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 [rDNA origin] injection) solution for subcutaneous injection
Initial U.S. Approval: 2005

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

Important Limitations of Use:
- Not recommended for treating diabetic ketoacidosis. Use intravenous, rapid-acting or short-acting insulin instead.

----------DOSAGE AND ADMINISTRATION----------
- The starting dose should be individualized based on the type of diabetes and whether the patient is insulin-naïve (2.1, 2.2, 2.3)
- Administer subcutaneously once daily or in divided doses twice daily. Once daily administration should be given with the evening meal or at bedtime (2.1)
- Rotate injection sites within an injection area (abdomen, thigh, or deltoid) to reduce the risk of lipodystrophy (2.1)
- Converting from other insulin therapies may require adjustment of timing and dose of LEVEMIR. Closely monitor glucoses especially upon converting to LEVEMIR and during the initial weeks thereafter (2.3)

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

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

----------WARNINGS AND PRECAUTIONS----------
- Dose adjustment and monitoring: Monitor blood glucose in all patients treated with insulin. Insulin regimens should be modified cautiously and only under medical supervision (5.1)
- Administration: Do not dilute or mix with any other insulin or solution. Do not administer subcutaneously via an insulin pump, intramuscularly, or intravenously because severe hypoglycemia can occur (5.2)
- Hypoglycemia is the most common adverse reaction of insulin therapy and may be life-threatening (5.3, 6.1)
- Allergic reactions: Severe, life-threatening, generalized allergy, including anaphylaxis, can occur (5.4)
- Renal or hepatic impairment: May require adjustment of the LEVEMIR dose (5.5, 5.6)

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

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

----------DRUG INTERACTIONS----------
- Certain drugs may affect glucose metabolism requiring insulin dose adjustment and close monitoring of blood glucose (7)
- The signs of hypoglycemia may be reduced or absent in patients taking anti-adrenergic drugs (e.g., beta-blockers, clonidine, guanethidine, and reserpine) (7)

----------USE IN SPECIFIC POPULATIONS----------
Pediatric: Has not been studied in children with type 2 diabetes. Has not been studied in children with type 1 diabetes < 6 years of age (8.4)

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

Revised: 3/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

LEVEMIR is indicated to improve glycemic control in adults and children with diabetes mellitus.

Important Limitations of Use:

- LEVEMIR is not recommended for the treatment of diabetic ketoacidosis. Intravenous rapid-acting or short-acting insulin is the preferred treatment for this condition.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing

LEVEMIR is a recombinant human insulin analog for once- or twice-daily subcutaneous administration.

Patients treated with LEVEMIR once-daily should administer the dose with the evening meal or at bedtime.

Patients who require twice-daily dosing can administer the evening dose with the evening meal, at bedtime, or 12 hours after the morning dose.

The dose of LEVEMIR must be individualized based on clinical response. Blood glucose monitoring is essential in all patients receiving insulin therapy.

Patients adjusting the amount or timing of dosing with LEVEMIR should only do so under medical supervision with appropriate glucose monitoring *[see Warnings and Precautions (5.1)]*.

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

As with all insulins, injection sites should be rotated within the same region (abdomen, thigh, or deltoid) from one injection to the next to reduce the risk of lipodystrophy *[see Adverse Reactions (6.1)]*.

LEVEMIR can be injected subcutaneously in the thigh, abdominal wall, or upper arm. As with all insulins, the rate of absorption, and consequently the onset and duration of action, may be affected by exercise and other variables, such as stress, intercurrent illness, or changes in co-administered medications or meal patterns.

2.2 Initiation of LEVEMIR Therapy

The recommended starting dose of LEVEMIR in patients with type 1 diabetes should be approximately one-third of the total daily insulin requirements. Rapid-acting or short-acting, pre-meal insulin should be used to satisfy the remainder of the daily insulin requirements.

The recommended starting dose of LEVEMIR in patients with type 2 diabetes who are not currently treated with insulin is 10 Units (or 0.1-0.2 Units/kg) given once daily in the evening or divided into a twice daily regimen.

LEVEMIR doses should subsequently be adjusted based on blood glucose measurements. The dosages of LEVEMIR should be individualized under the supervision of a healthcare provider.

2.3 Converting to LEVEMIR from other insulin therapies

If converting from insulin glargine to LEVEMIR, the change can be done on a unit-to-unit basis.

If converting from NPH insulin, the change can be done on a unit-to-unit basis. However, some patients with type 2 diabetes may require more LEVEMIR than NPH insulin, as observed in one trial *[see Clinical Studies (14)]*.

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

3 DOSAGE FORMS AND STRENGTHS

LEVEMIR solution for injection 100 Unit per mL is available as:

- 3 mL LEVEMIR FlexPen®
- 10 mL vial

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Dosage adjustment and monitoring

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

Changes in insulin strength, manufacturer, type, or method of administration may result in the need for a change in the insulin dose or an adjustment of concomitant anti-diabetic treatment.
As with all insulin preparations, the time course of action for LEVEMIR may vary in different individuals or at different times in the same individual and is dependent on many conditions, including the local blood supply, local temperature, and physical activity.

5.2 Administration

LEVEMIR should only be administered subcutaneously.

Do not administer LEVEMIR intravenously or intramuscularly. The intended duration of activity of LEVEMIR is dependent on injection into subcutaneous tissue. Intravenous or intramuscular

administration of the usual subcutaneous dose could result in severe hypoglycemia [*see Warnings and Precautions (5.3)*].

Do not use LEVEMIR in insulin infusion pumps.

Do not dilute or mix LEVEMIR with any other insulin or solution. If LEVEMIR is diluted or mixed, the pharmacokinetic or pharmacodynamic profile (e.g., onset of action, time to peak effect) of LEVEMIR and the mixed insulin may be altered in an unpredictable manner.

5.3 Hypoglycemia

Hypoglycemia is the most common adverse reaction of insulin therapy, including LEVEMIR. The risk of hypoglycemia increases with intensive glycemic control. Patients must be educated to recognize and manage hypoglycemia. Severe hypoglycemia can lead to unconsciousness or convulsions and may result in temporary or permanent impairment of brain function or death. Severe hypoglycemia requiring the assistance of another person or parenteral glucose infusion, or glucagon administration has been observed in clinical trials with insulin, including trials with LEVEMIR.

The timing of hypoglycemia usually reflects the time-action profile of the administered insulin formulations. Other factors such as changes in food intake (e.g., amount of food or timing of meals), exercise, and concomitant medications may also alter the risk of hypoglycemia *[see Drug Interactions (7)]*.

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

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

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

5.4 Hypersensitivity and allergic reactions

Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products, including LEVEMIR.

5.5 Renal Impairment

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

5.6 Hepatic Impairment

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

5.7 Drug interactions

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

6 ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere:

- Hypoglycemia *[see Warnings and Precautions (5.3)]*
- Hypersensitivity and allergic reactions *[see Warnings and Precautions (5.4)]*

6.1 Clinical trial experience

Because clinical trials are conducted under widely varying designs, the adverse reaction rates reported in one clinical trial may not be easily compared to 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.

