

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-536

APPROVED LABELING

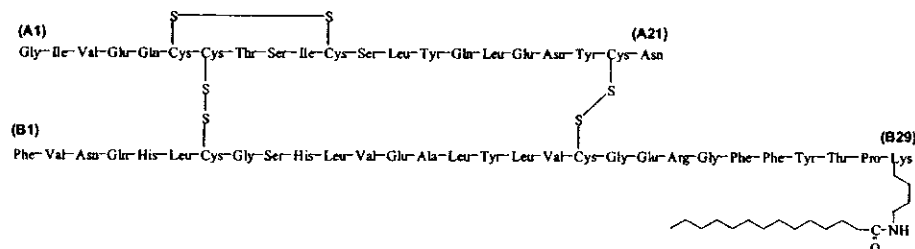
LEVEMIR

(insulin detemir [rDNA origin] injection)

DESCRIPTION

LEVEMIR® (insulin detemir [rDNA origin] injection) is a sterile solution of insulin detemir for use as an injection. Insulin detemir is a long-acting basal insulin analog, with up to 24 hours duration of action, 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:



LEVEMIR is a clear, colorless, aqueous, neutral sterile solution. Each milliliter of LEVEMIR contains 100 U (14.2 mg/mL) insulin detemir, 65.4 µg zinc, 2.06 mg m-cresol, 30.0 mg mannitol, 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.

CLINICAL PHARMACOLOGY

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 fat and by inhibiting the output of glucose from the liver. Insulin inhibits lipolysis in the adipocyte, inhibits proteolysis, and enhances protein synthesis.

Pharmacodynamics

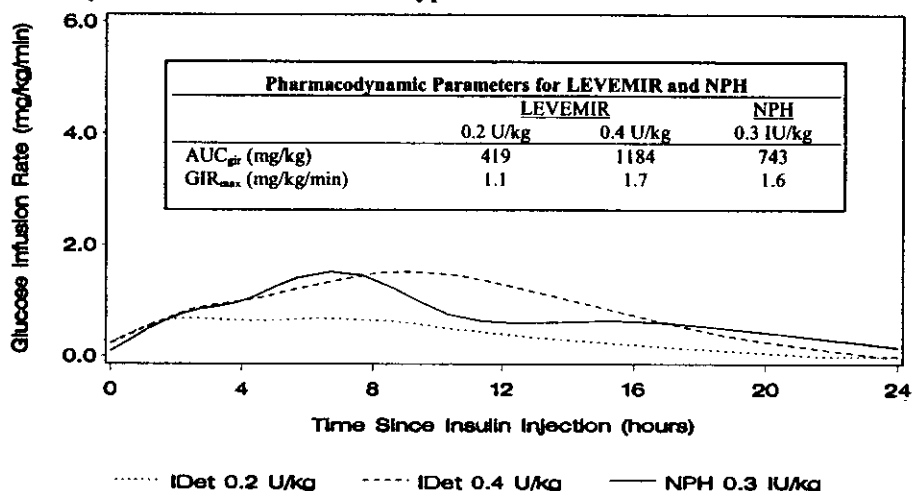
Insulin detemir is a soluble, long-acting basal human insulin analog with a relatively flat action profile. The mean duration of action of insulin detemir ranged from 5.7 hours at the lowest dose to 23.2 hours at the highest dose (sampling period 24 hours).

The prolonged action of LEVEMIR is mediated by the slow systemic absorption of insulin detemir molecules from the injection site due to strong self-association of the drug molecules,

and by slow distribution to peripheral target tissues since insulin detemir in the bloodstream is highly bound to albumin.

Figure 1 shows glucose infusion rate results from a glucose clamp study in patients with type 1 diabetes.

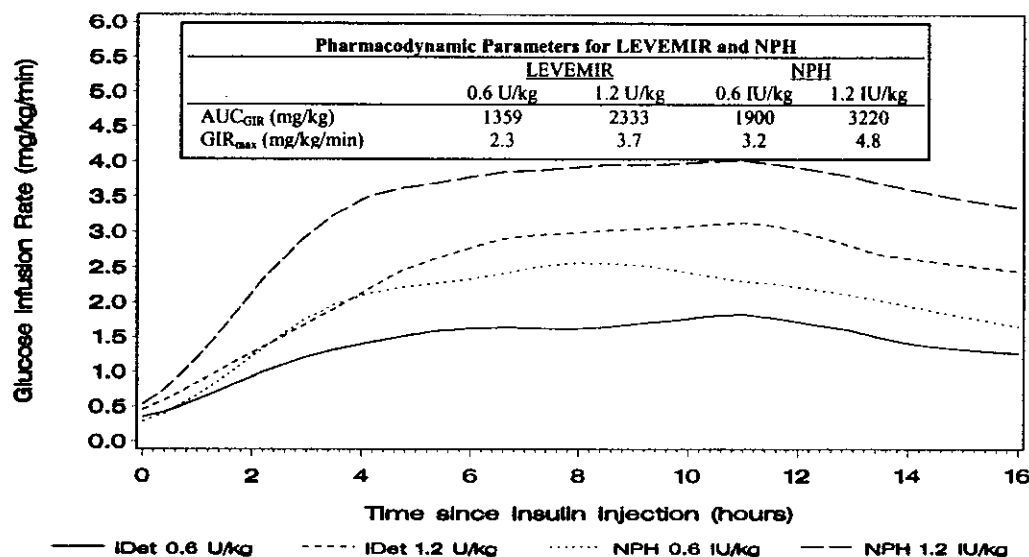
Figure 1: Activity Profiles in Patients with Type 1 Diabetes in a 24-hour Glucose Clamp Study



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



Mean Value Profiles

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

In a glucose clamp study, the overall glucodynamic effect ($AUC_{GIR\ 0-24h}$) [mean mg/kg $\pm$ SD (CV)] of four separate subcutaneous injections in the thigh was 1702.6 ± 489 mg/kg (29%) in the LEVEMIR group and 1922.8 ± 765 mg/kg (40%) for NPH. The clinical significance of this difference has not been established.

Pharmacokinetics

Absorption

After subcutaneous injection of insulin detemir in healthy subjects and in patients with diabetes, insulin detemir serum concentrations indicated a slower, more prolonged absorption over 24 hours in comparison to NPH human insulin.

Maximum serum concentration (C_{max}) is reached between 6 and 8 hours after administration. The absolute bioavailability of insulin detemir is approximately 60%.

Distribution and Elimination

More than 98% insulin detemir in bloodstream is bound to albumin. LEVEMIR has a small apparent volume of distribution of approximately 0.1 L/kg. LEVEMIR, after subcutaneous administration, has a terminal half-life of 5-7 hours depending on dose.

Special Populations

Children and Adolescents- The pharmacokinetic properties of LEVEMIR were investigated in children (6-12 years) and adolescents (13-17 years) and adults with Type 1 diabetes. Similar to NPH human insulin, slightly higher plasma Area Under the Curve (AUC) and C_{max} were observed in children by 10% and 24%, respectively, compared to adolescents and 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 (25 to 35 years) versus elderly (≥ 68 years) healthy subjects, higher insulin AUC levels (up to 35%) were found in elderly subjects due to a reduced clearance. As with other insulin preparations, LEVEMIR should always be titrated according to individual requirements.

Gender- In controlled clinical trials, no clinically relevant difference between genders is seen in pharmacokinetic parameters based on subgroup analyses.

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

Renal impairment- Individuals with renal impairment showed no difference in pharmacokinetic parameters as compared to healthy volunteers. However, literature reports have shown that clearance of human insulin is decreased in renally impaired patients. Careful glucose monitoring and dose adjustments of insulin, including LEVEMIR, may be necessary in patients with renal dysfunction (see PRECAUTIONS, Renal Impairment)

Hepatic impairment- Individuals with severe hepatic dysfunction, without diabetes, were observed to have lower AUCs as compared to healthy volunteers. Careful glucose monitoring and dose adjustments of insulin, including LEVEMIR, may be necessary in patients with hepatic dysfunction (see PRECAUTIONS, Hepatic Impairment).

Pregnancy- The effect of pregnancy on the pharmacokinetics and pharmacodynamics of LEVEMIR has not been studied (see PRECAUTIONS, Pregnancy).

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

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 human insulin or once-daily insulin glargine in non-blinded, randomized, parallel studies of 6004 patients with diabetes (3724 with type 1, and 2280 with type 2). In general, patients treated with LEVEMIR achieved levels of glycemic control similar to those treated with NPH human insulin or insulin glargine, as measured by glycosylated hemoglobin (HbA_{1c}).

Type 1 Diabetes

In one non-blinded clinical study (Study A, n=408), adult patients with type 1 diabetes were randomized to treatment with either LEVEMIR at 12-hour intervals, LEVEMIR morning and bedtime or NPH human insulin 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 FPG reductions to NPH-treated patients (Table 1). Differences in timing of LEVEMIR administration (or flexible dosing) had no effect on HbA_{1c}, FPG, body weight, or risk of having hypoglycemic episodes.

Overall glycemic control achieved with LEVEMIR was compared to that achieved with insulin glargine in a randomized, non-blinded, clinical study (Study B, n=320) in which patients with type 1 diabetes were treated for 26 weeks with either twice-daily (morning and bedtime) LEVEMIR or once-daily (bedtime) insulin glargine. 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 randomized, controlled clinical study (Study C, n=747), patients with type 1 diabetes were treated with once-daily (bedtime) LEVEMIR or NPH human insulin, both in combination with

human soluble insulin before each meal for 6 months. LEVEMIR and NPH human insulin had a similar effect on HbA_{1c}.

Table 1: Efficacy and Insulin Dosage in Type 1 Diabetes Mellitus

	<u>Study A</u>	
	16 weeks	
	NovoLog® (insulin aspart)	
	<u>LEVEMIR</u>	<u>NPH</u>
Treatment duration		
Treatment in combination with		
Number of subjects treated	276	132
HbA_{1c} (%)		
Baseline	8.64	8.51
End of study adjusted mean	7.76	7.94
Mean change from baseline	-0.82	-0.60
Fasting plasma glucose (mg/dL)		
End of study adjusted mean	168	202
Mean change from baseline	-42.48	-10.80
Daily Basal insulin dose (U/kg)		
Prestudy mean	0.36	0.39
End of study mean	0.49	0.45
Daily Bolus insulin dose (U/kg)		
Prestudy mean	0.40	0.40
End of study mean	0.38	0.38

Baseline values were included as covariates in an ANCOVA analysis.

Type 2 Diabetes

In a 24-week, non-blinded, randomized, clinical study (Study D, n= 475), LEVEMIR administered twice-daily (before breakfast and evening) was compared to a similar regimen of NPH human insulin as part of a regimen of combination therapy with one or two of the following oral antidiabetes agents (metformin, insulin secretagogue or α -glucosidase inhibitor). LEVEMIR and NPH similarly lowered HbA_{1c} from baseline (Table 2).

In a 26-week, non-blinded, randomized, clinical study (Study E, n=505) in adults with Type 2 diabetes, LEVEMIR and NPH human insulin were given once- or twice-daily as part of a basal-bolus regimen. As measured by HbA_{1c} or FPG, LEVEMIR had efficacy similar to NPH human insulin.

Table 2: Efficacy and Insulin Dosage in Type 2 Diabetes Mellitus

	<u>Study D</u>	
	24 weeks	
	OAD	
	<u>LEVEMIR</u>	<u>NPH</u>
Treatment duration		
Treatment in combination with		
Number of subjects treated	237	238
HbA_{1c} (%)		
Baseline	8.61	8.51
End of study adjusted mean	6.58	6.46
Mean change from baseline	-1.84	-1.90
Proportion achieving HbA _{1c} ≤ 7%	70%	74%
Fasting Plasma Glucose (mg/dL)		
End of study adjusted mean	119.16	113.40
Mean change from baseline	-75.96	-74.34
Daily Insulin Dose (U/kg)		
End of study mean	0.77	0.52

INDICATIONS AND USAGE

LEVEMIR is indicated for once or twice-daily subcutaneous administration in the treatment of adult patients with diabetes mellitus who require basal (long acting) insulin for the control of hyperglycemia.

CONTRAINDICATIONS

LEVEMIR is contraindicated in patients hypersensitive to insulin detemir or one of its excipients.

WARNINGS

Hypoglycemia is the most common adverse effect of insulin therapy, including LEVEMIR. As with all insulins, the timing of hypoglycemia may differ among various insulin formulations.

Glucose monitoring is recommended for all patients with diabetes.

LEVEMIR is not to be used in insulin infusion pumps.

