**Illegible text**
LEVEMIR® (insulin detemir) injection

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. [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® FlexPen® dials in 1-unit increments.
- Use the LEVEMIR® FlexPen® 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 glycosylated hemoglobin control.
- Dose adjustments may be needed with changes in physical activity, changes in meal patterns (e.g., 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 (5.5)].
- 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 U/kg of body weight can be used to calculate the 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 FlexPen® prefilled pen
- 10 mL multiple-dose vial

4 CONTRAINDICATIONS
LEVEMIR® is contraindicated:
- During episodes of hypoglycemia [see Warnings and Precautions (5.5) and Adverse Reactions (6.1)].
- 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® FlexPen®, Needle, or Insulin Syringe between Patients
LEVEMIR® FlexPen® prefilled pens must never be shared between patients. 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 Hyperglycemia or Hypoglycemia with Changes in Insulin Regimen
Changes in an insulin regimen (e.g., insulin strength, manufacturer, type, injection site or method of administration) may affect the glycemic control and predispose to hypoglycemia [see Warnings and Precautions (5.4)] or hyperglycemia. Repeated insulin injections into areas of lipodystrophy or localized cutaneous amyloidosis have been reported to result in hyperglycemia; and a sudden change in the injection site (to an unaffected area) has been reported to result in hypoglycemia [see Adverse Reactions (6)].

5.3 Hypoglycemia
Hypoglycemia is the most common adverse reaction of insulin, including LEVEMIR® [see Adverse Reactions (6.1)]. Severe hypoglycemia or hypoglycemic episodes that cause death, may occur in patients treated with LEVEMIR®. Hypoglycemia can impair concentration ability and reaction time; this may place the patient and others at risk in situations where these abilities are important (e.g., driving or operating other machinery). LEVEMIR®, or any insulin, should not be used during episodes of hypoglycemia [see Contraindications (4)].

5.4 Hypoglycemia Due to Medication Errors
Hypoglycemia can happen suddenly and symptoms may differ in each patient and change over time in the same patient. Symptomatic awareness of hypoglycemia may be less pronounced in patients with long-term diabetes or in patients with diabetic autonomic neuropathy, using drugs that block the sympathetic nervous system (e.g., beta-blockers) [see Drug Interactions (7)], or who experience recurrent hypoglycemia.

5.5 Risk Factors for Hypoglycemia
The risk of hypoglycemia generally increases with intensity of glycosylated hemoglobin control. The risk of hypoglycemia after an injection is related to the duration of action of the insulin [see Clinical Pharmacology (12.2)] and, in general, is highest when the glucose lowering effect time course is maximal. As with all insulin products, the glucose lowering effect time course of LEVEMIR® may vary among different patients or at different times in the same patient and depends on many conditions, including the area of injection as well as the injection site blood supply and temperature.

5.6 Risk Mitigation Strategies for Hypoglycemia
Patients and caregivers must be educated to recognize and manage hypoglycemia. Self-monitoring of blood glucose plays an essential role in the prevention and management of hypoglycemia. In patients at higher risk for hypoglycemia and patients who have reduced symptomatic awareness of hypoglycemia, increased frequency of blood glucose monitoring is recommended.

5.7 Fluid Retention and Heart Failure with Concomitant Use of PPAR-gamma Agonists
Triazolidinediones (TZDs), which are peroxisome proliferator-activator receptor (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 develops, LEVEMIR® should be managed according to current standards of care, and discontinuation or dose reduction of the PPAR-gamma agonist must be considered.

