

## HIGHLIGHTS OF PRESCRIBING INFORMATION

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

**LEVEMIR® (insulin detemir) injection, for subcutaneous use**  
**Initial U.S. Approval: 2005**

### INDICATIONS AND USAGE

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).

### DOSAGE FORMS AND STRENGTHS

Injection: 100 units/mL (U-100) of insulin detemir available as:

- 3 mL single-patient-use FlexPen® prefilled pen (3)
- 10 mL multiple-dose vial (3)

### CONTRAINDICATIONS

- During episodes of hypoglycemia (4)
- Hypersensitivity to insulin detemir or any of the excipients in LEVEMIR (4)

### WARNINGS AND PRECAUTIONS

- Never Share a LEVEMIR FlexPen, insulin syringe, or needle between patients, even if the needle is changed (5.1).
- *Hyperglycemia or hypoglycemia with changes in insulin regimen:* Make changes to a patient's insulin regimen (e.g., insulin strength, manufacturer, type, injection site or method of administration) under close medical supervision with increased frequency of blood glucose monitoring (5.2).
- *Hypoglycemia:* May be life-threatening. Increase frequency of glucose monitoring with changes to: insulin dosage, concomitant drugs, meal pattern, physical activity; and in patients with renal impairment or hepatic impairment or hypoglycemia unawareness (5.3).
- *Hypoglycemia due to medication errors:* Accidental mix-ups between insulin products can occur. Instruct patients to check insulin labels before injection (5.4).
- *Hypersensitivity reactions:* Severe, life-threatening, generalized allergy, including anaphylaxis, can occur. Discontinue LEVEMIR, monitor and treat if indicated (5.5).
- *Hypokalemia:* May be life-threatening. Monitor potassium levels in patients at risk for hypokalemia and treat if indicated (5.6).
- *Fluid retention and heart failure with concomitant use of thiazolidinediones (TZDs):* Observe for signs and symptoms of heart failure; consider dosage reduction or discontinuation if heart failure occurs (5.7).

### 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](http://www.fda.gov/medwatch).**

### DRUG INTERACTIONS

- *Drugs that Affect Glucose Metabolism:* Adjustment of insulin dosage may be needed. (7)
- *Antiadrenergic 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: 12/2022

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## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

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

#### Limitations of Use

LEVEMIR is not recommended for the treatment of diabetic ketoacidosis.

### 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 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 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 FlexPen prefilled pen
- 10 mL multiple-dose vial

## **4 CONTRAINDICATIONS**

LEVEMIR is contraindicated:

- During episodes of hypoglycemia [see *Warnings and Precautions (5.3)*]
- 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, even if the needle 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 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 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)*].

Make any changes to a patient's insulin regimen under close medical supervision with increased frequency of blood glucose monitoring. Advise patients who have repeatedly injected into areas of lipodystrophy or

localized cutaneous amyloidosis to change the injection site to unaffected areas and closely monitor for hypoglycemia. For patients with type 2 diabetes, dosage adjustments of concomitant antidiabetic products may be needed [see *Dosage and Administration (2.4)*].

### **5.3 Hypoglycemia**

Hypoglycemia is the most common adverse reaction of insulin, including LEVEMIR [see *Adverse Reactions (6.1)*]. Severe hypoglycemia can cause seizures, may be life-threatening or cause death. 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)*].

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 longstanding diabetes, in patients with diabetic neuropathy, using drugs that block the sympathetic nervous system (e.g., beta-blockers) [see *Drug Interactions (7)*], or who experience recurrent hypoglycemia.

#### Risk Factors for Hypoglycemia

The risk of hypoglycemia generally increases with intensity of glycemic 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 of the insulin is maximal. As with all insulins, 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.

Other factors which may increase the risk of hypoglycemia include changes in meal pattern (e.g., macronutrient content or timing of meals), changes in level of physical activity, or changes to concomitant drugs [see *Drug Interactions (7)*]. When a GLP-1 receptor agonist is used in combination with LEVEMIR, the LEVEMIR dose may need to be lowered or more conservatively titrated to minimize the risk of hypoglycemia [see *Adverse Reactions (6.1)*]. Patients with renal or hepatic impairment may be at higher risk of hypoglycemia [see *Use in Specific Populations (8.6, 8.7)*].

#### 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.

### **5.4 Hypoglycemia Due to Medication Errors**

Accidental mix-ups between insulin products have been reported. To avoid medication errors between LEVEMIR and other insulins, instruct patients to always check the insulin label before each injection.

### **5.5 Hypersensitivity Reactions**

Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulins, including LEVEMIR [see *Adverse Reactions (6.1)*]. If hypersensitivity reactions occur, discontinue LEVEMIR; treat per standard of care and monitor until symptoms and signs resolve. LEVEMIR is contraindicated in patients who have had hypersensitivity reactions to insulin detemir or any of the excipients.

### 5.6 Hypokalemia

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).

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

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

## 6 ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere:

- Hypoglycemia [see *Warnings and Precautions (5.3)*]
- 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=767) or NPH (n=388). The mean duration of exposure to LEVEMIR was 153 days, and the total exposure to LEVEMIR was 321 patient-years. The most common adverse reactions are summarized in Table 1.