Any change of insulin dose should be made cautiously and only under medical supervision. Changes in insulin strength, timing of dosing, manufacturer, type (e.g., regular, NPH, or

**insulin analogs), species (animal, human), or method of manufacture (rDNA versus animal-source insulin) may result in the need for a change in dosage.
Concomitant oral antidiabetic treatment may need to be adjusted.**

PRECAUTIONS

General

Inadequate dosing or discontinuation of treatment may lead to hyperglycemia and, in patients with type 1 diabetes, diabetic ketoacidosis. The first symptoms of hyperglycemia usually occur gradually over a period of hours or days. They include nausea, vomiting, drowsiness, flushed dry skin, dry mouth, increased urination, thirst and loss of appetite as well as acetone breath. Untreated hyperglycemic events are potentially fatal.

LEVEMIR is not intended for intravenous or intramuscular administration. The prolonged duration of activity of insulin detemir is dependent on injection into subcutaneous tissue. Intravenous administration of the usual subcutaneous dose could result in severe hypoglycemia. Absorption after intramuscular administration is both faster and more extensive than absorption after subcutaneous administration.

LEVEMIR should not be diluted or mixed with any other insulin preparations (see PRECAUTIONS, Mixing of Insulins).

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

Lipodystrophy and hypersensitivity are among potential clinical adverse effects associated with the use of all insulins.

As with all insulin preparations, the time course of LEVEMIR action may vary in different individuals or at different times in the same individual and is dependent on site of injection, blood supply, temperature, and physical activity.

Adjustment of dosage of any insulin may be necessary if patients change their physical activity or their usual meal plan.

Hypoglycemia

As with all insulin preparations, hypoglycemic reactions may be associated with the administration of LEVEMIR. Hypoglycemia is the most common adverse effect of insulins. Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as long duration of diabetes, diabetic nerve disease, use of medications such as beta-blockers, or intensified diabetes control (see PRECAUTIONS, Drug Interactions). Such situations may result in severe hypoglycemia (and, possibly, loss of consciousness) prior to patients' awareness of hypoglycemia.

The time of occurrence of hypoglycemia depends on the action profile of the insulins used and may, therefore, change when the treatment regimen or timing of dosing is changed. In patients being switched from other intermediate or long-acting insulin preparations to once- or twice-daily LEVEMIR, dosages can be prescribed on a unit-to-unit basis; however, as with all insulin preparations, dose and timing of administration may need to be adjusted to reduce the risk of hypoglycemia (see DOSAGE AND ADMINISTRATION, Changeover to LEVEMIR).

Renal Impairment

As with other insulins, the requirements for LEVEMIR may need to be adjusted in patients with renal impairment (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

Hepatic Impairment

As with other insulins, the requirements for LEVEMIR may need to be adjusted in patients with hepatic impairment (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

Injection Site and Allergic Reactions

As with any insulin therapy, lipodystrophy may occur at the injection site and delay insulin absorption. Other injection site reactions with insulin therapy may include redness, pain, itching, hives, swelling, and inflammation. Continuous rotation of the injection site within a given area may help to reduce or prevent these reactions. Reactions usually resolve in a few days to a few weeks. On rare occasions, injection site reactions may require discontinuation of LEVEMIR.

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.

Systemic allergy: Generalized allergy to insulin, which is less common but potentially more serious, may cause rash (including pruritus) over the whole body, shortness of breath, wheezing, reduction in blood pressure, rapid pulse, or sweating. Severe cases of generalized allergy, including anaphylactic reaction, may be life-threatening.

Intercurrent Conditions

Insulin requirements may be altered during intercurrent conditions such as illness, emotional disturbances, or other stresses.

Information for Patients

LEVEMIR must only be used if the solution appears clear and colorless with no visible particles (see DOSAGE AND ADMINISTRATION, Preparation and Handling). Patients should be informed about potential risks and advantages of LEVEMIR therapy, including the possible side effects. Patients should be offered continued education and advice on insulin therapies, injection technique, life-style management, regular glucose monitoring, periodic glycosylated hemoglobin testing, recognition and management of hypo- and hyperglycemia, adherence to meal planning, complications of insulin therapy, timing of dosage, instruction for use of injection devices and proper storage of insulin. Patients should be informed that frequent, patient-performed blood glucose measurements are needed to achieve effective glycemic control to avoid both hyperglycemia and hypoglycemia. Patients must 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, or skipped meals. Refer patients to the LEVEMIR "Patient Information" circular for additional information.

As with all patients who have diabetes, the ability to concentrate and/or react may be impaired as a result of hypoglycemia or hyperglycemia.

Patients with diabetes should be advised to inform their health care professional if they are pregnant or are contemplating pregnancy (see PRECAUTIONS, Pregnancy).

Laboratory Tests

As with all insulin therapy, the therapeutic response to LEVEMIR should be monitored by periodic blood glucose tests. Periodic measurement of HbA_{1c} is recommended for the monitoring of long-term glycemic control.

Drug Interactions

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

The following are examples of substances that may reduce the blood-glucose-lowering effect of insulin: corticosteroids, danazol, diuretics, sympathomimetic agents (e.g., epinephrine, albuterol, terbutaline), isoniazid, phenothiazine derivatives, somatropin, thyroid hormones, estrogens, progestogens (e.g., in oral contraceptives).

The following are examples of substances that may increase the blood-glucose-lowering effect of insulin and susceptibility to hypoglycemia: oral antidiabetic drugs, ACE inhibitors, disopyramide, fibrates, fluoxetine, MAO inhibitors, propoxyphene, salicylates, somatostatin analog (e.g., octreotide), and sulfonamide antibiotics.

Beta-blockers, clonidine, lithium salts, and alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia. In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine, and reserpine, the signs of hypoglycemia may be reduced or absent.

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.

Mixing of Insulins

If LEVEMIR is mixed with other insulin preparations, the profile of action of one or both individual components may change. Mixing LEVEMIR with insulin aspart, a rapid acting insulin analog, resulted in about 40% reduction in AUC_(0-2h) and C_{max} for insulin aspart compared to separate injections when the ratio of insulin aspart to LEVEMIR was less than 50%.

LEVEMIR should NOT be mixed or diluted with any other insulin preparations.

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.

Pregnancy: Teratogenic Effects: 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

the recommended human dose, 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 the recommended human dose based on AUC ratio) were given to rabbits during organogenesis. Drug-dose related increases in the incidence of fetuses with gall bladder abnormalities such as small, bilobed, bifurcated and missing gall bladders were observed at dose of 900 nmol/kg/day. The rat and rabbit embryofetal development studies that included concurrent human insulin control groups indicated that detemir and human insulin had similar effects regarding embryotoxicity and teratogenicity.

Nursing mothers

It is unknown whether LEVEMIR is excreted in significant amounts in human milk. For this reason, caution should be exercised when LEVEMIR is administered to a nursing mother. Patients with diabetes who are lactating may require adjustments in insulin dose, meal plan, or both.

Pediatric use

Information for the safe and effective use of LEVEMIR in children is not currently available.

Geriatric use

Of the total number of subjects in intermediate and long-term clinical studies of LEVEMIR, 85 (Type 1 studies) and 363 (Type 2 studies) were 65 years and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but 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 hypoglycemic reactions. Hypoglycemia may be difficult to recognize in the elderly.

ADVERSE REACTIONS

Adverse events commonly associated with human insulin therapy include the following:

Body as Whole: allergic reactions (see PRECAUTIONS, Allergy).

Skin and Appendages: lipodystrophy, pruritus, rash. Mild injection site reactions occurred more frequently with LEVEMIR than with NPH human insulin and usually resolved in a few days to a few weeks (see PRECAUTIONS, Allergy).

Other: Hypoglycemia (see WARNINGS and PRECAUTIONS). In trials of up to 6 months duration in patients with type 1 and type 2 diabetes, the incidence of severe hypoglycemia with LEVEMIR was comparable to the incidence with NPH, and, as expected, greater overall in patients with type 1 diabetes (Table 3).

Weight gain

In trials of up to 6 months duration in patients with type 1 and type 2 diabetes, LEVEMIR was associated with somewhat less weight gain than NPH (Table 3). Whether these observed differences represent true differences in the effects of LEVEMIR and NPH insulin is not known, since these trials were not blinded and the protocols (e.g., diet and exercise instructions and monitoring) were not specifically directed at exploring hypotheses related to

weight effects of the treatments compared. The clinical significance of the observed differences has not been established.

Table 3: Safety Information on Clinical Studies*

		Weight (kg)		Hypoglycemia (events/subject/month)		
	Treatment	# of subjects	Baseline	End of treatment	Major**	Minor***
Type 1						
<u>Study A</u>	LEVEMIR	N=263	75.0	75.1	0.04	2.14
	NPH	N=128	75.7	76.4	0.0335	2.9987
<u>Study C</u>	LEVEMIR	N=480	76.5	76.3	0.0286	2.3756
	NPH	N=247	76.1	76.5	0.0263	2.5344
Type 2						
<u>Study D</u>	LEVEMIR	N=237	82.7	83.7	0.0008	0.3083
	NPH	N=238	82.4	85.2	0.0063	0.5917
<u>Study E</u>	LEVEMIR	N=188	81.8	82.3	0.0029	0.1565
	NPH	N=194	79.6	80.9	0.0014	0.1735

* See CLINICAL STUDIES section for description of individual studies

** Major = requires assistance of another individual because of neurologic impairment

*** Minor = plasma glucose <56 mg/dl, subject able to deal with the episode him/herself

OVERDOSAGE

Hypoglycemia may occur as a result of an excess of insulin relative to food intake, energy expenditure, or both. 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 reoccurrence of hypoglycemia.

DOSAGE AND ADMINISTRATION

LEVEMIR can be administered once- or twice-daily. The dose of LEVEMIR should be adjusted according to blood glucose measurements. The dosage of LEVEMIR should be individualized based on the physician's advice, in accordance with the needs of the patient.

- For patients treated with Levemir once-daily, the dose should be administered with the evening meal or at bedtime.
- For patients who require twice-daily dosing for effective blood glucose control, the evening dose can be administered either with the evening meal, at bedtime, or 12 hours after the morning dose.

LEVEMIR should be administered by subcutaneous injection in the thigh, abdominal wall, or upper arm. Injection sites should be rotated within the same region. As with all insulins, the duration of action will vary according to the dose, injection site, blood flow, temperature, and level of physical activity.

Dose Determination for LEVEMIR

- For patients with type 1 or type 2 diabetes on basal-bolus treatment, changing the basal insulin to LEVEMIR can be done on a unit-to-unit basis. The dose of LEVEMIR should then be adjusted to achieve glycemic targets. In some patients with type 2 diabetes, more LEVEMIR may be required than NPH insulin. In a clinical study, the mean dose at end of treatment was 0.77 U/kg for LEVEMIR and 0.52 IU/kg for NPH human insulin (see Table 2).
- For patients currently receiving only basal insulin, changing the basal insulin to LEVEMIR can be done on a unit-to-unit basis.
- For insulin-naïve patients with type 2 diabetes who are inadequately controlled on oral antidiabetic drugs, LEVEMIR should be started at a dose of 0.1 to 0.2 U/kg once-daily in the evening or 10 units once- or twice-daily, and the dose adjusted to achieve glycemic targets.
- As with all insulins, close glucose monitoring is recommended during the transition and in the initial weeks thereafter. Dose and timing of concurrent short-acting insulins or other concomitant antidiabetic treatment may need to be adjusted.

Preparation and Handling:

LEVEMIR should be inspected visually prior to administration and should only be used if the solution appears clear and colorless.

LEVEMIR should not be mixed or diluted with any other insulin preparations.

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

HOW SUPPLIED

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

10 mL vial	NDC xxxx-xxxx-xx
3 mL PenFill cartridges*	NDC xxxx-xxxx-xx
3 mL InnoLet®	NDC xxxx-xxxx-xx
3 mL FlexPen®	NDC xxxx-xxxx-xx

*LEVEMIR PenFill® cartridges are for use with Novo Nordisk 3 mL PenFill® cartridge compatible insulin delivery devices and NovoFine® disposable needles.

RECOMMENDED STORAGE

Unused LEVEMIR should be stored between 2° and 8°C (36° to 46°F). *Do not freeze. Do not use LEVEMIR if it has been frozen.*

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), for up to 42 days, as long as it is kept as cool as possible and away from direct heat and light.

Unpunctured vials can be used until the expiration date printed on the label if they are stored in a refrigerator. Keep unused vials in the carton so they will stay clean and protected from light.

