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory tract infection</td>
<td>26.7</td>
</tr>
<tr>
<td>Headache</td>
<td>14.3</td>
</tr>
<tr>
<td>Back pain</td>
<td>8.1</td>
</tr>
<tr>
<td>Influenza-like illness</td>
<td>6.2</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>5.6</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>5.0</td>
</tr>
</tbody>
</table>

In two pooled trials, adults with type 2 diabetes were exposed to LEVEMIR® (n=430) or NPH (n=437). The mean duration of exposure to LEVEMIR® was 157 days, and the total exposure to LEVEMIR® was 185 patient-years. The most common adverse reactions were comparable to that observed in adult patients with type 1 diabetes mellitus; see Table 3.

For pediatric patients with type 1 diabetes who were exposed to individualized doses of LEVEMIR® (n=232) or NPH (n=115). The mean duration of exposure to LEVEMIR® was 180 days, and the total exposure to LEVEMIR® was 114 patient-years. The most common adverse reaction
Hypoglycemia

Hypoglycemia was the most commonly observed adverse reaction in patients treated with LEVEMIR®. The rates of reported hypoglycemia depend on the definition of hypoglycemia used, diabetes type, insulin dose, intensity of glucose control, background therapies, and other intrinsic and extrinsic patient factors. For these reasons, comparing rates of hypoglycemia in clinical trials for LEVEMIR® with the incidence of hypoglycemia for other products may be misleading and also, may not be representative of hypoglycemia rates that will occur in clinical practice.

Table 4 and Table 5 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 trial (Study D), non-severe hypoglycemia was defined as an asymptomatic or symptomatic plasma glucose <56 mg/dL (or equivalently blood glucose <50 mg/dL as used in Study A and C) that was self-treated by the patient. For pediatric Study I, non-severe hypoglycemia included asymptomatic events with plasma glucose <65 mg/dL as well as symptomatic events that the patient could self-treat or treat by taking oral therapy.

Hypersensitivity Reactions

Severe, life-threatening, generalized allergy, including anaphylaxis, generalized skin reactions, angioedema, bronchospasm, hypotension, and shock have occurred with insulin, including LEVEMIR®, and may be life-threatening.

Insulin Initiation and Intensification of Glucose Control

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

Lipoatrophy

Long-term use of insulin, including LEVEMIR®, can cause lipoatrophy at the site of repeated insulin injections. Lipoatrophy includes lipohypertrophy (thickening of adipose tissue) and lipoatrophy (thinning of adipose tissue), and may affect insulin absorption (see Dosage and Administration [2.1]).

Weight Gain

Weight gain can occur with insulin therapy, including LEVEMIR®, and has been attributed to the anabolic effects of insulin and the decrease in glucosuria (see Clinical Studies [14]). In the clinical program, the mean change in body weight from baseline in adult patients with type 1 diabetes (Study A, B, and C) treated with LEVEMIR® ranged from -0.3 kg to 0.5 kg. The mean change in body weight from baseline in adult patients with type 2 diabetes (Study E, F, and H) treated with LEVEMIR® ranged from 0.5 kg to 1.2 kg.

Peripheral Edema

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

Table 4: Hypoglycemia in Patients with Type 1 Diabetes

<table>
<thead>
<tr>
<th>Event</th>
<th>Percent of Patients with at least 1 Event (n/total N)</th>
<th>Event/ Patient/Year</th>
<th>Percent of Patients (n/total N)</th>
<th>Event/ Patient/Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study A</td>
<td>Type 1 Diabetes Adults 16 weeks In combination with insulin aspart</td>
<td>Twice-Daily LEVEMIR®</td>
<td>8.7</td>
<td>(24/276)</td>
</tr>
<tr>
<td>Study B</td>
<td>Type 1 Diabetes Adults 26 weeks In combination with insulin aspart</td>
<td>Twice-Daily LEVEMIR®</td>
<td>5.0</td>
<td>(8/161)</td>
</tr>
<tr>
<td>Study C</td>
<td>Type 1 Diabetes Adults 26 weeks In combination with regular insulin</td>
<td>Once-Daily LEVEMIR®</td>
<td>7.5</td>
<td>(37/491)</td>
</tr>
<tr>
<td>Study D</td>
<td>Type 1 Diabetes Pediatrics 26 weeks In combination with insulin aspart</td>
<td>Once- or Twice Daily LEVEMIR®</td>
<td>15.9</td>
<td>(37/232)</td>
</tr>
<tr>
<td>Study I</td>
<td>Type 1 Diabetes Pediatrics 52 weeks In combination with insulin aspart</td>
<td>Once- or Twice Daily LEVEMIR®</td>
<td>1.7</td>
<td>(3/177)</td>
</tr>
</tbody>
</table>