**Table 1: Adverse Reactions Occurring in  $\geq 5\%$  of LEVEMIR-Treated Adult Patients with Type 1 Diabetes Mellitus in Two Trials of 16 Weeks and 24 Weeks Duration**

	LEVEMIR, % (n = 767)
Upper respiratory tract infection	26.1

Headache	22.6
Pharyngitis	9.5
Influenza-like illness	7.8
Abdominal Pain	6.0

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  $\geq 5\%$  of LEVEMIR-Treated Adult Patients with Type 1 Diabetes Mellitus in a 26-week Trial**

	LEVEMIR, % (n = 161)
Upper respiratory tract infection	26.7
Headache	14.3
Back pain	8.1
Influenza-like illness	6.2
Gastroenteritis	5.6
Bronchitis	5.0

In two pooled trials, adults with type 2 diabetes were exposed to LEVEMIR (n=432) or NPH (n=437). The mean duration of exposure to LEVEMIR was 157 days, and the total exposure to LEVEMIR was 186 patient-years. The most common adverse reactions were comparable to that observed in adult patients with type 1 diabetes mellitus; see Table 1.

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 reactions are summarized in Table 3.

**Table 3: Adverse Reactions Occurring in  $\geq 5\%$  of LEVEMIR-Treated Pediatric Patients with Type 1 Diabetes Mellitus in a 26-week Trial**

	LEVEMIR, % (n = 232)
Upper respiratory tract infection	35.8
Headache	31.0
Pharyngitis	17.2
Gastroenteritis	16.8
Influenza-like illness	13.8
Abdominal pain	13.4
Pyrexia	10.3
Cough	8.2
Viral infection	7.3
Nausea	6.5
Rhinitis	6.5
Vomiting	6.5

### 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 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 provided by the caregiver.

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

		Severe Hypoglycemia		Non-Severe Hypoglycemia	
		Percent of patients with at least 1 event (n/total N)	Event/patient/year	Percent of patients (n/total N)	Event/patient/year
Study A Type 1 Diabetes Adults 16 weeks In combination with insulin aspart	Twice-Daily LEVEMIR	8.7 (24/276)	0.52	88.0 (243/276)	26.4
Study B Type 1 Diabetes Adults 26 weeks In combination with insulin aspart	Twice-Daily LEVEMIR	5.0 (8/161)	0.13	82.0 (132/161)	20.2
Study C Type 1 Diabetes Adults 24 weeks In combination with regular insulin	Once-Daily LEVEMIR	7.5 (37/491)	0.35	88.4 (434/491)	31.1
Study D Type 1 Diabetes Pediatrics 26 weeks In combination with insulin aspart	Once- or Twice Daily LEVEMIR	15.9 (37/232)	0.91	93.1 (216/232)	31.6
Study I Type 1 Diabetes Pediatrics 52 weeks In combination with insulin aspart	Once- or Twice Daily LEVEMIR	1.7 (3/177)	0.02	94.9 (168/177)	56.1

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

		Study E Type 2 Diabetes Adults 24 weeks In combination with oral agents	Study F Type 2 Diabetes Adults 22 weeks In combination with insulin aspart	Study H Type 2 Diabetes Adults 26 weeks in combination with Liraglutide and Metformin
		Twice-Daily LEVEMIR	Once- or Twice Daily LEVEMIR	Once Daily LEVEMIR + Liraglutide + Metformin
Severe hypoglycemia	Percent of patients with at least 1 event (n/total N)	0.4 (1/237)	1.5 (3/195)	0
	Event/patient/year	0.01	0.04	0
Non-severe hypoglycemia	Percent of patients (n/total N)	40.5 (96/237)	32.3 (63/195)	9.2 (15/163)
	Event/patient/year	3.5	1.6	0.29

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 transitory, reversible ophthalmologic refraction disorder, worsening of diabetic retinopathy, and acute painful peripheral neuropathy. However, long-term glycemic control decreases the risk of diabetic retinopathy and neuropathy.

Lipodystrophy

Long-term use of insulin, including LEVEMIR, can cause lipodystrophy at the site of repeated insulin injections. Lipodystrophy includes lipohypertrophy (thickening of adipose tissue) and lipoatrophy (thinning of adipose tissue), and may affect insulin absorption [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.

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 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.

**Table 6: Clinically Significant Drug Interactions with LEVEMIR**

<b>Drugs That May Increase the Risk of Hypoglycemia</b>	
Drugs:	Antidiabetic agents, ACE inhibitors, angiotensin II receptor blocking agents, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, pentoxifylline, pramlintide, salicylates, somatostatin analogs (e.g., octreotide), and sulfonamide antibiotics, GLP-1 receptor agonists, DPP-4 inhibitors, SGLT-2 inhibitors.
Intervention:	Dosage reductions and increased frequency of glucose monitoring may be required when LEVEMIR is co-administered with these drugs.
<b>Drugs That May Decrease the Blood Glucose Lowering Effect of LEVEMIR</b>	
Drugs:	Atypical antipsychotics (e.g., olanzapine and clozapine), corticosteroids, danazol, diuretics, estrogens, glucagon, isoniazid, niacin, oral contraceptives, phenothiazines, progestogens (e.g., in oral contraceptives), protease inhibitors, somatropin, sympathomimetic agents (e.g., albuterol, epinephrine, terbutaline), and thyroid hormones.
Intervention:	Dosage increases and increased frequency of glucose monitoring may be required when LEVEMIR is co-administered with these drugs.
<b>Drugs That May Increase or Decrease the Blood Glucose Lowering Effect of LEVEMIR</b>	

Drugs:	Alcohol, beta-blockers, clonidine, and lithium salts. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.
Intervention:	Dosage adjustment and increased frequency of glucose monitoring may be required when LEVEMIR is co-administered with these drugs.
<b>Drugs That May Blunt Signs and Symptoms of Hypoglycemia</b>	
Drugs:	Beta-blockers, clonidine, guanethidine, and reserpine
Intervention:	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

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 that included 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 20%, respectively. The estimated background risk of major birth defects is 6 to 10% in women with pre-gestational diabetes with a peri-conceptual  $HbA_{1c} >7$  and has been reported to be as high as 20 to 25% in women with a peri-conceptual  $HbA_{1c} >10$ . The estimated background risk of miscarriage for the indicated population is unknown.

