

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21-536/S-015

Trade Name: Levemir

Generic Name: insulin detemir [rDNA origin] injection

Sponsor: Novo Nordisk Inc.

Approval Date: May 16, 2007

Purpose: Provides for the following change in the drug product used to fill the 3 mL PenFill Cartridges: replacement of 30 mg mannitol with 16 mg glycerol

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21-536/S-015

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RESEARCH**

APPLICATION NUMBER:

21-536/S-015

APPROVAL LETTER



NDA 21-536/S-015

Novo Nordisk Inc.
Attention: Mary Ann McElligott, Ph.D.
Associate Vice President, Regulatory Affairs
100 College Road West
Princeton, NJ 08540

Dear Dr. McElligott:

Please refer to your supplemental new drug application dated January 17, 2007, received January 17, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Levemir (insulin detemir [rDNA origin] injection).

We acknowledge receipt of your submission dated January 19, 2007.

This supplemental new drug application provides for the following change in the drug product used to fill the 3 mL PenFill Cartridges: replacement of 30 mg mannitol with 16 mg glycerol.

We have completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

(b)(4)

Please submit the final printed carton labels electronically that are identical to the enclosed trade and sample FlexPen carton labels (submitted January 17, 2007.) For administrative purposes, designate this submission "**Final Printed Carton Labels for approved supplement NDA 21-536/S-015.**" Approval of this submission by FDA is not required before the labeling is used.

Marketing the products with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
5515 Security Lane
HFD-001, Suite 5100
Rockville, MD 20852

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Enid Galliers, Chief, Project Management Staff, at 301.796.1211.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology
Products (DMEP)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures:

Package Insert
Patient Package Insert – 3 mL PenFill Cartridge & 10 mL vial
Patient Package Insert – FlexPen 3 mL Prefilled Pen
Carton Label – FlexPen – Sample
Carton Label – FlexPen – Trade

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Mary Parks
5/16/2007 08:55:28 PM

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-536/S-015

LABELING

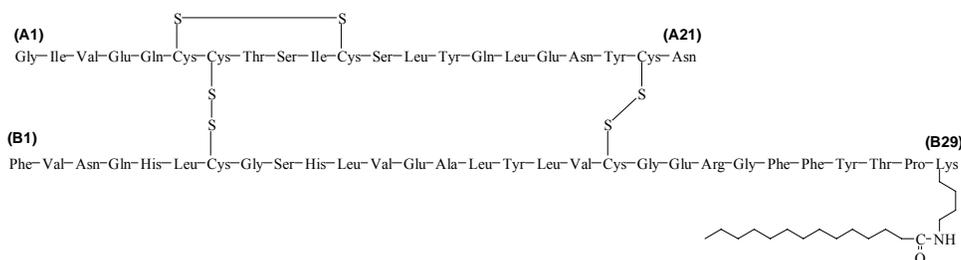
LEVEMIR[®]

(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.

Each milliliter of LEVEMIR 10 mL Vial contains the inactive ingredients 65.4 mcg 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. Each milliliter of LEVEMIR 3 mL PenFill[®] cartridge, FlexPen[™] and InnoLet[®] contains the inactive ingredients 65.4 mcg zinc, 2.06 mg m-cresol, 16.0 mg glycerol, 1.80 mg phenol, 0.89 mg disodium phosphate dihydrate, 1.17 mg sodium chloride, and water for injection.

Hydrochloric acid and/or sodium hydroxide may be added to adjust pH. LEVEMIR has a pH of approximately 7.4.

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 albumin binding. Insulin detemir is distributed more slowly 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

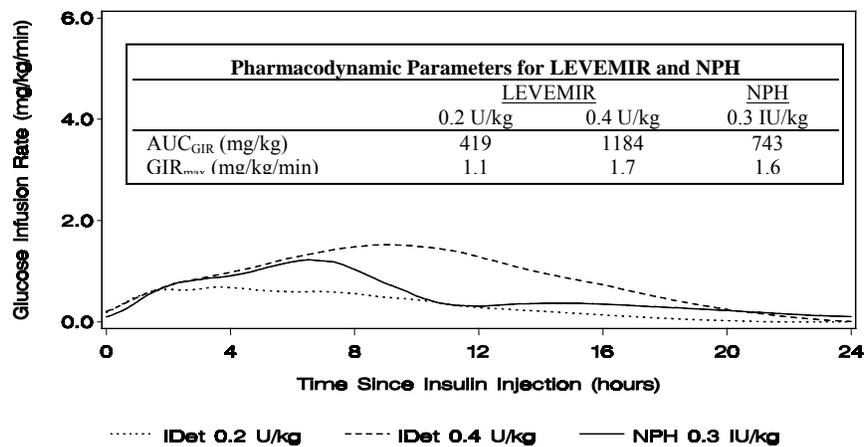
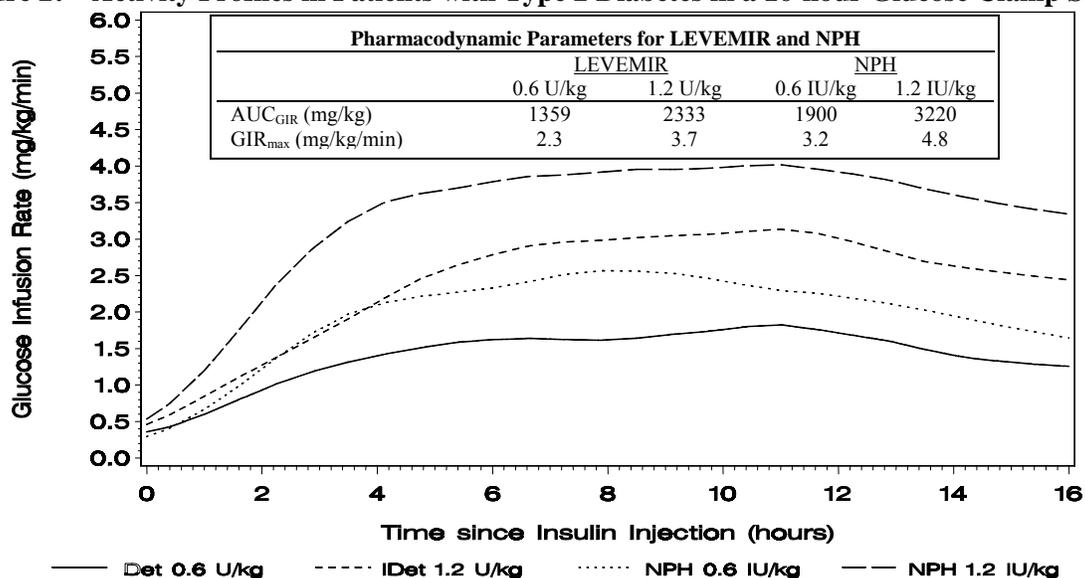


Figure 2 shows glucose infusion rate results from a 16-hour glucose clamp study in patients with type 2 diabetes. The clamp study was terminated at 16 hours according to protocol.

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



For doses in the interval of 0.2 to 0.4 U/kg, LEVEMIR exerts more than 50% of its maximum effect from 3 to 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 ± 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 the 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 to 7 hours depending on dose.

Special Populations

Children and Adolescents- The pharmacokinetic properties of LEVEMIR were investigated in children (6 to 12 years) and adolescents (13 to 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 – Adult

In one non-blinded clinical study (Study A, n=409), 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 fasting plasma glucose (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=749), 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 - Adult

	<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	133
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 1 Diabetes – Pediatric

In a non-blinded, randomized, controlled clinical study (Study D, n=347), pediatric patients (age range 6 to 17) with type 1 diabetes were treated for 26 weeks with a basal-bolus insulin regimen. LEVEMIR and NPH human insulin were administered once- or twice-daily (bedtime or morning and bedtime) according to pre-trial dose regimen. Bolus insulin aspart was administered before each meal. LEVEMIR-treated patients had a decrease in HbA_{1c} similar to that of NPH human insulin.

Table 2: Efficacy and Insulin Dosage in Type 1 Diabetes Mellitus - Pediatric

	<u>Study D</u>	
	26 weeks	
Treatment in combination with	NovoLog [®] (insulin aspart)	
	<u>LEVEMIR</u>	<u>NPH</u>
Treatment duration	26 weeks	
Number of subjects treated	232	115
HbA_{1c} (%)		
Baseline	8.75	8.77
End of study adjusted mean	8.02	7.93
Mean change from baseline	-0.72	-0.80
Fasting Plasma Glucose (mg/dL)		
End of study adjusted mean	151.92	172.44
Mean change from baseline	-45.00	-19.98
Daily Basal Insulin Dose (U/kg)		
Prestudy mean	0.48	0.49
End of study mean	0.67	0.64
Daily Bolus Insulin Dose (U/kg)		
Prestudy mean	0.52	0.47
End of study mean	0.52	0.51

Type 2 Diabetes – Adult

In a 24-week, non-blinded, randomized, clinical study (Study E, n=476), 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 3).