Table 5: Hypoglycemia in Patients with Type 2 Diabetes

<table>
<thead>
<tr>
<th>Event</th>
<th>Percent of Patients with at least 1 Event (n/total N)</th>
<th>Event/ Patient/Year</th>
<th>Percent of Patients (n/total N)</th>
<th>Event/ Patient/Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study E</td>
<td>Type 2 Diabetes Adults 24 weeks In combination with oral agents</td>
<td>Twice-Daily LEVEMIR®</td>
<td>0.4</td>
<td>(1/237)</td>
</tr>
<tr>
<td>Study F</td>
<td>Type 2 Diabetes Adults 22 weeks In combination with insulin aspart</td>
<td>Once- or Twice Daily LEVEMIR®</td>
<td>0.01</td>
<td>(3/237)</td>
</tr>
<tr>
<td>Study H</td>
<td>Type 2 Diabetes Adults 26 weeks In combination with Liraglutide and Metformin</td>
<td>Once-Daily LEVEMIR® + Liraglutide + Metformin</td>
<td>40.5</td>
<td>(6/153)</td>
</tr>
</tbody>
</table>

Injection Site Reactions

Patients taking LEVEMIR® may experience injection site reactions, including localized erythema, pain, pruritus, urticaria, edema, and inflammation. In clinical studies in adults, three patients treated with LEVEMIR® reported injection site pain (0.25%).

Immunogenicity

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

6.2 Postmarketing Experience

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

Medication errors have been reported in which rapid-acting or short-acting insulins and other insulin formulations have been accidentally administered instead of LEVEMIR®.

Localized cutaneous amyloidosis at the injection site has occurred. Hyperglycemia has been reported with repeated insulin injections into areas of localized cutaneous amyloidosis; hypoglycemia has been reported with a sudden change to an unalfeetected injection site.

7 DRUG INTERACTIONS

Table 6 includes clinically significant drug interactions with LEVEMIR®.

<table>
<thead>
<tr>
<th>LEVEMIR® % (n = 232)</th>
<th>Upper respiratory tract infection</th>
<th>Headache</th>
<th>Pharyngitis</th>
<th>Gastroenteritis</th>
<th>Influenza-like illness</th>
<th>Abdominal pain</th>
<th>Pyrexia</th>
<th>Cough</th>
<th>Viral infection</th>
<th>Nausea</th>
<th>Rhinitis</th>
<th>Vomiting</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>35.8</td>
<td>31.0</td>
<td>17.2</td>
<td>16.8</td>
<td>13.8</td>
<td>13.4</td>
<td>10.3</td>
<td>8.2</td>
<td>7.3</td>
<td>6.5</td>
<td>6.5</td>
<td>6.5</td>
</tr>
</tbody>
</table>
**Table 6: Clinically Significant Drug Interactions with LEVEMIR®**

**Drugs That May Increase the Risk of Hypoglycemia**

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiadrenergic agents, ACE inhibitors, angiotensin II receptor blockers, digoxin, diuretics, fluorouracil, methotrexate, pentoxifylline, propranolol, quinidine</td>
<td>Dosage reductions and increased frequency of glucose monitoring may be required when LEVEMIR® is co-administered with these drugs.</td>
</tr>
</tbody>
</table>

**Drugs That May Decrease the Blood Glucose Lowering Effect of LEVEMIR®**

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol, beta-blockers, clonidine, and lithium salts</td>
<td>Dosage increases and increased frequency of glucose monitoring may be required when LEVEMIR® is co-administered with these drugs.</td>
</tr>
</tbody>
</table>