#### Clinical Considerations

##### *Disease-Associated Maternal and/or Embryo/Fetal Risk*

Hypoglycemia and hyperglycemia occur more frequently during pregnancy in patients with pre-gestational diabetes. Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, preeclampsia, spontaneous abortions, preterm delivery, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia-related morbidity.

#### Data

##### *Human Data*

In an open-label clinical trial, pregnant females with type 1 diabetes (n=310) were treated with LEVEMIR (once or twice daily) or NPH insulin (once, twice, or thrice daily); both groups also received prandial insulin aspart. Approximately half of the study participants in each arm were randomized as pregnant and were exposed to NPH or to other insulins prior to conception and in the first 8 weeks of

gestation. The rates of preeclampsia observed in the study were within expected rates 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 above the lower level of quantification (<25 pmol/L).

#### *Animal Data*

In a fertility and embryonic development study, insulin detemir was administered to female rats before mating, during mating, and throughout pregnancy at doses up to 300 nmol/kg/day (3 times a human dose of 0.5 units/kg/day, based on plasma area under the curve (AUC) ratio). Doses of 150 and 300 nmol/kg/day produced numbers of litters with visceral anomalies. Doses up to 900 nmol/kg/day (approximately 135 times a human dose of 0.5 units/kg/day based on AUC ratio) were given to rabbits during organogenesis. Drug and dose related increases in the incidence of fetuses with gallbladder abnormalities such as small, bilobed, bifurcated, and missing gallbladders were observed at a dose of 900 nmol/kg/day. The rat and rabbit 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 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 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 I) in 694 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 and 309 of 1082 patients (29%) in the 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 safety or effectiveness were observed between these patients and younger patients, but small sample sizes limits 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 patients.

### **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 impairment. Careful glucose monitoring and dose adjustments 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. However, some studies 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**

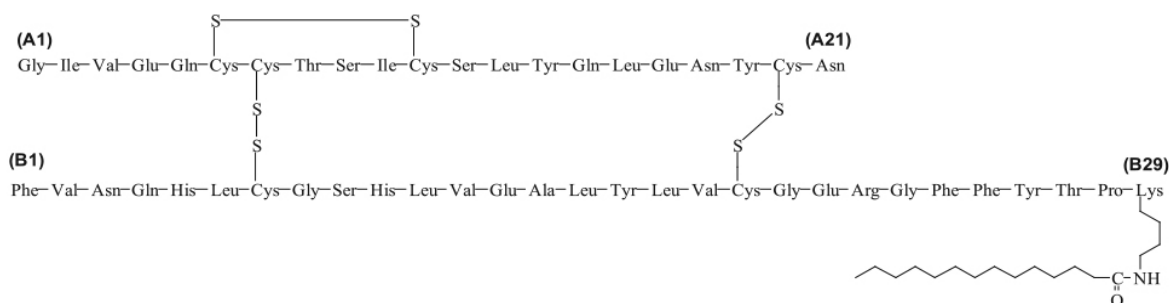
An excess of insulin relative to food intake, energy expenditure, or both may lead to severe and sometimes prolonged and life-threatening hypoglycemia and hypokalemia [*see Warnings and Precautions (5.3, 5.6)*]. Mild episodes of hypoglycemia usually can be treated with oral glucose. Lowering the insulin dosage, and adjustments in meal patterns, or exercise may be needed. More severe episodes with coma, seizure, 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 omitted, and a C14 fatty acid chain has been attached to the amino acid B29. Insulin detemir has a molecular formula of  $C_{267}H_{402}O_{76}N_{64}S_6$  and a molecular weight of 5.917 kDa. 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. Hydrochloric acid and/or sodium hydroxide may be added to adjust pH. LEVEMIR has a pH of approximately 7.4.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

The primary activity of insulin, 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 proteolysis, and enhances protein synthesis.