PenFill® cartridges, FlexPen® or InnoLet®:

After initial use, a cartridge (PenFill®) or a prefilled syringe (including FlexPen® or InnoLet®) may be used for up to 42 days if it is kept at room temperature, below 30°C (86°F). In-use cartridges and prefilled syringes in-use must NOT be stored in a refrigerator and must NOT be stored with the needle in place. Keep all cartridges and prefilled syringes away from direct heat and sunlight.

Not in-use (unopened) LEVEMIR PenFill®, FlexPen® or InnoLet® can be used until the expiration date printed on the label if they are stored in a refrigerator. Keep unused cartridges and prefilled syringes in the carton so they will stay clean and protected from light.

The storage conditions are summarized in the following table:

	Not in-use (unopened) Room Temperature (below 30°C)	Not in-use (unopened) Refrigerated	In-use (opened) Room Temperature (below 30°C)
10 mL vial	42 days	Until expiration date	42 days refrigerated/room temperature
3 mL PenFill cartridges®	42 days	Until expiration date	42 days (Do not refrigerate)
3 mL InnoLet®	42 days	Until expiration date	42 days (Do not refrigerate)
3 mL FlexPen®	42 days	Until expiration date	42 days (Do not refrigerate)

Rx Only.

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NDA 21-536
FDA revision 4 (6/16/05)
Page 14

Manufactured for Novo Nordisk Inc., Princeton, NJ 08540
Manufactured by Novo Nordisk A/S, 2880 Bagsvaerd, Denmark

www.novonordisk-us.com

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**Information For The Patient LEVEMIR (LEV uh mere)
Insulin detemir [rDNA origin] injection
3 mL PenFill® Disposable Cartridge (300 units per cartridge)
10 mL Vial (1000 units per vial)
100 Units/mL (U-100)**

Read this information carefully before you begin treatment and each time you get a refill because there may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. If you have any questions about **LEVEMIR** (LEV uh mere), ask your doctor. Only your doctor can determine if **LEVEMIR** is right for you.

What is the most important information I should know about LEVEMIR?

- **Do not change the insulin you are using without talking to your doctor.**
Any change of insulin should be made cautiously and only under medical supervision. Changes in insulin strength, manufacturer, type (for example: Regular, NPH, analogs), species (beef, pork, beef-pork, human) or method of manufacture (recombinant DNA versus animal source insulin) may need a change in the dose. This dose change may be needed right away or later on during the first several weeks or months on the new insulin. Doses of oral anti-diabetic medicines may also need to change, if your insulin is changed.
- **You must test your blood sugar levels while using an insulin, such as LEVEMIR.**
Your doctor will tell you how often you should test your blood sugar level, and what to do if it is high or low.
- **LEVEMIR should not be diluted or mixed with any other insulin or solution.**
- **LEVEMIR comes as U-100 insulin and contains 100 units of LEVEMIR per milliliter (mL). One milliliter of U-100 insulin contains 100 units of insulin. (1 mL = 1 cc).**

What is LEVEMIR?

- **LEVEMIR (insulin detemir [recombinant DNA origin]) is a long-acting insulin.** Because LEVEMIR is made by recombinant DNA technology (rDNA) and is chemically different from the insulin made by the human body, it is called an insulin analog. LEVEMIR is used to treat patients with diabetes for the control of high blood sugar. It is used once or twice a day to lower blood sugar.
- **LEVEMIR is a clear, colorless, sterile solution for injection under the skin (subcutaneously).**
- **The active ingredient in LEVEMIR is insulin detemir.** The concentration of insulin detemir is 100 units per milliliter (mL), or U-100. LEVEMIR also contains zinc, m-cresol, mannitol, phenol, disodium phosphate dihydrate, sodium chloride, and water for injection as inactive ingredients. Hydrochloric acid and/or sodium hydroxide may be added to adjust the final pH. LEVEMIR has a pH of approximately 7.4.

- You need a prescription to get LEVEMIR. Always be sure you receive the right insulin from the pharmacy.

LEVEMIR is available as:

- 10 mL vials (small bottles) for use with a syringe
- 3 mL PenFill® cartridges*
- 3 mL FlexPen®
- 3 mL InnoLet®

* PenFill® cartridges are for use with Novo Nordisk 3 mL PenFill® cartridge compatible insulin delivery devices and NovoFine® disposable needles.

Who should not take LEVEMIR?

Do not take LEVEMIR if:

- Your blood sugar is too low (hypoglycemia).
- You are allergic to LEVEMIR or any of its ingredients. Check with your doctor or pharmacist if you want information about the ingredients.

Before starting LEVEMIR, tell your doctor about all your medical conditions including if you:

- **have liver or kidney problems.** Your dose may need to be adjusted.
- **are pregnant or planning to become pregnant.** It is not known if LEVEMIR can cause any harm to your unborn baby if it is taken during pregnancy. It is very important to maintain control of your blood sugar levels during pregnancy. Your doctor will decide which insulin is best for you during your pregnancy.
- **are breast-feeding or planning to breast-feed.** It is not known whether LEVEMIR passes into your milk. Many medicines, including insulin, pass into human milk, and could affect your baby. Talk to your doctor about the best way to feed your baby.
- **take any other medicines,** including prescription and non-prescription medicines, vitamins, and herbal supplements. Be sure to mention about all medicines and supplements you are taking because some medicines, including non-prescription medicines and dietary supplements, may affect your diabetes. **Do not start any new medicines until you know how they may affect your insulin dose.**

How should I take LEVEMIR?

- Follow your doctor's instructions about monitoring your blood sugar. Do not make any changes with your insulin unless you have talked to your doctor. Your insulin needs may change because of illness, stress, other medicines, or changes in diet or activity level. Talk to your doctor about how to adjust your insulin dose.
- LEVEMIR can be taken once- or twice-daily. Your LEVEMIR dose and frequency of dosing should be individualized based on your doctor's advice.
- Before injecting LEVEMIR, make sure that you have the correct type and strength of insulin. Carefully follow the instructions on how to use your insulin syringe or insulin Pen.
- LEVEMIR should be inspected visually prior to administration and should only be used if the solution appears clear and colorless.
- Inject LEVEMIR under your skin (subcutaneously). Never inject it into a vein.

- The effect of an injected insulin dose may occur faster if the insulin is injected into your upper arm or abdomen (stomach area). However, you may also inject under the skin of your thigh.
- Change (rotate) injection sites within the same body area.
- Measure your blood sugar level as directed by your doctor.
- Carefully follow the instructions given by your doctor about the type of insulin you are using, its dose, and time of its injection. Any change in insulin should be made cautiously and only with your doctor's guidance. Your insulin needs may change due to a number of factors, such as illness, stress, medicines, or changes in diet or exercise routines. Follow your doctor's instructions to make these changes in your dose regimen.
- Clean your hands and the injection site with soap and water or with alcohol before you start the injection process.
- If you use insulin delivery device (insulin Pen), see the instructions on how to use the insulin Pen. It is important to read, understand, and follow the step-by-step instructions.

What should I use to take my LEVEMIR?

- 3 mL PenFill® cartridges*
*LEVEMIR PenFill® cartridges are for use with Novo Nordisk 3 mL PenFill® cartridge compatible insulin delivery devices and NovoFine® disposable needles.
- 10 mL vials (small bottles) for use with a syringe.
 - Always use a syringe that is marked for U-100 insulin. If you use other than U-100 insulin syringe, you may get the wrong dose of insulin causing serious problems for you, such as blood sugar level that is too low or too high. Always use a new needle and syringe each time you give LEVEMIR injection.
 - NEEDLES AND SYRINGERS MUST NOT BE SHARED
 - Disposable syringes and needles should only be used once. Used syringe and needle should be placed in "sharps" containers (such as red biohazard containers, hard plastic containers (such as detergent bottles), or metal containers (such as empty coffee cans). Such containers should be sealed and disposed of properly.

See the end of this patient information for instructions about preparing and giving the injection.

Mixing with LEVEMIR

LEVEMIR should NOT be mixed with any other insulin or solution. It will not work as intended and you may lose blood sugar control, which could be serious.

What should I know about using LEVEMIR?

- LEVEMIR can be taken once-daily in the evening. LEVEMIR can also be taken twice-daily in the morning and in the evening.
- Depending on dose, the effect of LEVEMIR can last for up to 24 hours after injection.

The effects of insulin may be different for different people. Even in the same person, the effects may vary from day to day. Because of this variation, the time periods listed here are general guidelines only.

What can affect how much insulin I need?

Illness. Illness may change how much insulin you need. It is a good idea to think ahead and make a "sick day" plan with your doctor in advance so you will be ready when this happens. Be sure to test your blood sugar more often and call your doctor if you are sick.

Medicines. Many medicines can affect your insulin needs. Other medicines, including prescription and non-prescription medicines, vitamins, and herbal supplements, can change the way insulin works. You may need a different dose of insulin when you are taking certain other medicines. **Know all the medicines you take**, including prescription and non-prescription medicines, vitamins and herbal supplements. You may want to keep a list of the medicines you take. You can show this list to your doctor and pharmacist anytime you get a new medicine or refill. Your doctor will tell you if your insulin dose needs to be changed.

Meals. The amount of food you eat can affect your insulin needs. If you eat less food, skip meals, or eat more food than usual, you may need to adjust your insulin dose. Talk to your doctor if you change your diet so that you know how to adjust your LEVEMIR and other insulin doses.

Alcohol. Alcohol, including beer and wine, may affect the way LEVEMIR works and affect your blood sugar levels. Talk to your doctor about drinking alcohol.

Exercise or Activity level. Exercise or activity level may change the way your body uses insulin. Check with your doctor before you start an exercise program because your dose may need to be changed.

Travel. If you travel across time zones, talk with your doctor about how to time your injections. When you travel, wear your medical alert identification. Take extra insulin and supplies with you.

Pregnancy or nursing. The effects of LEVEMIR on an unborn child or on a nursing baby are unknown. Therefore, tell your doctor if you planning to have a baby, are pregnant, or nursing a baby. Good control of diabetes is especially important during pregnancy and nursing.

What should I avoid while taking LEVEMIR?

- Alcohol, including beer and wine, may increase and lengthen the risk of hypoglycemia (too low blood sugar) when you take LEVEMIR.
- Be careful when you drive a car or operate machinery. Your ability to concentrate or react may be reduced if you have hypoglycemia. Ask your doctor if you should drive if you have frequent hypoglycemia or reduced or absent warning signs of hypoglycemia.

What are the possible side effects of LEVEMIR?

Insulins, including LEVEMIR, can cause hypoglycemia (low blood sugar), hyperglycemia (high blood sugar), allergy, and skin reactions.

Hypoglycemia (low blood sugar) This is the most common side effect. It occurs when there is a conflict between the amount of carbohydrates (source of glucose) from your food, the amount of glucose used by your body, and the amount and timing of insulin dosing. Therefore, **hypoglycemia can happen with:**

- **The wrong insulin dose.** This happens when too much insulin is injected.
- **Medicines that directly lower glucose or increase sensitivity to insulin.** This can happen with oral (taken by mouth) anti-diabetes drugs, sulfa antibiotics (for infections), ACE inhibitors (for blood pressure and heart failure), salicylates, including aspirin and NSAIDS (for pain), some antidepressants, and with other medicines.
- **Medical conditions that limit the body's glucose reserve, lengthen the time insulin stays in the body, or that increase sensitivity to insulin.** These conditions include diseases of the adrenal glands, the pituitary, the thyroid gland, the liver, and the kidney.
- **Not enough carbohydrate (sugar or starch) intake.** This can happen if:
 - a meal or snack is missed or delayed
 - you have vomiting or diarrhea that decreases the amount of glucose absorbed by your body
 - alcohol interferes with carbohydrate metabolism
- **Too much glucose use by the body.** This can happen from:
 - too much exercise
 - higher than normal metabolism rates due to fever or an overactive thyroid

What are symptoms of **mild to moderate** hypoglycemia:

- Sweating
- Dizziness
- Palpitation (fast heart beat)
- Tremor (shakiness)
- Hunger
- Restlessness
- Tingling in the hands, feet, lips, or tongue
- Lightheadedness
- Trouble concentrating
- Headache
- Drowsiness
- Sleep problems
- Anxiety
- Blurred vision
- Slurred speech
- Depressed mood
- Irritability
- Abnormal behavior

- Unsteady movement
- Personality change

What are symptoms of severe hypoglycemia:

- Disorientation
- Unconsciousness
- Seizures (convulsions)
- Death

If you develop serious hypoglycemic reactions, get medical help right away.