Table 1: Adverse reactions (excluding hypoglycemia) in two pooled clinical trials of 16 weeks and 24 weeks duration in adults with type 1 diabetes (adverse reactions with incidence ≥ 5%)

	LEVEMIR, % (n = 767)	NPH, % (n = 388)
Upper respiratory tract infection	26.1	21.4
Headache	22.6	22.7
Pharyngitis	9.5	8.0
Influenza-like illness	7.8	7.0
Abdominal Pain	6.0	2.6

Table 2: Adverse reactions (excluding hypoglycemia) in a 26-week trial comparing insulin aspart + LEVEMIR to insulin aspart + insulin glargine in adults with type 1 diabetes (adverse reactions with incidence ≥ 5%)

	LEVEMIR, % (n = 161)	Glargine, % (n = 159)
Upper respiratory tract infection	26.7	32.1
Headache	14.3	19.5
Back pain	8.1	6.3
Influenza-like illness	6.2	8.2
Gastroenteritis	5.6	4.4
Bronchitis	5.0	1.9

Table 3: Adverse reactions (excluding hypoglycemia) in two pooled clinical trials of 22 weeks and 24 weeks duration in adults with type 2 diabetes (adverse reactions with incidence ≥ 5%)

	LEVEMIR, % (n = 432)	NPH, % (n = 437)
Upper respiratory tract infection	12.5	11.2
Headache	6.5	5.3

Table 4: Adverse reactions (excluding hypoglycemia) in a 26-week clinical trial of children and adolescents with type 1 diabetes (adverse reactions with incidence ≥ 5%)

	LEVEMIR, % (n = 232)	NPH, % (n = 115)
Upper respiratory tract infection	35.8	42.6
Headache	31.0	32.2
Pharyngitis	17.2	20.9
Gastroenteritis	16.8	11.3
Influenza-like illness	13.8	20.9
Abdominal pain	13.4	13.0
Pyrexia	10.3	6.1
Cough	8.2	4.3
Viral infection	7.3	7.8
Nausea	6.5	7.0
Rhinitis	6.5	3.5
Vomiting	6.5	10.4

Pregnancy

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

- *Hypoglycemia*

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

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

The rates of hypoglycemia in the LEVEMIR clinical trials (see Section 14 for a description of the study designs) were comparable between LEVEMIR-treated patients and non-LEVEMIR-treated patients (see Tables 5 and 6).

Table 5: Hypoglycemia in Patients with Type 1 Diabetes

		Study A Type 1 Diabetes Adults 16 weeks In combination with insulin aspart		Study B Type 1 Diabetes Adults 26 weeks In combination with insulin aspart		Study C Type 1 Diabetes Adults 24 weeks In combination with regular insulin		Study D Type 1 Diabetes Pediatrics 26 weeks In combination with insulin aspart	
		Twice-Daily LEVEMIR	Twice-Daily NPH	Twice-Daily LEVEMIR	Once-Daily Glargine	Once-Daily LEVEMIR	Once-Daily NPH	Once- or Twice Daily LEVEMIR	Once- or Twice Daily NPH
Severe hypoglycemia	Percent of patients with at least 1 event (n/total N)	8.7 (24/276)	10.6 (14/132)	5.0 (8/161)	10.1 (16/159)	7.5 (37/491)	10.2 (26/256)	15.9 (37/232)	20.0 (23/115)
	Event/patient/ year	0.52	0.43	0.13	0.31	0.35	0.32	0.91	0.99
Non-severe hypoglycemia	Percent of patients (n/total N)	88.0 (243/276)	89.4 (118/132)	82.0 (132/161)	77.4 (123/159)	88.4 (434/491)	87.9 (225/256)	93.1 (216/232)	95.7 (110/115)
	Event/patient/ year	26.4	37.5	20.2	21.8	31.1	33.4	31.6	37.0

Table 6: 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	
		Twice-Daily LEVEMIR	Twice-Daily NPH	Once- or Twice Daily LEVEMIR	Once- or Twice Daily NPH
Severe hypoglycemia	Percent of patients with at least 1 event (n/total N)	0.4 (1/237)	2.5 (6/238)	1.5 (3/195)	4.0 (8/199)
	Event/patient/year	0.01	0.08	0.04	0.13
Non-severe hypoglycemia	Percent of patients (n/total N)	40.5 (96/237)	64.3 (153/238)	32.3 (63/195)	32.2 (64/199)
	Event/patient/year	3.5	6.9	1.6	2.0

- *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 adsorption. Rotate insulin injection sites within the same region to reduce the risk of lipodystrophy *[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.

- *Peripheral Edema*

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

- *Allergic Reactions*

Local Allergy

As with any insulin therapy, patients taking LEVEMIR may experience injection site reactions, including localized erythema, pain, pruritis, urticaria, edema, and inflammation. In clinical studies in adults, three patients treated with LEVEMIR reported injection site pain (0.25%) compared to one patient treated with NPH insulin (0.12%). The reports of pain at the injection site did not result in discontinuation of therapy.

Rotation of the injection site within a given area from one injection to the next may help to reduce or prevent these reactions. In some instances, these reactions may be related to factors other than insulin, such as irritants in a skin cleansing agent or poor injection technique. Most minor reactions to insulin usually resolve in a few days to a few weeks.

Systemic Allergy

Severe, life-threatening, generalized allergy, including anaphylaxis, generalized skin reactions, angioedema, bronchospasm, hypotension, and shock may occur with any insulin, including LEVEMIR, and may be life-threatening *[see Warnings and Precautions (5.4)]*.

- *Antibody Production*

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 phase 3 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 during post-approval use of LEVEMIR in which other insulins, particularly rapid-acting or short-acting insulins, have been accidentally administered instead of LEVEMIR *[see Patient Counseling Information (17)]*. To avoid medication errors between LEVEMIR and other insulins, patients should be instructed always to verify the insulin label before each injection.

7 DRUG INTERACTIONS

A number of medications affect glucose metabolism and may require insulin dose adjustment and particularly close monitoring.

The following are examples of medications that may increase the blood-glucose-lowering effect of insulins including LEVEMIR and, therefore, increase the susceptibility to hypoglycemia: oral antidiabetic medications, pramlintide acetate, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, propoxyphene, pentoxifylline, salicylates, somatostatin analogs, and sulfonamide antibiotics.

The following are examples of medications that may reduce the blood-glucose-lowering effect of insulins including LEVEMIR: corticosteroids, niacin, danazol, diuretics, sympathomimetic agents (e.g., epinephrine, albuterol, terbutaline), glucagon, isoniazid, phenothiazine derivatives, somatropin, thyroid hormones, estrogens, progestogens (e.g., in oral contraceptives), protease inhibitors and atypical antipsychotic medications (e.g. olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts, and alcohol may either increase or decrease the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.

The signs of hypoglycemia may be reduced or absent in patients taking anti-adrenergic drugs such as beta-blockers, clonidine, guanethidine, and reserpine.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

Risk Summary

The background risk of birth defects, pregnancy loss, or other adverse events that exists for all pregnancies is increased in pregnancies complicated by hyperglycemia. Female patients should be advised to tell their physician if they intend to become, or if they become pregnant while taking LEVEMIR. A randomized controlled clinical trial of pregnant women with type I diabetes using LEVEMIR during pregnancy did not show an increase in the risk of fetal abnormalities. Reproductive toxicology studies in non-diabetic rats and rabbits that included concurrent human insulin control groups indicated that insulin detemir and human insulin had similar effects regarding embryotoxicity and teratogenicity that were attributed to maternal hypoglycemia.

Clinical Considerations

The increased risk of adverse events in pregnancies complicated by hyperglycemia may be decreased with good glucose control before conception and throughout pregnancy. Because insulin requirements vary throughout pregnancy and in the post-partum period, careful monitoring of glucose control is essential in pregnant women.