6 ADVERSE REACTIONS
The following adverse reactions are discussed elsewhere:
- Hypoglycemia [see Warnings and Precautions (5.3)]
- 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 155 days, and the total exposure to LEVEMIR® was 351 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>
<tr>
<td>Adults with type 1 diabetes were exposed to LEVEMIR® (n=161) or NPH (n=159). The mean duration of exposure to LEVEMIR® was 176 days, and the total exposure to LEVEMIR® was 351 patient-years. The most common adverse reactions are summarized in Table 2.</td>
<td></td>
</tr>
</tbody>
</table>

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>14.1</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>
<tr>
<td>In two pooled trials, adults with type 2 diabetes were exposed to LEVEMIR® (n=430) or NPH (n=457). 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 2.</td>
<td></td>
</tr>
</tbody>
</table>

Table 3: Adverse Reactions occurring in ≥5% of LEVEMIR®-Treated Pediatric Patients with Type 1 Diabetes Mellitus in a 26-week Trial

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>LEVEMIR®, % (n = 232)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory tract infection</td>
<td>26.7</td>
</tr>
<tr>
<td>Headache</td>
<td>14.1</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>
| Pediatric patients with type 1 diabetes were exposed to individualized doses of LEVEMIR® (n=232) or NPH (n=115). The mean duration of exposure to LEVEMIR® was 180 days, and the total exposure to LEVEMIR® was 114 patient-years. The most common adverse
Table 3: Adverse Reactions Occurring in ≥5% of LEVEMIR®-Treated Pediatric Patients with Type 1 Diabetes Mellitus in a 26-week Trial

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

**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 (type 1 diabetes) and Table 5 (type 2 diabetes) 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 also, may not be representative of hypoglycemia rates that will occur in clinical practice.

Table 4 (type 1 diabetes) and Table 5 (type 2 diabetes) summarize the incidence of severe and non-severe hypoglycemia in the LEVEMIR® clinical trials.

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

### Table 4: Hypoglycemia in Patients with Type 1 Diabetes

<table>
<thead>
<tr>
<th>Study</th>
<th>Type 1 Diabetes</th>
<th>Percent of patients with at least 1 event (%)</th>
<th>Event/patient/year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study A</td>
<td>Adults 16 weeks</td>
<td>Twice-Daily LEVEMIR® 8.7 (24/276)</td>
<td>0.52</td>
</tr>
<tr>
<td>Study B</td>
<td>Adults 26 weeks</td>
<td>Twice-Daily LEVEMIR® 5.0 (8/161)</td>
<td>0.13</td>
</tr>
<tr>
<td>Study C</td>
<td>Adults 24 weeks</td>
<td>Once-Daily LEVEMIR® 7.5 (37/491)</td>
<td>0.35</td>
</tr>
<tr>
<td>Study D</td>
<td>Pediatrics 26 weeks</td>
<td>Once- or Twice Daily LEVEMIR® 15.9 (37/232)</td>
<td>0.91</td>
</tr>
<tr>
<td>Study I</td>
<td>Pediatrics 52 weeks</td>
<td>Once- or Twice Daily LEVEMIR® 1.7 (3/177)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

### Table 5: Hypoglycemia in Patients with Type 2 Diabetes

<table>
<thead>
<tr>
<th>Study</th>
<th>Type 2 Diabetes</th>
<th>Percent of patients with at least 1 event (%)</th>
<th>Event/patient/year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study E</td>
<td>Adults 24 weeks</td>
<td>Twice-Daily LEVEMIR® 0.4 (1/237)</td>
<td>1.5</td>
</tr>
<tr>
<td>Study F</td>
<td>Adults 22 weeks</td>
<td>Once- or Twice Daily LEVEMIR® 1.5 (3/195)</td>
<td>0</td>
</tr>
<tr>
<td>Study H</td>
<td>Adults 26 weeks</td>
<td>Once Daily LEVEMIR® + Liraglutide 40.5 (66/237)</td>
<td>9.2</td>
</tr>
</tbody>
</table>

#### 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 lipoatrophy (thickening of adipose tissue) and lipoatrophy (thinning of adipose tissue), and may affect insulin absorption (see Dosage and Administration). 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. 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.

### 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, 3 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 insulins, 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 unaffected injection site.