Without recognition of early warning symptoms, you may not be able to take steps to avoid more serious hypoglycemia. Be alert for all of the various types of symptoms that may indicate hypoglycemia. Patients who experience hypoglycemia without early warning symptoms should monitor their blood glucose frequently, especially prior to activities such as driving. If the blood glucose is below your normal fasting glucose, you should consider eating or drinking sugar-containing foods to treat your hypoglycemia. Mild to moderate hypoglycemia may be treated by eating foods or drinks that contain sugar. Patients should always carry a quick source of sugar, such as candy mints or glucose tablets. More severe hypoglycemia may require the assistance of another person. Patients who are unable to take sugar orally or who are unconscious require an injection of glucagon or should be treated with intravenous administration of glucose at a medical facility. You should learn to recognize your own symptoms of hypoglycemia. If you are uncertain about these symptoms, you should monitor your blood glucose frequently to help you learn to recognize the symptoms that you experience with hypoglycemia.

If you have frequent episodes of hypoglycemia or experience difficulty in recognizing the symptoms, you should consult your doctor to discuss possible changes in therapy, meal plans, and/or exercise programs to help you avoid hypoglycemia.

Hyperglycemia (high blood sugar) is another common side effect. It also occurs when there is a conflict between the amount of carbohydrates (source of glucose) from your food, the amount of glucose used by your body, and the amount and timing of insulin dosing. Therefore, **hyperglycemia can occur with:**

- **The wrong insulin dose.** This can happen when too little or no insulin is injected.
- the insulin's ability to lower glucose is changed by incorrect storage (freezing, excessive heat), or usage after the expiration date
- **Medicines that directly increase glucose or decrease sensitivity to insulin.** This can happen, for example, with thiazide water pills (used for blood pressure), corticosteroids, birth control pills, and protease inhibitors (used for AIDS).
- **Medical conditions that increase the body's production of glucose or decrease sensitivity to insulin.** These medical conditions include fevers, infections, heart attacks, and stress.
- **Too much carbohydrate intake.** This can happen if you:
 - eat larger meals
 - eat more often
 - increase the proportion of carbohydrate in your meals

In patients with type 1 or insulin-dependent diabetes, long-lasting hyperglycemia can cause diabetic ketoacidosis (DKA). The first symptoms of DKA usually come on slowly, over a period of hours or days, and include feeling drowsy, flushed face, thirst, loss of appetite, and fruity odor on the breath. With DKA, urine tests show large amounts of glucose and ketones. Heavy breathing and a rapid pulse are more severe symptoms. If uncorrected, long-lasting hyperglycemia or DKA can lead to nausea, vomiting, stomach pains, dehydration, loss of consciousness, or even death. Therefore, it is important that you obtain medical help right away.

Other possible side effects include the following:

- **Serious allergic reaction.**
Get medical help right away if you develop a rash over your whole body, have trouble breathing, a fast heartbeat, or sweating. These are signs of a dangerous allergic reaction (systemic allergic reaction). These reactions are not common.
- **Reaction at the injection site (local allergic reaction).** You may get redness, swelling and itching at the injection site. If you have serious or continuing reactions, you may need to stop using LEVEMIR and use another insulin. Do not inject insulin into skin sites with these reactions. No type of insulin should be injected into skin sites with these reactions.
- **Skin thickens or pits at the injection site,** especially if the injection site is not rotated (changed).
- **Vision changes** that may require evaluation by an ophthalmologist (medical doctor specializing in eye disease) or changes in your eyeglasses or contact lens prescription.
- **Fluid retention or swelling of your hands and feet.**
- **Low potassium in your blood (hypokalemia)**

There are other possible side effects from LEVEMIR. Ask your doctor or pharmacist for further information. Tell your doctor or pharmacist if you have any other unwanted effects that you believe are caused by this insulin.

How should I store LEVEMIR?

- **Unopened vials and PenFill cartridges:**
Store unopened vials and PenFill cartridges in a refrigerator (36°F to 46°F; 2°C to 8°C) but not in the freezer. Do not use LEVEMIR if it has been frozen. Keep unopened LEVEMIR vials and PenFill® cartridges in the carton so they will stay clean and protected from light because the product is light sensitive.
- **Punctured vials:**
After initial use, the punctured vials should be stored in a refrigerator but not in a freezer. If refrigeration is not possible, the vial that you are currently using can be kept at room temperature up to 42 days, as long as it is kept below 30°C [86°F]. **Throw away unrefrigerated vials after 42 days from the first use, even if it still contains LEVEMIR.**
- **Punctured cartridges:**

After initial use (the rubber membrane has been punctured), do not refrigerate the punctured LEVEMIR PenFill® cartridges. However, keep them as cool as possible (below 30°C [86°F]). PenFill® cartridge that you are currently using can be kept at room temperature up to 42 days, as long as they are kept below 30°C [86°F]. **Throw away unrefrigerated disposable LEVEMIR PenFill® cartridges after 42 days from the cartridges first use, even if it still contains LEVEMIR.**

Keep all disposable PenFill® cartridges and vials away from direct heat and sunlight.

These storage conditions are summarized in the following table:

	Not in-use (unopened) Room Temperature (below 30°C)	Not in-use (unopened) Refrigerated	In-use (opened) Room Temperature (below 30°C)
10 mL vial	42 days	Until expiration date	42 days refrigerated/room temperature
3 mL PenFill cartridges®	42 days	Until expiration date	42 days (Do not refrigerate)

General information about LEVEMIR

Use LEVEMIR only to treat your diabetes. **Do not** give it to any other person. Ask your doctor or pharmacist about any concerns you have. They can answer your questions and give you written information about LEVEMIR written for health care professionals.

Doses of insulin are measured in units. **LEVEMIR** is available as a U-100 insulin. One milliliter (mL) of U-100 contains 100 units of insulin detemir. (1 mL = 1 cc). Only U-100 type syringes should be used for injection to ensure proper dosing.

Disposable syringes and needles are sterile if the package is sealed. They should be used only once and thrown away properly, to protect others from harm.

How should I prepare and deliver the injection using different insulin delivery devices?

Using the 10 mL vial:

1. At your first use, remove the tamper-resistant cap from the vial. If the cap has already been removed, do not use this vial and return it to your pharmacy.
2. Wipe the rubber membrane with an alcohol swab.
3. Do not roll or shake the vial. Vigorous shaking right before the dose is drawn into the syringe may cause bubbles or froth, which could cause dosage errors. The insulin should be used only if it is clear and colorless.
4. Pull back the plunger on your syringe until the black tip reaches the marking for the number of units you will inject.
5. Push the needle through the rubber membrane into the vial.
6. Push the plunger all the way in. This inserts air into the vial.
7. Turn the vial and syringe upside down together and slowly pull the plunger back to a few units beyond the correct dose.

8. If there are air bubbles, tap the syringe gently with your finger to raise the air bubbles to the needle. Then slowly push the plunger to the correct unit marking.
9. Lift the vial off the syringe.
10. Inject right away.
11. The syringe and vial should be disposed of properly without recapping the needle. After each injection, patients must **remove the needle without recapping** and dispose of it in a puncture-resistant container. Used syringes, needles, or 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.

Using the LEVEMIR 3 mL PenFill® cartridge in 3 mL PenFill® cartridge delivery devices* (*see 3 mL PenFill® cartridge compatible delivery devices section):

1. Read the instruction manuals for the 3 mL PenFill® cartridge compatible delivery device* before the device is used.
2. The insulin should be used only if it is clear and colorless. Insert the PenFill® cartridge into the 3 mL PenFill® cartridge compatible delivery device*.
3. Place the needle onto the 3 mL PenFill® cartridge compatible delivery device* immediately before use
4. Airshots should be done prior to each injection. Directions for performing an airshot and setting the dose are provided in your insulin delivery device instruction manual.
5. Discard needle after each dose. The needle should not be recapped to avoid needlesticks. After each injection, patients must **remove the needle without recapping** and dispose of it in a puncture-resistant container. Used syringes, needles, or 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.

After the first use of PenFill® cartridge:

1. Airshots should be done prior to each injection. Directions for performing an airshot and setting the dose are provided in your insulin delivery device instruction manual.
2. To avoid needle sticks, **do not recap** the needle. Throw away the needle safely after each injection

How should I inject LEVEMIR insulin with a syringe or 3 mL PenFill® cartridge compatible delivery device*?

1. Pinch your skin between two fingers, push the needle into the skinfold, and push the plunger to inject the insulin under your skin. The needle should be perpendicular to the skin. This means 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.
3. If blood appears after you pull the needle from your skin, press the injection site lightly with a finger. Do not rub the area.

* LEVEMIR PenFill® cartridges are for use with Novo Nordisk 3 mL PenFill® cartridge compatible insulin delivery devices and NovoFine® disposable needles.

For additional information regarding diabetes, contact the American Diabetes Association (ADA) at 1-800-DIABETES (1-800-342-2383), or visit the ADA website (www.diabetes.org).

For information about LEVEMIR contact:

Novo Nordisk Inc.
100 College Road West
Princeton, New Jersey 08540
1-800-727-6500

www.novonordisk-us.com/

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

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Date of Issue: XXXX

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Information For The Patient
LEVEMIR (LEV uh mere) FlexPen®
insulin detemir [rDNA origin] injection
in a 3 mL Prefilled Syringe
100 Units/mL (U-100)

Read this information carefully before you begin treatment and each time you get a refill because there may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. If you have any questions about LEVEMIR (LEV uh mere), ask your doctor. Only your doctor can determine if LEVEMIR is right for you.

What is the most important information I should know about LEVEMIR?

- **Do not change the insulin you are using without talking to your doctor.**
Any change of insulin should be made cautiously and only under medical supervision. Changes in insulin strength, manufacturer, type (for example: Regular, NPH, analogs), species (beef, pork, beef-pork, human) or method of manufacture (recombinant DNA versus animal source insulin) may need a change in the dose. This dose change may be needed right away or later on during the first several weeks or months on the new insulin. Doses of oral anti-diabetic medicines may also need to change, if your insulin is changed.
- **You must test your blood sugar levels while using an insulin, such as LEVEMIR.**
Your doctor will tell you how often you should test your blood sugar level, and what to do if it is high or low.
- **LEVEMIR should not be diluted or mixed with any other insulin or solution.**
- **LEVEMIR comes as U-100 insulin and contains 100 units of LEVEMIR per milliliter (mL). One milliliter of U-100 insulin contains 100 units of insulin. (1 mL = 1 cc).**

What is LEVEMIR?

- **LEVEMIR (insulin detemir [recombinant DNA origin]) is a long-acting insulin.** Because LEVEMIR is made by recombinant DNA technology (rDNA) and is chemically different from the insulin made by the human body, it is called an insulin analog. LEVEMIR is used to treat patients with diabetes for the control of high blood sugar. It is used once or twice a day to lower blood sugar.
- **LEVEMIR is a clear, colorless, sterile solution for injection under the skin (subcutaneously).**
- **The active ingredient in LEVEMIR is insulin detemir.** The concentration of insulin detemir is 100 units per milliliter (mL), or U-100. LEVEMIR also contains zinc, m-cresol, mannitol, phenol, disodium phosphate dihydrate, sodium chloride, and water for injection as inactive ingredients. Hydrochloric acid and/or sodium hydroxide may be added to adjust the final pH. LEVEMIR has a pH of approximately 7.4.

- You need a prescription to get LEVEMIR. Always be sure you receive the right insulin from the pharmacy.

LEVEMIR is available as:

- 10 mL vials (small bottles) for use with a syringe
- 3 mL PenFill® cartridges*
- 3 mL FlexPen®
- 3 mL InnoLet®

* PenFill® cartridges are for use with Novo Nordisk 3 mL PenFill® cartridge compatible insulin delivery devices and NovoFine® disposable needles.

Who should not take LEVEMIR?

Do not take LEVEMIR if:

- Your blood sugar is too low (hypoglycemia).
- You are allergic to LEVEMIR or any of its ingredients. Check with your doctor or pharmacist if you want information about the ingredients.

Before starting LEVEMIR, tell your doctor about all your medical conditions including if you:

- **have liver or kidney problems.** Your dose may need to be adjusted.
- **are pregnant or planning to become pregnant.** It is not known if LEVEMIR can cause any harm to your unborn baby if it is taken during pregnancy. It is very important to maintain control of your blood sugar levels during pregnancy. Your doctor will decide which insulin is best for you during your pregnancy.
- **are breast-feeding or planning to breast-feed.** It is not known whether LEVEMIR passes into your milk. Many medicines, including insulin, pass into human milk, and could affect your baby. Talk to your doctor about the best way to feed your baby.
- **take any other medicines,** including prescription and non-prescription medicines, vitamins, and herbal supplements. Be sure to mention about all medicines and supplements you are taking because some medicines, including non-prescription medicines and dietary supplements, may affect your diabetes. **Do not start any new medicines until you know how they may affect your insulin dose.**

How should I take LEVEMIR?

