Levemir®
insulin detemir (rDNA origin) injection

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use LEVEMIR® safely and effectively. See full prescribing information for LEVEMIR®.
LEVEMIR® (insulin detemir [rDNA origin]) solution for subcutaneous injection
Initial U.S. Approval: 2005

—- RECENT MAJOR CHANGES ——-
• Warnings and Precautions (5.1)  02/2015

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

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

—- DOSAGE AND ADMINISTRATION ——-
• The starting dose should be individualized based on the type of diabetes and whether the patient is insulin- naïve (2.1, 2.2, 2.3)
• Administer subcutaneously once daily or in divided doses twice daily. Once daily administration should be given with the evening meal or at bedtime (2.1)
• Rotate injection sites within an injection area (abdomen, thigh, or deltoid) to reduce the risk of lipodystrophy (2.1)
• Converting from other insulin therapies may require adjustment of timing and dose of LEVEMIR®. Closely monitor glucoses and insulin, including LEVEMIR® (5.1).
• Use intravenous, rapid-acting or short-acting insulin instead. Not recommended for treating diabetic ketoacidosis.

—- USE IN SPECIFIC POPULATIONS ———

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

—- WARNINGS AND PRECAUTIONS ——-
Never Share a LEVEMIR® FlexTouch® between patients, even if the needle is changed (5.1).
• Dose adjustment and monitoring: Monitor blood glucose in all patients treated with insulin. Insulin regimens should be modified cautiously and only under medical supervision (5.2)
• Administration: Do not dilute or mix with any other insulin or solution. Do not administer subcutaneously via an insulin pump, intramuscularly, or intravenously because severe hypoglycemia can occur (5.3)
• Hypoglycemia is the most common adverse reaction of insulin therapy and may be life-threatening (5.4, 6.1)
• Allergic reactions: Severe, life-threatening, generalized allergy, including anaphylaxis, can occur (5.5)
• Renal or hepatic impairment: May require adjustment of the LEVEMIR® dose (5.6, 5.7)
• Fluid retention and heart failure can occur with concomitant use of thiazolidinediones (TZDs), which are PPAR-gamma agonists, and insulin, including LEVEMIR® (5.9)

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

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

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

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

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling. Revised: 02/2015

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LEVEMIR® (insulin detemir [rDNA origin] injection)

5.2 Dosage adjustment and monitoring
Glucose monitoring is essential for all patients receiving insulin therapy. Changes in insulin strength, manufacturer, type, or method of administration may result in the need for a change in the insulin dose or an adjustment of concomitant anti-diabetic treatment.

As with all insulin preparations, the titration course of action for LEVEMIR® may vary in different individuals or at different times in the same individual and is dependent on many conditions, including the local blood supply, local temperature, and physical activity.

5.3 Administration
LEVEMIR® should only be administered subcutaneously.

Do not administer LEVEMIR® intravenously or intramuscularly. The intended duration of activity of LEVEMIR® is dependent on injection into subcutaneous tissue. Intravenous or intramuscular administration of the usual subcutaneous dose may result in severe hyperglycemia (see Warnings and Precautions (5.4)).

Do not use LEVEMIR® in insulin infusion pumps.

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

5.4 Hypoglycemia
Hypoglycemia is the most common adverse reaction of insulin therapy, including LEVEMIR®. The risk of hypoglycemia increases with intensive glycemic control.

When GLP-1 receptor agonist is used in combination with LEVEMIR®, the LEVEMIR® dose may need to be lowered or more conservatively titrated to minimize the risk of hypoglycemia (see Adverse Reactions (6.1)).

All patients must be educated to recognize and manage hypoglycemia. Patients with hypoglycemia can lead to unconsciousness or convulsions and may result in temporary or permanent impairment of brain function or death. Severe hypoglycemia requiring the assistance of another person or parenteral glucose infusion, or insulin administration has been observed in clinical trials with insulin, including trials with LEVEMIR®.

The timing of hypoglycemia usually reflects the time-action profile of the administered insulin formulations. Other factors such as changes in food intake (e.g., amount of food or timing of meals), exercise, and other variables, such as stress, intercurrent illness, or changes in co-administered medications or meal patterns.

5.5 Hyposensitiveness and allergic reactions

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

6. ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere:

Hypoglycemia [see Warnings and Precautions (5.4)]

Hypersensitivity and allergic reactions [see Warnings and Precautions (5.5)]

6.1 Clinical trial experience

Because clinical trials are conducted under widely varying designs, the adverse reaction rates reported in one clinical trial may not be easily compared to those rates reported in another clinical trial, and may not reflect the rates actually observed in clinical practice.

The frequencies of adverse reactions (excluding hypoglycemia) reported during LEVEMIR® clinical trials in patients with type 1 diabetes mellitus and type 2 diabetes mellitus are listed in Tables 1–4 below. See Tables 5 and 6 for the hypoglycemia findings.