**Drugs That May Blunt Signs and Symptoms of Hypoglycemia**

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-blockers, clonidine, guanethidine, and reserpine</td>
<td>Increased frequency of glucose monitoring may be required when LEVEMIR® is co-administered with these drugs.</td>
</tr>
</tbody>
</table>

**8 USE IN SPECIFIC POPULATIONS**

**8.1 Pregnancy**

**Risk Summary**

Available data from published studies and postmarketing case reports with LEVEMIR® use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In a randomized, parallel-group, open-label clinical trial, 1,152 pregnant women with type 1 diabetes who were administered LEVEMIR® once or twice daily, beginning in gestational weeks 8 to 12 or prior to conception, no clear evidence of maternal or fetal risk associated with LEVEMIR® was observed (see Data). There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy (see Clinical Considerations).

Animal reproduction studies were conducted in non-diabetic pregnant rats and rabbits with insulin detemir administration at 3 and 135 times the human dose of 0.5 units/kg/day, respectively, throughout pregnancy. Overall, the effects of insulin detemir did not generally differ from those observed with regular human insulin (see Data). In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 25%, respectively. The estimated background risk of major birth defects is 6 to 10% in women with pre-gestational diabetes with a peri-conceptional HbA₁c >7 and has been reported to be as high as 20 to 25% in women with a per-conceptional HbA₁c >10. The estimated background risk of miscarriage for the indicated population is unknown. Clinical Considerations

**8.2 Lactation**

**Risk Summary**

Available data from published literature demonstrate that exogenous human insulin products, including biosynthetic insulins such as insulin detemir, are transferred into human milk. There are no published reports of adverse reactions including hypoglycemia, in breastfed infants exposed to exogenous human insulin products, including insulin detemir, in breastmilk. There are no data on the effects of exogenous human insulin products, including insulin detemir, on milk production. The developmental and functional capacity of breastfeeding should be considered along with the mother's clinical need for LEVEMIR® and any potential adverse effects on the breastfed infant from LEVEMIR® or from the underlying maternal condition.

**8.4 Pediatric Use**

The safety and effectiveness of LEVEMIR® to improve glycemic control in pediatric patients with diabetes mellitus have been established. The use of LEVEMIR® for this indication is supported by evidence from adequate and well-controlled trials (Studies D and F) with pediatric populations aged 2 to 17 years with type 1 diabetes mellitus (see Clinical Studies (14.2)) and from other studies in pediatric patients and adults with diabetes mellitus (see Pharmacology (12.3), Clinical Studies (14.3)).

**8.5 Geriatric Use**

In clinical trials of LEVEMIR®, 64 of 1624 patients (4%) in the age group 65 and older who had type 2 diabetes trials were 65 years or older. A total of 52 (7 type 1 and 45 type 2 patients) (2%) were 75 years or older. No overall differences in the safety or effectiveness were observed between these patients and younger patients, but small sample sizes limit conclusions. Greater sensitivity of some older individuals cannot be ruled out. In geriatric patients, the initial dosing, dosage increments, and any potential adverse effects on the geriatric population should be considered.

**8.6 Renal Impairment**

No difference was observed in the pharmacokinetics of LEVEMIR® between non-diabetic patients with kidney impairment and healthy volunteers. However, some studies with human insulin have shown increased circulating insulin concentrations in patients with kidney disease. Patients with renal impairment may be necessary in patients with kidney impairment (see Clinical Pharmacology (12.3)).

**8.7 Hepatic Impairment**

Non-diabetic patients with severe hepatic impairment had lower systemic exposures to insulin detemir compared to healthy volunteers. However, with human insulin have shown increased circulating insulin concentrations in patients with liver impairment. Careful glucose monitoring and dosage adjustments of LEVEMIR®, may be necessary in patients with hepatic impairment (see Clinical Pharmacology (12.3)).