- Follow your doctor's instructions about monitoring your blood sugar. Do not make any changes with your insulin unless you have talked to your doctor. Your insulin needs may change because of illness, stress, other medicines, or changes in diet or activity level. Talk to your doctor about how to adjust your insulin dose.
- LEVEMIR can be taken once- or twice-daily. Your LEVEMIR dose and frequency of dosing should be individualized based on your doctor's advice.
- Before injecting LEVEMIR, make sure that you have the correct type and strength of insulin. Carefully follow the instructions on how to use your FlexPen Prefilled Syringe.

- LEVEMIR should be inspected visually prior to administration and should only be used if the solution appears clear and colorless.
- Inject LEVEMIR under your skin (subcutaneously). Never inject it into a vein.
- The effect of an injected insulin dose may occur faster if the insulin is injected into your upper arm or abdomen (stomach area). However, you may also inject under the skin of your thigh.
- Change (rotate) injection sites within the same body area.
- Measure your blood sugar level as directed by your doctor.
- Carefully follow the instructions given by your doctor about the type of insulin you are using, its dose, and time of its injection. Any change in insulin should be made cautiously and only with your doctor's guidance. Your insulin needs may change due to a number of factors, such as illness, stress, medicines, or changes in diet or exercise routines. Follow your doctor's instructions to make these changes in your dose regimen.
- Clean your hands and the injection site with soap and water or with alcohol before you start the injection process.

See the end of this patient information for instructions about preparing and giving the injection.

What should I know about using LEVEMIR?

- LEVEMIR can be taken once-daily in the evening. LEVEMIR can also be taken twice-daily in the morning and in the evening.
- Depending on dose, the effect of LEVEMIR can last for up to 24 hours after injection.

The effects of insulin may be different for different people. Even in the same person, the effects may vary from day to day. Because of this variation, the time periods listed here are general guidelines only.

What can affect how much insulin I need?

Illness. Illness may change how much insulin you need. It is a good idea to think ahead and make a "sick day" plan with your doctor in advance so you will be ready when this happens. Be sure to test your blood sugar more often and call your doctor if you are sick.

Medicines. Many medicines can affect your insulin needs. Other medicines, including prescription and non-prescription medicines, vitamins, and herbal supplements, can change the way insulin works. You may need a different dose of insulin when you are taking certain other medicines. **Know all the medicines you take**, including prescription and non-prescription medicines, vitamins and herbal supplements. You may want to keep a list of the medicines you take. You can show this list to your doctor and pharmacists anytime you get a new medicine or refill. Your doctor will tell you if your insulin dose needs to be changed.

Meals. The amount of food you eat can affect your insulin needs. If you eat less food, skip meals, or eat more food than usual, you may need to adjust your insulin dose. Talk to your doctor if you change your diet so that you know how to adjust your LEVEMIR and other insulin doses.

Alcohol. Alcohol, including beer and wine, may affect the way LEVEMIR works and affect your blood sugar levels. Talk to your doctor about drinking alcohol.

Exercise or Activity level. Exercise or activity level may change the way your body uses insulin. Check with your doctor before you start an exercise program because your dose may need to be changed.

Travel. If you travel across time zones, talk with your doctor about how to time your injections. When you travel, wear your medical alert identification. Take extra insulin and supplies with you.

Pregnancy or nursing. The effects of LEVEMIR on an unborn child or on a nursing baby are unknown. Therefore, tell your doctor if you planning to have a baby, are pregnant, or nursing a baby. Good control of diabetes is especially important during pregnancy and nursing.

What should I avoid while taking LEVEMIR?

- Alcohol, including beer and wine, may increase and lengthen the risk of hypoglycemia (too low blood sugar) when you take LEVEMIR.
- Be careful when you drive a car or operate machinery. Your ability to concentrate or react may be reduced if you have hypoglycemia. Ask your doctor if you should drive if you have frequent hypoglycemia or reduced or absent warning signs of hypoglycemia.

What are the possible side effects of LEVEMIR?

Insulins, including LEVEMIR, can cause hypoglycemia (low blood sugar), hyperglycemia (high blood sugar), allergy, and skin reactions.

Hypoglycemia (low blood sugar). This is the most common side effect. It occurs when there is a conflict between the amount of carbohydrates (source of glucose) from your food, the amount of glucose used by your body, and the amount and timing of insulin dosing. Therefore, hypoglycemia can occur with:

- **The wrong insulin dose.** This happens when too much insulin is injected.
- **Medicines that directly lower glucose or increase sensitivity to insulin.** This can happen with oral (taken by mouth) antidiabetes drugs, sulfa antibiotics (for infections), ACE inhibitors (for blood pressure and heart failure), salicylates, including aspirin and NSAIDS (for pain), some antidepressants, and with other medicines.
- **Medical conditions that limit the body's glucose reserve, lengthen the time insulin stays in the body, or that increase sensitivity to insulin.** These conditions include diseases of the adrenal glands, the pituitary, the thyroid gland, the liver, and the kidney.
- **Not enough carbohydrate (sugar or starch) intake.** This can happen if:
 - a meal or snack is missed or delayed
 - you have vomiting or diarrhea that decreases the amount of glucose absorbed by your body
 - alcohol interferes with carbohydrate metabolism
- **Too much glucose use by the body.** This can happen from:
 - too much exercise
 - higher than normal metabolism rates due to fever or an overactive thyroid

What are symptoms of **mild to moderate** hypoglycemia:

- Sweating
- Dizziness
- Palpitation (fast heart beat)
- Tremor (shakiness)
- Hunger
- Restlessness
- Tingling in the hands, feet, lips, or tongue
- Lightheadedness
- Trouble concentrating
- Headache
- Drowsiness
- Sleep problems
- Anxiety
- Blurred vision
- Slurred speech
- Depressed mood
- Irritability
- Abnormal behavior
- Unsteady movement
- Personality change

What are symptoms of **severe** hypoglycemia:

- Disorientation
- Unconsciousness
- Seizures (convulsions)
- Death

If you develop serious hypoglycemic reactions, get medical help right away.

Without recognition of early warning symptoms, you may not be able to take steps to avoid more serious hypoglycemia. Be alert for all of the various types of symptoms that may indicate hypoglycemia. Patients who experience hypoglycemia without early warning symptoms should monitor their blood glucose frequently, especially prior to activities such as driving. If the blood glucose is below your normal fasting glucose, you should consider eating or drinking sugar-containing foods to treat your hypoglycemia. Mild to moderate hypoglycemia may be treated by eating foods or drinks that contain sugar. Patients should always carry a quick source of sugar, such as candy mints or glucose tablets. More severe hypoglycemia may require the assistance of another person. Patients who are unable to take sugar orally, or who are unconscious, require an injection of glucagon or should be treated with intravenous administration of glucose at a medical facility. You should learn to recognize your own symptoms of hypoglycemia. If you are uncertain about these symptoms, you should monitor your blood glucose frequently to help you learn to recognize the symptoms that you experience with hypoglycemia.

If you have frequent episodes of hypoglycemia or experience difficulty in recognizing the symptoms, you should consult your doctor to discuss possible changes in therapy, meal plans, and/or exercise programs to help you avoid hypoglycemia.

Hyperglycemia (high blood sugar) is another common side effect. It also occurs when there is a conflict between the amount of carbohydrates (source of glucose) from your food, the amount of glucose used by your body, and the amount and timing of insulin dosing. Therefore, **hyperglycemia can occur with:**

- **The wrong insulin dose.** This can happen from any of the following:
 - too little or no insulin is injected
 - the insulin's ability to lower glucose is changed by incorrect storage (freezing, excessive heat), or usage after the expiration date
- **Medicines that directly increase glucose or decrease sensitivity to insulin.** This can happen, for example, with thiazide water pills (used for blood pressure), corticosteroids, birth control pills, and protease inhibitors (used for AIDS).
- **Medical conditions that increase the body's production of glucose or decrease sensitivity to insulin.** These medical conditions include fevers, infections, heart attacks, and stress.
- **Too much carbohydrate intake.** This can happen if you
 - eat larger meals
 - eat more often
 - increase the proportion of carbohydrate in your meals

In patients with type 1 or insulin-dependent diabetes, long-lasting hyperglycemia can cause diabetic ketoacidosis (DKA). The first symptoms of DKA usually come on slowly, over a period of hours or days, and include feeling drowsy, flushed face, thirst, loss of appetite, and fruity odor on the breath. With DKA, urine tests show large amounts of glucose and ketones. Heavy breathing and a rapid pulse are more severe symptoms. If uncorrected, long-lasting hyperglycemia or DKA can lead to nausea, vomiting, stomach pains, dehydration, loss of consciousness, or even death. Therefore, it is important that you obtain medical help right away.

Other possible side effects include the following:

- **Serious allergic reaction.**
Get medical help right away if you develop a rash over your whole body, have trouble breathing, a fast heartbeat, or sweating. These are signs of a dangerous allergic reaction (systemic allergic reaction). These reactions are not common.
- **Reaction at the injection site** (local allergic reaction). You may get redness, swelling and itching at the injection site. If you have serious or continuing reactions, you may need to stop using LEVEMIR and use another insulin. Do not inject insulin into skin sites with these reactions. No type of insulin should be injected into skin sites with these reactions.
- **Skin thickens or pits at the injection site**, especially if the injection site is not rotated (changed).

- **Vision changes** that may require evaluation by an ophthalmologist (medical doctor specializing in eye disease) or changes in your eyeglasses or contact lens prescription.
- **Fluid retention or swelling of your hands and feet.**
- **Low potassium in your blood (hypokalemia)**

There are other possible side effects from LEVEMIR. Ask your doctor or pharmacist for further information. Tell your doctor or pharmacist if you have any other unwanted effects that you believe are caused by this insulin.

How should I store LEVEMIR?

- **Unopened LEVEMIR FlexPen:**

Store unopened LEVEMIR FlexPen in a refrigerator (36°F to 46°F; 2°C to 8°C), but not in the freezer. Do not use LEVEMIR FlexPen if it has been frozen. Keep unopened disposable LEVEMIR FlexPen in the carton so they will stay clean and protected from light because the product is light sensitive.

- **Punctured LEVEMIR FlexPen:**

After initial use (the rubber membrane has been punctured), do not refrigerate disposable LEVEMIR FlexPen. However, keep them as cool as possible (below 30°C [86°F]). LEVEMIR FlexPen that you are currently using can be used for 42 days after the first use if it is kept at room temperature (below 30°C [86°F]). **Throw away unrefrigerated disposable LEVEMIR FlexPen after 42 days, even if it still contains LEVEMIR.**

Keep all disposable LEVEMIR FlexPen away from direct heat and sunlight.

These storage conditions are summarized in the following table:

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

General information about LEVEMIR

Use LEVEMIR only to treat your diabetes. **Do not** give it to any other person. Ask your doctor or pharmacist about any concerns you have. They can answer your questions and give you written information about LEVEMIR written for health care professionals.

LEVEMIR FlexPen (3mL) directions for use

LEVEMIR FlexPen is a disposable dial-a-dose insulin delivery system able to deliver 1 to a maximum of 60 units. The dose can be adjusted in increments of 1 unit. LEVEMIR FlexPen is designed for use with NovoFine® single-use needles. LEVEMIR FlexPen is not recommended

Novo's submission date: June 16, 2005

308 for the blind or severely visually impaired patients without the assistance of a sighted individual
309 trained in the proper use of the product.