In the LEVEMIR® add-on to liraglutide+metformin trial, all patients received liraglutide 1.8 mg + metformin during a 12-week run-in period. During the run-in period, 167 patients (17% of enrolled total) withdrew from the trial: 76 (46% of withdrawals) of these patients doing so because of gastrointestinal adverse reactions and 15 (9% of withdrawals) doing so due to other adverse events. Of these patients, 76 patients who completed the run-in period with inadequate glycemic control were randomized to 26 weeks of add-on therapy with LEVEMIR® or continued, unchanged treatment with liraglutide 1.8 mg + metformin. During this randomized 26-week period, diabetes was the only adverse reaction reported in 25% of patients treated with liraglutide 1.8 mg + metformin (11.7%) and greater than in patients treated with liraglutide 1.8 mg and metformin alone (6.9%). In two pooled trials, a total of 1155 adults with type 1 diabetes were exposed to individualized doses of LEVEMIR® (n=767) or NPH (n=388). The mean duration of exposure to LEVEMIR® was 153 days, and the total exposure to LEVEMIR® was 321 patient-years. The most common adverse reactions are summarized in Table 1.

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

<table>
<thead>
<tr>
<th>Condition</th>
<th>LEVEMIR®, % (n=767)</th>
<th>NPH®, % (n=388)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory tract infection</td>
<td>26.1</td>
<td>21.4</td>
</tr>
<tr>
<td>Headache</td>
<td>22.6</td>
<td>22.7</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>9.5</td>
<td>8.0</td>
</tr>
<tr>
<td>Influenza-like illness</td>
<td>7.8</td>
<td>7.0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>6.0</td>
<td>2.6</td>
</tr>
</tbody>
</table>

A total of 320 adults with type 1 diabetes were exposed to individualized doses of LEVEMIR® (n=161) or insulin glargine (n=159). The mean duration of exposure to LEVEMIR® was 176 days, and the total exposure to LEVEMIR® was 186 patient-years. The most common adverse reactions are summarized in Table 2.

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

<table>
<thead>
<tr>
<th>Condition</th>
<th>LEVEMIR®, % (n=161)</th>
<th>NPH®, % (n=159)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory tract infection</td>
<td>25.7</td>
<td>32.1</td>
</tr>
<tr>
<td>Headache</td>
<td>14.3</td>
<td>19.5</td>
</tr>
<tr>
<td>Back pain</td>
<td>8.1</td>
<td>6.3</td>
</tr>
<tr>
<td>Influenza-like illness</td>
<td>6.2</td>
<td>8.9</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>5.6</td>
<td>4.4</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>5.0</td>
<td>4.9</td>
</tr>
</tbody>
</table>

In two pooled trials, a total of 869 adults with type 2 diabetes were exposed to individualized doses of LEVEMIR® (n=432) or NPH (n=437). The mean duration of exposure to LEVEMIR® was 157 days, and the total exposure to LEVEMIR® was 186 patient-years. The most common adverse reactions are summarized in Table 3.

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

<table>
<thead>
<tr>
<th>Condition</th>
<th>LEVEMIR®, % (n=432)</th>
<th>NPH®, % (n=437)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory tract infection</td>
<td>12.5</td>
<td>11.2</td>
</tr>
<tr>
<td>Headache</td>
<td>8.5</td>
<td>5.3</td>
</tr>
</tbody>
</table>
Table 6: Hypoglycemia in Patients with Type 2 Diabetes

| Study | Type 2 Diabetes | Adults 24 weeks | In combination with insulin aspart |
|-------|-----------------|----------------|
|       | Levidis®        |                |
|       | Twice-Daily     | 10.5 (14/132)  |
|       | Once-Daily      | 10.1 (16/159)  |
| Study E | Levidis®    | 15.9 (37/232)  |
| Study F | Levidis®    | 20.9 (22/115)  |
| Study H | Levidis®    | 1.7 (3/177)    |
|        | NPH            | 10.2 (26/255)  |
|        | NPH            | 10.2 (26/255)  |

*One subject is an outlier and was excluded due to 25 hypoglycemic episodes that the patient was able to self-treat. This patient had a history of frequent hypoglycemia prior to the study.*

Specific Populations (8.1)

- **Hypoglycemia**
  - Hypoglycemia is the most commonly observed adverse reaction in patients using insulin, including LEVEMIR®.[8][9]

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

- **Allergic Reactions**
  - Local Allergy
    - As with any insulin therapy, patients taking LEVEMIR® may experience local allergic reactions, including local erythema, pain, pruritus, urticaria, edema, and inflammation.

  - Systemic Allergy
    - Severe, life-threatening, generalized allergy, including anaphylaxis, generalized skin reactions, angioedema, bronchospasm, hypotension, and shock may occur with any insulin, including LEVEMIR®, and may be life-threatening.[8][9]

- **Antibody Production**
  - All insulin products can elicit the formation of insulin antibodies. These insulin antibodies may increase or decrease the efficacy of insulin and may require adjustment of the insulin dose.