**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 and hypokalemia [see Warnings and Precautions (5.3, 5.6)]. Mild episodes of hypoglycemia usually can be treated with oral glucose. Lowering the insulin dosage, and adjustments in meal patterns, or exercise may be needed. More severe episodes with coma, seizures, or neurologic impairment may be treated with a glucagon product for emergency use or concentrated intravenous glucose. After apparent clinical recovery from hypoglycemia, continued observation and additional carbohydrate intake may be necessary to avoid recurrence of hypoglycemia. Hypokalemia must be corrected appropriately.
The effect of smoking on the pharmacokinetics and pharmacodynamics of LEVEMIR® has not been studied.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Standard 2-year carcinogenicity studies in animals have not been performed. Insulin detemir tested negative for genotoxic potential in the in vitro reverse mutation study in bacteria, human peripheral blood lymphocyte chromosome aberration test, and the in vivo mouse micronucleus test.

In a fertility and embryonic development study, insulin detemir was administered to female rats before mating, during mating, and throughout pregnancy at dosages up to 330 nmol/kg/day (3 times a human therapeutic dose 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) was compared to that of once-daily or twice-daily NPH insulin in open-label, randomized, parallel trials 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 trial of 320 patients with type 1 diabetes. The evening LEVEMIR® dose was titrated in all trials according to pre-defined targets for fasting blood glucose. The pre-dinner blood glucose was used to titrate the morning LEVEMIR® dose in those trials that also administered LEVEMIR® in the morning. In general, the reduction in HbA1c with LEVEMIR® was similar to that with NPH insulin or insulin glargine.

14.1 Clinical Studies in Adult Patients with Type 1 Diabetes

In a 16-week open-label clinical trial (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 7). 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 trial (Study B, n=320), adults with type 1 diabetes were randomized to once-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 trial (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 human regular insulin before each meal. LEVEMIR® and NPH insulin had a similar effect on HbA1c.

Table 7: Type 1 Diabetes Mellitus – Adult

<table>
<thead>
<tr>
<th>Treatment duration</th>
<th>Study A</th>
<th>Study B</th>
<th>Study C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>16 weeks</td>
<td>26 weeks</td>
<td>24 weeks</td>
</tr>
<tr>
<td>Treatment in combination with</td>
<td>NovoLog® (insulin aspart)</td>
<td>NovoLog® (insulin aspart)</td>
<td>Human Soluble Insulin (regular insulin)</td>
</tr>
<tr>
<td>Twice-daily LEVEMIR®</td>
<td>Twice-daily NPH</td>
<td>Twice-daily LEVEMIR®</td>
<td>Once-daily LEVEMIR®</td>
</tr>
<tr>
<td>Baseline</td>
<td>9.6</td>
<td>8.3</td>
<td>8.4</td>
</tr>
<tr>
<td>Adj. mean change from baseline</td>
<td>-0.8</td>
<td>-0.9</td>
<td>-0.1</td>
</tr>
<tr>
<td>LEVEMIR® vs NPH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% CI for Treatment difference</td>
<td>(-0.3, -0.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting blood glucose (mg/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline mean</td>
<td>209</td>
<td>220</td>
<td>213</td>
</tr>
<tr>
<td>Adj. mean change from baseline</td>
<td>-44</td>
<td>-9</td>
<td>-30</td>
</tr>
</tbody>
</table>

Table 8: Type 1 Diabetes Mellitus – Pediatric

<table>
<thead>
<tr>
<th>Treatment duration</th>
<th>Study D</th>
<th>Study I</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>26 weeks</td>
<td>52 weeks</td>
</tr>
<tr>
<td>Treatment in combination with</td>
<td>NovoLog® (insulin aspart)</td>
<td>NovoLog® (insulin aspart)</td>
</tr>
<tr>
<td>Once- or Twice Daily LEVEMIR®</td>
<td>Once- or Twice Daily NPH</td>
<td>Once- or Twice Daily LEVEMIR®</td>
</tr>
<tr>
<td>Baseline</td>
<td>8.8</td>
<td>8.4</td>
</tr>
<tr>
<td>Adj. mean change from baseline</td>
<td>-0.7</td>
<td>-0.8</td>
</tr>
<tr>
<td>LEVEMIR® vs NPH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% CI for Treatment difference</td>
<td>-0.1</td>
<td>0.3</td>
</tr>
<tr>
<td>Fasting blood glucose (mg/dL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline mean</td>
<td>181</td>
<td>141</td>
</tr>
<tr>
<td>Adj. mean change from baseline</td>
<td>-39</td>
<td>-10</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.