### 7 DRUG INTERACTIONS

Table 6 includes clinically significant drug interactions with LEVEMIR®.
Preparitional insulin aspart. Approximately half of the study participants in both arms were women with normal or impaired glucose tolerance (WHO criteria) to NPH or to other insulins prior to conception and in the first 8 weeks of gestation. The rates of preeclampsia observed in the study were within expected ranges for pregnancy complicated by diabetes.

No differences in pregnancy outcomes or the health of the fetus and newborn were seen between the two groups. In this study, the proportion of subjects with severe hypoglycemia and non-severe hypoglycemia was similar between the two treatment arms; for the definitions of severe hypoglycemia and non-severe hypoglycemia (see Adverse Reactions (6.1)).

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


dose Reductions and increased frequency of glucose monitoring may be required when LEVEMIR® is co-administered with these drugs.

Drugs that May Decrease the Blood Glucose Lowering Effect of LEVEMIR®

**Drugs:** Alcohol, beta-blockers, clonidine, and lithium salts.

**Intervention:** Dosage adjustments and increased frequency of glucose monitoring may be required when LEVEMIR® is co-administered with these drugs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

**Risk Summary:**

<table>
<thead>
<tr>
<th>Glucose Infusion Rate (mg/kg/min)</th>
<th>GIRmax (mg/kg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>1.1</td>
</tr>
<tr>
<td>0.2</td>
<td>1.7</td>
</tr>
<tr>
<td>0.4</td>
<td>2.1</td>
</tr>
</tbody>
</table>

**Drug and dose related increases in the incidence of fetuses with visceral anomalies.** Doses up to 900 nmol/kg/day (approximately 13 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 visceral anomalies such as small, bilobed, bifurcated, and missing gallbladders were observed at a dose of 900 nmol/kg/day. The rat and rabbit embryo-fetal development studies that included concurrent human insulin control groups indicated that insulin detemir and human insulin had similar effects regarding embryotoxicity and teratogenicity suggesting that the effects seen were the result of hypoglycemia resulting from insulin exposure in normal animals.

8.2 Lactation

**Risk Summary:**

Available data from published literature demonstrate that exogenous human insulin products, including biosynthetic insulins such as insulin aspart, are transferred into human milk. In 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 health benefits 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 E) with pediatric patients 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 Clinical Pharmacology (12.3), Clinical Studies (14.3)).

8.5 Geriatric Use

In clinical trials of LEVEMIR®, 64 of 1624 patients (4%) in the type 1 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 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 maintenance dosage should be conservative to avoid hypoglycemia. Hypoglycemia may be difficult to recognize in the geriatric patient.

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 show increased circulating insulin concentrations in patients with kidney disease; the effects of insulin detemir and human insulin may be different. Dosages of LEVEMIR®, 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. In patients with hepatic impairment and normal insulin sensitivity, the systemic exposures to insulin detemir and normal insulin are similar. This similarity may be maintained in patients with hepatic impairment (see Clinical Pharmacology (12.3)).

10 OVERDOSE

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.

11 DESCRIPTION

Insulin detemir is a long-acting recombinant human insulin analog produced by a process that includes expression of recombinant DNA in Saccharomyces cerevisiae followed by chemical modification.

Insulin detemir differs from human insulin in that the amino acid threonine in position B30 has been replaced, and a C14 fatty acid chain has been attached to the amino acid B39. Insulin detemir has a molecular formula of C_{40}H_{64}O_{24}N_{6}S_{2} and a molecular weight of 5917 Da. It has the following structure:

Figure 1: Structural Formula of Insulin Detemir

LEVEMIR® (insulin detemir) injection is a clear, colorless, aqueous, neutral sterile solution for subcutaneous use. Each milliliter of LEVEMIR® contains 100 units insulin detemir, dibasic sodium phosphate (0.71 mg), glycerin (16 mg), metacresol (2.06 mg), phenol (1.8 mg), sodium chloride (1.17 mg), zinc (65.4 mcg), and Water for injection. USP. Lactose hydrochloride and sodium hydroxide may be added to adjust pH. LEVEMIR® has a pH of approximately 7.4.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The primary activity of insulin, including LEVEMIR®, is regulation of glucose metabolism. Insulins and its analogs lower blood glucose by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin also inhibits lipolysis 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 slow systemic absorption of insulin detemir molecules from the injection site due to self-association of the drug molecules. In addition, the distribution of insulin detemir to peripheral target tissues is slowed because of binding to albumin.