6.2 Postmarketing experience

The following adverse reactions have been identified during post approval use of LEVEMIR®. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Medication errors have been reported during post-release use of LEVEMIR® in which other insulins, particularly rapid-acting or short-acting insulins, have been accidentally administered instead of LEVEMIR®.[8][9]

- The signs of hypoglycemia may be reduced or absent in patients atypical antipsychotic medications (e.g., olanzapine and clozapine), progestogens (e.g., in oral contraceptives), protease inhibitors and non-nucleoside reverse transcriptase inhibitors, and some combinations of antidiabetic medications, pramlintide acetate, angiotensin converting enzyme (ACE) inhibitors, diuretics, levodopa, fluoxetine, monoamine oxidase (MAO) inhibitors, propranolol, pentoxifylline, salicylates, somatostatin analogs, and sulfonamide antibiotics.

7. DRUG INTERACTIONS

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

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

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

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

Signs of hypoglycemia may be reduced or absent in patients taking anti-platelet and anti-thrombotic drugs such as beta-blockers, clonidine, guanethidine, and reserpine.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

Risk Summary

The background risk of birth defects, pregnancy loss, or other adverse events that exist for all pregnant women is increased in pregnancies complicated by hyperglycemia. Female patients should be advised to tell their physician if they intend to become, or if they become pregnant while taking LEVEMIR®. A randomized controlled clinical trial of pregnant women with type 1 diabetes using LEVEMIR® during pregnancy did not show an increase in the risk of fetal abnormalities.

Reproductive toxicity studies in non-diabetic rats and rabbits that included concurrent human insulin control groups indicated
that insulin detemir and human insulin had similar effects regarding embryotaxicity and teratogenicity that were attributed to maternal hypoglycemia.

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

Human Data
In an, open-label, clinical study, women with type 1 diabetes who were (between weeks 8 and 12 of gestation) or intended to become pregnant were randomized 1:1 to LEVEMIR® (once or twice daily) or NPH insulin (once, twice or thrice daily). Insulin aspart was administered before each meal. A total of 152 women in the LEVEMIR® arm and 158 women in the NPH arm were or became pregnant during the study (Total pregnant women = 310). Approximately one half of the study participants in each arm were randomized as pregnant and were exposed to NPH or to other insulins prior to conception and in the first 8 weeks of gestation. In the 310 pregnant women, the mean glycoylated hemoglobin (HbA1c) was <7% at 10, 12, and 24 weeks of gestation in both arms. In the intent-to-treat population, the adjusted mean HbA1c (standard error) at gestational week 36 was 6.2% (0.052) in LEVEMIR®-treated patient (n=153) and 6.33% (0.056) in NPH-treated patients (n=145); the difference was not clinically significant.

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

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

In the NPH insulin group there were 6 serious adverse reactions in four mothers of the following placental disorders, 'Placenta previa', 'Placenta previa hemorrhage', 'Premature separation of placenta' and 'Premature separation of placenta and cervical incompetence'. There were none reported in the LEVEMIR® group.

The incidence of early fetal death (abortions) was similar in LEVEMIR® and NPH treated patients. 6.6% and 5.1%, respectively. The proportions were 4/78 (5.1%) and 4/76 (5.3%) in the LEVEMIR® and NPH insulin groups respectively. The rate of severe hypoglycemia was 1.1 and 1.2 events per patient-year in LEVEMIR® and NPH treated patients respectively. The proportion of subjects experiencing severe hypoglycemia was 16.4% and 20.9% in LEVEMIR® and NPH treated patients respectively. The rate of severe hypoglycemia was 1.1 and 1.2 events per patient-year in LEVEMIR® and NPH treated patients respectively. The proportion of patients experiencing severe hypoglycemia was similar in both treatment groups (Table 8).

Table 8: Hypoglycemia in Pregnant Women with Type 1 Diabetes

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Type 1 Diabetes Pregnancy</th>
<th>Hypoglycemia *</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEVEMIR®</td>
<td>NPH</td>
<td>LEVEMIR®</td>
</tr>
<tr>
<td>Severe hypoglycemia*</td>
<td>Percent of patients with at least 1 event/total N</td>
<td>16.4 (152/936)</td>
</tr>
<tr>
<td>Event/patient/year</td>
<td>1.1</td>
<td>1.2</td>
</tr>
<tr>
<td>Non-severe hypoglycemia*</td>
<td>Percent of patients with at least 1 event/total N</td>
<td>94.7 (144/152)</td>
</tr>
<tr>
<td>Event/patient/year</td>
<td>114.2</td>
<td>108.4</td>
</tr>
</tbody>
</table>

*For definition regarding severe and non-severe hypoglycemia see section 6.2.

In about a quarter of infants, LEVEMIR® was detected in the infant cord blood at levels above the lower level of quantification (<25 pmol/L). No differences in pregnancy outcomes or the health of the fetus and newborn were seen with LEVEMIR® use.

Animal Data
Data from studies and embryonic development study, insulin detemir was administered to female rats before mating, during mating, and throughout pregnancy at doses up to 300 nmol/kg/day (3 times a human dose of 0.5 Units/kg/day, based on plasma area under the curve (AUC) ratio). Doses of 150 and 300 nmol/kg/day produced numbers of litters with visceral anomalies. Doses up to 900 nmol/kg/day (approximately 135 times a human dose of 0.5 Units/kg/day based on AUC ratio) were given to rabbits during organogenesis. Dose related increases in the incidence of fetuses with galbladder abnormalities such as, small, bilobed, bifurcated, and missing gallbladders were observed at a dose of 900 nmol/kg/day. The rat and rabbit embryotrofetal development studies that include human and rabbit insulin control groups indicated that insulin detemir and human insulin had similar effects regarding embryotoxicity and teratogenicity suggesting that the effects seen were the result of hypoglycemia resulting from insulin exposure in normal animals.