Table 3: Efficacy and Insulin Dosage in Type 2 Diabetes Mellitus

	<u>Study E</u>	
	24 weeks	
Treatment in combination with	OAD	
	<u>LEVEMIR</u>	<u>NPH</u>
Number of subjects treated	237	239
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

In a 22-week, non-blinded, randomized, clinical study (Study F, n=395) 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.

INDICATIONS AND USAGE

LEVEMIR is indicated for once- or twice-daily subcutaneous administration for the treatment of adult and pediatric patients with type 1 diabetes mellitus or adult patients with type 2 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 a dose of 900 nmol/kg/day. The rat and rabbit embryofetal development studies that included concurrent human insulin control groups indicated that insulin detemir and human insulin had similar effects regarding embryotoxicity and teratogenicity.

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

In a controlled clinical study, HbA_{1c} concentrations and rates of hypoglycemia were similar among patients treated with LEVEMIR and patients treated with NPH human insulin.

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 4).

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 4). 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 4: Safety Information on Clinical Studies*

	Treatment	# of subjects	Weight (kg)		Hypoglycemia (events/subject/month)	
			Baseline	End of treatment	Major**	Minor***
Type 1						
Study A	LEVEMIR	N=276	75.0	75.1	0.045	2.184
	NPH	N=133	75.7	76.4	0.035	3.063
Study C	LEVEMIR	N=492	76.5	76.3	0.029	2.397
	NPH	N=257	76.1	76.5	0.027	2.564
Study D Pediatric	LEVEMIR	N=232	N/A	N/A	0.076	2.677
	NPH	N=115	N/A	N/A	0.083	3.203
Type 2						
Study E	LEVEMIR	N=237	82.7	83.7	0.001	0.306
	NPH	N=239	82.4	85.2	0.006	0.595
Study F	LEVEMIR	N=195	81.8	82.3	0.003	0.193
	NPH	N=200	79.6	80.9	0.006	0.235

* 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 3).
- 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 0169-3687-12
3 mL PenFill cartridges*	NDC 0169-3305-11
3 mL InnoLet®	NDC 0169-2312-11
3 mL FlexPen®	NDC 0169-6439-10

*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.

Date of Issue: June 16, 2005

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, glycerol (mannitol for vial product), 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 insulin?

- 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 something 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 SYRINGES 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) 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 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 they still contain insulin.**
- **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 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.

Date of Issue: June 16, 2005

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).

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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).

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- 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, glycerol (mannitol for vial product), 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.

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- 10 mL vials (small bottles) for use with a syringe
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- 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.

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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.
- 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 are 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.

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).

Date of Issue: June 16, 2005

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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

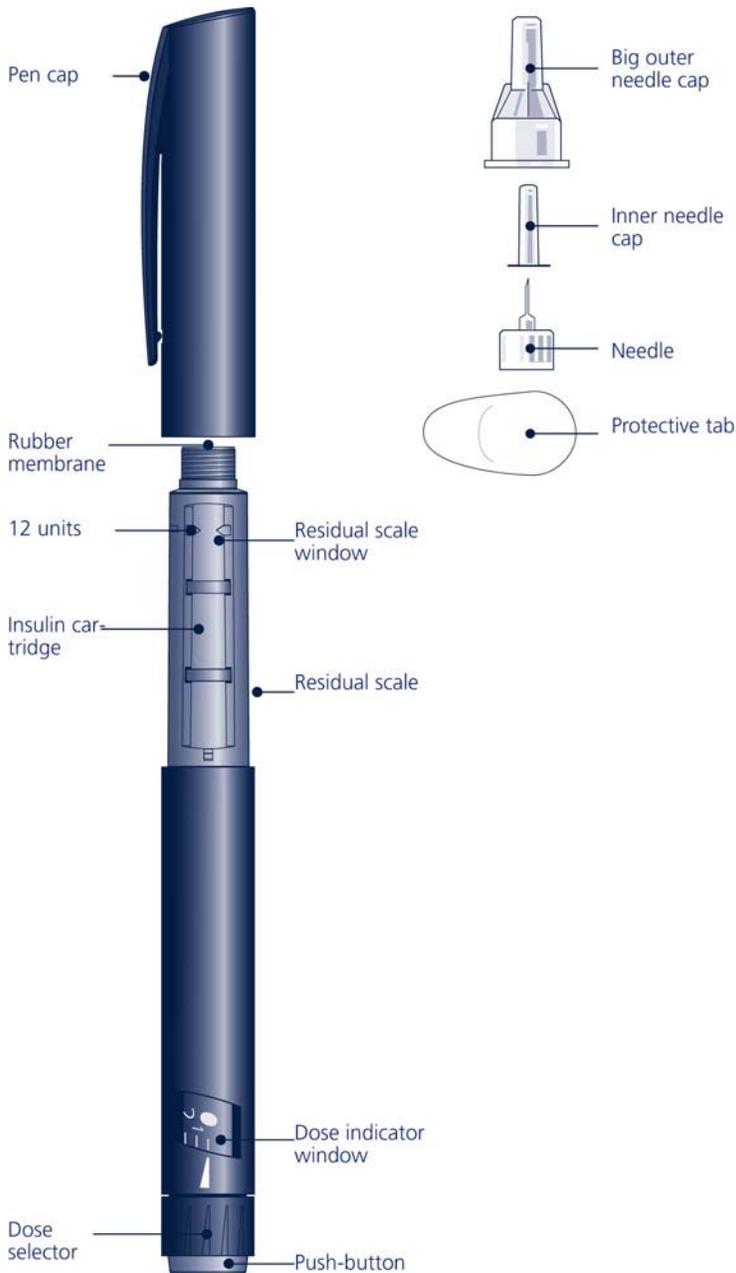
LEVEMIR FlexPen (3mL) directions for use

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 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.

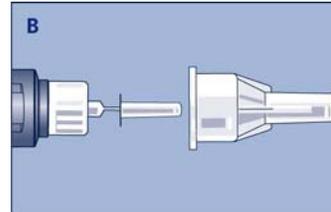
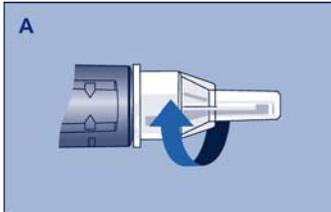
Every time you give an injection using LEVEMIR FlexPen:

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



1. PREPARING THE LEVEMIR FLEXPEN

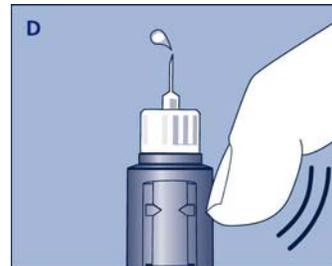
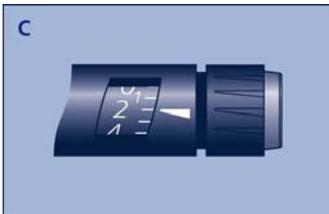
- a. Pull off the cap.
- b. Wipe the rubber membrane with an alcohol swab.



- 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.

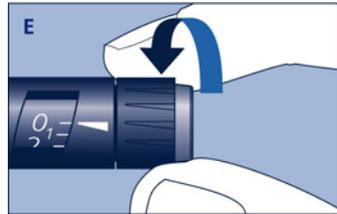
The numbers on the insulin reservoir can be used to estimate the amount of insulin left in the LEVEMIR FlexPen. Do not use these numbers to measure the insulin dose. You cannot set a dose greater than the number of units remaining in the insulin reservoir.



- 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.

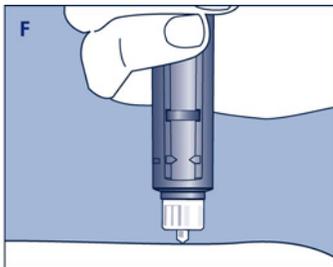
2. SETTING THE DOSE



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.

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

To avoid needlesticks, **do not** recap the needle. 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.