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

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

**Graph:**

**Pharmacodynamic Parameters for LEVEMIR®**

<table>
<thead>
<tr>
<th>LEVEMIR®</th>
<th>0.2 Units/kg</th>
<th>0.4 Units/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUCGIR (mg/kg)</td>
<td>419</td>
<td>1184</td>
</tr>
<tr>
<td>GIRmax (mg/kg/min)</td>
<td>1.1</td>
<td>1.7</td>
</tr>
</tbody>
</table>

**Glucose Infusion Rate (mg/kg/min)**

<table>
<thead>
<tr>
<th>Time Since Insulin Injection (hours)</th>
<th>---</th>
<th>---</th>
</tr>
</thead>
<tbody>
<tr>
<td>---</td>
<td>---</td>
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</tr>
</tbody>
</table>

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**Figure 3:** 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.
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 studied 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 of LEVEMIR® was administered to healthy subjects and those with varying degrees of renal impairment (mild, moderate, severe, and hemodialysis-dependant). In this study, there were no differences in the pharmacokinetics of LEVEMIR® between healthy subjects and those with renal impairment [see Use in Specific Populations (8.6)].

Hepatic impairment
A single subcutaneous dose of 0.2 units/kg of LEVEMIR® was administered to healthy subjects and those with varying degrees of hepatic impairment (mild, moderate and severe). LEVEMIR® exposure as estimated by AUC decreased with increasing degrees of hepatic impairment with a corresponding increase in apparent clearance [see Use in Specific Populations (8.7)].

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 a 26-week trial of LEVEMIR® in type 1 diabetes (≤18 years). The other trial (Study I) was a 52 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. Bolus 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 (≤5 years, >5 and ≤12 years, >12 and ≤16 years, ≥16 years) and the mean HbA1c in the LEVEMIR®- and NPH insulin-treated groups was 3.8% lower at week 52. In both trials, LEVEMIR® and NPH insulin were administered to all patients at each meal, and no clinically relevant differences in renal or hepatic function were observed.

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>Treatment in combination with</td>
<td>NovoLog® (insulin aspart)</td>
<td>NovoLog® (insulin aspart)</td>
</tr>
<tr>
<td></td>
<td>Once- or Twice Daily LEVEMIR®</td>
<td>Once- or Twice Daily NPH</td>
</tr>
<tr>
<td></td>
<td>26 weeks</td>
<td>52 weeks</td>
</tr>
<tr>
<td>Number of patients treated</td>
<td>332</td>
<td>115</td>
</tr>
<tr>
<td>HBAlc (%)</td>
<td>10.2</td>
<td>9.7</td>
</tr>
<tr>
<td>Baseline HBAlc</td>
<td>8.8</td>
<td>8.8</td>
</tr>
<tr>
<td>Adj. mean change from baseline</td>
<td>0.6**</td>
<td>0.5**</td>
</tr>
<tr>
<td>LEVEMIR® - NPH 95% CI for Treatment difference</td>
<td>-0.3 (-0.5, -0.1)</td>
<td>-0.3 (-0.5, -0.1)</td>
</tr>
<tr>
<td>Fasting blood glucose (mg/dL)</td>
<td>190</td>
<td>180</td>
</tr>
<tr>
<td>Baseline mean</td>
<td>99</td>
<td>99</td>
</tr>
<tr>
<td>Adj. mean change from baseline</td>
<td>-41**</td>
<td>-41**</td>
</tr>
</tbody>
</table>