8.3 Nursing Mothers
It is unknown whether LEVEMIR® is excreted in human milk. Because many drugs, including human insulin, are excreted in human milk, use caution when administering LEVEMIR® to a nursing woman.

8.4 Dosage of Insulin in pregnancy

8.4.1 Pregnancy

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

12 CLINICAL PHARMACOLOGY

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

12.2 Pharmacodynamics
Insulin detemir is a soluble, long-acting basal human insulin analog with a 24-hour duration of action. The pharmacodynamic profile of LEVEMIR® is relatively constant with no pronounced peak. The duration of action of LEVEMIR® is mediated by slowed systemic absorption of insulin detemir molecules from the injection site due to self-association of the drug molecules. In addition, the distribution of insulin detemir to peripheral target tissues is slowed because of binding to albumin.

Figure 2 shows results from a study in patients with type 1 diabetes conducted for a maximum of 24 hours after the subcutaneous injection of LEVEMIR® or NPH insulin. The mean time between injection and the end of pharmacological effect for insulin detemir ranged from 7.6 hours to 24 hours (24 hours was the end of the observation period).

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

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

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

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

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

More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. After apparent clinical recovery from hypoglycemia, continued observation and additional carbohydrate intake may be necessary to avoid recurrence of hypoglycemia (see Warnings and Precautions (5.4)).

11 DESCRIPTION
LEVEMIR® (insulin detemir [rDNA origin]) injection is a sterile solution of insulin detemir for use as a subcutaneous injection. Insulin detemir is a long-acting (up to 24-hour duration of action) recombinant human insulin analog. LEVEMIR® is produced by a process that includes expression of recombinant DNA in Saccharomyces cerevisiae followed by chemical modification. Insulin detemir differs from human insulin in that the amino acid threonine in position B30 has been omitted, and a C14 fatty acid chain has been attached to the amino acid B29. Insulin detemir has a molecular formula of C27H48O37N6S6E5 and a molecular weight of 961.9. It has the following structure.
**Hepatic impairment** - A single subcutaneous dose of 0.2 Units/kg (1.2 nmol/kg) of LEVEMIR® was administered to healthy subjects and those with varying degrees of hepatic impairment (mild, moderate and severe). LEVEMIR® exposure as estimated by AUC decreased with increasing degrees of hepatic impairment with a corresponding increase in apparent clearance. However, some studies with human insulin have shown increased circulating levels of insulin in patients with liver impairment. Careful glucose monitoring and dose adjustments of insulin, including LEVEMIR®, may be necessary in patients with hepatic impairment (see Warnings and Precautions (5.7)).

**Pregnancy** - The effect of pregnancy on the pharmacokinetics and pharmacodynamics of LEVEMIR® has not been studied (see Use In Specific Populations (8.17)).

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

### 12.3 Pharmacokinetics

**Absorption and Bioavailability**

After subcutaneous injection of LEVEMIR® in healthy subjects and in patients with diabetes, insulin detemir serum concentrations had a relatively constant concentration/time profile over 24 hours with the maximum serum concentration (Cmax) reached between 6-8 hours post-dose. Insulin detemir was more slowly absorbed after subcutaneous administration to the thigh where AUC0-inf was 30-40% lower and AUC0-inf was 10% lower than the corresponding AUCs with subcutaneous injections to the deltoid and abdominal regions. The absolute bioavailability of insulin detemir is approximately 60%.

**Distribution and Elimination**

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

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

**Specific Populations**

**Children and Adolescents** - The pharmacokinetic properties of LEVEMIR® were investigated in children (≤12 years), adolescents (13-17 years), and adults with type 1 diabetes. In children, the insulin detemir plasma area under the curve (AUC) and Cmax were increased by 10% and 24%, respectively, as compared to adults. There was no difference in pharmacokinetics between adolescents and adults.

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

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

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

**Renal impairment** - A single subcutaneous dose of 0.2 Units/kg (1.2 nmol/kg) of LEVEMIR® was administered to healthy subjects and those with varying degrees of renal impairment (mild, moderate, severe, and hemodialysis-dependent). In this study, there were no differences in the pharmacokinetics of LEVEMIR® between healthy subjects and those with renal impairment. However, some studies with human insulin have shown increased circulating levels of insulin in patients with renal impairment. Careful glucose monitoring and dose adjustments of insulin, including LEVEMIR®, may be necessary in patients with renal impairment (see Warnings and Precautions (5.6)).
Once- or Twice Daily NPH

