

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

Pregnancy category C: Use during pregnancy only if the potential benefit justifies the potential risk to the fetus (8.1)

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: 1/2012

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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 \geq 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 \geq 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 \geq 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 \geq 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 |

- *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 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 ($<$ 50 mg/dL 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 C: 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-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.

There are no well-controlled clinical studies of the use of LEVEMIR in pregnant women. Patients should be advised to discuss with their healthcare provider if they intend to, or if they become, pregnant. Because animal reproduction studies are not always predictive of human response, LEVEMIR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is essential for patients with diabetes or a history of gestational diabetes to maintain good metabolic control before conception and throughout pregnancy. Insulin requirements may decrease during the first trimester, generally increase during the second and third trimesters, and rapidly decline after delivery. Careful monitoring of glucose control is essential in these patients.

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. Use of LEVEMIR is compatible with breastfeeding, but 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.

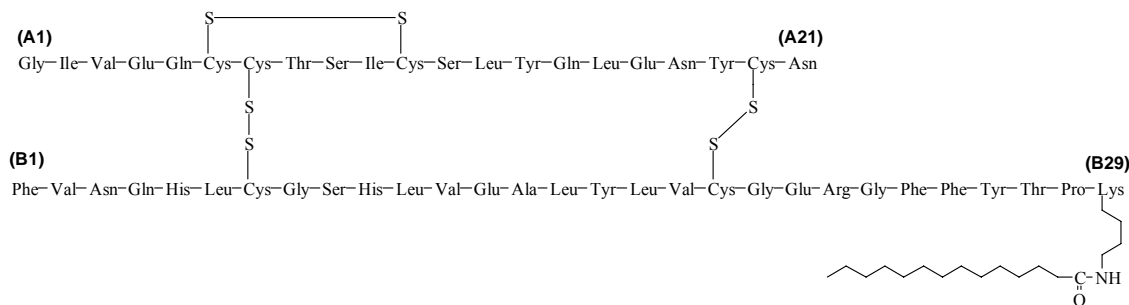
More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. After apparent clinical recovery from hypoglycemia, continued observation and additional carbohydrate intake may be necessary to avoid recurrence 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.

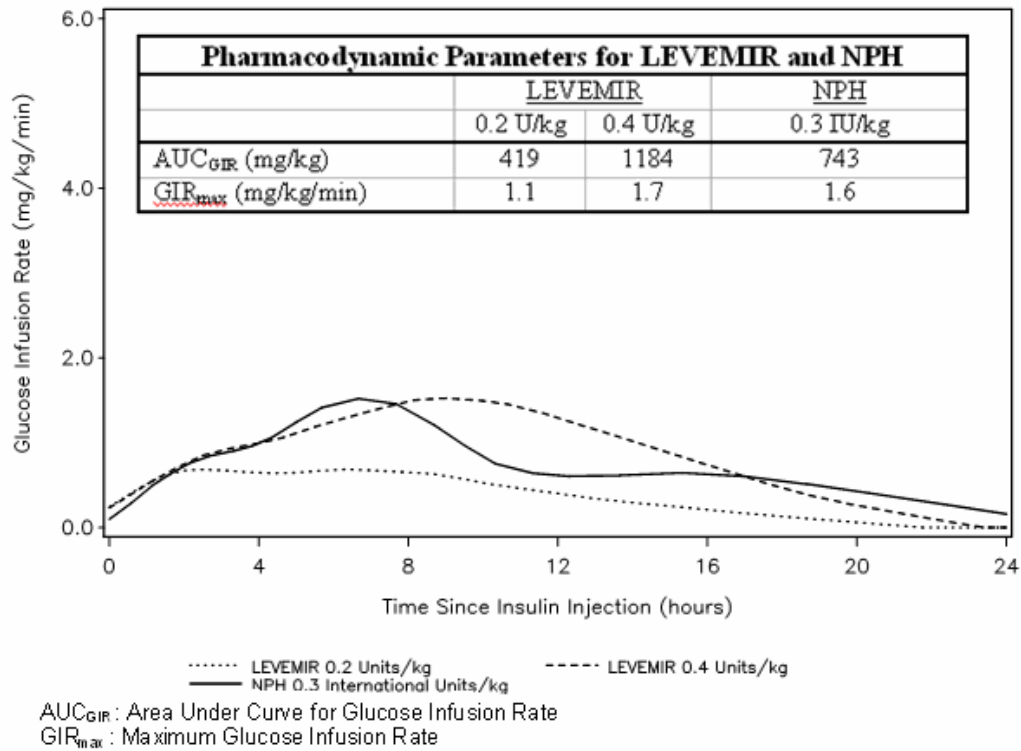
12.2 Pharmacodynamics

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).