14.2 Clinical Studies in Pediatric Patients with Type 1 Diabetes

Two open-label, randomized, controlled clinical trials have been conducted in pediatric patients with type 1 diabetes. One trial (Study D) was 26 weeks in duration and enrolled patients 2 to 16 years of age. In both trials, LEVEMIR® and NPH insulin were administered once- or twice-daily. Basol insulin aspart was administered before each meal. In the 26-week trial, LEVEMIR®-treated patients had a mean decrease in HbA1c similar to that of NPH insulin (Table 8). In the 52-week trial, the randomization was stratified by age (2-5 years, n=82, and 6-16 years, n=263) and the mean HbA1c increased in both treatments with similar findings in the 2-5 year-old age group (n=80) and the 6-18 year-old age group (n=285) (Table 8).
14.3 Clinical Studies in Adult Patients with Type 2 Diabetes

In a 24-week, open-label, randomized, clinical trial (Study E, n=476), LEVEMIR® administered twice-daily (before breakfast and evening) was compared to NPH insulin administered twice-daily (before breakfast and evening) as part of a regimen of stable combination therapy with one or two of the following oral antidiabetic medications: metformin, an insulin secretagogue, or a glitazone inhibitor. All patients were insulin-naïve at the time of randomization. LEVEMIR® and NPH insulin similarly lowered Hba1C from baseline (Table 9). In a 22-week, open-label, randomized, clinical trial (Study F, n=395) in adults with type 2 diabetes, LEVEMIR® and NPH insulin were given once-or twice-daily as part of a basal-bolus regimen with insulin aspart. As measured by Hba1C or FPG, LEVEMIR® had efficacy similar to that of NPH insulin.

Table 9: Type 2 Diabetes Mellitus – Adult

<table>
<thead>
<tr>
<th></th>
<th>Study E</th>
<th>Study F</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment duration</td>
<td>Treatment in combination with oral agents</td>
</tr>
<tr>
<td></td>
<td>24 weeks</td>
<td>twice-daily LEVEMIR®</td>
</tr>
<tr>
<td>Baseline HbA1C</td>
<td>8.6</td>
<td>8.5</td>
</tr>
<tr>
<td>Adj. mean change from baseline</td>
<td>-2.1*</td>
<td>-0.6**</td>
</tr>
<tr>
<td>Fasting blood glucose (mg/dL)</td>
<td>179</td>
<td>173</td>
</tr>
<tr>
<td>Baseline</td>
<td>166</td>
<td>159</td>
</tr>
</tbody>
</table>

Combination Therapy with Metformin and Liraglutide

This 26-week open-label trial enrolled 988 patients with inadequate glycemic control (HbA1C ≥10%) on metformin (≥1500 mg/day) alone or inadequate glycemic control (HbA1C ≥7.5%) 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. The remaining 323 patients with HbA1C ≥7% (33% of those who entered the run-in period) were randomized to 26 weeks of once-daily LEVEMIR® administered in the evening as add-on therapy (n=164) or to unchanged treatment with liraglutide 1.8 mg and metformin (n=161). The starting dose of LEVEMIR® was 10 units/day and the mean dose at the end of the 26-week randomized period was 39 units/day. During the 26-week randomized treatment period, the percentage of patients who discontinued due to ineffective therapy was 11.2% in the group randomized to continued treatment with liraglutide 1.8 mg and metformin and 1.2% in the group randomized to add-on therapy with LEVEMIR®.

Treatment with LEVEMIR® as add-on to liraglutide 1.8 mg + metformin resulted in statistically significant reductions in FPG and HbA1C compared to unchanged treatment with liraglutide 1.8 mg + metformin alone (Table 10). From a mean baseline body weight of 96 kg after randomization, there was a mean reduction of 0.3 kg in the patients who received LEVEMIR® add-on therapy compared to a mean reduction of 1.1 kg in the patients who continued on unchanged treatment with liraglutide 1.8 mg + metformin alone.