Human Data

In an, open-label, clinical study, women with type 1 diabetes who were (between weeks 8 and 12 of gestation) or intended to become pregnant were randomized 1:1 to LEVEMIR (once or twice daily) or NPH insulin (once, twice or thrice daily). Insulin aspart was administered before each meal. 152 women in the LEVEMIR arm and 158 women in the NPH arm were or became pregnant during the

study (Total pregnant women = 310). Approximately one 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. In the 310 pregnant women, the mean glycosylated hemoglobin (HbA_{1c}) was < 7% at 10, 12, and 24 weeks of gestation in both arms. In the intent-to-treat population, the adjusted mean HbA_{1c} (standard error) at gestational week 36 was 6.27% (0.053) in LEVEMIR-treated patient (n=138) and 6.33% (0.052) in NPH-treated patients (n=145); the difference was not clinically significant.

Adverse reactions in pregnant patients occurring at an incidence of ≥5% are shown in Table 7. The two most common adverse reactions were nasopharyngitis and headache. These are consistent with findings from other type 1 diabetes trials (see Table 1, Section 6.1.),and are not repeated in Table 7.

The incidence of adverse reactions of pre-eclampsia was 10.5% (16 cases) and 7.0% (11 cases) in the Levemir and NPH insulin groups respectively. Out of the total number of cases of pre-eclampsia, eight (8) cases in the LEVEMIR group and 1 case in the NPH insulin group required hospitalization. The rates of pre-eclampsia observed in the study are within expected rates for pregnancy complicated by diabetes. Pre-eclampsia is a syndrome defined by symptoms, hypertension and proteinuria; the definition of pre-eclampsia was not standardized in the trial making it difficult to establish a link between a given treatment and an increased risk of pre-eclampsia. All events were considered unlikely related to trial treatment. In all nine (9) cases requiring hospitalization the women had healthy infants. Events of hypertension, proteinuria and edema were reported less frequently in the LEVEMIR group than in the NPH insulin group as a whole. There was no difference between the treatment groups in mean blood pressure during pregnancy and there was no indication of a general increase in blood pressure.

In the NPH insulin group there were 6 serious adverse reactions in four mothers of the following placental disorders, ‘Placenta previa’, ‘Placenta previa hemorrhage’, and ‘Premature separation of placenta’ and 1 serious adverse reaction of ‘Antepartum haemorrhage’. There were none reported in the LEVEMIR group.

The incidence of early fetal death (abortions) was similar in LEVEMIR and NPH treated patients; 6.6% and 5.1%, respectively. The abortions were reported under the following terms: ‘Abortion spontaneous’, ‘Abortion missed’, ‘Blighted ovum’, ‘Cervical incompetence’ and ‘Abortion incomplete’.

Table 7: Adverse reactions during pregnancy in a trial comparing insulin aspart + LEVEMIR to insulin aspart + NPH insulin in pregnant women with type 1 diabetes (adverse reactions with incidence ≥ 5%)*

	LEVEMIR, % (n = 152)	**NPH, % (n = 158)**
Anaemia	13.2	10.8
Diarrhoea	11.8	5.1
Pre-eclampsia	10.5	7.0
Urinary tract infection	9.9	5.7
Gastroenteritis	8.6	5.1
Abdominal pain upper	5.9	3.8
Vomiting	5.3	4.4
Abortion spontaneous	5.3	2.5

Abdominal pain	5.3	6.3
Oropharyngeal pain	5.3	6.3

* 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 proportion of subjects experiencing severe hypoglycemia was 16.4% and 20.9% in LEVEMIR and NPH treated patients respectively. The rate of severe hypoglycemia was 1.1 and 1.2 events per patient-year in LEVEMIR and NPH treated patients respectively. Proportion and incidence rates for non-severe episodes of hypoglycemia were similar in both treatment groups (Table 8).

Table 8: Hypoglycemia in Pregnant Women with Type 1 Diabetes

		Study G Type 1 Diabetes Pregnancy In combination with insulin aspart	
		LEVEMIR	NPH
Severe hypoglycemia*	Percent of patients with at least 1 event (n/total N)	16.4 (25/152)	20.9 (33/158)
	Events/patient/year	1.1	1.2
Non-severe hypoglycemia*	Percent of patients with at least 1 event (n/total N)	94.7 (144/152)	92.4 (146/158)
	Events/patient/year	114.2	108.4

* For definition regarding severe and non-severe hypoglycemia see section 6, Hypoglycemia.

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

No differences in pregnancy outcomes or the health of the fetus and newborn were seen with LEVEMIR use.

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 embryofetal 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.

8.3 Nursing Mothers

It is unknown whether LEVEMIR is excreted in human milk. Because many drugs, including human insulin, are excreted in human milk, use caution when administering LEVEMIR to a nursing woman. Women with diabetes who are lactating may require adjustments of their insulin doses.

8.4 Pediatric Use

The pharmacokinetics, safety and effectiveness of subcutaneous injections of LEVEMIR have been established in pediatric patients (age 6 to 17 years) with type 1 diabetes *[see Clinical Pharmacology (12.3) and Clinical Studies (14)]*. LEVEMIR has not been studied in pediatric patients younger than 6 years of age with type 1 diabetes. LEVEMIR has not been studied in pediatric patients with type 2 diabetes.

The dose recommendation when converting to LEVEMIR is the same as that described for adults *[see Dosage and Administration (2) and Clinical Studies (14)]*. As in adults, the dosage of LEVEMIR must be individualized in pediatric patients based on metabolic needs and frequent monitoring of blood glucose.

8.5 Geriatric Use

In controlled clinical trials comparing LEVEMIR to NPH insulin or insulin glargine, 64 of 1624 patients (3.9%) in the type 1 diabetes trials and 309 of 1082 patients (28.6%) in the type 2 diabetes trials were ≥65 years of age. A total of 52 (7 type 1 and 45 type 2) patients (1.9%) were ≥75 years of age. No overall differences in safety or effectiveness were observed between these patients and younger patients, but small sample sizes, particularly for patients ≥65 years of age in the type 1 diabetes trials and for patients ≥75 years of age in all trials limits conclusions. Greater sensitivity of some older individuals cannot be ruled out. In elderly patients with diabetes, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemia. Hypoglycemia may be difficult to recognize in the elderly.

10 OVERDOSAGE

An excess of insulin relative to food intake, energy expenditure, or both may lead to severe and sometimes prolonged and life-threatening hypoglycemia. Mild episodes of hypoglycemia usually can be treated with oral glucose. Adjustments in drug dosage, meal patterns, or exercise may be needed.

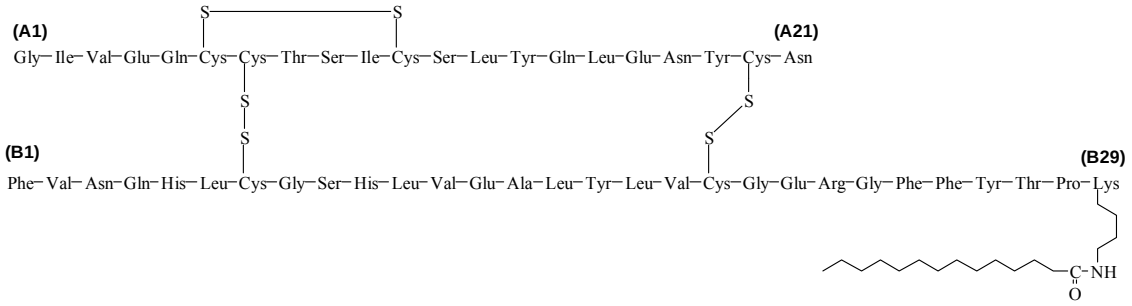
More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. After apparent clinical recovery from hypoglycemia, continued observation and additional carbohydrate intake may be necessary to avoid recurrence of hypoglycemia [*see Warnings and Precautions (5.3)*].