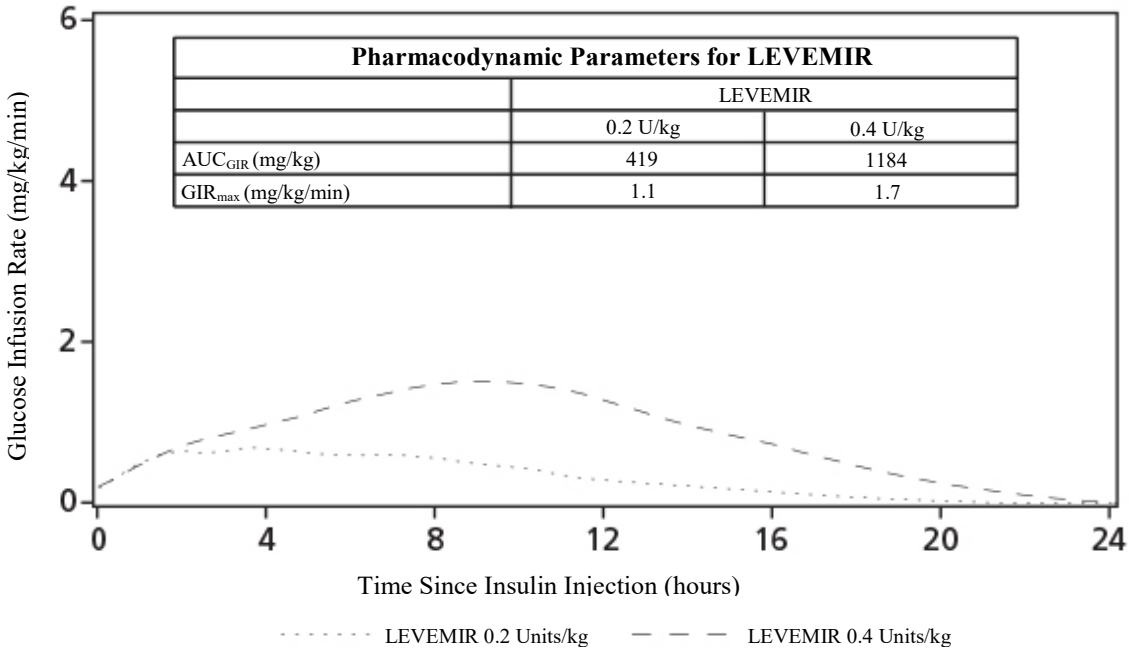
### 12.2 Pharmacodynamics

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

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

Figure 2 shows results from a study in patients with type 1 diabetes conducted for a maximum of 24 hours after the subcutaneous injection of LEVEMIR. 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**

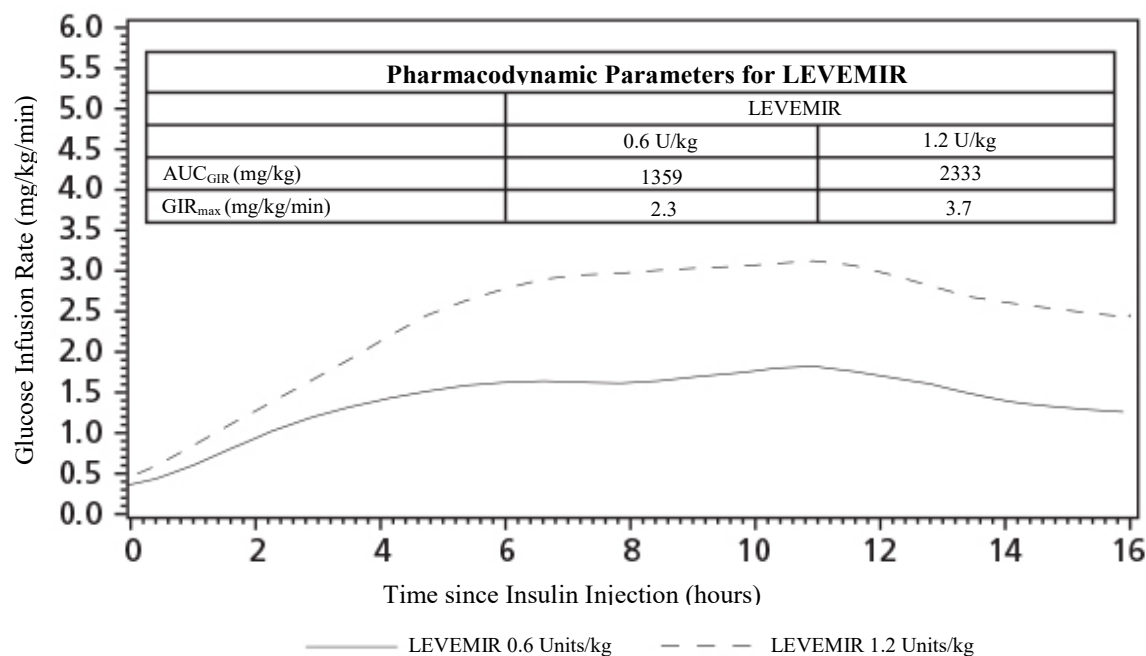


AUC<sub>GIR</sub>: Area Under Curve Glucose Infusion Rate  
GIR<sub>max</sub>: Maximum Glucose Infusion Rate

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

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

**Figure 3: Glucose Lowering Effect in Patients with Type 2 Diabetes in a 16-hour Glucose Clamp Study**



AUC<sub>GIR</sub>: Area Under Curve Glucose Infusion Rate  
GIR<sub>max</sub>: Maximum Glucose Infusion Rate

### 12.3 Pharmacokinetics

#### Absorption

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

The absolute bioavailability of insulin detemir is approximately 60%.

#### Distribution

Insulin detemir has an apparent volume of distribution of approximately 0.1 L/kg. More than 98% of insulin detemir in the bloodstream is bound to albumin. The results of *in vitro* and *in vivo* protein binding studies demonstrate that there is no clinically relevant interaction between insulin detemir and fatty acids or other protein-bound drugs.

#### Elimination

After subcutaneous administration in patients with type 1 diabetes, insulin detemir has a terminal half-life of 5 to 7 hours depending on dose.

#### Specific Populations

### *Pediatric Patients*

The pharmacokinetic properties of LEVEMIR were studied in pediatric patients 6-12 years, 13-17 years, and adults with type 1 diabetes. In pediatric patients 6-12 years, the insulin detemir plasma area under the curve (AUC) and  $C_{\max}$  were increased by 10% and 24%, respectively, as compared to adults. There was no difference in pharmacokinetics between pediatric patients 13-17 years and adults.

### *Geriatrics*

In a clinical trial studying differences in pharmacokinetics of a single subcutaneous dose of LEVEMIR in young (20 to 35 years) versus elderly ( $\geq 68$  years) healthy subjects, the insulin detemir AUC was up to 35% higher among the elderly subjects due to reduced clearance [see *Use in Specific Populations (8.5)*].