*From an ANCOVA model adjusted for baseline value and age.
**From an ANCOVA model adjusted for baseline value, age, and gender.
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 an alpha-glucosidase 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>Treatment duration</th>
<th>Study E</th>
<th>Study F</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>22 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment in combination with</td>
<td>oral agents</td>
<td>insulin aspart</td>
</tr>
<tr>
<td>Twice-daily LEVEMIR®</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Twice-daily NPH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Once- or Twice Daily LEVEMIR®</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Once- or Twice Daily NPH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of subjects treated</td>
<td>237</td>
<td>239</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.6</td>
<td>8.5</td>
</tr>
<tr>
<td>Adj. mean change from baseline</td>
<td>-2.0*</td>
<td>-2.1*</td>
</tr>
<tr>
<td>LEVEMIR® – NPH 95% CI for Treatment difference</td>
<td>-0.0, 0.3</td>
<td>-0.2, 0.1</td>
</tr>
<tr>
<td>Fasting blood glucose (mg/dL)</td>
<td>179</td>
<td>173</td>
</tr>
<tr>
<td>Baseline mean</td>
<td>179</td>
<td>173</td>
</tr>
<tr>
<td>Adj. mean change from baseline</td>
<td>-69*</td>
<td>-74*</td>
</tr>
</tbody>
</table>

*From an ANCOVA model adjusted for baseline value, country and oral antidiabetic treatment category.
**From an ANCOVA model adjusted for baseline value.
**From an ANCOVA model adjusted for baseline value and country.

Combination Therapy with Metformin and Liraglutide

This 26-week open-label trial enrolled 988 patients with inadequate glycemic control (HbA1c >7.5%) 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=162) or to continued, unchanged treatment with liraglutide 1.8 mg and metformin (n=161). The starting dose of LEVEMIR® was 10 units/day and the mean dose at the end of the 26-week randomized period was 39 units/day. During the 26-week randomized treatment period, the percentage of patients who discontinued due to ineffective therapy was 11.2% in the group randomized to continued treatment with liraglutide 1.8 mg and metformin and 12.1% in the group randomized to add-on therapy with LEVEMIR®.

Treatment with LEVEMIR® as add-on to liraglutide 1.8 mg + metformin resulted in statistically significant reductions in HbA1c and FPG compared to continued, unchanged treatment with liraglutide 1.8 mg + metformin alone (Table 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>
<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>Baseline (week 0)</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) 95% Confidence Interval</td>
<td>-0.5*** (-0.7, -0.4)</td>
<td>-0.7*** (-0.9, -0.5)</td>
</tr>
<tr>
<td>Percentage of patients achieving A1c &lt;7%</td>
<td>43**</td>
<td>17**</td>
</tr>
<tr>
<td>Fasting Plasma Glucose (mg/dL) (Mean)</td>
<td></td>
<td></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) 95% Confidence Interval</td>
<td>-31*** (-39, -23)</td>
<td>-23*** (-31, -15)</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® Prefilled Pen.

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

Advise patients that they must never share a LEVEMIR® Prefilled 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)].

Hyperglycemia or Hypoglycemia

Inform patients that hyperglycemia is the most common adverse reaction with insulin. Inform patients of the symptoms of hyperglycemia (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 hyperglycemia or reduced or absent warning signs of hypoglycemia to exercise caution when driving or operating machinery [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

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 exercise caution when driving or operating machinery [see Warnings and Precautions (5.2)].
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 for people with diabetic ketoacidosis (increased ketones in the blood or urine).

Who should not take LEVEMIR®?
Do not take LEVEMIR® if you:
- are having an episode of low blood sugar (hypoglycemia).
- have an allergy to LEVEMIR® or any of the ingredients in LEVEMIR®. See the end of this Patient Information leaflet for a complete list of ingredients in LEVEMIR®.