11 DESCRIPTION

LEVEMIR (insulin detemir [rDNA origin] injection) is a sterile solution of insulin detemir for use as a subcutaneous injection. Insulin detemir is a long-acting (up to 24-hour duration of action) recombinant human insulin analog. LEVEMIR is produced by a process that includes expression of recombinant DNA in *Saccharomyces cerevisiae* followed by chemical modification.

Insulin detemir differs from human insulin in that the 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 5916.9. It has the following structure:

Figure 1: Structural Formula of insulin detemir



LEVEMIR is a clear, colorless, aqueous, neutral sterile solution. Each milliliter of LEVEMIR contains 100 units (14.2 mg/mL) insulin detemir, 65.4 mcg zinc, 2.06 mg m-cresol, 16.0 mg glycerol, 1.80 mg phenol, 0.89 mg disodium phosphate dihydrate, 1.17 mg sodium chloride, and water for injection. Hydrochloric acid and/or sodium hydroxide may be added to adjust pH. LEVEMIR has a pH of approximately 7.4.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The primary activity of insulin detemir is the regulation of glucose metabolism. Insulins, including insulin detemir, exert their specific action through binding to insulin receptors. Receptor-bound insulin lowers blood glucose by facilitating cellular uptake of glucose into skeletal muscle and adipose tissue and by inhibiting the output of glucose from the liver. Insulin inhibits lipolysis in the adipocyte, inhibits proteolysis, and enhances protein synthesis.

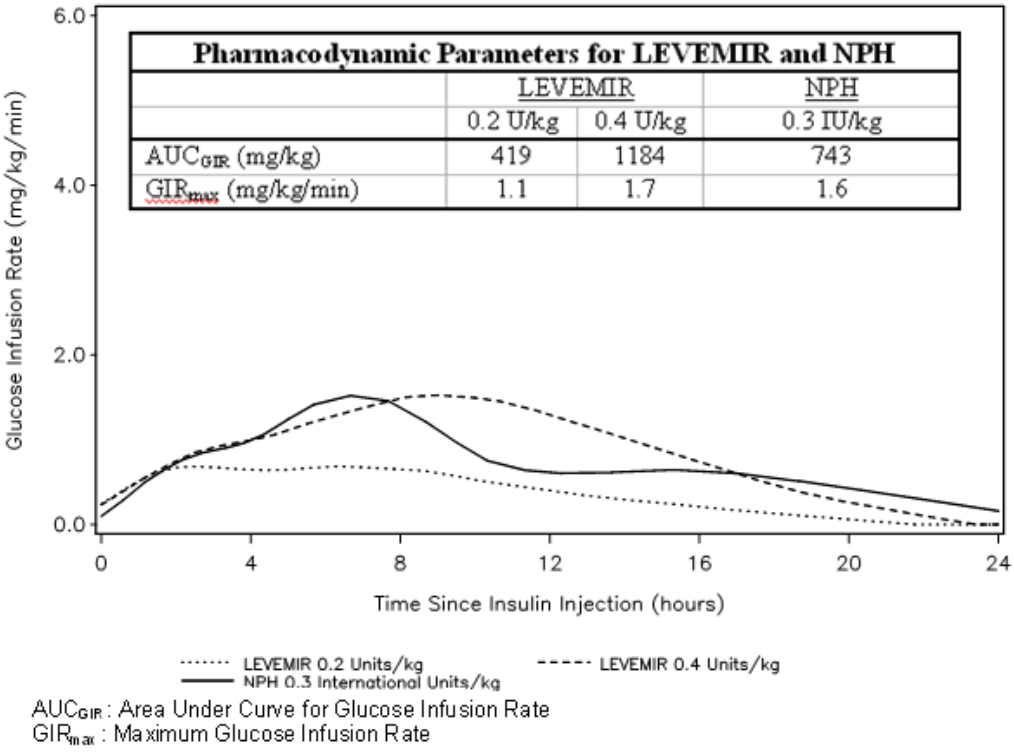
12.2 Pharmacodynamics

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

The duration of action of LEVEMIR is mediated by slowed systemic absorption of insulin detemir molecules from the injection site due to 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 or NPH insulin. The mean time between injection and the end of pharmacological effect for insulin detemir ranged from 7.6 hours to > 24 hours (24 hours was the end of the observation period).

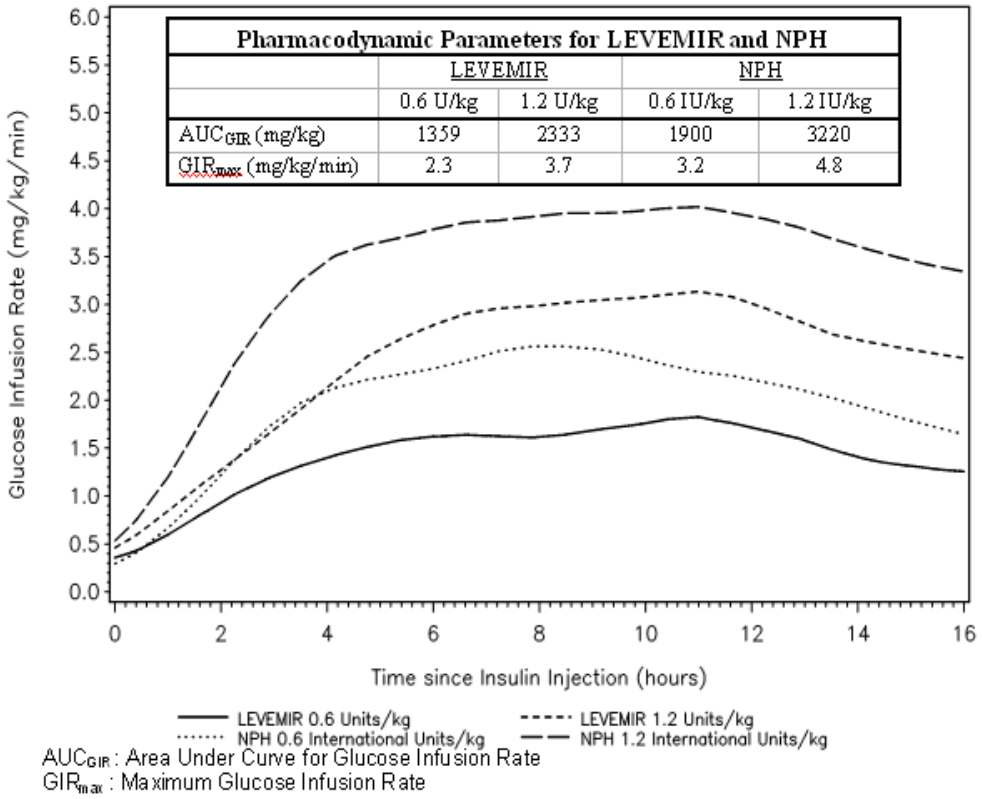
Figure 2: Activity Profiles in Patients with Type 1 Diabetes in a 24-hour Glucose Clamp Study



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

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

Figure 3: Activity Profiles in Patients with Type 2 Diabetes in a 16-hour Glucose Clamp Study



12.3 Pharmacokinetics

Absorption and Bioavailability

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

The absolute bioavailability of insulin detemir is approximately 60%.