### *Gender*

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

### *Race*

In two clinical pharmacology studies conducted in healthy Japanese and Caucasian subjects, there were no clinically relevant differences seen in pharmacokinetic parameters. The pharmacokinetics and pharmacodynamics of LEVEMIR were 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-dependent). 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)*].

### *Smoking*

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

### *Liraglutide*

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

## **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 doses up to 300 nmol/kg/day (3 times a human dose of 0.5 units/kg/day, based on plasma AUC ratio). There were no effects on fertility in the rat.

## 14 CLINICAL STUDIES

The efficacy and safety of LEVEMIR given once-daily at bedtime or twice-daily (before breakfast and at bedtime, before breakfast and with the evening meal, or at 12-hour intervals) was compared to that of once-daily or twice-daily NPH insulin in open-label, randomized, parallel 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 HbA<sub>1c</sub> 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 HbA<sub>1c</sub> and fasting plasma glucose (FPG) reductions compared to the NPH-treated patients (Table 7). Differences in timing of LEVEMIR administration had no effect on HbA<sub>1c</sub>, 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 twice-daily LEVEMIR (administered in the morning and bedtime) or once-daily insulin glargine (administered at bedtime). Insulin aspart was administered before each meal. LEVEMIR-treated patients had a decrease in HbA<sub>1c</sub> 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 regular human insulin before each meal. LEVEMIR and NPH insulin had a similar effect on HbA<sub>1c</sub>.

**Table 7: Type 1 Diabetes Mellitus – Adult**

	Study A		Study B		Study C	
Treatment duration	16 weeks		26 weeks		24 weeks	
Treatment in combination with	NovoLog (insulin aspart)		NovoLog (insulin aspart)		Human Soluble Insulin (regular insulin)	
	<u>Twice-daily LEVEMIR</u>	<u>Twice-daily NPH</u>	<u>Twice-daily LEVEMIR</u>	<u>Once- daily insulin glargine</u>	<u>Once-daily LEVEMIR</u>	<u>Once- daily NPH</u>
Number of patients treated	276	133	161	159	492	257
HbA <sub>1c</sub> (%)						

Baseline HbA <sub>1c</sub>	8.6	8.5	8.9	8.8	8.4	8.3
Adj. mean change from baseline	-0.8*	-0.7*	-0.6**	-0.5**	-0.1*	0.0*
LEVEMIR – NPH 95% CI for Treatment difference	-0.2 (-0.3, -0.0)		-0.0 (-0.2, 0.2)		-0.1 (-0.3, 0.0)	
Fasting blood glucose (mg/dL)						
Baseline mean	209	220	153	150	213	206
Adj. mean change from baseline	-44*	-9*	-38**	-41**	-30*	-9*

\*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 6 to 17 years of age. The other trial (Study I) was 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 HbA<sub>1c</sub> 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=265) and the mean HbA<sub>1c</sub> increased in both treatment arms, with similar findings in the 2-5 year-old age group (n=80) and the 6-16 year-old age group (n=258) (Table 8).

**Table 8: Type 1 Diabetes Mellitus – Pediatric**

	Study D		Study I	
Treatment duration	26 weeks		52 weeks	
Treatment in combination with	NovoLog (insulin aspart)		NovoLog (insulin aspart)	
	Once- or Twice Daily <u>LEVEMIR</u>	Once- or Twice Daily <u>NPH</u>	Once- or Twice Daily <u>LEVEMIR</u>	Once- or Twice Daily <u>NPH</u>
Number of subjects treated	232	115	177	170
HbA <sub>1c</sub> (%)				
Baseline HbA <sub>1c</sub>	8.8	8.8	8.4	8.4
Adj. mean change from baseline	-0.7*	-0.8*	0.3**	0.2**
LEVEMIR – NPH 95% CI for Treatment difference	0.1 -0.1; 0.3		0.1 -0.1; 0.4	
Fasting blood glucose (mg/dL)				
Baseline mean	181	181	135	141
Adj. mean change from baseline	-39	-21	-10**	0**

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

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

## 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 HbA<sub>1c</sub> 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 HbA<sub>1c</sub> or FPG, LEVEMIR had efficacy similar to that of NPH insulin.

**Table 9: Type 2 Diabetes Mellitus – Adult**

	Study E		Study F	
Treatment duration	24 weeks		22 weeks	
Treatment in combination with	oral agents		insulin aspart	
	<u>Twice-daily LEVEMIR</u>	<u>Twice-daily NPH</u>	Once- or Twice Daily <u>LEVEMIR</u>	Once- or Twice Daily <u>NPH</u>
Number of subjects treated	237	239	195	200
HbA <sub>1c</sub> (%)				
Baseline HbA <sub>1c</sub>	8.6	8.5	8.2	8.1
Adj. mean change from baseline	-2.0*	-2.1*	-0.6**	-0.6**
LEVEMIR – NPH 95% CI for Treatment difference	0.1 (-0.0, 0.3)		-0.1 (-0.2, 0.1)	
Fasting blood glucose <sup>1</sup> (mg/dL)				
Baseline mean	179	173	-	-
Adj. mean change from baseline	-69*	-74*	-	-