310

311 **Please read and follow these instructions completely each time you use this device.**

312 **If you do not follow these instructions completely, you may get too much or too**
313 **little insulin.**

314

315 **Every time you give an injection using LEVEMIR FlexPen:**

316

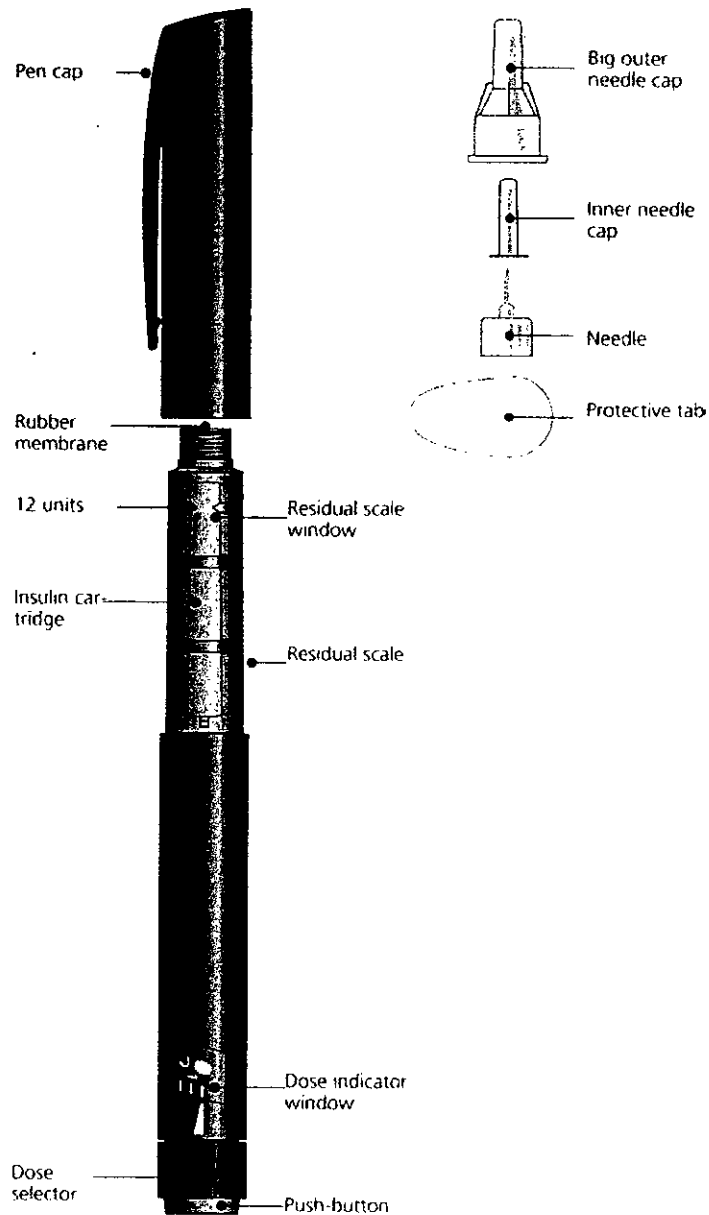
- **Use a new needle**

317

- **Prime to make sure the FlexPen is ready to dose**

318

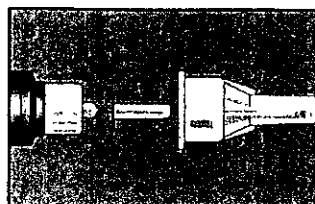
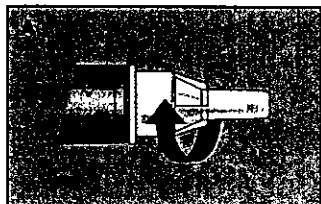
- **Make sure you got your full dose**



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1. PREPARING THE FLEXPEN PREFILLED SYRINGE

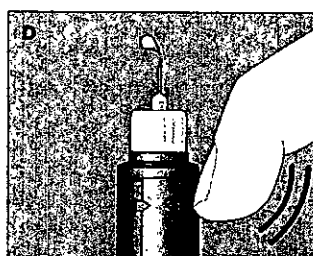
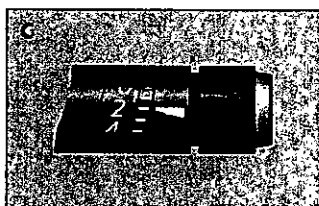
- a. Pull off the cap.
- b. Wipe the rubber membrane with an alcohol swab.



- c. Remove the protective tab from the disposable needle and screw the needle onto the FlexPen[®] (see diagram A). Never place a disposable needle on your FlexPen until you are ready to give an injection. Remove the needle from FlexPen immediately after the use. If the needle is not removed, some liquid may leak from the FlexPen.

Pull off the outer and inner needle caps (see diagram B). Do not discard the outer needle cap.

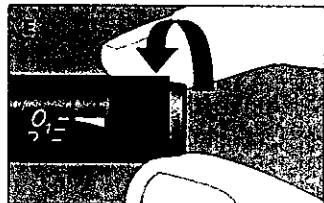
The numbers on the insulin reservoir *[show on the diagram]* can be used to estimate the amount of insulin left in the LEVEMIR FlexPen. Do not use these numbers to measure the insulin dose. You cannot set a dose greater than the number of units remaining in the insulin reservoir.



- d. **Giving the airshot before each injection:**
Small amounts of air may collect in the needle and insulin reservoir during normal use. **To avoid injecting air and to ensure proper dosing, follow steps (e) and (f) described below.**
- e. Dial 2 units (see diagram C).
- f. Holding the LEVEMIR FlexPen with the needle pointing up, tap the insulin reservoir gently with your finger a few times (see diagram D). Still with the needle pointing up, press the push button as far as it will go and see if a drop of insulin appears at the needle tip. If not, repeat the procedure until insulin appears. Before the first use of each disposable LEVEMIR FlexPen, you may need to perform up to 6 airshots to get a droplet of insulin at the needle tip. If you need to make more than 6 airshots, do not use the LEVEMIR FlexPen, and contact Novo Nordisk at 1-800-727-6500. A small air bubble

may remain but it will not be injected because the operating mechanism prevents the insulin reservoir from being completely emptied.

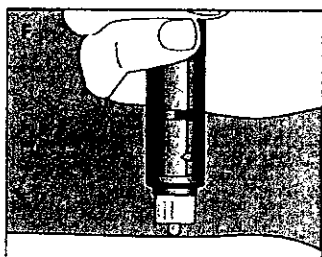
2. SETTING THE DOSE



Always check that the dose selector is set at 0 (see diagram E). Dial the number of dose you need to inject. The dose can be corrected either up or down by turning the dose selector in either direction. When dialing back, be careful not to push the push button as insulin will come out. You cannot set a dose larger than the number of units left in the reservoir. You will hear a click for every single unit dialed. Do not set the dose by counting the number of clicks you hear.

3. GIVING THE INJECTION

Use the injection technique recommended by your doctor or health care professionals.



- a. Pinch the skin between two fingers; push the needle into the skinfold (see diagram F).
- b. Deliver the dose by pressing the push button all the way in (see diagram G). Be careful only to push the push button when injecting.

- 381
382 c. After the injection, the needle should remain under the skin for at least 6 seconds. Keep
383 the push button fully pressed until the needle is withdrawn from the skin. This will
384 ensure that the full dose has been delivered. If blood appears after you pull the needle
385 from your skin, press the injection site lightly with a finger. **Do not rub the area.**
386

387 To avoid needlesticks, **do not** recap the needle. After each injection, you must **remove the**
388 **needle before replacing the device cap** and dispose of the needle in a puncture-resistant
389 container. Used syringes, needles, or lancets should be placed in "sharps" containers (such
390 as red biohazard containers), hard plastic containers (such as detergent bottles), or metal
391 containers (such as an empty coffee can). Such containers should be sealed and disposed of
392 properly.
393

394 **It is important that you use a new needle for each injection. Health care professionals,**
395 **relatives, and other caregivers, should follow general precautionary measures for removal**
396 **and disposal of needles to eliminate the risk of unintended needle stick.**
397

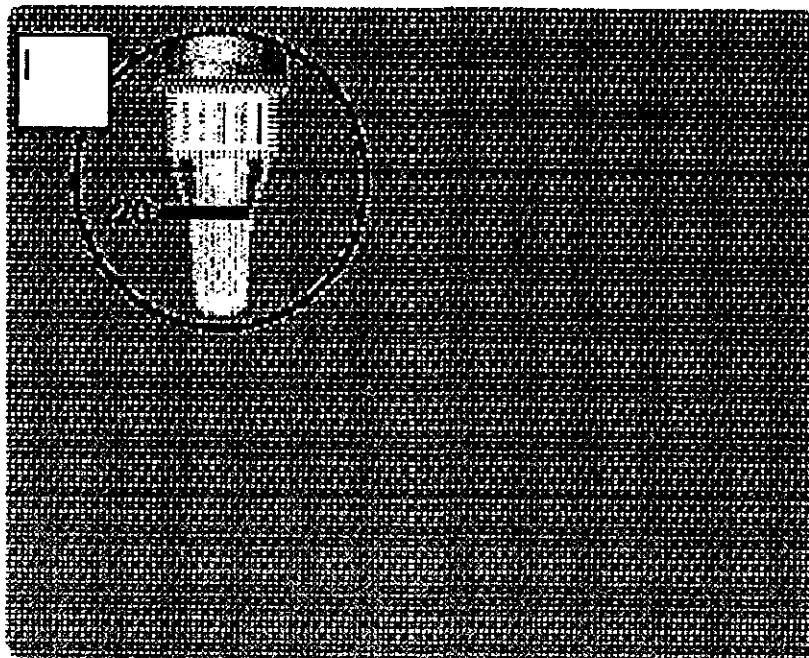
398 4. LATER (SUBSEQUENT) INJECTIONS

399

400 **It is important that you use a new needle for each injection. Follow the directions in steps 1**
401 **to 3.**
402

403 The numbers on the insulin reservoir can be used to estimate the amount of insulin left in the
404 LEVEMIR FlexPen. Do not use these numbers to measure the insulin dose. You cannot set a
405 dose greater than the number of units remaining in the reservoir.
406
407

408 **5. FUNCTION CHECK**



- 409
410 If your LEVEMIR FlexPen is not working properly, follow the following procedures:
411 - Screw on a new NovoFine needle
412 - Give an air shot as described in section **1. PREPARING THE FLEXPEN**
413 **PREFILLED SYRINGE**, steps (e) through (f). Put the outer needle cap
414 onto the needle
415 - Dispense 20 units into the outer needle cap, holding the LEVEMIR FlexPen
416 with the needle pointing down.

417 The insulin should fill the lower part of the cap (as shown in figure I). If LEVEMIR
418 FlexPen has released too much or too little insulin, repeat the test. If it happens again,
419 do not use your LEVEMIR FlexPen and contact Novo Nordisk at 1-800-727-6500.
420 Dispose of the empty LEVEMIR FlexPen carefully without the needle attached.
421

422

423

423 **6. IMPORTANT NOTES**

424

- 425 • If you need to perform more than 6 air shots before the first use of each disposable
426 LEVEMIR FlexPen to get a droplet of insulin at the needle tip, do not use the FlexPen and
427 contact Novo Nordisk at 1-800-727-6500.
428 • Remember to perform an air shot before each injection. See Section **1. PREPARING THE**
429 **FLEXPEN PREFILLED SYRINGE**, steps (e) through (f).
430 • Do not drop, damage, or crush the disposable LEVEMIR FlexPen.
431 • Remember to keep the disposable LEVEMIR FlexPen Prefilled syringe with you. Don't
432 leave it in a car or other location where it can get too hot or too cold.

- LEVEMIR FlexPen is not supplied with needles. NovoFine® disposable needles are designed and recommended for use with Novo Nordisk® insulin delivery devices, including LEVEMIR FlexPen.
- Never place a disposable needle on the LEVEMIR FlexPen until you are ready to use it. Remove the needle right after the use without recapping.
- **Discard the needle after each injection. After each injection, remove the needle before replacing the device cap and dispose of the needle in a puncture-resistant container. Used syringes, needles, or 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.**
- Throw away the empty LEVEMIR FlexPen without the needle attached.
- Always carry an extra LEVEMIR FlexPen with you in case your LEVEMIR FlexPen you are using is damaged or lost.
- To avoid possible transmission of disease, do not share your LEVEMIR FlexPen with anyone, even if you attach a new needle.
- **Novo Nordisk is not responsible for harm due to using this insulin delivery system with products not recommended by Novo Nordisk.**
- Keep this disposable LEVEMIR FlexPen out of the reach of children.

For additional information regarding diabetes, contact the American Diabetes Association (ADA) at 1-800-DIABETES (1-800-342-2383), or visit the ADA website (www.diabetes.org).

For information about LEVEMIR contact:

Novo Nordisk Inc.
100 College Road West,
Princeton, New Jersey 08540
1-800-727-6500

www.novonordisk-us.com

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

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License under U.S. Patent No. 5,618,913 and Des. 347,894

Date of Issue: ???????

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Novo's submission date: June 16, 2005

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Information For The Patient
LEVEMIR (LEV uh mere)InnoLet®
insulin detemir [rDNA origin] injection
in a 3 mL Prefilled Syringe
100 Units/mL (U-100)

Read this information carefully before you begin treatment and each time you get a refill because there may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. If you have any questions about LEVEMIR (LEV uh mere), ask your doctor. Only your doctor can determine if LEVEMIR is right for you.

What is the most important information I should know about LEVEMIR?