Distribution and Elimination

More than 98% of insulin detemir in the bloodstream is bound to albumin. The results of *in vitro* and *in vivo* protein binding studies demonstrate that there is no clinically relevant interaction between insulin detemir and fatty acids or other protein-bound drugs.

Insulin detemir has an apparent volume of distribution of approximately 0.1 L/kg. After subcutaneous administration in patients with type 1 diabetes, insulin detemir has a terminal half-life of 5 to 7 hours depending on dose.

Specific Populations

Children and Adolescents- The pharmacokinetic properties of LEVEMIR were investigated in children (6-12 years), adolescents (13-17 years), and adults with type 1 diabetes. In children, the insulin detemir

plasma area under the curve (AUC) and C_{max} were increased by 10% and 24%, respectively, as compared to adults. There was no difference in pharmacokinetics between adolescents and adults.

Geriatrics- In a clinical trial investigating differences in pharmacokinetics of a single subcutaneous dose of LEVEMIR in young (20 to 35 years) versus elderly (≥68 years) healthy subjects, the insulin detemir AUC was up to 35% higher among the elderly subjects due to reduced clearance. As with other insulin preparations, LEVEMIR should always be titrated according to individual requirements.

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

Race- In two clinical pharmacology studies conducted in healthy Japanese and Caucasian subjects, there were no clinically relevant differences seen in pharmacokinetic parameters. The pharmacokinetics and pharmacodynamics of LEVEMIR were investigated in a clamp study comparing patients with type 2 diabetes of Caucasian, African-American, and Latino origin. Dose-response relationships for LEVEMIR were comparable in these three populations.

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

Hepatic impairment- A single subcutaneous dose of 0.2 Units/kg (1.2 nmol/kg) of LEVEMIR was administered to healthy subjects and those with varying degrees of hepatic impairment (mild, moderate and severe). LEVEMIR exposure as estimated by AUC decreased with increasing degrees of hepatic impairment with a corresponding increase in apparent clearance. However, some studies with human insulin have shown increased circulating levels of insulin in patients with liver impairment. Careful glucose monitoring and dose adjustments of insulin, including LEVEMIR, may be necessary in patients with hepatic impairment [*see Warnings and Precautions (5.6)*].

Pregnancy- The effect of pregnancy on the pharmacokinetics and pharmacodynamics of LEVEMIR has not been studied [*see Use in Specific Populations (8.1*)].

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenicity, Mutagenicity, Impairment of Fertility

Standard 2-year carcinogenicity studies in animals have not been performed. Insulin detemir tested negative for genotoxic potential in the *in vitro* reverse mutation study in bacteria, human peripheral blood lymphocyte 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 studies of 1155 adults with type 1 diabetes mellitus, 347 pediatric patients with type 1 diabetes mellitus, and 869 adults with type 2 diabetes mellitus. The efficacy and safety of LEVEMIR given twice-daily was compared to once-daily insulin glargine in an open-label, randomized, parallel study of 320 patients with type 1 diabetes. The evening LEVEMIR dose was titrated in all trials according to 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 glycosylated hemoglobin (HbA_{1c}) with LEVEMIR was similar to that with NPH insulin or insulin glargine.

Type 1 Diabetes – Adult

In a 16-week open-label clinical study (Study A, n=409), adults with type 1 diabetes were randomized to treatment with either LEVEMIR at 12-hour intervals, LEVEMIR administered in the morning and bedtime or NPH insulin administered in the morning and bedtime. Insulin aspart was also administered before each meal. At 16 weeks of treatment, the combined LEVEMIR-treated patients had similar HbA_{1c} and fasting plasma glucose (FPG) reductions compared to the NPH-treated patients (Table 9). Differences in timing of LEVEMIR administration had no effect on HbA_{1c}, fasting plasma glucose (FPG), or body weight.

In a 26-week, open-label clinical study (Study B, n=320), adults with type 1 diabetes were randomized to twice-daily LEVEMIR (administered in the morning and bedtime) or once-daily insulin glargine (administered at bedtime). Insulin aspart was administered before each meal. LEVEMIR-treated patients had a decrease in HbA_{1c} similar to that of insulin glargine-treated patients.

In a 24-week, non-blinded clinical study (Study C, n=749), adults with type 1 diabetes were randomized to once-daily LEVEMIR or once-daily NPH insulin, both administered at bedtime and in combination with regular human insulin before each meal. LEVEMIR and NPH insulin had a similar effect on HbA_{1c}.

Table 9: 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)	
	Twice-daily LEVEMIR	Twice-daily NPH	Twice-daily LEVEMIR	Once-daily insulin glargine	Once-daily LEVEMIR	Once-daily NPH
Number of patients treated	276	133	161	159	492	257
HbA1c (%)						
Baseline HbA1c	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	-0.2		-0.0		-0.1	
95% CI for Treatment difference	(-0.3, -0.0)		(-0.2, 0.2)		(-0.3, 0.0)	
Basal insulin dose (units/day)						
Baseline mean	21	24	27	23	12	24
Mean change from baseline	16	10	10	4	9	2
Total insulin dose (units/day)						
Baseline mean	48	54	56	51	46	57
Mean change from baseline	17	10	9	6	11	3
Fasting blood glucose (mg/dL)						
Baseline mean	209	220	153	150	213	206
Adj. mean change from baseline	-44	-9	-38	-41	-30	-9
Body weight (kg)						
Baseline mean	74.6	75.5	77.5	75.1	76.5	76.9
Mean change from baseline	0.2	0.8	0.5	1.0	-0.3	0.3

Baseline values were included as covariates in an ANCOVA analysis.

Type 1 Diabetes – Pediatric

In an open-label clinical study (Study D, n=347), pediatric patients (age range 6 to 17) with type 1 diabetes were randomized to 26 weeks of treatment with LEVEMIR or NPH insulin both of which were administered either once- or twice-daily (bedtime or morning and bedtime), at a dosing frequency consistent with the number of daily basal insulin injections a patient was taking prior to trial entry. Insulin aspart was administered before each meal. LEVEMIR-treated patients had a decrease in HbA_{1c} similar to that of NPH insulin (Table 10).

Table 10: Type 1 Diabetes Mellitus – Pediatric

	Study D	
Treatment duration	26 weeks	
Treatment in combination with	NovoLog® (insulin aspart)	
	Once- or Twice Daily LEVEMIR	Once- or Twice Daily NPH
Number of subjects treated	232	115
HbA1c (%)		
Baseline HbA1c	8.8	8.8
Adj. mean change from baseline	-0.7	-0.8
LEVEMIR – NPH	0.1	
95% CI for Treatment difference	(-0.1, 0.3)	
Basal insulin dose (units/day)		
Baseline mean	24	26
Mean change from baseline	8	6
Total insulin dose (units/day)		
Baseline mean	48	50
Mean change from baseline	9	7
Fasting blood glucose (mg/dL)		
Baseline mean	181	181
Adj. mean change from baseline	-39	-21
Body weight (kg)		
Baseline mean	46.3	46.2
Mean change from baseline	1.6	2.7

Type 2 Diabetes – Adult

In a 24-week, open-label, randomized, clinical study (Study E, n=476), LEVEMIR administered twice-daily (before breakfast and evening) was compared to NPH insulin administered twice-daily (before breakfast and evening) as part of a regimen of stable combination therapy with 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_{1c} from baseline (Table 11).

In a 22-week, open-label, randomized, clinical study (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_{1c} or FPG, LEVEMIR had efficacy similar to that of NPH insulin.