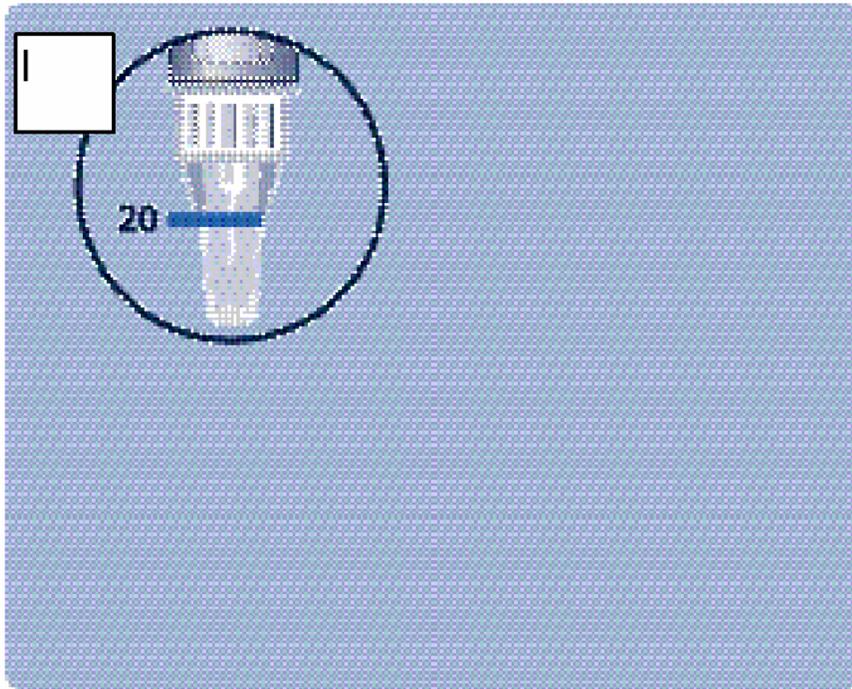
It is important that you use a new needle for each injection. Health care professionals, relatives, and other caregivers, should follow general precautionary measures for removal and disposal of needles to eliminate the risk of unintended needle stick.

4. LATER (SUBSEQUENT) INJECTIONS

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

The numbers on the insulin reservoir 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 reservoir.

5. FUNCTION CHECK



If your LEVEMIR FlexPen is not working properly, follow the following procedures:

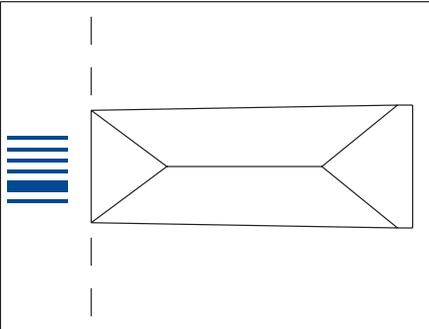
- Screw on a new NovoFine needle
- Give an air shot as described in section **1. PREPARING THE LEVEMIR FLEXPEN**, steps (e) and (f). Put the outer needle cap onto the needle
- Dispense 20 units into the outer needle cap, holding the LEVEMIR FlexPen with the needle pointing down.

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

6. IMPORTANT NOTES

- If you need to perform more than 6 air shots before the first use of each disposable LEVEMIR FlexPen to get a droplet of insulin at the needle tip, do not use the FlexPen and contact Novo Nordisk at 1-800-727-6500.
- Remember to perform an air shot before each injection. Follow the instructions in section **1. PREPARING THE LEVEMIR FLEXPEN**, steps (e) and (f).
- Do not drop, damage, or crush the disposable LEVEMIR FlexPen.
- Remember to keep the disposable LEVEMIR FlexPen with you. Don't 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.



**Levemir®
FlexPen®**
Insulin detemir (rDNA origin) injection
100 units/mL (U-100)
1×3 mL
Prefilled Pen

Warning
Any change of insulin should be made cautiously and only under medical supervision.

Levemir® FlexPen® is for single person use only.

Usual Dosage: See package insert
Needles not included.

FlexPen® and NovoFine® are trademarks of Novo Nordisk A/S. U.S. patent No. 4,973,318

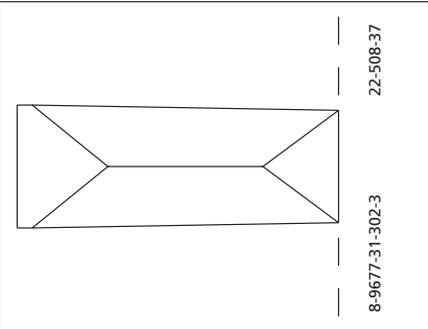
Each mL contains 100 Units (14.20 mg/mL) of insulin detemir, 65.40 mcg zinc, 2.06 mg m-cresol, 16.00 mg glycerol, 1.80 mg phenol, 0.89 mg disodium phosphate dihydrate, 1.17 mg sodium chloride, and water for injection.

Manufactured for:
Novo Nordisk Inc.
Princeton, NJ 08540
www.novonordisk-us.com
1-800-727-6500

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



Expiry/Control:



22-508-37
8-9677-31-302-3



Sample Not For Resale

**Levemir®
FlexPen®**
Insulin detemir (rDNA origin) injection
1×3 mL Prefilled Pen

NDC 0169-6439-90 List 643990

**Levemir®
FlexPen®**
Insulin detemir (rDNA origin) injection

100 units/mL (U-100)
1×3 mL Prefilled Pen
For subcutaneous use only
Rx Only

For use with NovoFine® disposable needles or other products specifically recommended by Novo Nordisk.

Keep in a cold place.
Store at 2° - 8°C (36° - 46°F).

Avoid freezing.
Protect from light.



Sample Not For Resale

**Levemir®
FlexPen®**
Insulin detemir (rDNA origin) injection
100 units/mL (U-100) 1×3 mL Prefilled Pen



Sample Not For Resale

8-9677-31-301-3

Levemir® FlexPen®
Insulin detemir (rDNA origin) Injection
100 units/mL (U-100) 5x3 mL Prefilled Pens

Levemir® FlexPen®

Insulin detemir (rDNA origin) Injection
100 units/mL (U-100) 5x3 mL Prefilled Pens

22-503-57

Levemir® FlexPen®
Insulin detemir (rDNA origin) Injection
100 units/mL (U-100) 5x3 mL Prefilled Pens

NDC 0169-6439-10 List 643910

Levemir® FlexPen®

Insulin detemir (rDNA origin) injection

100 units/mL (U-100)
5x3 mL Prefilled Pens
For subcutaneous use only
Rx Only



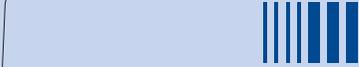
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Expiry/Control:



Warning
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Needles not included.

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FlexPen® and NovoFine® are trademarks of Novo Nordisk A/S.
U.S. patent No. 4,973,318



Novo Nordisk Inc.
Princeton, NJ 08540
www.novonordisk-us.com

1-800-727-6500

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



2
8

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-536/S-015

CHEMISTRY REVIEW(S)

DIVISION OF POST-MARKETING VALUATION
Review of Chemistry, Manufacturing, and Controls

NDA # 21-536 **SUPPLEMENT:** SCF-015

REVIEW DATE: 11-Apr-2007

SUPPLEMENT(S) PROVIDE(S) FOR: a change of the formulation for 3 ml PenFill cartridge presentation by replacing mannitol with glycerol as the isotonic agent in the drug product and (b) (4).

TYPE of SUPPLEMENT:

SUPAC CBE-0 CBE-30 Prior Approval Bundled Review Expedited Review

THE USER FEE GOAL DATE: 17-May-2007

<u>SUBMISSION DATE:</u>	<u>SUB. TYPE</u>	<u>DOC. DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
17-Jan-2007	electronic	17-Jan-2007	17-Jan-2007	15-Feb-2007
19-Jan-2007, C				N/A

NAME & ADDRESS OF APPLICANT:

Representative: Mary Ann McElligott, Ph. D.
Associate Vice President, Regulatory Affairs
Novo Nordisk, Inc.
100 College Road West, Princeton, New Jersey 08540
T: 609-987-5831, F-609-987-3916

NDA 21-536	
DRUG PRODUCT NAME: Proprietary:	LEVEMIR®
Nonproprietary/Established/USAN:	Insulin detemir (rDNA origin) injection
Code Name: Chem. Type/Therapeutic Class:	1/S
PHARMACOL. CATEGORY/INDICATION	Insulins / Treatment of diabetes melitus
DOSAGE FORM:	Parenteral
STRENGTHS:	100 Units/mL
ROUTE OF ADMINISTRATION:	Subcutaneous
DISPENSED:	<u>xx</u> Rx <u> </u> OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA(M.F.), MOLECULAR WEIGHT(M.W.):

This human insulin (recombinant DNA origin) is structurally identical to the insulin produced by the human pancreas. This human insulin is produced by recombinant DNA technology utilizing *Saccharomyces cerevisiae* (bakers' yeast) as the production organism.