Table 10: Results of a 26-week Open-label Trial of LEVEMIR® as Add-on to Liraglutide + Metformin Compared to Continued Treatment with Liraglutide + Metformin Alone in Patients Not Achieving Hba1C <7% After 12 Weeks of Metformin and Liraglutide

<table>
<thead>
<tr>
<th>Study H</th>
<th>LEVEMIR® + Liraglutide + Metformin</th>
<th>Liraglutide + Metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intent-to-Treat Population (N)</td>
<td>162</td>
<td>157</td>
</tr>
<tr>
<td>Hba1C (%) (Mean)</td>
<td>7.6</td>
<td>7.6</td>
</tr>
<tr>
<td>Adjusted mean change from baseline</td>
<td>-0.5</td>
<td>0*</td>
</tr>
<tr>
<td>Difference from liraglutide + metformin arm (LS mean)*</td>
<td>-0.5***</td>
<td>(-0.7, -0.4)</td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td>Percentage of patients achieving Hba1C &lt;7%</td>
<td>43**</td>
</tr>
<tr>
<td>Fasting Plasma Glucose (mg/dL) (Mean)</td>
<td>166</td>
<td>159</td>
</tr>
<tr>
<td>Baseline (week 0)</td>
<td>166</td>
<td>159</td>
</tr>
<tr>
<td>Adjusted mean change from baseline</td>
<td>-38*</td>
<td>-7*</td>
</tr>
<tr>
<td>Difference from liraglutide + metformin arm (LS mean)*</td>
<td>-31***</td>
<td>(-39, -23)</td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td>Percentage of patients achieving Hba1C &lt;7%</td>
<td>43**</td>
</tr>
</tbody>
</table>

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied
LEVEMIR® (insulin detemir) injection 100 units/mL (U-100) is a clear and colorless solution available in the following presentations:

<table>
<thead>
<tr>
<th>Presentation</th>
<th>NDC</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 mL Single-patient-use FlexTouch® pen</td>
<td>0169-6438-10</td>
</tr>
<tr>
<td>10 mL Multiple-dose vial</td>
<td>0169-3657-12</td>
</tr>
</tbody>
</table>

Additional Information about LEVEMIR® FlexTouch®:
- The pen dials in 1-unit increments.
- Use NovoFin® or NovoTwist® disposable needles.
- Each pen for use by a single patient. LEVEMIR® FlexTouch® must never be shared between patients, even if the needle is changed.

16.2 Storage
Dispense in the original sealed carton with the enclosed Instructions for Use.

Store unused (unopened) LEVEMIR® in the refrigerator between 36° to 46°F (2° to 8°C). 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. Keep unused LEVEMIR® in the carton so that it stays clean and protected from light.

Remove the needle from the LEVEMIR® FlexTouch® pen after each injection and store without a needle attached. Use a new needle for each injection.

The storage conditions for vials and LEVEMIR® FlexTouch® pens are summarized in Table 11:

Table 11: Storage Conditions for LEVEMIR® FlexTouch® and Vial

<table>
<thead>
<tr>
<th>LEVEMIR® Presentation</th>
<th>Not in-use (unopened)</th>
<th>In-use (opened)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refrigerated (36°F to 46°F [2°C and 8°C])</td>
<td>Room Temperature (up to 86°F [30°C])</td>
<td>Refrigerated (36°F to 46°F [2°C and 8°C])</td>
</tr>
<tr>
<td>3 mL single-patient-use LEVEMIR® FlexTouch® pen</td>
<td>Until expiration date</td>
<td>42 days</td>
</tr>
<tr>
<td>10 mL multiple-dose vial</td>
<td>Until expiration date</td>
<td>42 days</td>
</tr>
</tbody>
</table>

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (Patient Information and Instructions for Use). There are separate Instructions for Use for the Vials and LEVEMIR® FlexTouch® Pen.

Never Share a LEVEMIR® FlexTouch® Pen or Insulin Syringe Between Patients

Advise patients that they must never share a LEVEMIR® FlexTouch® pen with another person, even if the needle is changed. Advise patients using LEVEMIR® vials not to share needles or insulin syringes with another person. Sharing poses a risk for transmission of blood-borne pathogens (see Warnings and Precautions (5.1)).