<table>
<thead>
<tr>
<th>Number of subjects treated</th>
<th>Baseline HbA1c (%)</th>
<th>Adj. mean change from baseline</th>
<th>Change from baseline difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Once- or Twice Daily NovoLog®</td>
<td>8.8</td>
<td>-0.7**</td>
<td>-0.1; 0.3</td>
</tr>
<tr>
<td>Once- or Twice Daily NPH</td>
<td>8.8</td>
<td>-0.8</td>
<td>-0.1</td>
</tr>
<tr>
<td>Once- or Twice Daily NovoLog®</td>
<td>8.4</td>
<td>0.3**</td>
<td>0.1</td>
</tr>
<tr>
<td>Once- or Twice Daily NPH</td>
<td>8.4</td>
<td>0.2**</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Baseline insulin dose (units/day)

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Mean change from baseline</th>
<th>Total insulin dose (units/day)</th>
<th>Mean change from baseline</th>
<th>Fasting blood glucose (mg/dL)</th>
<th>Body weight (kg)</th>
<th>Mean change from baseline</th>
<th>Adj. mean change from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>24</td>
<td>26</td>
<td>17</td>
<td>17</td>
<td>8</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Total insulin</td>
<td>48</td>
<td>50</td>
<td>35</td>
<td>34</td>
<td>9</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Baseline</td>
<td>181</td>
<td>181</td>
<td>181</td>
<td>181</td>
<td>181</td>
<td>181</td>
<td>181</td>
</tr>
<tr>
<td>Baseline</td>
<td>139</td>
<td>212</td>
<td>108</td>
<td>8</td>
<td>166</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td>Baseline</td>
<td>563</td>
<td>606</td>
<td>374</td>
<td>355</td>
<td>36.5</td>
<td>2.7**</td>
<td>36.5</td>
</tr>
<tr>
<td>Baseline</td>
<td>1.6**</td>
<td>2.7**</td>
<td>2.7**</td>
<td>3.6**</td>
<td>0.3**</td>
<td>0**</td>
<td>0.3**</td>
</tr>
</tbody>
</table>

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

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

### Type 2 Diabetes – Adult

In a 24-week, open-label, randomized, clinical study (Study E, n=476), LEVEMIR® administered twice-daily (before breakfast and evening) was compared to NPH insulin administered twice-daily (before breakfast and evening) as part of a regimen of stable combination therapy with one or two of the following oral antidiabetic medications: metformin, an insulin secretagogue, or an alpha-glucosidase inhibitor. All patients were insulin-naive at the time of randomization. LEVEMIR® and NPH insulin similarly lowered HbA1c from baseline (Table 11).

Table 11: Type 2 Diabetes Mellitus – Adult

<table>
<thead>
<tr>
<th>Treatment duration</th>
<th>Body weight (kg)</th>
<th>Total insulin dose (units/day)</th>
<th>Fasting blood glucose (mg/dL)</th>
<th>Baseline insulin dose (units/day)</th>
<th>Number of subjects treated</th>
<th>Study E</th>
<th>Study F</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 weeks</td>
<td>16.3</td>
<td>24</td>
<td>104</td>
<td>6.3</td>
<td>237</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>22 weeks</td>
<td>16.3</td>
<td>24</td>
<td>97</td>
<td>6.3</td>
<td>239</td>
<td>24</td>
<td>24</td>
</tr>
</tbody>
</table>

### Table 10: Type 1 Diabetes Mellitus – Pediatric

<table>
<thead>
<tr>
<th>Treatment duration</th>
<th>Treatment in combination with</th>
<th>Number of subjects treated</th>
<th>LEVEMIR®</th>
<th>NovoLog®</th>
<th>Baseline HbA1c (%)</th>
<th>Adj. mean change from baseline</th>
<th>Change from baseline difference</th>
<th>LEVEMIR® – NPH</th>
<th>95% CI for Treatment difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>26 weeks</td>
<td>NovoLog®</td>
<td>232</td>
<td>0.4</td>
<td>0.0**</td>
<td>8.8</td>
<td>-0.7**</td>
<td>-0.1; 0.3</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>52 weeks</td>
<td>NovoLog®</td>
<td>115</td>
<td>0.4</td>
<td>0.0**</td>
<td>8.8</td>
<td>-0.8</td>
<td>-0.1</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>22 weeks</td>
<td>NovoLog®</td>
<td>177</td>
<td>0.3**</td>
<td>0.2**</td>
<td>8.4</td>
<td>0.3**</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>42 days*</td>
<td>NovoLog®</td>
<td>170</td>
<td>0.2**</td>
<td>0.1</td>
<td>8.6</td>
<td>0.2</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
</tr>
</tbody>
</table>

### Table 13: Storage Conditions for LEVEMIR® and Vial

<table>
<thead>
<tr>
<th>Study</th>
<th>LEVEMIR®</th>
<th>FlexTouch®</th>
<th>Storage Temperature (below 30°C)</th>
<th>Room Temperature</th>
<th>In-use (opened)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
<td>FlexTouch®</td>
<td>Until expiration date</td>
<td>FlexTouch®</td>
<td>Until expiration date</td>
<td>FlexTouch®</td>
</tr>
<tr>
<td>Study</td>
<td>FlexTouch®</td>
<td>Room Temperature (below 30°C)</td>
<td>Room Temperature</td>
<td>Room Temperature</td>
<td>Room Temperature</td>
</tr>
<tr>
<td>Study</td>
<td>FlexTouch®</td>
<td>In-use</td>
<td>Room Temperature</td>
<td>In-use</td>
<td>Room Temperature</td>
</tr>
<tr>
<td>Study</td>
<td>FlexTouch®</td>
<td>Room Temperature (below 30°C)</td>
<td>Room Temperature</td>
<td>Room Temperature</td>
<td>Room Temperature</td>
</tr>
</tbody>
</table>

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

### 16.3 Preparation and handling

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. LEVEMIR® should be inspected visually prior to administration and should only be used if the solution appears clear and colorless. Mixing and diluting LEVEMIR® must NOT be done with any other insulin or solution (See Warnings and Precautions (3.3)).