SUPPORTING DOCUMENTS: N/A

RELATED DOCUMENTS (if applicable): N/A

CONSULTS: Microbiology, requested 02-Apr-2007; completed: 11-Apr-2007, referred to N21-172/SCF-034.

REMARKS/COMMENTS: (see review notes as well)

This change formulation submission is for replacing mannitol with glycerol. The change has been found adequate by the followings:

- The manufacturing process has been validated with 3 production batches and no change in the release specifications. No changes are made for the shelf life based on stability data which have shown comparable trend at all storage conditions to the mannitol formulation.
- Although the change causes freezing point depression, it is still within the approved specification. This formulation is compatible with current approved container closure system and does not affect the dose accuracy.
- No significant changes are noted for the assay, impurity levels, and pH during storage. The stability trend is comparable with the mannitol formulation.
- Analytical procedures, Package Insert, Carton and Container Labels have been updated with the new formulation.
- Regulatory requirements for stability commitment is provided..

Overall, from a chemist standpoint, this supplement is approved.

CONCLUSIONS & RECOMMENDATIONS: Approval

Li-Shan Hsieh, Ph.D., Review Chemist,

James Vidra, Ph.D., Chief of Branch VII

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Li-Shan Hsieh
4/25/2007 06:59:53 AM
CHEMIST

Jim Vidra
4/25/2007 01:03:41 PM
CHEMIST

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-536/S-015

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW

NDA: 21-536 (SCF015) Submission Date(s): January 17, 2007
Brand Name Levemir®
Generic Name insulin detemir injection, [rDNA origin]
Reviewer Sally Y. Choe, Ph.D.
Team Leader S. W. Johnny Lau, Ph.D. (Acting)
OCP Division Clinical Pharmacology II
OND division Metabolism and Endocrinology Products (HFD-510)
Sponsor Novo Nordisk
Submission Type; Code Prior Approval Supplement (CMC)
Formulation; Strength(s) Sterile parenteral solution, 100 U/mL
Indication Diabetes mellitus

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1. EXECUTIVE SUMMARY

1.1 RECOMMENDATION

The Office of Clinical Pharmacology / Division of Clinical Pharmacology II (OCP/DCP-II) has reviewed NDA 21-536 for Levemir® and finds it acceptable. The following comments, however, should be sent to the sponsor.

COMMENTS TO THE SPONSOR:

Related to the serum samples analysis and pharmacokinetic analysis in study NN304-1685, it appears that you have not provided: (i) complete report of bioanalytical analytical validation (ii) adequate discussion on hemolyzed blood samples in terms of the extent of hemolysis and the criteria used in including or omitting those samples for pharmacokinetic analysis and (iii) pharmacokinetic analysis excluding the samples with hemolysis issues (even though there was a notation that these samples should be viewed with caution).

In future submissions containing similar data, you should include complete report of bioanalytical method validation data, thorough discussion of samples with hemolysis issues, and pharmacokinetic analysis including and excluding samples with hemolysis issues. Submissions containing pivotal bioequivalence studies should contain all available data as outlined above to facilitate the Agency's assessment of the impact of formulation changes.

1.2 PHASE IV COMMITMENTS

None

1.3 SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS

Novo Nordisk proposes to change the formulation for the 3 mL PenFill® cartridge presentations by replacing mannitol with glycerol as the isotonic agent in the drug product. It has been noted that mannitol was (b) (4). To (b) (4), glycerol was proposed to replace the mannitol as the isotonic agent. In order to show that no difference in pharmacokinetic properties exists between the two formulations, a bioequivalence (BE) trial was conducted comparing key pharmacokinetic (PK) parameters obtained after a single subcutaneous (SC) injection of 0.375 U/kg of the reference product (insulin detemir with mannitol) and of the test product (insulin detemir with glycerol). The BE study has demonstrated that the test product containing glycerol is bioequivalent to the currently marketed reference product containing mannitol.

Hemolysis occurred in 11.5% of the serum samples analyzed. A separate BE analysis excluding these hemolyzed samples was conducted by the reviewer; the results were consistent that the insulin detemir with mannitol and the insulin detemir with glycerol were bioequivalent.

Insulin detemir (glycerol) / Insulin detemir (mannitol)	
AUC_(0-48h)	
N	34
Estimate of Ratio	98.1*
Lower 90% Confidence Limit	91.9*
Upper 90% Confidence Limit	104.7*
C_{max}	
N	34
Estimate of Ratio	92.0*
Lower 90% Confidence Limit	81.1*
Upper 90% Confidence Limit	104.4*

*The insulin detemir (glycerol)/insulin detemir (mannitol) ratio is given in percent.

2. QUESTION-BASED REVIEW (QBR)

2.1 GENERAL ATTRIBUTES

Insulin detemir is a derivative of human insulin (Lys^{B29}(N^ε-tetradecanoyl) des(B30) human insulin), in which the threonine residue at position B30 of the human insulin molecule has been removed and a C₁₄ fatty acid side-chain has been attached to position B29. Novo Nordisk proposes to change the marketed formulation of the insulin detemir, 3 mL PenFill® cartridge presentations by replacing mannitol with glycerol as the isotonic agent. The formulation change results in a minor change to the specification for freezing point depression of the product. Products involved PenFill® 3.0 mL cartridges which are included in the disposable insulin injection device Levemir FlexPen®.

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 *Has the sponsor demonstrated the bioequivalence between the reference product (insulin detemir with mannitol formulation) and the test product (insulin detemir with glycerol formulation)?*

The isotonic agent used in the current formulation of the 3 mL PenFill® cartridge presentation is being changed from mannitol to glycerol to (b) (4). Mannitol was previously used as the isotonic agent. However, it had been noted that mannitol was a (b) (4). To (b) (4) it was decided to replace mannitol with glycerol as the isotonic agent, a component well known from other insulin products. The change proved to have no impact on product stability. In order to show that no difference in pharmacokinetic properties exists between the two formulations, a bioequivalence (BE) trial was conducted comparing key pharmacokinetic (PK) parameters obtained after a single subcutaneous (SC) injection of 0.375 U/kg of the reference product (insulin detemir with mannitol) and of the test product (insulin detemir with glycerol). Differences between the two formulations are shown in Table 1.

Table 1 Composition of insulin detemir 100 U/mL

Name of ingredients	Insulin detemir 100 U/ml with mannitol (current) Quantity per ml	Insulin detemir 100 U/ml with glycerol (new) Quantity per ml
Insulin detemir	2400 nmol = 100U	2400 nmol = 100U
Phenol	1.80 mg ^{1,2}	1.80 mg ^{1,2}
Metacresol	2.06 mg ¹	2.06 mg ¹
Glycerol	-	16.0 mg
Mannitol	30.0 mg	-
Disodium phosphate, dihydrate	0.89 mg	0.89 mg
Sodium chloride	1.17 mg	1.17 mg
Zinc (b) (4)	65.4 µg (b) (4)	65.4 µg (b) (4)
Hydrochloric acid (b) (4)	Approx. (b) (4)	Approx. (b) (4)
Sodium hydroxide (b) (4)	+	+
Water for injections	To make 1.0 ml	To make 1.0 ml

⁴ If necessary, pH is adjusted with sodium hydroxide (b) (4) or hydrochloric acid (b) (4)

The sponsor conducted a randomized, single centre, two-way crossover trial investigating the bioequivalence between a single subcutaneous (SC) injection of 0.375 U/kg of the reference product (insulin detemir with mannitol) and of the test product (insulin detemir with glycerol) in healthy subjects. The BE study has demonstrated that the test product containing glycerol is bioequivalent to the currently marketed reference product containing mannitol. Mean serum insulin detemir profiles are presented below in Figure 1 and the PK parameter summary and BE analysis are presented in Tables 2 and 3.