- **Do not change the insulin you are using without talking to your doctor.**
Any change of insulin should be made cautiously and only under medical supervision. Changes in insulin strength, manufacturer, type (for example: Regular, NPH, analogs), species (beef, pork, beef-pork, human) or method of manufacture (recombinant DNA versus animal source insulin) may need a change in the dose. This dose change may be needed right away or later on during the first several weeks or months on the new insulin. Doses of oral anti-diabetic medicines may also need to change, if your insulin is changed.
- **You must test your blood sugar levels while using an insulin, such as LEVEMIR.**
Your doctor will tell you how often you should test your blood sugar level, and what to do if it is high or low.
- **LEVEMIR should not be diluted or mixed with any other insulin or solution.**
- **LEVEMIR comes as U-100 insulin and contains 100 units of LEVEMIR per milliliter (mL). One milliliter of U-100 insulin contains 100 units of insulin. (1 mL = 1 cc).**

What is LEVEMIR?

- LEVEMIR (insulin detemir [recombinant DNA origin]) is a long-acting insulin. Because LEVEMIR is made by recombinant DNA technology (rDNA) and is chemically different from the insulin made by the human body, it is called an insulin analog. LEVEMIR is used to treat patients with diabetes for the control of high blood sugar. It is used once or twice a day to lower blood sugar.
- LEVEMIR is a clear, colorless, sterile solution for injection under the skin (subcutaneously).
- The active ingredient in LEVEMIR is insulin detemir. The concentration of insulin detemir is 100 units per milliliter (mL), or U-100. LEVEMIR also contains zinc, m-cresol, mannitol, phenol, disodium phosphate dihydrate, sodium chloride, and water for injection as inactive ingredients. Hydrochloric acid and/or sodium hydroxide may be added to adjust the final pH. LEVEMIR has a pH of approximately 7.4.
- You need a prescription to get LEVEMIR. Always be sure you receive the right insulin from the pharmacy.

LEVEMIR is available as:

- 10 mL vials (small bottles) for use with a syringe
- 3 mL PenFill® cartridges*
- 3 mL FlexPen®
- 3 mL InnoLet®

* PenFill® cartridges are for use with Novo Nordisk 3 mL PenFill® cartridge compatible insulin delivery devices and NovoFine® disposable needles.

Who should not take LEVEMIR?

Do not take LEVEMIR if:

- Your blood sugar is too low (hypoglycemia).
- You are allergic to LEVEMIR or any of its ingredients. Check with your doctor or pharmacist if you want information about the ingredients.

Before starting LEVEMIR, tell your doctor about all your medical conditions including if you:

- **have liver or kidney problems.** Your dose may need to be adjusted.
- **are pregnant or planning to become pregnant.** It is not known if LEVEMIR can cause any harm to your unborn baby if it is taken during pregnancy. It is very important to maintain control of your blood sugar levels during pregnancy. Your doctor will decide which insulin is best for you during your pregnancy.
- **are breast-feeding or planning to breast-feed.** It is not known whether LEVEMIR passes into your milk. Many medicines, including insulin, pass into human milk, and could affect your baby. Talk to your doctor about the best way to feed your baby.
- **take any other medicines,** including prescription and non-prescription medicines, vitamins, and herbal supplements. Be sure to mention about all medicines and supplements you are taking because some medicines, including non-prescription medicines and dietary supplements, may affect your diabetes. **Do not start any new medicines until you know how they may affect your insulin dose.**

How should I take LEVEMIR?

- Follow your doctor's instructions about monitoring your blood sugar. Do not make any changes with your insulin unless you have talked to your doctor. Your insulin needs may change because of illness, stress, other medicines, or changes in diet or activity level. Talk to your doctor about how to adjust your insulin dose.
- LEVEMIR can be taken once- or twice-daily. Your LEVEMIR dose and frequency of dosing should be individualized based on your doctor's advice.
- Before injecting LEVEMIR, make sure that you have the correct type and strength of insulin. Carefully follow the instructions on how to use your InnoLet.
- LEVEMIR should be inspected visually prior to administration and should only be used if the solution appears clear and colorless.
- Inject LEVEMIR under your skin (subcutaneously). Never inject it into a vein.
- The effect of an injected insulin dose may occur faster if the insulin is injected into your upper arm or abdomen (stomach area). However, you may also inject under the skin of your thigh.

- Change (rotate) injection sites within the same body area.
- Measure your blood sugar level as directed by your doctor.
- Carefully follow the instructions given by your doctor about the type of insulin you are using, its dose, and time of its injection. Any change in insulin should be made cautiously and only with your doctor's guidance. Your insulin needs may change due to a number of factors, such as illness, stress, medicines, or changes in diet or exercise routines. Follow your doctor's instructions to make these changes in your dose regimen.
- Clean your hands and the injection site with soap and water or with alcohol before you start the injection process.

See the end of this patient information for instructions about preparing and giving the injection.

What should I know about using LEVEMIR?

- LEVEMIR can be taken once-daily in the evening. LEVEMIR can also be taken twice-daily in the morning and in the evening.
- Depending on dose, the effect of LEVEMIR can last for up to 24 hours after injection.

The effects of insulin may be different for different people. Even in the same person, the effects may vary from day to day. Because of this variation, the time periods listed here are general guidelines only.

What can affect how much insulin I need?

Illness. Illness may change how much insulin you need. It is a good idea to think ahead and make a "sick day" plan with your healthcare provider in advance so you will be ready when this happens. Be sure to test your blood sugar more often and call your healthcare provider if you are sick.

Medicines. Many medicines can affect your insulin needs. Other medicines, including prescription and non-prescription medicines, vitamins, and herbal supplements, can change the way insulin works. You may need a different dose of insulin when you are taking certain other medicines. **Know all the medicines you take**, including prescription and non-prescription medicines, vitamins and herbal supplements. You may want to keep a list of the medicines you take. You can show this list to your healthcare provider and pharmacists anytime you get a new medicine or refill. Your healthcare provider will tell you if your insulin dose needs to be changed.

Meals. The amount of food you eat can affect your insulin needs. If you eat less food, skip meals, or eat more food than usual, you may need to adjust your insulin dose. Talk to your healthcare provider if you change your diet so that you know how to adjust your LEVEMIR and other insulin doses.

Alcohol. Alcohol, including beer and wine, may affect the way LEVEMIR works and affect your blood sugar levels. Talk to your healthcare provider about drinking alcohol.

Exercise or Activity level. Exercise or activity level may change the way your body uses insulin. Check with your healthcare provider before you start an exercise program because your dose may need to be changed.

Travel. If you travel across time zones, talk with your healthcare provider about how to time your injections. When you travel, wear your medical alert identification. Take extra insulin and supplies with you.

Pregnancy or nursing. The effects of LEVEMIR on an unborn child or on a nursing baby are unknown. Therefore, tell your healthcare provider if you planning to have a baby, are pregnant, or nursing a baby. Good control of diabetes is especially important during pregnancy and nursing.

What should I avoid while taking LEVEMIR?

- Alcohol, including beer and wine, may increase and lengthen the risk of hypoglycemia (too low blood sugar) when you take LEVEMIR.
- Be careful when you drive a car or operate machinery. Your ability to concentrate or react may be reduced if you have hypoglycemia. Ask your doctor if you should drive if you have frequent hypoglycemia or reduced or absent warning signs of hypoglycemia.

What are the possible side effects of LEVEMIR?

Insulins, including LEVEMIR, can cause hypoglycemia (low blood sugar), hyperglycemia (high blood sugar), allergy, and skin reactions.

Hypoglycemia (low blood sugar) This is the most common side effect. It occurs when there is a conflict between the amount of carbohydrates (source of glucose) from your food, the amount of glucose used by your body, and the amount and timing of insulin dosing. Therefore, hypoglycemia can occur with:

- **The wrong insulin dose.** This happens when too much insulin is injected
- **Medicines that directly lower glucose or increase sensitivity to insulin.** This can happen with oral (taken by mouth) antidiabetes drugs, sulfa antibiotics (for infections), ACE inhibitors (for blood pressure and heart failure), salicylates, including aspirin and NSAIDS (for pain), some antidepressants, and with other medicines.
- **Medical conditions that limit the body's glucose reserve, lengthen the time insulin stays in the body, or that increase sensitivity to insulin.** These conditions include diseases of the adrenal glands, the pituitary, the thyroid gland, the liver, and the kidney.
- **Not enough carbohydrate (sugar or starch) intake.** This can happen if:
 - a meal or snack is missed or delayed
 - you have vomiting or diarrhea that decreases the amount of glucose absorbed by your body
 - alcohol interferes with carbohydrate metabolism
- **Too much glucose use by the body.** This can happen from:
 - too much exercise
 - higher than normal metabolism rates due to fever or an overactive thyroid

What are symptoms of mild to moderate hypoglycemia:

- Sweating
- Dizziness
- Palpitation (fast heart beat)
- Tremor (shakiness)
- Hunger

- Restlessness
- Tingling in the hands, feet, lips, or tongue
- Lightheadedness
- Trouble concentrating
- Headache
- Drowsiness
- Sleep problems
- Anxiety
- Blurred vision
- Slurred speech
- Depressed mood
- Irritability
- Abnormal behavior
- Unsteady movement
- Personality change

What are symptoms of severe hypoglycemia:

- Disorientation
- Unconsciousness
- Seizures (convulsions)
- Death

If you develop serious hypoglycemic reactions, get medical help right away.

Without recognition of early warning symptoms, you may not be able to take steps to avoid more serious hypoglycemia. Be alert for all of the various types of symptoms that may indicate hypoglycemia. Patients who experience hypoglycemia without early warning symptoms should monitor their blood glucose frequently, especially prior to activities such as driving. If the blood glucose is below your normal fasting glucose, you should consider eating or drinking sugar-containing foods to treat your hypoglycemia. Mild to moderate hypoglycemia may be treated by eating foods or drinks that contain sugar. Patients should always carry a quick source of sugar, such as candy mints or glucose tablets. More severe hypoglycemia may require the assistance of another person. Patients who are unable to take sugar orally or who are unconscious require an injection of glucagon or should be treated with intravenous administration of glucose at a medical facility. You should learn to recognize your own symptoms of hypoglycemia. If you are uncertain about these symptoms, you should monitor your blood glucose frequently to help you learn to recognize the symptoms that you experience with hypoglycemia.

If you have frequent episodes of hypoglycemia or experience difficulty in recognizing the symptoms, you should consult your doctor to discuss possible changes in therapy, meal plans, and/or exercise programs to help you avoid hypoglycemia.

Hyperglycemia (high blood sugar) is another common side effect. It also occurs when there is a conflict between the amount of carbohydrates (source of glucose) from your food, the amount of glucose used by your body, and the amount and timing of insulin dosing. Therefore, **hyperglycemia can occur with:**

- **The wrong insulin dose.** This can happen from any of the following:
 - too little or no insulin is injected
 - the insulin's ability to lower glucose is changed by incorrect storage (freezing, excessive heat), or usage after the expiration date
- **Medicines that directly increase glucose or decrease sensitivity to insulin.** This can happen, for example, with thiazide water pills (used for blood pressure), corticosteroids, birth control pills, and protease inhibitors (used for AIDS).
- **Medical conditions that increase the body's production of glucose or decrease sensitivity to insulin.** These medical conditions include fevers, infections, heart attacks, and stress.
- **Too much carbohydrate intake.** This can happen if you
 - eat larger meals
 - eat more often
 - increase the proportion of carbohydrate in your meals

In patients with type 1 or insulin-dependent diabetes, long-lasting hyperglycemia can cause diabetic ketoacidosis (DKA). The first symptoms of DKA usually come on slowly, over a period of hours or days, and include feeling drowsy, flushed face, thirst, loss of appetite, and fruity odor on the breath. With DKA, urine tests show large amounts of glucose and ketones. Heavy breathing and a rapid pulse are more severe symptoms. If uncorrected, long-lasting hyperglycemia or DKA can lead to nausea, vomiting, stomach pains, dehydration, loss of consciousness, or even death. Therefore, it is important that you obtain medical help right away.

Other possible side effects include the following:

- **Serious allergic reaction.**
Get medical help right away if you develop a rash over your whole body, have trouble breathing, a fast heartbeat, or sweating. These are signs of a dangerous allergic reaction (systemic allergic reaction). These reactions are not common.
- **Reaction at the injection site** (local allergic reaction). You may get redness, swelling and itching at the injection site. If you have serious or continuing reactions, you may need to stop using LEVEMIR and use another insulin. Do not inject insulin into skin sites with these reactions. No type of insulin should be injected into skin sites with these reactions.
- **Skin thickens or pits at the injection site**, especially if the injection site is not rotated (changed).
- **Vision changes** that may require evaluation by an ophthalmologist (medical doctor specializing in eye disease) or changes in your eyeglasses or contact lens prescription.
- **Fluid retention or swelling of your hands and feet.**
- **Low potassium in your blood** (hypokalemia)

There are other possible side effects from LEVEMIR. Ask your doctor or pharmacist for further information. Tell your doctor or pharmacist if you have any other unwanted effects that you believe are caused by this insulin.