### 17. Patient Counseling Information

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

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

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

LEVEMIR® must only be used if the solution is clear and colorless with no particles visible. Patients must be advised that LEVEMIR® must NOT be diluted or mixed with any other insulin or solution. Patients should be instructed on self-management procedures including glucose monitoring, proper injection technique, and management of hypoglycemia and hyperglycemia. Patients should be instructed on handling of special situations such as intercurrent conditions (illness, stress, or emotional disturbances), an inadequate or skipped insulin dose, inadvertent administration of an increased insulin dose, inadequate food intake, and skipped meals.

Patients should receive proper training on how to use Levemir®. Instruct patients that when injecting Levemir®, they must press and hold down the dose button until the dose counter shows 0 and then keep the needle in the skin and count slowly to 6. When the dose counter returns to 0, the prescribed dose is not completely delivered until 6 seconds later. If the needle is removed earlier, they may see a stream of insulin coming from the needle tip. If so, the full dose will not be delivered (a possible under-dose may occur by as much as 20%), and they should increase the frequency of checking their blood glucose levels and possible additional insulin administration may be necessary.

- If 0 does not appear in the dose counter after continuously pressing the dose button, the patient may have used a blocked needle. In this case they would not have received any insulin—even though the dose counter has moved from the original dose that was set.
- If the patient did have a blocked needle, instruct them to change the needle as described in Section 5 of the Instructions for Use and repeat all steps in the IFU starting with Section 1: Prepare your pen with a new needle. Make sure the patient selects the full dose needed.

Patients with diabetes should be advised to inform their healthcare professional if they are pregnant or are contemplating pregnancy. Refer patients to the LEVEMIR® “Patient Information” for additional information.
Patient Information
LEVEMIR® (LEV–uh-mere) (insulin detemir [rDNA origin] injection)

Do not share your Levemir® FlexTouch® with other people, even if the needle has been changed. You may give other people a serious infection, or get a serious infection from them.

What is Levemir®?
• Levemir® is a man-made insulin that is used to control high blood sugar in adults and children with diabetes mellitus.
• Levemir® is not meant for use to treat diabetic ketoacidosis.

Who should not take Levemir®?
Do not take Levemir® if you:
• have an allergy to Levemir® or any of the ingredients in Levemir®.

Before taking Levemir®, tell your healthcare provider about all your medical conditions including, if you are:
• pregnant, planning to become pregnant, or are breastfeeding.
• taking new prescription or over-the-counter medicines, vitamins, or herbal supplements.

Before you start taking Levemir®, talk to your healthcare provider about low blood sugar and how to manage it.

How should I take Levemir®?
• Read the Instructions for Use that come with your Levemir®.
• Take Levemir® exactly as your healthcare provider tells you to.
• Know the type and strength of insulin you take. Do not change the type of insulin you take unless your healthcare provider tells you to. The amount of insulin and the best time for you to take your insulin may need to change if you take different types of insulin.
• Check your blood sugar levels. Ask your healthcare provider what your blood sugars should be and when you should check your blood sugar levels.
• Do not reuse or share your needles or syringes with other people. You may give other people a serious infection, or get a serious infection from them.
• Never inject Levemir® into a vein or muscle.

What should I avoid while taking Levemir®?
While taking Levemir® do not:
• Drive or operate heavy machinery, until you know how Levemir® affects you.
• Drink alcohol or use prescription or over-the-counter medicines that contain alcohol.

What are the possible side effects of Levemir®?
Levemir® may cause serious side effects that can lead to death, including:
Low blood sugar (hypoglycemia). Signs and symptoms that may indicate low blood sugar include:
• dizziness or light-headedness
• sweating
• confusion
• headache
• blurred vision
• slurred speech
• Shakiness
• fast heart beat
• anxiety, irritability, or mood changes
• hunger

Your insulin dose may need to change because of:
• change in level of physical activity or exercise
• weight gain or loss
• increased stress
• illness
• change in diet

Other common side effects of Levemir® may include:
• Reactions at the injection site, itching, rash, serious allergic reactions (whole body reactions), skin thickening or pits at the injection site (lipodystrophy), weight gain, and swelling of your hands and feet.

Get emergency medical help if you have:
• trouble breathing, shortness of breath, fast heartbeat, swelling of your face, tongue, or throat, sweating, extreme drowsiness, dizziness, confusion.