<sup>1</sup>Study F - Fasting blood glucose data not collected

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

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

### Combination Therapy with Metformin and Liraglutide

This 26-week open-label trial enrolled 988 patients with inadequate glycemic control (HbA<sub>1c</sub> 7-10%) on metformin (≥1500 mg/day) alone or inadequate glycemic control (HbA<sub>1c</sub> 7-8.5%) on metformin (≥1500 mg/day) and a sulfonylurea. Patients who were on metformin and a sulfonylurea discontinued the sulfonylurea then all patients entered a 12-week run-in period during which they received add-on therapy with liraglutide titrated to 1.8 mg once-daily. At the end of the run-in period, 498 patients (50%) achieved HbA<sub>1c</sub> <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 HbA<sub>1c</sub> ≥7% (33% of those who entered the run-in period) were randomized to 26 weeks of once-daily LEVEMIR administered in the evening as add-on therapy (n=162) or to continued, unchanged treatment with liraglutide 1.8 mg and metformin (n=161). The starting dose of LEVEMIR was 10 units/day and the mean dose at the end of the 26-week randomized period was 39 units/day. During the 26-week randomized treatment period, the percentage of patients who discontinued due to ineffective therapy was 11.2% in the group randomized to continued treatment with liraglutide 1.8 mg and metformin and 1.2% in the group randomized to add-on therapy with LEVEMIR.

Treatment with LEVEMIR as add-on to liraglutide 1.8 mg + metformin resulted in statistically significant reductions in HbA<sub>1c</sub> 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 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 HbA<sub>1c</sub> <7% After 12 Weeks of Metformin and Liraglutide**

	Study H	
	LEVEMIR + Liraglutide +Metformin	Liraglutide+ Metformin
<b>Intent-to-Treat Population (N)<sup>a</sup></b>	162	157
<b>HbA<sub>1c</sub> (%) (Mean)</b>		
Baseline (week 0)	7.6	7.6
Adjusted mean change from baseline	-0.5*	0*
Difference from liraglutide + metformin arm (LS mean) <sup>b</sup> 95% Confidence Interval	-0.5*** (-0.7, -0.4)	
Percentage of patients achieving A <sub>1c</sub> <7%	43**	17**
<b>Fasting Plasma Glucose (mg/dL) (Mean)</b>		
Baseline (week 0)	166	159
Adjusted mean change from baseline	-38*	-7*
Difference from liraglutide + metformin arm (LS mean) <sup>b</sup> 95% Confidence Interval	-31*** (-39, -23)	

<sup>a</sup>Intent-to-treat population using last observation on study

<sup>b</sup>Least squares mean adjusted for baseline value

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

\*\*From a logistic regression model adjusted for baseline HbA<sub>1c</sub>.

\*\*\*p-value <0.0001

## 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:

Presentation	NDC
3 mL Single-patient-use FlexPen pen	0169-6432-10
10 mL Multiple-dose vial	0169-3687-12

Additional Information about LEVEMIR FlexPen:

- The pen dials in 1-unit increments.
- Use NovoFine<sup>®</sup> or NovoFine Plus<sup>®</sup> disposable needles.
- Each pen for use by a single patient. LEVEMIR FlexPen 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° and 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 FlexPen pen after each injection and store without a needle attached. Use a new needle for each injection.

The storage conditions for vials and LEVEMIR FlexPen prefilled pens are summarized in Table 11:

**Table 11: Storage Conditions for LEVEMIR FlexPen and Vial**

LEVEMIR Presentation	Not in-use (unopened)		In-use (opened)	
	Refrigerated (36°F to 46°F [2°C and 8°C])	Room Temperature (up to 86°F [30°C])	Refrigerated (36°F to 46°F [2°C and 8°C])	Room Temperature (up to 86°F [30°C])
3 mL single-patient-use LEVEMIR FlexPen	Until expiration date	42 days	Do not refrigerate	42 days
10 mL multiple-dose vial	Until expiration date	42 days	42 days	42 days

## 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 FlexPen Prefilled Pen.

### *Never Share a LEVEMIR FlexPen or Insulin Syringe Between Patients*

Advise patients that they must never share a LEVEMIR FlexPen 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 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)*].

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Patent Information: <https://www.novonordisk-us.com/products/product-patents.html>

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Manufactured by:

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Plainsboro, NJ 08536  
U.S. License Number 1261

For information about LEVEMIR contact:

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800 Scudders Mill Road  
Plainsboro, New Jersey 08536  
1-800-727-6500

[www.novonordisk-us.com](http://www.novonordisk-us.com)

**PATIENT INFORMATION**  
**LEVEMIR® (LEV–uh–mere)**  
**(insulin detemir)**  
**injection, for subcutaneous use**

**Do not share your LEVEMIR FlexPen with other people, even if the needle has been changed. Do not share needles or syringes with another person. 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 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
  - blurred vision
  - anxiety, irritability, or mood changes
  - sweating
  - slurred speech
  - hunger
  - confusion
  - shakiness
  - headache
  - fast heartbeat

- **severe allergic reactions.** Severe allergic reactions are a potential side effect of LEVEMIR. Get emergency medical help if you have:
  - trouble breathing
  - fast heartbeat
  - swelling of your face, tongue, or throat
  - extreme drowsiness
  - shortness of breath
  - swelling
  - sweating
  - dizziness
  - confusion
- **low potassium in your blood (hypokalemia).**
- **heart failure.** Taking certain diabetes pills called TZDs (thiazolidinediones) with LEVEMIR may cause heart failure in some people. This can happen even if you have never had heart failure or heart problems before. If you already have heart failure, it may get worse while you take TZDs with LEVEMIR. Tell your healthcare provider if you have any new or worse symptoms of heart failure including:
  - shortness of breath
  - swelling of ankles or feet
  - sudden weight gainTreatment with TZDs and LEVEMIR may need to be changed or stopped by your healthcare provider if you have new or worse heart failure.