Figure 1 Mean Serum Insulin Detemir Profile

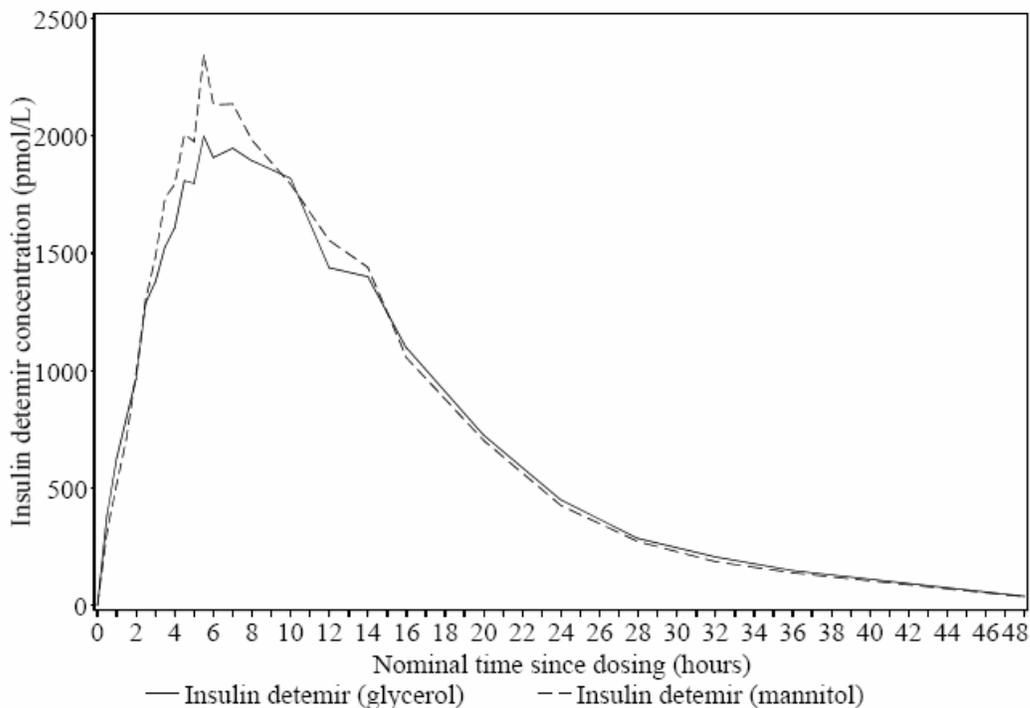


Table 2 Summary Table of PK Parameters

	Insulin detemir (mannitol)	Insulin detemir (glycerol)
AUC_(0-48h) ((nmol/L) x min)		
N	33	34
Mean	2082.9	2038.9
SD	414.4	416.5
Geometric Mean	2042.3	1997.5
CV %	19.9	20.4
Median	2120.6	1968.6
Min;Max	1306.5;2957.6	1320.7;2838.9
C_{max} (nmol/L)		
N	33	34
Mean	2.58	2.43
SD	0.69	0.88
Geometric Mean	2.49	2.29
CV %	26.57	36.12
Median	2.56	2.26
Min;Max	1.21;4.09	1.16;4.69

Table 3 Bioequivalence Analysis

Insulin detemir (glycerol) / Insulin detemir (mannitol)	
AUC_(0-48h)	
N	34
Estimate of Ratio	98.1 ^a
Lower 90% Confidence Limit	91.9 ^a
Upper 90% Confidence Limit	104.7 ^a
C_{max}	
N	34
Estimate of Ratio	92.0 ^a
Lower 90% Confidence Limit	81.1 ^a
Upper 90% Confidence Limit	104.4 ^a

^aThe insulin detemir (glycerol)/insulin detemir (mannitol) ratio is given in percent.

In addition, the sponsor compared the pharmacodynamic profiles of two formulations. The mean glucose infusion rate (GIR) profiles following administration of the reference product (insulin detemir with mannitol) and of the test product (insulin detemir with glycerol) were considered to be similar. These profiles can be found in Appendix 4.2.1.

2.3 ANALYTICAL SECTION

2.3.1 *What bioanalytical methods are used to assess concentrations?*

A validated enzyme immunoassay (ELISA) method was employed for the analysis of insulin detemir in human serum. For each calibration curve, 6 calibrators (0, 25, 50, 100, 200, and 400 pmol/L) were assayed in duplicate. The lower limit of quantitation was 25 pmol/L. The precision and the mean inaccuracy of the quality control samples were at or below 8.5% and 3.6%, respectively. The precision and the mean inaccuracy of the assay based on calibrator concentrations were at or below 3.0% and 5.9%, respectively.

3. DETAILED LABELING RECOMMENDATIONS

The sponsor did not propose clinical pharmacology related changes in the label for this submission.

4. APPENDICES

4.1 PROPOSED LABELING (ORIGINAL)

The sponsor's proposed changes in labeling are in yellow highlight and reside in only DESCRIPTION section.

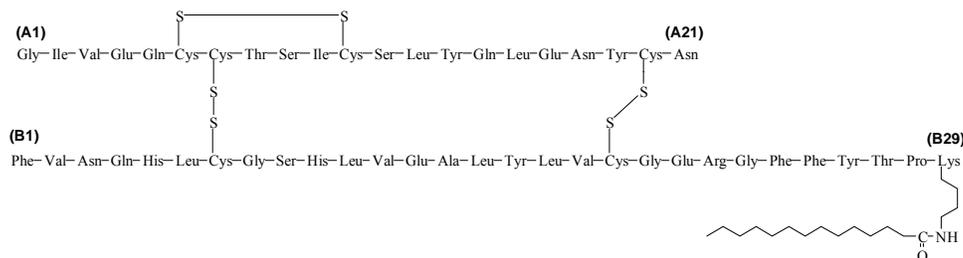
LEVEMIR[®]

(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.

Each milliliter of LEVEMIR 10 mL Vial contains the inactive ingredients 65.4 mcg 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. Each milliliter of LEVEMIR 3 mL PenFill[®] cartridge, FlexPen[™] and InnoLet[®] contains the inactive ingredients 65.4 mcg zinc, 2.06 mg m-cresol, 16.0 mg glycerol, 1.80 mg phenol, 0.89 mg disodium phosphate dihydrate, 1.17 mg sodium chloride, and water for injection.

Hydrochloric acid and/or sodium hydroxide may be added to adjust pH. LEVEMIR has a pH of approximately 7.4.

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 albumin binding. Insulin detemir is distributed more slowly 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

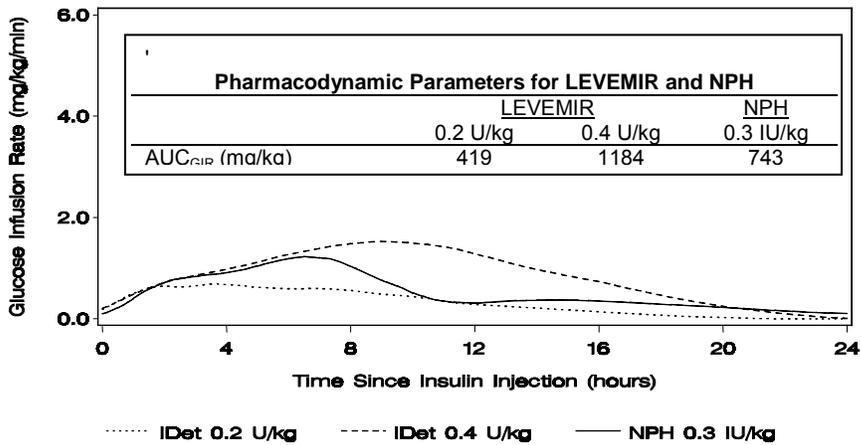
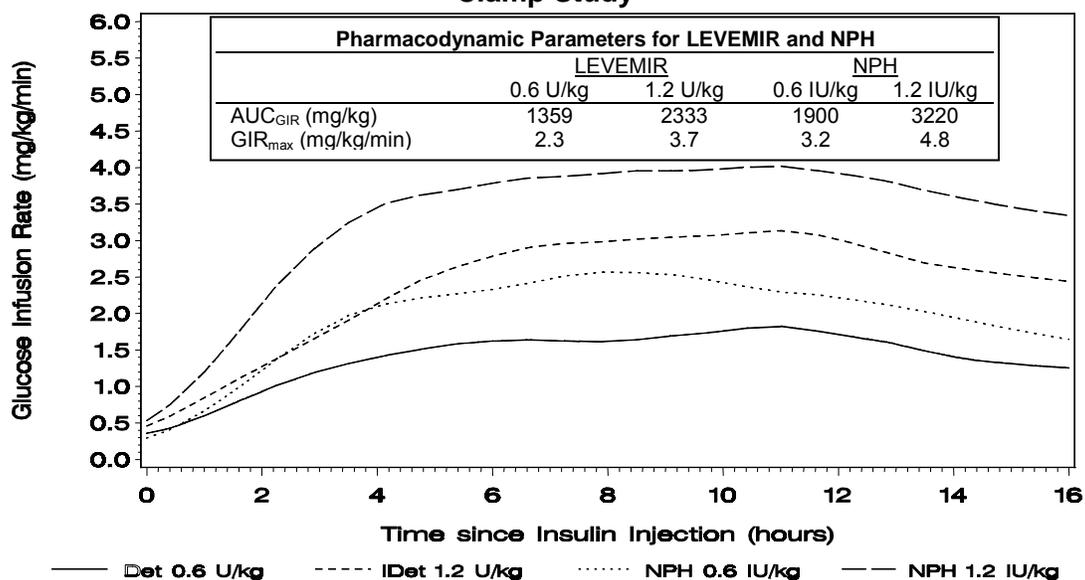


Figure 2 shows glucose infusion rate results from a 16-hour glucose clamp study in patients with type 2 diabetes. The clamp study was terminated at 16 hours according to protocol.