Table 11: Type 2 Diabetes Mellitus – Adult

	Study E		Study F	
Treatment duration	24 weeks		22 weeks	
Treatment in combination with	oral agents		insulin aspart	
	Twice-daily LEVEMIR	Twice-daily NPH	Once- or Twice Daily LEVEMIR	Once- or Twice Daily NPH
Number of subjects treated	237	239	195	200
HbA1c (%)				
Baseline HbA1c	8.6	8.5	8.2	8.1
Adj. mean change from baseline	-2.0	-2.1	-0.6	-0.6
LEVEMIR – NPH	0.1		-0.1	
95% CI for Treatment difference	(-0.0, 0.3)		(-0.2, 0.1)	
Basal insulin dose (units/day)				
Baseline mean	18	17	22	22
Mean change from baseline	48	28	26	15
Total insulin dose[1] (units/day)				
Baseline mean	-	-	22	22
Mean change from baseline	-	-	57	42
Fasting blood glucose[2] (mg/dL)				
Baseline mean	179	173	-	-
Adj. mean change from baseline	-69	-74	-	-
Body weight (kg)				
Baseline mean	82.7	82.5	82.0	79.6
Mean change from baseline	1.2	2.7	0.5	1.2

[1]Study E – Conducted in insulin-naïve patients
[2]Study F - Fasting blood glucose data not collected

Pregnancy

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

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

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

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

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

16.2 Storage:
Unused (unopened) LEVEMIR should be stored in the refrigerator between 2° and 8°C (36° to 46°F). Do not store in the freezer or directly adjacent to the refrigerator cooling element. Do not freeze. Do not use LEVEMIR if it has been frozen.

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

If refrigeration is not possible, unused (unopened) LEVEMIR can be kept unrefrigerated at room temperature, below 30°C (86°F) as long as it is kept as cool as possible and away from direct heat and light. Unrefrigerated LEVEMIR should be discarded 42 days after it is first kept out of the refrigerator, even if the FlexPen or vial still contains insulin.

Vials:
After initial use, vials should be stored in a refrigerator, never in a freezer. If refrigeration is not possible, the in-use vial can be kept unrefrigerated at room temperature, below 30°C (86°F) as long as it is kept as cool as possible and away from direct heat and light. Refrigerated LEVEMIR vials should be discarded 42 days after initial use. Unrefrigerated LEVEMIR vials should be discarded 42 days after they are first kept out of the refrigerator.

LEVEMIR FlexPen:
After initial use, the LEVEMIR FlexPen must NOT be stored in a refrigerator and must NOT be stored with the needle in place. Keep the opened (in use) LEVEMIR FlexPen away from direct heat and light at room temperature, below 30°C (86°F). Unrefrigerated LEVEMIR FlexPens should be discarded 42 days after they are first kept out of the refrigerator.

The storage conditions are summarized in Table 12:

Table 12: Storage Conditions for LEVEMIR FlexPen and vial

	Not in-use (unopened) **Refrigerated**	**Not in-use (unopened)** **Room Temperature (below 30°C)**	**In-use (opened)**
3 mL LEVEMIR FlexPen	Until expiration date	42 days*	42 days* Room Temperature (below 30°C) **(Do not refrigerate)**
10 mL vial	Until expiration date	42 days*	42 days* Refrigerated or Room Temperature (below 30°C)

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

16.3 Preparation and handling

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

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

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (Patient Information and Instructions for Use)

17.1 Instructions for Patients

Patients should be informed that changes to insulin regimens must be made cautiously and only under medical supervision. Patients should be informed about the potential side effects of insulin therapy, including hypoglycemia, weight gain, lipodystrophy (and the need to rotate injection sites within the same body region), and allergic reactions. Patients should be informed that the ability to concentrate and react may be impaired as a result of hypoglycemia. This may present a risk in situations where these abilities are especially important, such as driving or operating other machinery. Patients who have frequent hypoglycemia or reduced or absent warning signs of hypoglycemia should be advised to use caution when driving or operating machinery.

Accidental mix-ups between LEVEMIR and other insulins, particularly short-acting insulins, have been reported. To avoid medication errors between LEVEMIR and other insulins, patients should be instructed to always check the insulin label before each injection.

LEVEMIR must only be used if the solution is clear and colorless with no particles visible. Patients must be advised that LEVEMIR must NOT be diluted or mixed with any other insulin or solution.

Patients should be instructed on self-management procedures including glucose monitoring, proper injection technique, and management of hypoglycemia and hyperglycemia. Patients should be instructed on handling of special situations such as intercurrent conditions (illness, stress, or emotional disturbances), an inadequate or skipped insulin dose, inadvertent administration of an increased insulin dose, inadequate food intake, and skipped meals.

Patients with diabetes should be advised to inform their healthcare professional if they are pregnant or are contemplating pregnancy. Refer patients to the LEVEMIR "Patient Information" for additional information.

17.2 Never Share a LEVEMIR FlexPen Between Patients

Counsel patients that they should never share a LEVEMIR FlexPen with another person, even if the needle is changed. Sharing of the FlexPen between patients may pose a risk of transmission of infection.

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

For information about LEVEMIR contact:
Novo Nordisk Inc.
100 College Road West
Princeton, NJ 08540
1-800-727-6500

www.novonordisk-us.com

Patient Information

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

Read the Patient Information that comes with LEVEMIR® before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your healthcare provider about your diabetes or your treatment. Make sure that you know how to manage your diabetes. Ask your healthcare provider, if you have any questions about managing your diabetes.

What is LEVEMIR?
LEVEMIR is a man-made long-acting insulin, that is used to control high blood sugar in adults and children with diabetes mellitus.

It is not recommended to use LEVEMIR to treat diabetic ketoacidosis.

Who should not use LEVEMIR?

Do not take LEVEMIR if:
- you are allergic to any of the ingredients in LEVEMIR. See the end of this leaflet for a complete list of ingredients in LEVEMIR.

What should I tell my healthcare provider before taking LEVEMIR?

Before you take LEVEMIR, tell your healthcare provider if you:
- have liver or kidney problems
- have any other medical conditions. Some medical conditions can affect your insulin needs and your dose of LEVEMIR.
- are pregnant or plan to become pregnant. It is not known, if LEVEMIR would harm your unborn baby. Talk to your healthcare provider, if you are pregnant or plan to become pregnant. You and your healthcare provider should talk about the best way to manage your diabetes while you are pregnant.
- are breastfeeding or plan to breast-feed. It is not known if LEVEMIR passes into breast milk. You and your healthcare provider should decide if you will take LEVEMIR while you breastfeed.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins and herbal supplements. LEVEMIR may affect the way other medicines work, and other medicines may affect how LEVEMIR works.

Know the medicines you take. Keep a list of your medicines with you to show your healthcare provider and pharmacist when you get a new medicine.

How should I take LEVEMIR?

- Take LEVEMIR exactly as your healthcare provider told you to take it.
- Your healthcare provider will tell you how much LEVEMIR to take and when to take it.
- Do not make any changes to your dose or type of insulin unless you are told to do so by your healthcare provider.

  Know your insulin. **Make sure you know:**
  - the type and strength of insulin prescribed for you.
  - the amount of insulin you take.
  - the best time for you to take your insulin. This may change if you take a different type of insulin.

- Do not dilute or mix LEVEMIR with any other insulin or solution. Your LEVEMIR will not work the right way and you may lose blood sugar control, which can be serious.