Hypoglycemia or Hypoglycemia

Inform patients that hypoglycemia is the most common adverse reaction with insulin. Inform patients of the symptoms of hypoglycemia (e.g., impaired ability to concentrate and react). This may present a risk in situations where these abilities are especially important, such as driving or operating other machinery.

Advise patients who have frequent hypoglycemia or reduced or absent warning signs of hypoglycemia to use caution when driving or operating machinery (see Warnings and Precautions (5.3)).

Advise patients that changes in insulin regimen can predispose to hyperglycemia or hypoglycemia and that changes in insulin regimen should be made under close medical supervision (see Warnings and Precautions (5.2)).

Hypersensitivity Reactions

Advise patients that hypersensitivity reactions have occurred with LEVEMIR®. Inform patients on the symptoms of hypersensitivity reactions (see Warnings and Precautions (5.5)).

Hypoglycemia Due to Medication Errors

Instruct patients to always check the insulin label before each injection to avoid mix-ups between insulin products (see Warnings and Precautions (5.4)).
**PATIENT INFORMATION**

**LEVEMIR® (LEV–uh-mere)**

(insulin detemir) injection, for subcutaneous use

---

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

---

**What is Levemir®?**

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

---

**Who should not take Levemir®?**

**Do not take Levemir® if you:**

- have an allergy to Levemir® or any of the ingredients in Levemir®.

---

**Before taking Levemir®, tell your healthcare provider about all your medical conditions including, if you are:**

- pregnant, planning to become pregnant, or are breastfeeding.
- taking new prescription or over-the-counter medicines, vitamins, or herbal supplements.

---

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

---

**How should I take Levemir®?**

- Read the Instructions for Use that come with your Levemir®.
- Take Levemir® exactly as your healthcare provider tells you to.
- Know the type and strength of insulin you take. Do not change the type of insulin you take unless your healthcare provider tells you to. The amount of insulin and the best time for you to take your insulin may need to change if you take different types of insulin.
- Check your blood sugar levels. Ask your healthcare provider what your blood sugars should be and when you should check your blood sugar levels.
- Do not reuse or share your needles or syringes with other people. You may give other people a serious infection, or get a serious infection from them.
- Never inject Levemir® into a vein or muscle.
- Change (rotate) your injection sites within the area you choose with each dose to reduce your risk of getting lipodystrophy (pits in skin or thickened skin) and localized cutaneous amyloidosis (skin with lumps) at the injection sites.
- Do not use the exact same spot for each injection.
- Do not inject where the skin has pits, is thickened, or has lumps.
- Do not inject where the skin is tender, bruised, scaly or hard, or into scars or damaged skin.

---

**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

*Your insulin dose may need to change because of:*

- change in level of physical activity or exercise
- weight gain or loss

**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.
- 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.

---

**What are the ingredients in Levemir®?**

**Active Ingredient:** insulin detemir

**Inactive Ingredients:** dibasic sodium phosphate, glycerin, metacresol, phenol, sodium chloride, zinc and Water for Injection, USP. Hydrochloric acid or sodium hydroxide may be added.

**Manufactured by:**

Novo Nordisk Inc.
800 Scudders Mill Road
Plainsboro, NJ 08536
U.S. License Number 1261

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: 07/2022
INSTRUCTIONS FOR USE

LEVEMIR® (LEV–uh-mer) injection, for subcutaneous use
10 mL multiple-dose vial

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

How should I use the LEVEMIR® vial?

Using the 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. LEVEMIR® can be injected under the skin (subcutaneously) of your stomach area (abdomen), upper legs (thighs) or upper arms. For each injection, change (rotate) your injection site within the area of skin that you use to reduce your risk of getting lipodystrophy (pits in skin or thickened skin) and localized cutaneous amyloidosis (skin with lumps) at the injection sites. Do not use the same injection site for each injection. Do not inject where the skin has pits, is thickened, or has bumps. Do not inject where the skin is tender, bruised, scaly or hard, or into scars or damaged skin.