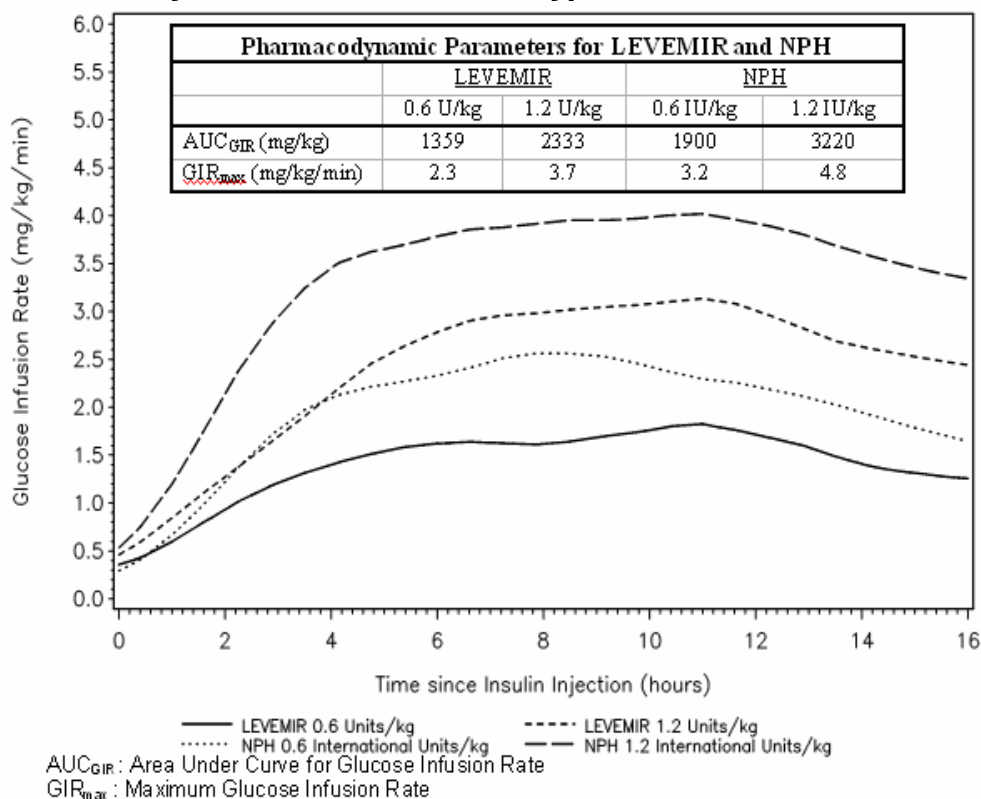
Figure 2: Activity Profiles in Patients with Type 1 Diabetes in a 24-hour Glucose Clamp Study



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 (C_{max}) reached between 6-8 hours post-dose. Insulin detemir was more slowly absorbed after subcutaneous administration to the thigh where AUC_{0-5h} was 30-40% lower and AUC_{0-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 7). 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 7: Type 1 Diabetes Mellitus – Adult

| Treatment duration Treatment in combination with | Study A 16 weeks NovoLog [®] (insulin aspart) | | Study B 26 weeks NovoLog [®] (insulin aspart) | | Study C 24 weeks 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 |
| HbA _{1c} (%) | | | | | | |
| Baseline HbA _{1c} | 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) | |
|--|----------------------|------|---------------------|------|---------------------|------|
| 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 8).

Table 8: Type 1 Diabetes Mellitus – Pediatric

| Treatment duration Treatment in combination with | Study D 26 weeks NovoLog [®] (insulin aspart) | |
|---|---|--|
| | Once- or Twice Daily <u>LEVEMIR</u> | Once- or Twice Daily <u>NPH</u> |
| Number of subjects treated | 232 | 115 |
| HbA _{1c} (%) | | |
| Baseline HbA _{1c} | 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 9).

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 9: Type 2 Diabetes Mellitus – Adult

| Treatment duration Treatment in combination with | Study E 24 weeks oral agents | | Study F 22 weeks 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 _{1c} (%) | | | | |
| Baseline HbA _{1c} | 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 |

¹Study E – Conducted in insulin-naïve patients

²Study F - Fasting blood glucose data not collected

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 10:

Table 10: 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.

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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, 6,235,400 and other patents pending.

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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