- Do not use LEVEMIR in an insulin pump.

- Inject LEVEMIR under your skin (subcutaneously) in your upper arm, abdomen (stomach area), or thigh. Never inject LEVEMIR into a vein or muscle.

- Change injection sites within the area you choose with each dose. Do not inject into the exact same spot for each injection.

- **Read the instructions for use that comes with your LEVEMIR.** Talk to your healthcare provider if you have any questions. Your healthcare provider should show you how to inject LEVEMIR before you start taking it.

- Your healthcare provider will decide which type of LEVEMIR to prescribe for you.
  LEVEMIR comes in:
  - 10 mL vials (small bottles) for use with a syringe
  - 3 mL LEVEMIR FlexPen®

Ask your healthcare provider how you should use LEVEMIR.

- **If you take too much LEVEMIR, your blood sugar may fall low (hypoglycemia).** You can treat mild low blood sugar (hypoglycemia) by drinking or eating something sugary right away (fruit juice, sugar candies, or glucose tablets). It is important to treat low blood sugar (hypoglycemia) right away because it could get worse and you could pass out (lose consciousness).

  If you pass out you will need help from another person or emergency medical services right away. See "What are the possible side effects of LEVEMIR?" for more information on low blood sugar (hypoglycemia).

- **If you forget to take your dose of LEVEMIR, your blood sugar may go too high (hyperglycemia).** If high blood sugar (hyperglycemia) is not treated it can lead to serious problems, like loss of consciousness (passing out), coma or even death.

  Follow your healthcare provider's instructions for treating high blood sugar.

  Know your symptoms of high blood sugar, which may include:
  - increased thirst
  - frequent urination
  - drowsiness
  - loss of appetite
  - a hard time breathing
  - fruity smell on the breath
  - high amounts of sugar and ketones in your urine
  - nausea, vomiting (throwing up) or stomach pain

- Do not share needles, insulin pens or syringes with others.

- **Check your blood sugar levels.** Ask your healthcare provider what your blood sugars should be and when you should check your blood sugar levels.

Your insulin dosage may need to change because of:

- illness
- stress
- other medicines you take
- change in diet
- change in physical activity or exercise

What should I avoid while taking LEVEMIR?

- **Alcohol.** Drinking alcohol may affect your blood sugar when you take LEVEMIR.

- **Driving and operating machinery.** You may have trouble paying attention or reacting if you have low blood sugar (hypoglycemia). Be careful when you drive a car or operate machinery. Ask your healthcare provider if it is alright for you to drive if you often have:
  - low blood sugar (hypoglycemia)
  - decreased or no warning signs of low blood sugar

What are the possible side effects of LEVEMIR?
LEVEMIR can cause serious side effects, including:

- **Low blood sugar (hypoglycemia).** Symptoms of low blood sugar may include:
  - dizziness or lightheadedness
  - shakiness
  - hunger
  - fast heart beat
  - tingling in your hands, feet, lips or tongue
  - trouble concentrating or confusion
  - blurred vision
  - slurred speech
  - anxiety or mood changes
  - headache
  - sweating

Very low blood sugar (hypoglycemia) can cause loss of consciousness (passing out), seizures, and death. Talk to your healthcare provider about how to tell if you have low blood sugar and what to do if this happens while taking LEVEMIR. Know your symptoms of low blood sugar. Follow your healthcare provider's instructions for treating low blood sugar.

Talk to your healthcare provider if low blood sugar is a problem for you. Your dose of LEVEMIR may need to be changed.

- **Skin thickening or pits at the injection site (lipodystrophy).** Change (rotate) the area where you inject your insulin to help prevent these skin changes from happening. Do not inject insulin into areas of skin that have thickening or pits.

- **Serious allergic reactions. LEVEMIR can cause life threatening symptoms.** Get medical help right away if you have any of these symptoms of an allergic reaction:
  - a rash all over your body
  - itching
  - shortness of breath
  - trouble breathing (wheezing)
  - fast heartbeat
  - sweating
  - feel faint

Common side effects of LEVEMIR include:

- **Low blood sugar (hypoglycemia). See "What are the possible side effects of LEVEMIR?" for more information on low blood sugar (hypoglycemia).**
- **Reactions at the injection site (local allergic reaction)**. You may get redness, swelling, and itching at the injection site. If you keep having skin reactions or they are serious, talk to your healthcare provider.
- **Weight gain.** This can occur with any insulin therapy. Talk to your healthcare provider about how LEVEMIR can affect your weight.

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

These are not all of the possible side effects from LEVEMIR. Ask your healthcare provider or pharmacist for more information.

Call your doctor for medical advice about side effects.
You may report side effects to FDA at 1-800-FDA-1088.

How should I store LEVEMIR?

Unopened LEVEMIR:

- **Keep all unopened LEVEMIR in the refrigerator between 36°F to 46°F (2°C to 8°C).**
- Unopened LEVEMIR can be kept until the expiration date on the label if the medicine has been stored in a refrigerator.
- If refrigeration is not possible, you can keep the unopened LEVEMIR at room temperature below 86°F (30°C).
- Throw away LEVEMIR 42 days after it is first kept out of the refrigerator.
- Do not freeze. Do not use LEVEMIR if it has been frozen.
- Keep unopened LEVEMIR in the carton to protect it from light.

LEVEMIR in use:

- **Vials**

- Keep opened vials of LEVEMIR in the refrigerator or at room temperature below 86°F (30°C) away from direct heat or light.
- Throw away a vial that has always been kept in the refrigerator after 42 days of use, even if there is insulin left in the vial.
- Throw away a vial that has been kept at room temperature 42 days after it is first kept out of the refrigerator, even if there is insulin left in the vial.

- **LEVEMIR FlexPen**
  - Keep at room temperature below 86°F (30°C) for up to 42 days.
  - Do not store a LEVEMIR FlexPen that you are using in the refrigerator.
  - Do not store LEVEMIR with the needle attached.
  - Keep LEVEMIR FlexPen away from direct heat or light.
  - Throw away used LEVEMIR FlexPens after 42 days, even if there is insulin left in them.

Keep LEVEMIR and all medicines out of the reach of children.

General information about LEVEMIR

Medicines are sometimes prescribed for conditions that are not mentioned in the patient 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 you have. It may harm them.

This leaflet summarizes the most important information about LEVEMIR. If you would like more information about LEVEMIR or diabetes, talk with your healthcare provider. You can ask your healthcare provider for information about LEVEMIR that is written for healthcare professionals.

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

What are the ingredients in LEVEMIR?
Active Ingredient: Insulin detemir
Inactive Ingredients: zinc, m-cresol, glycerol, phenol, disodium phosphate dehydrate, sodium chloride and water for injection. Hydrochloric acid or sodium hydroxide may be added.

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

Administration.

Revised: January 2012

LEVEMIR® is covered by US Patent Nos. 5,750,497, 5,866,538, 6,011,007, 6,869,930 and other patents pending.

FlexPen® is covered by US Patent Nos. 6,582,404, 6,004,297, 6,235,004 and other patents pending.

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

For information about LEVEMIR® contact:
Novo Nordisk Inc.
100 College Road West
Princeton, New Jersey 08540
www.novonordisk-us.com
1-800-727-6500

Patient Instructions For Use
LEVEMIR® 10 mL vial

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

How should I use the LEVEMIR 10 mL vial?