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 vials, 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 store LEVEMIR®?

• Do not freeze LEVEMIR®. Do not use LEVEMIR® if it has been frozen.

• Keep LEVEMIR® away from heat or light.

• All unopened vials:
  - Store unopened LEVEMIR® vials in the refrigerator at 36°F to 46°F (2°C to 8°C).
  - Unopened vials may be used until the expiration date printed on the label, if they have been stored in the refrigerator.
  - Unopened vials should be thrown away after 42 days, if they are stored at room temperature up to 86°F (30°C).

• After vials have been opened:
  - Opened LEVEMIR® vials can be stored in the refrigerator at 36°F to 46°F (2°C to 8°C) or at room temperature up to 86°F (30°C).
  - Throw away all opened LEVEMIR® vials after 42 days, even if they still have insulin left in them.

Revised: 07/2022
Novo Nordisk® and LEVEMIR® are registered trademarks of Novo Nordisk A/S.


Manufactured by:
Novo Nordisk Inc.
800 Scudders Mill Road
Plainboro, NJ 08536
U.S. License Number 1261
© 2005-2022 Novo Nordisk
US22LV00003 7/2022
INSTRUCTION FOR USE

Levemir® (LEV–uh–mere) (insulin detemir) injection, for subcutaneous use

FlexTouch® Pen

Please read the following instructions carefully before using your Levemir® FlexTouch® Pen®.

- Do not share your Levemir® FlexTouch® Pen with other people, even if the needle has been changed. You may give other people a serious infection, or get a serious infection from them.
- Levemir® FlexTouch® Pen (“Pen”) is a prefilled disposable, single-patient-use insulin pen containing 300 units insulin detemir. You can inject from 1 to 80 units in a single injection.
- People who are blind or have vision problems should not use this Pen without help from a person trained to use the Pen.

Supplies you will need to give your Levemir® injection:
- Levemir® FlexTouch® Pen
- a new NovoFine®, NovoFine® Plus, or NovoTwist® needle
- alcohol swab
- 1 sharps container for throwing away used Pens and needles.

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

Preparing your Levemir® FlexTouch® Pen:
- Wash your hands with soap and water.
- Before you start to prepare your injection, check the Levemir® FlexTouch® Pen label to make sure you are taking the right type of insulin. This is especially important if you take more than 1 type of insulin.
- Levemir® should look clear and colorless. Do not use Levemir® if it is thick, cloudy, or 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.

Insertion of the needle into the skin:

Step 1:
- 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 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.

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 light (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.

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.

- The Levemir® FlexTouch® Pen insulin scale will show you how much insulin is left in your Pen (See Figure L).
  - 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), upper legs (thighs) or upper arms.**
- For each injection, change (rotate) your injection site within the area of skin that you use to reduce your risk of getting lipodystrophy (pits in skin or thickened skin) and localized cutaneous amyloidosis (skin with lumps) at the injection sites.
- Do not use the same injection site for each injection. Do not inject where the skin has pits, is thickened, or has lumps. Do not inject where the skin is tender, bruised, scaly or hard, or into scars or damaged skin.

**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.
- 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 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.
- Do not share your Levemir® FlexTouch® Pen or needles with other people. You may give other people a serious infection, or get a serious infection from them.

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

**Step 11:**
- Choose your injection site (abdomen, thighs or upper arms) 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.

**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.
- 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 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:
- The used Levemir® FlexTouch® Pen may be thrown away in your household trash after you have removed the needle.
- You can put your used needles in a FDA-cleared sharps disposal container right away after use. Do not throw away (dispose of) loose needles 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
  - leak-resistant
  - properly labeled to warn of hazardous waste inside the container
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. Do not reuse or share your needles or syringes with other people. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA’s website at: http://www.fda.gov/safesharpsdisposal.
- Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.

**How should I store my Levemir® FlexTouch® Pen?**
- Store unused Levemir® FlexTouch® Pens in the refrigerator at 36°F to 46°F (2°C to 8°C).
- Store the Pen you are currently using out of the refrigerator up to 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 your Levemir® FlexTouch® Pen or needles with other people. You may give other people a serious infection, or get a serious infection from them.