Before taking LEVEMIR®, tell your healthcare provider about all your medical conditions including, if you:
- take any other medicines, especially medicines commonly called TZDs (thiazolidinediones).
- are pregnant, planning to become pregnant, or are breastfeeding.

Tell your healthcare provider all the medicines you take, including prescription and 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 comes 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.
- LEVEMIR® is injected under the skin (subcutaneously) of your upper legs (thighs), upper arms, or stomach area (abdomen).
- Do not 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). Low blood sugar can be a serious, but common side effect of LEVEMIR®. Signs and symptoms that may indicate low blood sugar include:
  - dizziness or light-headedness
  - anxiety, irritability, or mood changes
  - slurred speech
  - shakiness
  - severe allergic reactions. Severe allergic reactions are a potential side effect of LEVEMIR®. Get emergency medical help if you have:
    - trouble breathing
    - swelling of your face, tongue, or throat
    - rash
    - swelling of your hands and feet
    - itching
    - shearing
    - dizziness or light-headedness

Other common side effects of LEVEMIR® include:
- injection site reactions
- skin thickening or pits at the injection site (lipodystrophy)
- swelling of your hands and feet
- swelling of ankles or feet
- weight gain
- rash
- shortness of breath
- shortness of breath
- skin thickening or pits at the injection site (lipodystrophy)
- swelling of your hands and feet
- itching

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

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. 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. You can ask your pharmacist or healthcare provider for information about LEVEMIR® that is written for health professionals.

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: 12/2022
INSTRUCTIONS FOR USE

LEVEMIR® (LEV-uh-merge) 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 lumps. 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.
Instructions For Use
LEVEMIR® (LEV-uh-mere) FlexPen®
(insulin detemir) injection, for subcutaneous use

Please read the following instructions carefully before using your LEVEMIR® FlexPen®.

Do not share your LEVEMIR® FlexPen® 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® FlexPen® is a prefilled disposable, single-patient-use, 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® or NovoFine® Plus needles.

People who are blind or have vision problems should not use this Pen without help from a person trained to use the Pen.

Getting ready
Make sure you have the following items:
• LEVEMIR® FlexPen®
• NovoFine® or NovoFine® Plus disposable needles
• Alcohol swab
• Sharps disposal container (see After the Injection)

LEVEMIR® FlexPen®

Pen cap

Rubber stopper

Cartridge scale

Pointer

Push-button selector

NovoFine®

Big outer needle cap

Inner needle cap

Needle

Protective tab

NovoFine® Plus

Big outer needle cap

Inner needle cap

Needle

Protective tab

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® helps prevent leakage, infection, and will help to make sure you inject the right dose of insulin.

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

B. Wipe the rubber stopper with an alcohol swab.

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

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

E. Turn the dose selector to select 2 units (see diagram E).

F. Hold your LEVEMIR® FlexPen® with the needle point ing 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. Keep the needle point ing upwards, press the green push-button all the way in (see diagram G). The dose selector returns to 0.

H. 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 green push-button as insulin will come out.

I. You cannot select a dose larger than the number of units left in the cartridge.

J. You will hear a click for every single unit dialed.

K. You cannot select a dose larger than the number of units left in the cartridge.

L. If blood appears after you take the needle out of your skin, press the injection site tightly with an alcohol swab. Do not rub the area.

After the injection
Do not recap the needle. Recapping can lead to a needle stick injury. Remove the needle from the LEVEMIR® FlexPen® after each injection and dispose of it. This helps to prevent infection, leakage of insulin, and will help to make sure you inject the right dose of insulin.

• If you do not have a sharps container, carefully slip the needle into the outer needle cap using 1 hand. Use your other hand to pinch the base of the big outer needle cap and unscrew the used needle from the FlexPen® and throw it away as soon as you can.

• 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
  • leak-resistant, and
  • 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.

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

Storing without the needle attached helps prevent leaking, blocking of the needle, and air from entering the LEVEMIR® FlexPen®.

How should I store LEVEMIR® FlexPen®?