**Other common side effects of LEVEMIR include:**

- injection site reactions
- skin thickening or pits at the injection site (lipodystrophy)
- weight gain
- swelling of your hands and feet
- rash
- itching

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

- change in level of physical activity or exercise
- weight gain or loss
- increased stress
- illness
- change in diet

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

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

**General information about the safe and effective use of LEVEMIR.**

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information Leaflet. 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](http://www.novonordisk-us.com) or call 1-800-727-6500.

**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.

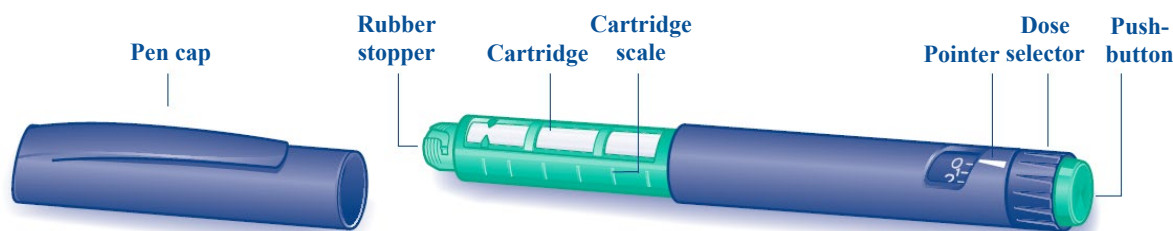
△ People who are blind or have vision problems should not use this Pen without help from a person trained to use the Pen.

**Getting ready**

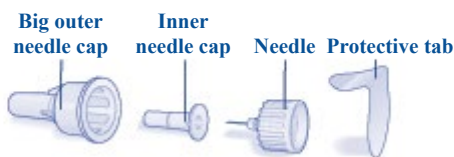
Make sure you have the following items:

- LEVEMIR FlexPen
- NovoFine or NovoFine Plus disposable needles
- Alcohol swab
- Sharps disposal container (see **After the Injection**)

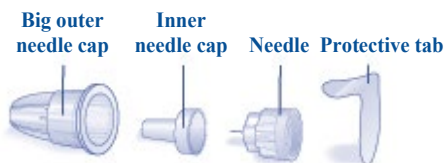
**LEVEMIR FlexPen**



**NovoFine**



**NovoFine Plus**

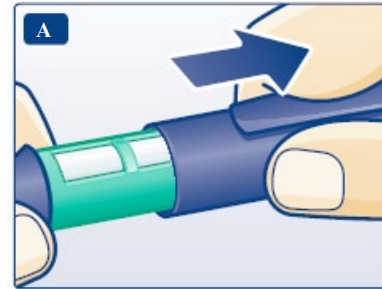


### Preparing your LEVEMIR FlexPen

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

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

Wipe the rubber stopper with an alcohol swab.

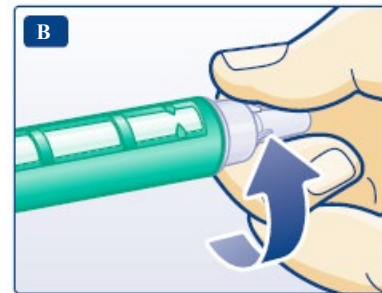


**B.** Attaching the needle

Remove the protective tab from a new disposable needle.

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

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



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



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

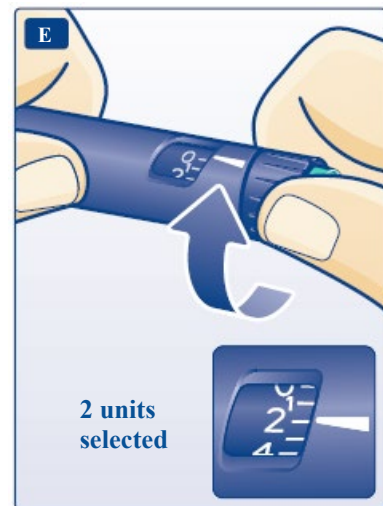


- ⚠ Always use a new needle for each injection to make sure the needle is free of germs (sterile) and to prevent blocked needles. **Do not** reuse or share your needles with other people. You may give other people a serious infection or get a serious infection from them.
- ⚠ Be careful not to bend or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

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



- F. Hold your LEVEMIR FlexPen with the needle pointing up. Tap the cartridge gently with your finger a few times to make any air bubbles collect at the top of the cartridge (see diagram F).



- G. 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. If not, change the needle and repeat the procedure no more than 6 times.

If you do not see a drop of insulin after 6 times, do not use the LEVEMIR FlexPen and contact Novo Nordisk at 1-800-727-6500.

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



### Selecting your dose

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

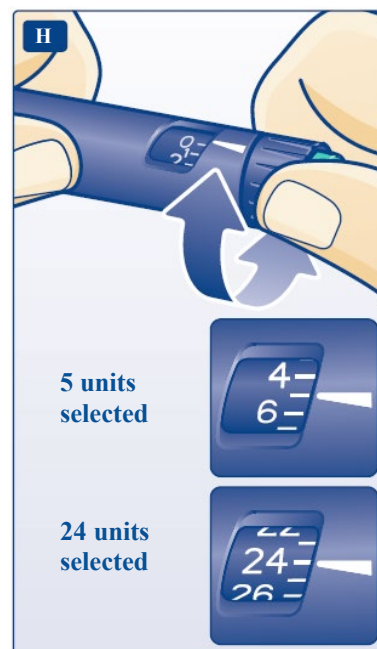
- H.** Turn the dose selector to the number of units you need to inject. The pointer should line up with your dose.