Submission date: June 16, 2005

How should I store LEVEMIR?**• Unopened LEVEMIR InnoLet:**

Store unopened LEVEMIR InnoLet in a refrigerator (36°F to 46°F; 2°C to 8°C), but not in the freezer. Do not use LEVEMIR InnoLet if it has been frozen. Keep unopened disposable LEVEMIR InnoLet in the carton so they will stay clean and protected from light.

• Opened (in-use) LEVEMIR InnoLet:

After initial use (the rubber membrane has been punctured), do not refrigerate disposable LEVEMIR InnoLet. However, keep them as cool as possible (below 30°C [86°F]). LEVEMIR InnoLet that you are currently using can be used for 42 days after the first use if it is kept at room temperature (below 30°C [86°F]). **Throw away unrefrigerated disposable LEVEMIR InnoLet after 42 days, even if it still contains Levemir.**

Keep disposable LEVEMIR InnoLet away from direct heat and sunlight.

These storage conditions are summarized in the following table:

	Not in-use (unopened) Room Temperature (below 30°C)	Not in-use (unopened) Refrigerated	In-use (opened) Room Temperature (below 30°C)
3 mL InnoLet®	42 days	Until expiration date	42 days (Do not refrigerate)

General information about LEVEMIR

Use LEVEMIR only to treat your diabetes. **Do not** give it to any other person. Ask your doctor or pharmacist about any concerns you have. They can answer your questions and give you written information about LEVEMIR written for health care professionals.

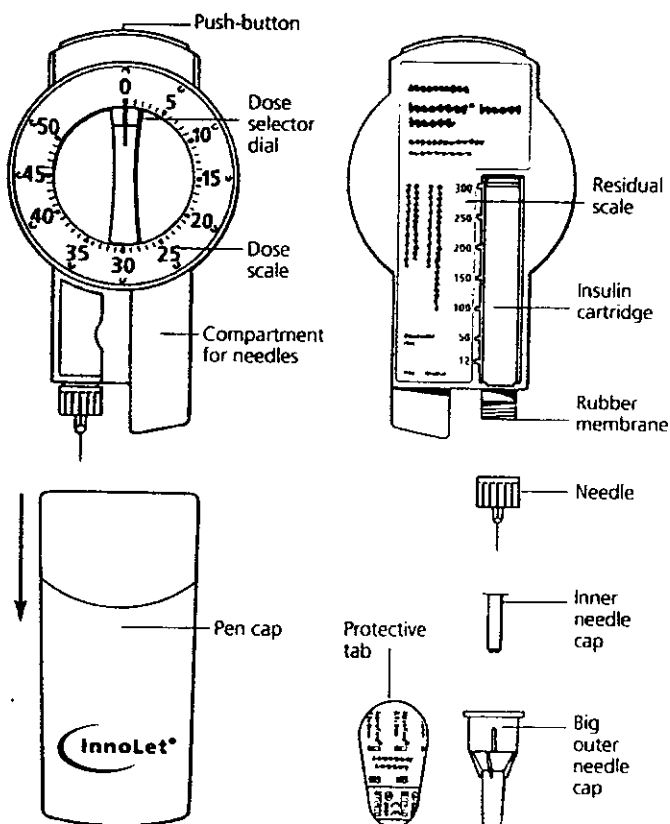
LEVEMIR InnoLet (3 mL) directions for use

LEVEMIR InnoLet is a disposable dial-a-dose insulin delivery system able to deliver 1 to a maximum of 50 units. The dose can be adjusted in increments of 1 unit. LEVEMIR InnoLet is designed for use with NovoFine® single-use needles. LEVEMIR InnoLet is not recommended for the blind or severely visually impaired patients without the assistance of a sighted individual trained in the proper use of the product.

Please read and follow these instructions completely each time you use this device. If you do not follow these instructions completely, you may get too much or too little insulin.

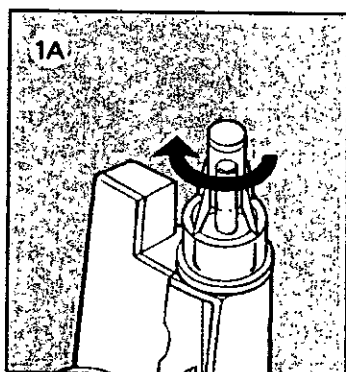
Every time you give an injection using LEVEMIR InnoLet:

- Use a new needle
- Prime to make sure the InnoLet is ready to dose
- Make sure you got your full dose



1. PREPARING THE LEVEMIR INNOLET

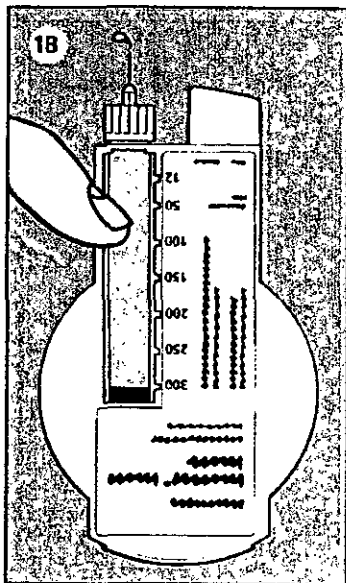
- a. Pull off the cap.
- b. Wipe the rubber membrane with an alcohol swab.



- c. Remove the protective tab from the disposable needle and screw the needle onto the InnoLet (see diagram 1A). Never place a disposable needle on your InnoLet until you are ready to give an injection. Remove the needle from InnoLet immediately after the use. If the needle is not removed, some liquid may leak from the LEVEMIR InnoLet.

d. **Giving the air shot before each injection**

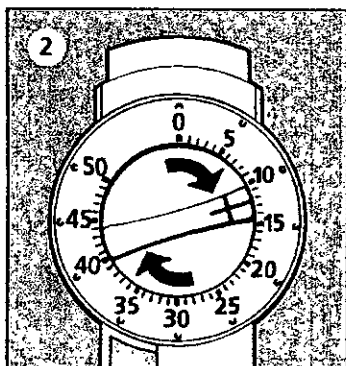
Small amounts of air may collect in the needle and insulin reservoir during normal use. **To avoid injecting air and to ensure proper dosing**, dial 2 units by turning the dose selector clockwise. Hold the LEVEMIR InnoLet with the needle pointing up and tap the LEVEMIR InnoLet gently with your finger so any air bubbles collect in the top of the reservoir. Remove both the plastic outer and inner needle cap.



- e. With the needle pointing up, press the push button as far as it will go and the dose selector returns to zero. See if a drop of insulin appears at the needle tip (see Figure 1B). If not, repeat the procedure until insulin appears.

Before the first use of LEVEMIR InnoLet, you may need to perform up to 6 airshots to get a droplet of insulin at the needle tip. If you need to make more than 6 airshots, do not use the LEVEMIR InnoLet, and contact Novo Nordisk® at 1-800-727-6500. A small air bubble may remain but it will not be injected because the operating mechanism prevents the reservoir from being completely emptied.

2. SETTING THE DOSE

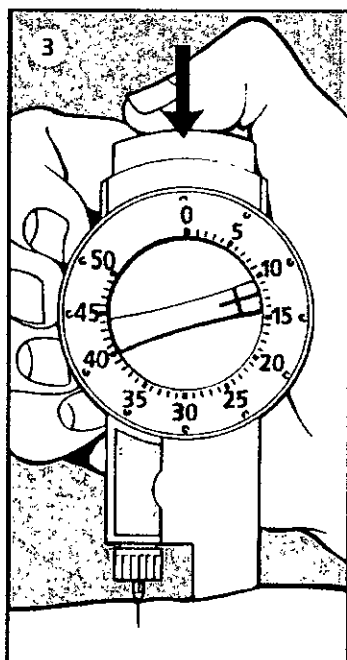


Always check that the push button is fully depressed and the dose selector is set at 0. Hold the LEVEMIR InnoLet® in front of you and dial the dose selector clockwise to set the required dose. Do not put your hand over the push button when dialing the dose. If the button is not allowed to rise freely, insulin will be pushed out of the needle. You will hear a click for every single unit dialed. Do not rely on the clicking sound as a means for setting your dose. If you have set a wrong dose, simply dial the dose selector forward or backwards until the right number of dose has been set.

50 units is the maximum dose.

3. GIVING THE INJECTION

Use the injection technique recommended by your doctor or health care professionals.



- a. Check that you have set the proper dose and depress the push button as far as it will go. Make sure not to block the dose selector while injecting, as the dose selector must be allowed

to return to zero when you press the push button. When depressing the push button, you may hear a clicking sound. Do not rely on this clicking sound as a means of confirming delivery of your dose.

After making the injection, unscrew the needle and discard appropriately. After each injection, you must **remove the needle before replacing the device cap** and dispose of the needle in a puncture-resistant container. Used syringes, needles, or 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.

It is important that you use a new needle for each injection. Health care professionals, relatives, and other caregivers, should follow general precautionary measures for removal and disposal of needles to eliminate the risk of unintended needlestick.

4. LATER (SUBSEQUENT) INJECTIONS

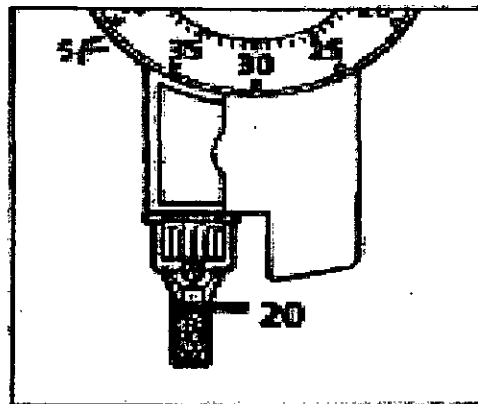
Always check that the push button is fully depressed before using the LEVEMIR InnoLet® again. If not, turn the dose selector until the push button is completely down. Then proceed as stated in steps 1-3.

The numbers on the insulin reservoir can be used to estimate the amount of insulin left in the LEVEMIR InnoLet. Do not use these numbers to measure the insulin dose. You cannot set a dose greater than the number of units remaining in the reservoir.

5. FUNCTION CHECK

If you think that your LEVEMIR InnoLet is not working properly, follow this procedure:

- Screw on a new NovoFine needle
- Perform air shot as described in Section 1. **PREPARING THE LEVEMIR INNOLET®, steps (d) through (e) and Figure 1B**
- Put the outer needle cap onto the needle
- Dispense 20 units into the needle cap.



The insulin will fill the lower part of the cap (as shown in the figure above).

If the LEVEMIR InnoLet has released too much or too little insulin, repeat the test. If it happens again, do not use your LEVEMIR InnoLet and contact Novo Nordisk at 1-800-727-6500.

6. IMPORTANT NOTES

- If you need to perform more than 6 air shots before the first use of the disposable LEVEMIR InnoLet to get a droplet of insulin at the needle tip, do not use your LEVEMIR InnoLet and contact Novo Nordisk at 1-800-727-6500.
- Remember to perform an air shot before each injection. See figure 1B.
- Do not drop, damage, or crush the disposable LEVEMIR InnoLet.
- Remember to keep the disposable LEVEMIR InnoLet with you. Don't leave it in a car or other location where it can get too hot or too cold.
- LEVEMIR InnoLet is not supplied with needles. NovoFine® disposable needles are designed and recommended for use with Novo Nordisk® insulin delivery devices, including LEVEMIR InnoLet.
- Never place a disposable needle on the LEVEMIR InnoLet until you are ready to use it. Remove the needle right after the use without recapping.
- **Discard the needle after each injection. After each injection, remove the needle before replacing the device cap and dispose the needle in a puncture-resistant container. Used syringes, needles, or 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.**
- Throw away the empty LEVEMIR InnoLet without the needle attached.
- Always carry an extra LEVEMIR InnoLet with you in case your LEVEMIR InnoLet you are using is damaged or lost.
- To avoid possible transmission of disease, do not share your LEVEMIR InnoLet with anyone, even if you attach a new needle.
- **Novo Nordisk is not responsible for harm due to using this insulin delivery system with products not recommended by Novo Nordisk.**
- Keep this disposable LEVEMIR InnoLet out of the reach of children.

For additional information regarding diabetes, contact the American Diabetes Association (ADA) at 1-800-DIABETES (1-800-342-2383), or visit the ADA website (www.diabetes.org).

For information about LEVEMIR InnoLet contact:

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Date of Issue: ???????

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