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

General information about the safe and effective use of Levemir®.
Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. You can ask your pharmacist or healthcare provider for information about Levemir® that is written for health professionals. Do not use Levemir® for a condition for which it was not prescribed. Do not give Levemir® to other people, even if they have the same symptoms that you have. It may harm them.

What are the ingredients in Levemir®?
Active Ingredient: insulin detemir (rDNA origin)
Inactive Ingredients: zinc, m-cresol, glycerol, phenol, disodium phosphate dihydrate, sodium chloride and water for injection. Hydrochloric acid or sodium hydroxide may be added.

Manufactured by:
Novo Nordisk A/S
DK-2880 Bagsvaerd, Denmark
For more information, go to www.novonordisk-us.com or call 1-800-727-6500.

This Patient Information has been approved by the U.S. Food and Drug Administration
Revised: 02/2015
Patient Instructions For Use
LEVEMIR® 10 mL vial

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

How should I use the LEVEMIR® 10 mL vial?

Using the 10 mL vial:

1. Check to make sure that you have the correct type of insulin. This is especially important if you use different types of insulin.
2. Look at the vial and the insulin. The LEVEMIR® insulin should be clear and colorless. The tamper-resistant cap should be in place before the first use. If the cap has been removed before your first use of the vial, or if the insulin is cloudy or colored, Do not use the insulin and return it to your pharmacy.
3. Wash your hands with soap and water.
4. If you are using a new vial, pull off the tamper-resistant cap.
5. Do not roll or shake the vial. Shaking the vial right before the dose is drawn into the syringe may cause bubbles or foam. This can cause you to draw up the wrong dose of insulin. The insulin should be used only if it is clear and colorless.
6. Pull back the plunger on your syringe until the black tip reaches the marking for the number of units you will inject.
7. Push the needle through the rubber stopper into the vial.
8. Push the plunger all the way in. This inserts air into the vial.
9. Turn the vial and syringe upside down and slowly pull the plunger back to a few units beyond the correct dose that you need.
10. If there are air bubbles, tap the syringe gently with your finger to raise the air bubbles to the top of the needle. Then slowly push the plunger to the correct unit marking for your dose.
11. Check to make sure you have the right dose of LEVEMIR® in the syringe.
12. Pull the syringe out of the vial.
13. Inject your LEVEMIR® right away as instructed by your healthcare provider.

How should I inject LEVEMIR® with a syringe?

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

1. Pinch your skin between two fingers, push the needle into the skinfold, using a dart-like motion and push the plunger to inject the insulin under your skin. The needle will be straight in.
2. Keep the needle under your skin for at least 6 seconds to make sure you have injected all the insulin. After you pull the needle from your skin you may see a drop of Levemir® at the needle tip. This is normal and has no effect on the dose you just received.
3. If blood appears after you pull the needle from your skin, press the injection site lightly with an alcohol swab. Do not rub the area.
4. After each injection, remove the needle without recapping and dispose of it in a puncture-resistant container. Used syringes, needles, and lancets should be placed in sharps containers (such as red biohazard containers), hard plastic containers (such as detergent bottles), or metal containers (such as an empty coffee can). Such containers should be sealed and disposed of properly.
Read before first use

Instructions for Use

Levemir® (LEV-uh-mere) FlexTouch® Pen
(insulin detemir [rDNA origin] injection)

- Do not share your Levemir® FlexTouch® Pen with other people, even if the needle has been changed. You may give other people a serious infection, or get a serious infection from them.
- Levemir® FlexTouch® Pen (“Pen”) is a prefilled disposable pen containing 300 units of U-100 Levemir® (insulin detemir [rDNA origin] injection) insulin. You can inject from 1 to 80 units in a single injection.
- This Pen is not recommended for use by the blind or visually impaired without the assistance of a person trained in the proper use of the product.

Supplies you will need to give your Levemir® injection:
- Levemir® FlexTouch® Pen
- a new NovoFine®, NovoFine® Plus, or NovoTwist® needle
- alcohol swab
- a new NovoFine® Plus, or NovoTwist® needle
- 1 sharps container for throwing away used Pens and needles.
- a new NovoFine® Plus, or NovoTwist® needle
- This Pen is not recommended for use by the blind or visually impaired without the assistance of a person trained in the proper use of the product.

Preparing your Levemir® FlexTouch® Pen:
- Wash your hands with soap and water.
- Before you start to prepare your injection, check the Levemir® FlexTouch® Pen label to make sure you are taking the right type of insulin. This is especially important if you take more than 1 type of insulin.
- Levemir® should look clear and colorless. Do not use Levemir® if it is thick, cloudy, or is colored.
- Do not use Levemir® past the expiration date printed on the label or 42 days after you start using the Pen.
- Always use a new needle for each injection to help ensure sterility and prevent blocked needles. Do not reuse or share your needles with other people. You may give other people a serious infection, or get a serious infection from them.

NovoFine®

- Outer needle cap
- Inner needle cap
- Needle
- Paper tab

NovoFine® Plus

- Outer needle cap
- Inner needle cap
- Needle
- Paper tab

NovoTwist®

- Outer needle cap
- Inner needle cap
- Needle
- Paper tab

Step 1:
- Pull Pen cap straight off
- (See Figure B).