• Store the unused (unopened) LEVEMIR® FlexPen® in the refrigerator between 36°F to 46°F (2°C to 8°C).

• Store the LEVEMIR® FlexPen® you are currently using out of the refrigerator up to 86°F.

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

• Keep the LEVEMIR® FlexPen® away from heat or light.

Always use a new needle for each injection to make sure the needle is free of germs (sterile) and to prevent blocked needles. Do not reuse or share your needles with other people. You may give other people a serious infection or get a serious infection from them.

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

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 proper dosing:

• Turn the dose selector to select 2 units (see diagram E).

• 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).

• Keep the needle pointing upwards, press the green push-button all the way in (see diagram G). The dose selector returns to 0.

• A drop of insulin should appear 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.

I. 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 green push-button as insulin will come out.

J. You cannot select a dose larger than the number of units left in the cartridge.

K. You will hear a click for every single unit dialed. Do not set the dose by counting the number of clicks you hear because you may get an incorrect dose.

L. Do not use the cartridge scale printed on the cartridge to measure your dose of insulin.

Giving the injection

Give the injection exactly as shown to you by your healthcare provider. Your healthcare provider should tell you if you need to pinch the skin before injecting. Wipe the skin with an alcohol swab and let the area dry.

LEVEMIR® can be injected under the skin (subcutaneously) of your stomach area (abdomen), upper legs (thighs), or upper arms.

Change (rotate) your injection sites within the area you choose for 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 same injection site for each injection. Do not inject where the skin has pits, is thickened,
• Unused LEVEMIR® FlexPens may be used until the expiration date printed on the label, if kept in the refrigerator. The LEVEMIR® FlexPen® you are using should be thrown away after 42 days, even if it still has insulin left in it.

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

Maintenance
For the safe and proper use of your LEVEMIR® FlexPen®, be sure to handle it with care. Avoid dropping your LEVEMIR® FlexPen® as it may damage it. If you are concerned that your LEVEMIR® FlexPen® is damaged, use a new one. You can clean the outside of your LEVEMIR® FlexPen® by wiping it with a damp cloth. Do not soak or wash your LEVEMIR® FlexPen® as it may damage it. Do not refill your LEVEMIR® FlexPen®.

△ Remove the needle from the LEVEMIR® FlexPen® after each injection. This helps to ensure sterility, prevent leakage of insulin, and will help to make sure you inject the right dose of insulin for future injections.

△ Be careful when handling used needles to avoid needle sticks and transfer of infectious diseases. Use the LEVEMIR® FlexPen® exactly as your healthcare provider tells you to.

△ Do not share your LEVEMIR® FlexPen® or needles with other people. You may give other people a serious infection, or get a serious infection from them.

△ 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 precautionary 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.
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® 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. Do not re-use or share your needles with other people. You may give other people a serious infection, or get a serious infection from them.

NovoFine®

Outer needle cap
Inner needle cap
Needle
Paper tab

NovoFine® Plus

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

Step 1:
• Pull Pen cap straight off (See 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.

Step 3:
• Select a new needle.
• Pull off the paper tab from the outer needle cap (See Figure D).

Step 4:
• Push the capped needle straight onto the Pen and twist the needle on until it is tight (See Figure E).

Step 5:
• Pull off the outer needle cap. Do not throw it away (See Figure F).

Step 6:
• Pull off the inner needle cap and throw it away (See Figure G).

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

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

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

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).

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 Insulin exactly as your healthcare provider has shown you. Your healthcare provider should tell you if you need to pinch the skin before injecting.
• Insulin 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 site.
• 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 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 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 rotating it clockwise (See Figure T).

After your injection:
• The used InsulinFlexTouch® 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, without sharps being able to come out
  • upright and stable during use
  • leak-resistant
  • properly labeled to warn of hazardous waste inside the container
• When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. Do not reuse or share your needles or syringes with other people. You may give other people a serious infection, or get a serious infection from them.