The dose can be corrected either up or down by turning the dose selector in either direction until the correct dose lines up with the pointer (see diagram H). When turning the dose selector, be careful not to press the green push-button as insulin will come out.

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

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

- ⚠ **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, buttocks, 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, or has lumps. **Do not** inject where the skin is tender, bruised, scaly or hard, or into scars or damaged skin.

- I.** Insert the needle into your skin.

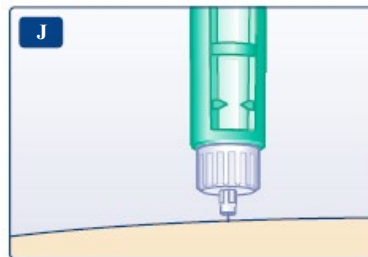
Inject the dose by pressing the green push-button all the way in until the 0 lines up with the pointer (see diagram I). Be careful only to push the green push-button when injecting.

Turning the dose selector will not inject the insulin.



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

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



### After the injection

**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 Pen and throw it away as soon as you can.
- The used LEVEMIR FlexPen may be thrown away in your household trash after you have removed the needle.
- Put your used needles in an 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, 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>.

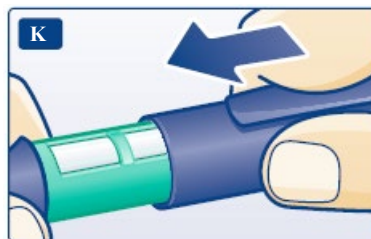
**Do not** dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. **Do not** recycle your used sharps disposal container.

When there is not enough medicine left in your LEVEMIR FlexPen for your prescribed dose, the LEVEMIR FlexPen may be thrown away in your household trash after you have removed the needle.

The LEVEMIR FlexPen prevents the cartridge from being completely emptied. It is designed to deliver 300 units.

- 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.
- 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.

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

### **Manufactured by:**

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

**Revised: 12/2022**

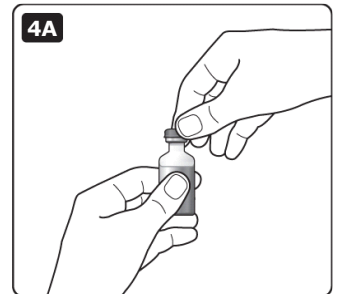
**INSTRUCTIONS FOR USE  
LEVEMIR® (LEV-uh-mere)  
injection, for subcutaneous use  
10 mL multiple-dose vial**

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.

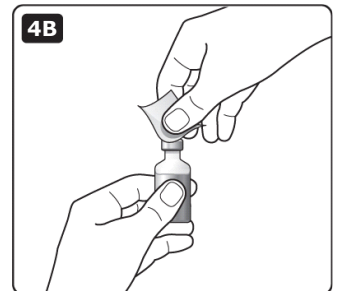
**How should I use the LEVEMIR vial?**

**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.

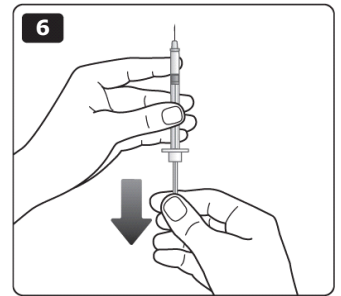


Before each use, wipe the rubber stopper with an alcohol wipe.

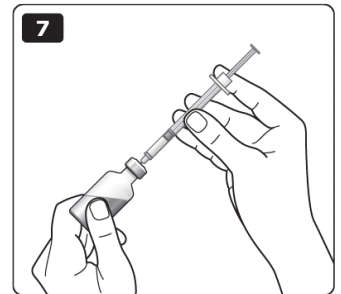


5. Do not roll or shake the vial. Shaking the vial right before the dose is drawn into the syringe may cause bubbles or foam. This can cause you to draw up the wrong dose of insulin. The insulin should be used only if it is clear and colorless.

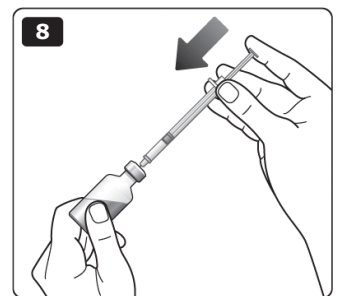
6. Pull back the plunger on your syringe until the black tip reaches the marking for the number of units you will inject.



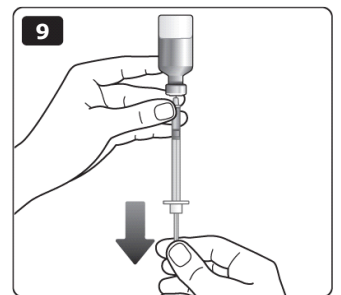
7. Push the needle through the rubber stopper into the vial.



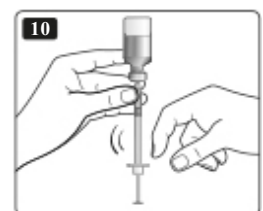
8. Push the plunger all the way in. This inserts air into the vial.



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



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



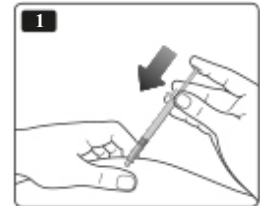
11. Check to make sure you have the right dose of LEVEMIR in the syringe.

12. Pull the syringe out of the vial.
13. Inject your LEVEMIR right away as instructed by your healthcare provider. 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.

Revised: 07/2022

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PATENT Information: <https://www.novonordisk-us.com/products/product-patents.html>

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