Step 2:
- Check the liquid in the Pen (See Figure C). Levemir® should look clear and colorless. Do not use if it looks cloudy or colored.

Step 3:
- Always
- Select a new needle.
- Pull off the paper tab from the outer needle cap (See Figure D).

Step 4:
- Push the capped needle straight onto the Pen and twist the needle on until it is tight (See Figure E).

Step 5:
- Pull off the outer needle cap and do not throw it away (See Figure F).

Step 6:
- Pull off the inner needle cap and do not throw it away (See Figure G).

Step 7:
- Turn the dose selector to select 2 units (See Figure H).

Step 8:
- Hold the Pen with the needle pointing up. Tap the top of the Pen gently a few times to let any air bubbles rise to the top (See Figure I).

Step 9:
- Hold the Pen with the needle pointing up. Press and hold in the dose button until the dose counter shows “0.” The “0” must line up with the dose pointer.
- A drop of insulin should be seen at the needle tip (See Figure J).
- If you do not see a drop of insulin, repeat steps 7 to 9, no more than 6 times.
- If you still do not see a drop of insulin, change the needle and repeat steps 7 to 9.

Step 10:
- Turn the dose selector to select the number of units you need to inject. The dose pointer should line up with your dose (See Figure K).
- If you select the wrong dose, you can turn the dose selector forwards or backwards to the correct dose.
- The even numbers are printed on the dial.
- The odd numbers are shown as lines.

- The Levemir® FlexTouch® Pen insulin scale will show you how much insulin is left in your Pen (See Figure L).
- To see how much insulin is left in your Levemir® FlexTouch® Pen:
  - Turn the dose selector until it stops. The dose counter will line up with the number of units of insulin that is left in your Pen. If the dose counter shows 80, there are at least 80 units left in your Pen.
  - If the dose counter shows less than 80, the number shown in the dose counter is the number of units left in your Pen.
Giving your injection:
• Inject your Levemir® exactly as your healthcare provider has shown you. Your healthcare provider should tell you if you need to pinch the skin before injecting.
• Levemir® can be injected under the skin (subcutaneously) of your stomach area (abdomen), upper legs (thighs) or upper arms.
• For each injection, change (rotate) your injection site within the area of skin that you use. Do not use the same injection site for each injection.

Step 11:
• Choose your injection site and wipe the skin with an alcohol swab. Let the injection site dry before you inject your dose (See Figure M).

Step 12:
• Insert the needle into your skin (See Figure N).
  - Make sure you can see the dose counter. Do not cover it with your fingers, this can stop your injection.

Step 13:
• Press and hold down the dose button until the dose counter shows “0” (See Figure Q).
  - The “0” must line up with the dose pointer. You may then hear or feel a click.
  - Keep the needle in your skin after the dose counter has returned to “0” and slowly count to 6 (See Figure P).
  - When the dose counter returns to “0”, you will not get your full dose until 6 seconds later.
  - If the needle is removed before you count to 6, you may see a stream of insulin coming from the needle tip.
  - If you see a stream of insulin coming from the needle tip you will not get your full dose. If this happens you should check your blood sugar levels more often because you may need more insulin.

Step 14:
• Pull the needle out of your skin (See Figure Q).
  - If you see blood after you take the needle out of your skin, press the injection site lightly with a piece of gauze or an alcohol swab. Do not rub the area.

Step 15:
• Carefully remove the needle from the Pen and throw it away (See Figure R).
  - Do not recap the needle. Recapping the needle can lead to needle stick injury.
  - If you do not have a sharps container, carefully slip the needle into the outer needle cap (See Figure S). Safely remove the needle and throw it away as soon as you can.
  - Do not store the Pen with the needle attached. Storing without the needle attached helps prevent leaking, blocking of the needle, and air from entering the Pen.

Step 16:
• Replace the Pen cap by pushing it straight on (See Figure T).

After your injection:
• You can put your used Levemir® FlexTouch® Pen and needles in a FDA-cleared sharps disposal container right away after use. Do not throw away (dispose of) loose needles and Pens in your household trash.
• If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
  - made of a heavy-duty plastic
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out
  - upright and stable during use
  - leak-resistant
  - properly labeled to warn of hazardous waste inside the container
• If your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. Do not reuse or share your needles or syringes with other people. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal
• Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.

How should I store my Levemir® FlexTouch® Pen?
• Store unused Levemir® FlexTouch® Pens in the refrigerator at 36°F to 46°F (2°C to 8°C).
• Store the Pen you are currently using out of the refrigerator below 86°F.
• Do not freeze Levemir®. Do not use Levemir® if it has been frozen.
• Keep Levemir® away from heat or light.
• Unused Pens may be used until the expiration date printed on the label, if kept in the refrigerator.
• The Levemir® FlexTouch® Pen you are using should be thrown away after 42 days, even if it still has insulin left in it.

General Information about the safe and effective use of Levemir®
• Keep Levemir® FlexTouch® Pens and needles out of the reach of children.
• Always use a new needle for each injection.
• Do not share your Levemir® FlexTouch® Pen or needles with other people. You may give other people a serious infection, or get a serious infection from them.