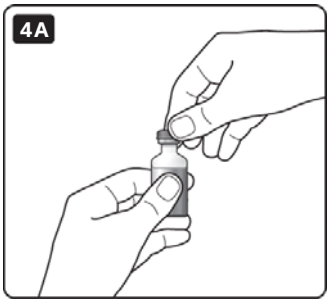
Using the 10 mL vial:

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

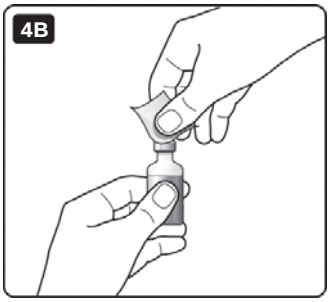
2. Look at the vial and the insulin. The LEVEMIR insulin should be clear and colorless. The tamper-resistant cap should be in place before the first use. If the cap has been removed before your first use of the vial, or if the insulin is cloudy or colored, **Do not** use the insulin and return it to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

3. Wash your hands with soap and water.

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

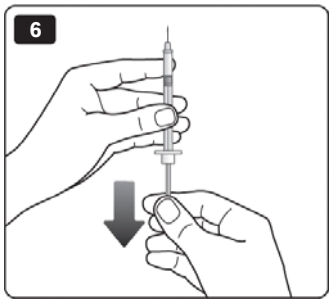


   Before each use, wipe the rubber stopper with an alcohol wipe.

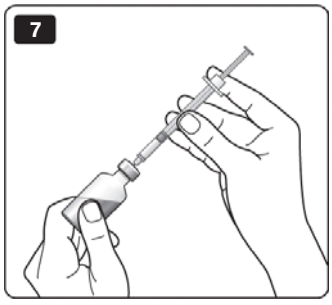


5. Do not roll or shake the vial. Shaking the vial right before the dose is drawn into the syringe may cause bubbles or foam. This can cause you to draw up the wrong dose of insulin. The insulin should be used only if it is clear and colorless.

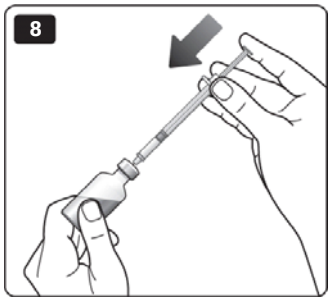
6. Pull back the plunger on your syringe until the black tip reaches the marking for the number of units you will inject.



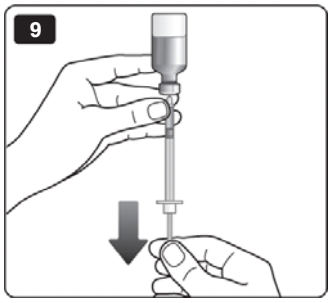
7. Push the needle through the rubber stopper into the vial.



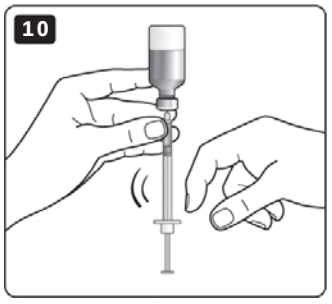
8. Push the plunger all the way in. This inserts air into the vial.



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



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



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

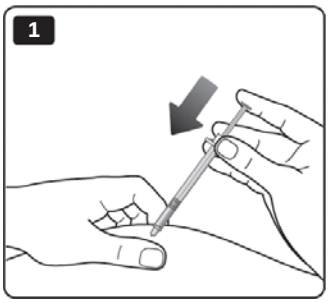
12. Pull the syringe out of the vial.

13. Inject your LEVEMIR right away as instructed by your healthcare provider.

How should I inject LEVEMIR with a syringe?

If you clean your injection site with an alcohol swab, let the injection site dry before you inject. Talk with your healthcare provider about how to rotate injection sites and how to give an injection.

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



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

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

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

Revised: January 2012

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

For information about LEVEMIR® contact:
Novo Nordisk Inc.
100 College Road West,
Princeton, New Jersey 08540

Instructions For Use
LEVEMIR® FlexPen®

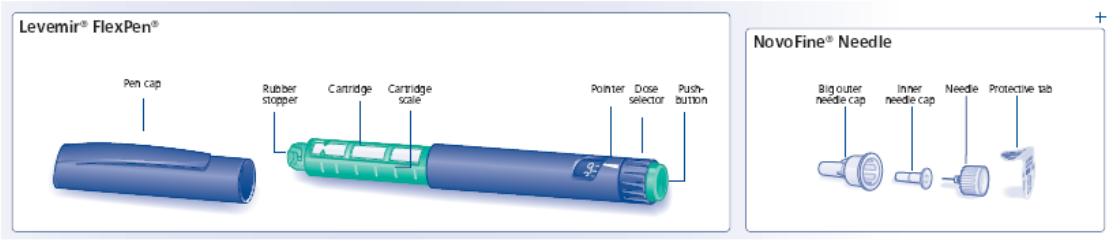
Please carefully read the following Instructions for use before using your LEVEMIR® FlexPen® and each time you get a refill. You should read the instructions in this manual even if you have used a LEVEMIR FlexPen before.

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

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

Getting ready
Make sure you have the following items:

- LEVEMIR FlexPen
- NovoFine disposable needles
- Alcohol swab



PREPARING YOUR LEVEMIR FLEXPEN
Wash your hands with soap and water. Before you start to prepare your injection, check the label to make sure that you are taking the right type of insulin. This is especially important if you take more than 1 type of insulin. LEVEMIR should look clear and colorless.

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

Wipe the rubber stopper with an alcohol swab.

B. Attaching the needle
Remove the protective tab from a new disposable needle.

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

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

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

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

- ⚠ Always use a new needle for each injection to cut down the chance of infection and to prevent blocked needles.
- ⚠ 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 you take the right dose of insulin:

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

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

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

A drop of insulin should appear at the needle tip. If not, change the needle and repeat the procedure no more than 6 times.

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

6500.

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

SELECTING YOUR DOSE

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

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

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

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

You will hear a click for every single unit dialed. Do not set the dose by counting the number of clicks you hear.

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

GIVING THE INJECTION

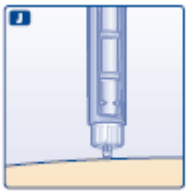
Do the injection exactly as shown to you by your healthcare provider. Your healthcare provider should tell you if you need to pinch the skin before injecting. Wipe the skin with an alcohol swab and let the area dry.

I. Insert the needle into your skin.

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

Turning the dose selector will not inject insulin.

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



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

After the injection

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

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

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

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

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

FUNCTION CHECK

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

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

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

Maintenance

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

- ⚠ Remove the needle from the LEVEMIR FlexPen after each injection. This helps to cut down your chance of infection, prevent leakage of insulin. Be careful when handling used needles to avoid needle sticks and transfer of infections.
- ⚠ Keep your LEVEMIR FlexPen and needles out of the reach of children.
- ⚠ Use LEVEMIR FlexPen as directed to treat your diabetes. Needles and LEVEMIR FlexPen must not be shared.
- ⚠ Always use a new needle for each injection.
- ⚠ Novo Nordisk is not responsible for harm due to using this insulin pen with products not recommended by Novo Nordisk.
- ⚠ As a safety measure, always carry a spare insulin delivery device in case your LEVEMIR FlexPen is lost or damaged.
- ⚠ Remember to keep the disposable LEVEMIR FlexPen with you. Do not leave it in a car or other location where it can get too hot or too cold.

Revised: January 2012

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

For information about LEVEMIR® contact:
Novo Nordisk Inc.
100 College Road West,
Princeton, New Jersey 08540