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



For doses in the interval of 0.2 to 0.4 U/kg, LEVEMIR exerts more than 50% of its maximum effect from 3 to 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 ± 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 the 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 to 7 hours depending on dose.

Special Populations

Children and Adolescents- The pharmacokinetic properties of LEVEMIR were investigated in children (6 to 12 years) and adolescents (13 to 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 – Adult

In one non-blinded clinical study (Study A, n=409), 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 fasting plasma glucose (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=749), 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 - Adult

	<u>Study A</u>	
	16 weeks	
Treatment duration	16 weeks	
Treatment in combination with	NovoLog® (insulin aspart)	
	<u>LEVEMIR</u>	<u>NPH</u>
Number of subjects treated	276	133
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 1 Diabetes – Pediatric

In a non-blinded, randomized, controlled clinical study (Study D, n=347), pediatric patients (age range 6 to 17) with type 1 diabetes were treated for 26 weeks with a basal-bolus insulin regimen. LEVEMIR and NPH human insulin were administered once- or twice-daily (bedtime or morning and bedtime) according to pre-trial dose regimen. Bolus insulin aspart was administered before each meal. LEVEMIR-treated patients had a decrease in HbA_{1c} similar to that of NPH human insulin.

Table 2: Efficacy and Insulin Dosage in Type 1 Diabetes Mellitus - Pediatric

	<u>Study D</u>	
	26 weeks	
Treatment duration	26 weeks	
Treatment in combination with	NovoLog [®] (insulin aspart)	
	<u>LEVEMIR</u>	<u>NPH</u>
Number of subjects treated	232	115
HbA_{1c} (%)		
Baseline	8.75	8.77
End of study adjusted mean	8.02	7.93
Mean change from baseline	-0.72	-0.80
Fasting Plasma Glucose (mg/dL)		
End of study adjusted mean	151.92	172.44
Mean change from baseline	-45.00	-19.98
Daily Basal Insulin Dose (U/kg)		
Prestudy mean	0.48	0.49
End of study mean	0.67	0.64
Daily Bolus Insulin Dose (U/kg)		
Prestudy mean	0.52	0.47
End of study mean	0.52	0.51

Type 2 Diabetes – Adult

In a 24-week, non-blinded, randomized, clinical study (Study E, n=476), 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 3).

Table 3: Efficacy and Insulin Dosage in Type 2 Diabetes Mellitus

	<u>Study E</u>	
Treatment duration	24 weeks	
Treatment in combination with	OAD	
	<u>LEVEMIR</u>	<u>NPH</u>
Number of subjects treated	237	239
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

In a 22-week, non-blinded, randomized, clinical study (Study F, n=395) 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.

INDICATIONS AND USAGE

LEVEMIR is indicated for once- or twice-daily subcutaneous administration for the treatment of adult and pediatric patients with type 1 diabetes mellitus or adult patients with type 2 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 a dose of 900 nmol/kg/day. The rat and rabbit embryofetal development studies that included concurrent human insulin control groups indicated that insulin detemir and human insulin had similar effects regarding embryotoxicity and teratogenicity.

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

In a controlled clinical study, HbA_{1c} concentrations and rates of hypoglycemia were similar among patients treated with LEVEMIR and patients treated with NPH human insulin.

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 4).

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 4). 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 4: Safety Information on Clinical Studies*

	Treatment	# of subjects	Weight (kg)		Hypoglycemia (events/subject/month)	
			Baseline	End of treatment	Major**	Minor***
Type 1						
Study A	LEVEMIR	N=276	75.0	75.1	0.045	2.184
	NPH	N=133	75.7	76.4	0.035	3.063
Study C	LEVEMIR	N=492	76.5	76.3	0.029	2.397
	NPH	N=257	76.1	76.5	0.027	2.564
Study D Pediatric	LEVEMIR	N=232	N/A	N/A	0.076	2.677
	NPH	N=115	N/A	N/A	0.083	3.203
Type 2						
Study E	LEVEMIR	N=237	82.7	83.7	0.001	0.306
	NPH	N=239	82.4	85.2	0.006	0.595
Study F	LEVEMIR	N=195	81.8	82.3	0.003	0.193
	NPH	N=200	79.6	80.9	0.006	0.235

* 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 3).
- 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 0169-3687-12
3 mL PenFill cartridges*	NDC 0169-3305-11
<i>3 mL InnoLet®</i>	<i>NDC 0169-2312-11</i>
<i>3 mL FlexPen®</i>	<i>NDC 0169-6439-10</i>

*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)	Not in-use (unopened)	In-use (opened)
	Room Temperature (below 30°C)	Refrigerated	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.

Date of Issue: June 16, 2005

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

www.novonordisk-us.com

NovoLog[®], FlexPen[®], InnoLet[®], PenFill[®], and NovoFine[®] are registered trademarks owned by Novo Nordisk A/S.

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4.2 INDIVIDUAL STUDY REVIEWS

4.2.1 Bioequivalence Study

Clinical Study NN304-1685

TITLE: A randomised, single centre, two-period cross-over, glucose clamp trial to test for bioequivalence between two insulin detemir formulations containing mannitol and glycerol as isotonic agents respectively, in healthy subjects

INVESTIGATOR: Cyril Clarke, B.Sc., MB BS, MFPM

STUDY CENTER: Medeval Ltd., Skelton House,
Manchester Science Park, Lloyd Street North,
Manchester M15 6SH, UK

PHARMACOKINETIC AND STATISTICAL ANALYSIS:

Novo Nordisk A/S.
Krogshøjvej 53A
DK-2880 Bagsværd
Denmark

BIOANALYTICAL ANALYSIS:

 (b) (4)

STUDY PERIOD: November 7, 2005 to February 3, 2006

OBJECTIVE: The primary objective of the study was to test for bioequivalence based on AUC_{48h} and C_{max} between two formulations of insulin detemir, containing mannitol and glycerol as isotonic agents. The secondary objective was to compare the pharmacokinetic and pharmacodynamics profiles of these two formulations.

STUDY DESIGN: This was a single center, randomized, single dose, 2-period, crossover study in healthy male and female subjects. A euglycaemic glucose clamp setting was chosen for safety reasons and in order to assess the pharmacodynamics. The washout period ranged from 7 to 28 days between the dosing visits. At each dosing visit basal blood samples were obtained for measurement of pre-dose insulin detemir and glucose concentrations. A single dose of trial product was then administered after which blood samples for insulin detemir measurements were taken at several time-points up to 48 hr after dosing. A euglycaemic lamp was initiated and continued for 16 hr. The trial product is a single injection (0.375 U/kg) of insulin detemir 100 U/mL, 2400 nmol/mL (supplied in Penfill® 3.0 mL cartridges) using either mannitol or glycerol as an isotonic agent. This trial product was injected subcutaneously into a lifted skin fold of the anterior aspect of the thigh using NovoPEN® 3 with a NovoFine® 30 gauge 8 mm needle. The following table shows the composition of each formulation.

Name of ingredients	Insulin detemir 100 U/ml with mannitol (current) Quantity per ml	Insulin detemir 100 U/ml with glycerol (new) Quantity per ml
Insulin detemir	2400 nmol = 100U	2400 nmol = 100U
Phenol	1.80 mg ^{1, 2}	1.80 mg ^{1, 2}
Metacresol	2.06 mg ¹	2.06 mg ¹
Glycerol	-	16.0 mg
Mannitol	30.0 mg	-
Disodium phosphate, dihydrate	0.89 mg	0.89 mg
Sodium chloride	1.17 mg	1.17 mg
Zinc	65.4 µg (b) (4)	65.4 µg (b) (4)
Hydrochloric acid (b) (4)	Approx. (b) (4)	Approx. (b) (4)
Sodium hydroxide (b) (4)	+	+
Water for injections	To make 1.0 ml	To make 1.0 ml

(b) (4)

⁴If necessary, pH is adjusted with sodium hydroxide (b) (4) or hydrochloric acid (b) (4)

BLOOD SAMPLE COLLECTION: 4 mL of blood were collected for measurement of insulin detemir at pre-dose (-30, -15, and -5 min) and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 10, 12, 14, 16, 20, 24, 28, 32, 36, and 48 hours post-dose. The first 16 hr of blood samples (except 2.5, 3.5, 4.5, 5.5, and 14 hr samples) were also used for measurement of serum C-peptide. In addition, blood samples were drawn every 10 minutes for 16 hours post-dosing, and continuously analyzed by a Yellow Springs glucose analyzer using 0.5 mL blood.

SAFETY ASSESSMENT: The safety evaluation was based on adverse events, hypoglycaemic episodes, vital signs, clinical laboratory tests (hematology, biochemistry and urinalysis), physical examination, ECGs, and local tolerability at injection site.

SUBJECTS: Thirty-four normal healthy, male and female subjects (21 males and 13 females) were randomized and 33 subjects completed the study. Subjects were between the ages of 19 and 51 years (mean ± SD = 27.1 ± 8.1 years).

ANALYTICAL METHOD: A validated enzyme immunoassay (ELISA) method was employed for the analysis of insulin detemir in human serum. The calibrator-fitting algorithm was a 3 order absorbance versus log concentration equation for concentrations in the interval 25 - 400 pmol/L and linear equation (absorbance vs. concentration) for concentrations in the interval 0 - ≤ 25 pmol/L. For each calibration curve, 6 calibrators (0, 25, 50, 100, 200, and 400 pmol/L) were assayed in duplicate. The lower limit of quantitation was 25 pmol/L. The precision and the mean inaccuracy of the quality control samples were at or below 8.5% and 3.6%, respectively. The precision and the mean inaccuracy of the assay based on calibrator concentrations were at or below 3.0% and 5.9%, respectively.

There were 207 repeat samples out of 1804 samples analyzed mainly due to improper dilution, excessive deviation in duplicates, and technical errors. These repeats did not seem to have significant impact on conclusion of the study.

There also were 207 samples out of 1804 samples analyzed that were hemolyzed. Five samples out of 207 hemolyzed samples were not able to be analyzed and the remaining 202 samples had comments stating that the results should be regarded with reservation.

The concentrations of C-peptide were measured in a total of 1069 serum samples by enzyme immunoassays (ELISA) using a commercially available C-peptide kit. The lower limit of quantification was 0.09 nmol/L and the limit of detection was 0.04 nmol/L. The inter-assay precision of quality control samples was at or below 10.2% and the mean inaccuracy from the quality control samples was at or below 4.6%.

PHARMACOKINETICS

Statistical Methods: A sample size of 32 was needed to meet the 80 – 125% confidence interval limits with a statistical power of at least 85% for both C_{max} and AUC_{48h}. The primary pharmacokinetic endpoints were C_{max} and AUC_{48h}. The secondary endpoints were AUC_∞, AUC_{16h}, T_{max}, T_{1/2el}, AUC_{GIR16h}, maximum glucose infusion rate (GIR_{max}), and tGIR_{max}.

Statistical and PK analyses were performed using SAS® Release version 8.2.

AUC_{48h} and C_{max} were subjected to an analysis of variance (ANOVA) using log transformed values in order to account for heteroscedasticity. The statistical model for each ANOVA had treatment and period as fixed effects and subject as a random effect.

The secondary pharmacokinetic and pharmacodynamic endpoints were compared for the two insulin formulations using descriptive statistics.

Results:

The summary of the pharmacokinetic parameters for insulin detemir and the results of bioequivalence testing are given in the following tables.

Table 9–1 Summary Table of Primary Endpoints

	Insulin detemir (mannitol)	Insulin detemir (glycerol)
AUC_(0-48h) ((nmol/L) x min)		
N	33	34
Mean	2082.9	2038.9
SD	414.4	416.5
Geometric Mean	2042.3	1997.5
CV %	19.9	20.4
Median	2120.6	1968.6
Min;Max	1306.5;2957.6	1320.7;2838.9
C_{max} (nmol/L)		
N	33	34
Mean	2.58	2.43
SD	0.69	0.88
Geometric Mean	2.49	2.29
CV %	26.57	36.12
Median	2.56	2.26
Min;Max	1.21;4.09	1.16;4.69

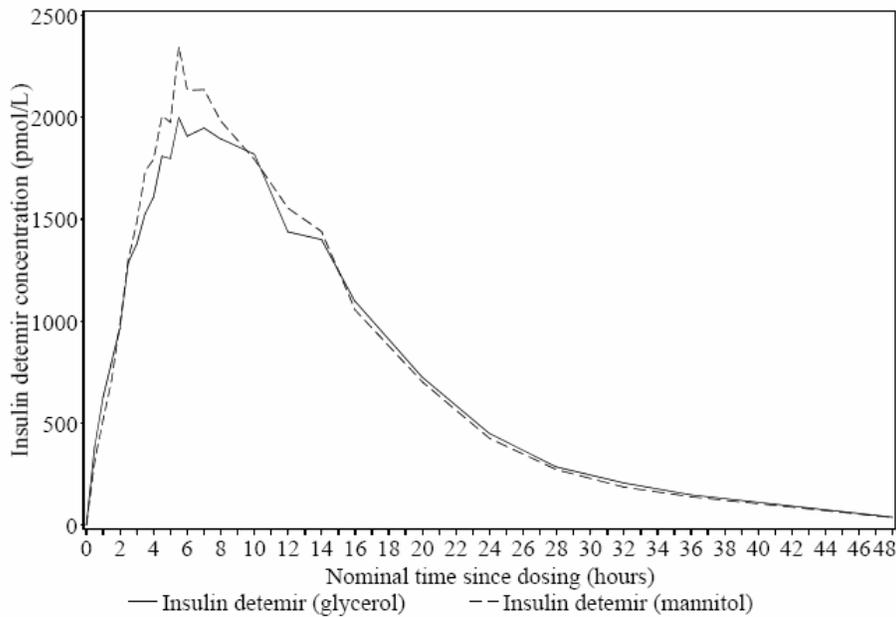
Cross-reference: EOT Table 3

Table 9–2 Analysis of Primary Endpoints

Insulin detemir (glycerol) / Insulin detemir (mannitol)	
AUC_(0-48h)	
N	34
Estimate of Ratio	98.1 ^a
Lower 90% Confidence Limit	91.9 ^a
Upper 90% Confidence Limit	104.7 ^a
C_{max}	
N	34
Estimate of Ratio	92.0 ^a
Lower 90% Confidence Limit	81.1 ^a
Upper 90% Confidence Limit	104.4 ^a

^aThe insulin detemir (glycerol)/insulin detemir (mannitol) ratio is given in percent.
 Cross-reference: EOT Table 4

The mean insulin detemir concentration-time curves for the two insulin detemir formulation are shown in the following graph.



w304-1605freze_27jun2006-27jun2006 - (report)_mean_serum_pk_meanprofiles.qm

Cross-reference: EOT Figure 68

Figure 9–1 Mean Serum Insulin Detemir Profile

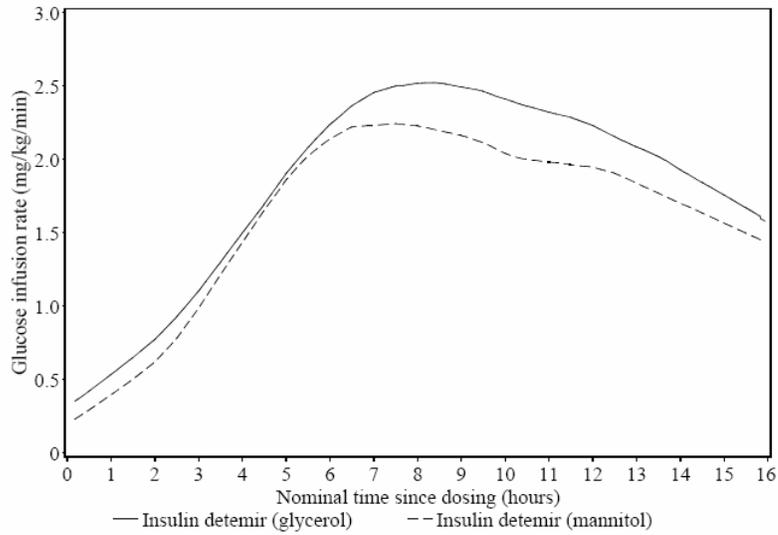
The summary of the secondary pharmacokinetic parameters for insulin detemir is given in the following tables.

Table 9–3 Summary Table of Secondary Pharmacokinetic Endpoints

	Insulin detemir (mannitol)	Insulin detemir (glycerol)
AUC_(0-∞) ((nmol/L) x min)		
N	33	34
Mean	2106.9	2067.9
SD	413.9	411.9
Geometric Mean	2066.9	2027.8
CV %	19.6	19.9
Median	2142.5	2001.6
Min;Max	1332.4;2991.6	1324.4;2846.6
AUC_(0-16h) ((nmol/L) x min)		
N	33	34
Mean	1485.3	1402.1
SD	359.9	439.3
Geometric Mean	1442.8	1339.3
CV %	24.2	31.3
Median	1393.1	1336.9
Min;Max	834.2;2222.5	738.1;2451.1
t_{max} (min)		
N	33	34
Median	330	420
Lower Quartile	330	330
Upper Quartile	420	600
Min;Max	180;960	150;960
t_{1/2} (min)		
N	33	34
Mean	410.0	406.8
SD	64.7	92.4
Harmonic Mean	401.4	384.8
Median	405.0	406.5
Min;Max	309.1;649.6	221.4;557.5

Cross-reference: EOT Table 9

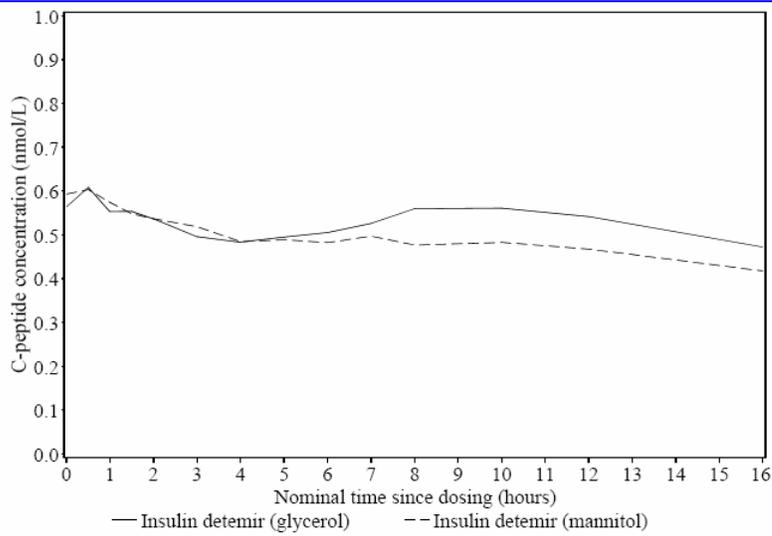
The mean glucose infusion rate (GIR), mean serum C-peptide, and the mean blood glucose concentration profiles following administration of the two insulin detemir formulations are shown in the following graphs.



m304-1655base_27jun2006 - 27JUN2006 - 1_girprofiles_mean.sasfig_meanGIRprofiles.qm

Cross-reference: EOT Figure 136

Figure 9-2 Mean GIR Profile



m304-1655base_27jun2006 - 27JUN2006 - 1_cpeptide_mean.sasfig_meancpeptide.qm

Cross-reference: EOT Figure 137

Figure 9-3 Mean Serum C-peptide Profile

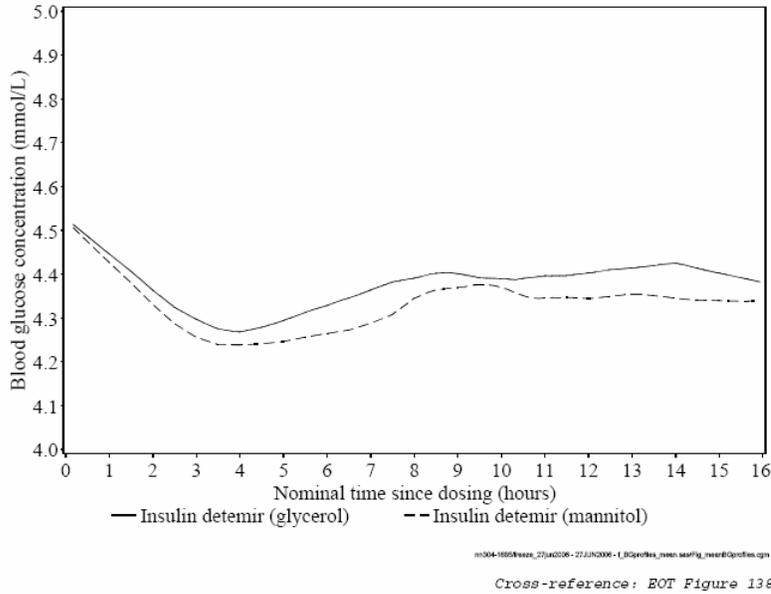


Figure 9-4 Mean Blood Glucose Concentration

SAFETY ASSESSMENT: A total of 74 treatment emergent adverse events (TEAEs) were reported by 27 of 34 subjects. There was one withdrawal caused by an AE, which was a syncope occurring at the first dosing visit approximately 10 min after termination of the euglycaemic glucose clamp. The subject fully recovered, completed the first dosing visit and was then withdrawn. This AE was judged by the investigator as “unlikely” to be related to trial product. Headache, hypoglycemia, dizziness, and nausea were the most frequent AEs and the incidence was similar following the two formulations. There were no clinically relevant findings in other safety parameters including laboratory variables.

SPONSOR’S CONCLUSIONS:

- The test product of insulin detemir with glycerol is bioequivalent to the reference product, insulin detemir with mannitol based on primary endpoints, C_{max} and AUC_{48h} .
- No relevant differences were observed between the two insulin detemir formulations for the secondary endpoints, AUC_{∞} , AUC_{16h} , T_{max} , $T_{1/2el}$, AUC_{GIR16h} , GIR_{max} , and $tGIR_{max}$.
- There were no significant safety issues in either treatment of insulin detemir with glycerol or mannitol.

REVIEWER’S COMMENTS:

- The sponsor did not address the issue of hemolyzed blood samples adequately in their submission. The concern for these 207 hemolyzed samples out of 1804 analyzed samples is whether these samples’ concentration data that should be “regarded with reservation” would have any significant impact on the overall results of the equivalency. Therefore, the reviewer performed the bioequivalence testing on the sponsor’s dataset excluding the 207 hemolyzed sample data. The result of this BE testing is summarized in the following table.

Parameters	LowerCL	Difference	UpperCL	Ratio	U_LCI	L_LCI
LCMAX	-0.219	-0.087	0.046	91.689	104.666	80.322
LAUC _{48h}	-0.083	-0.015	0.052	98.465	105.338	92.040

The result of this bioequivalence testing showed that the insulin detemir with glycerol is bioequivalent to the insulin detemir with mannitol, which is consistent with the sponsor's conclusion.

- Guidance for Industry titled, "Bioanalytical Method Validation" mentions that the calibration curve should consist of a six to eight non-zero samples covering the expected range, including LLOQ. The calibration curve generated by the sponsor contained only five non-zero samples (25, 50, 100, 200, and 400 pmol/L). However, this deviation did not seem to impact the overall result of the study.
- The sponsor did not submit the validation report of ELISA on insulin detemir.

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this page is the manifestation of the electronic signature.**

/s/

Sally Choe
5/11/2007 02:10:13 PM
BIOPHARMACEUTICS

S.W. Johnny Lau
5/11/2007 02:24:04 PM
BIOPHARMACEUTICS

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-536/S-015

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS



NDA 21-536/S-015

PRIOR APPROVAL SUPPLEMENT

Novo Nordisk, Inc.
Attn: Mary Ann McElligott, Ph.D.
Associate Vice President, Regulatory Affairs
100 College Road West
Princeton, NJ 08540

Dear Dr. McElligott:

We have received your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Levemir[®] (insulin detemir [rDNA origin]) for Injection
NDA Number: 21-536
Supplement number: S-015
Date of supplement: January 17, 2007
Date of receipt: January 17, 2007

This supplemental application proposes to change the formulation for the 3 ml PenFill[®] cartridge presentation by replacing mannitol with glycerol as the isotonic agent in the drug product.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on March 18, 2007, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be May 17, 2007.

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

U.S. Postal Service/Courier/Overnight Mail:
Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
Attention: Document and Records Section
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA 21-536/S-015

Page 2

If you have any questions, call me at (301) 796-1211.

Sincerely,

{See appended electronic signature page}

Enid Galliers
Chief, Project Management Staff
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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this page is the manifestation of the electronic signature.**

/s/

Enid Galliers

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