Novo Nordisk

Prescribing Information

1. NAME OF THE MEDICINAL PRODUCT

Levemir®

Solution for injection in pre-filled pen.
Solution for injection in cartridge.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of the solution contains 100 U insulin detemir* (equivalent to 14.2 mg).
1 pre-filled pen contains 3 ml equivalent to 300 U.
1 cartridge contains 3 ml equivalent to 300 U.

*Insulin detemir is produced by recombinant DNA technology in *Saccharomyces cerevisiae*.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled pen- FlexPen®.
Solution for injection in cartridge- Penfill®
Clear, colourless, neutral solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of diabetes mellitus

4.2 Posology and method of administration

Posology

The potency of insulin analogues, including insulin detemir, is expressed in units (U), whereas the potency of insulin human is expressed in international units

(IU). 1 unit (U) insulin detemir corresponds to 1 international unit (IU) of insulin human

In combination with oral antidiabetic medicines it is recommended to use **Levemir®** once daily, initially at a dose of 10 U or 0.1-0.2 U/kg. The dose of **Levemir®** should be titrated based on individual patients' needs.

Based on study results, the following titration guideline is recommended:

Average pre-breakfast SMPG*	**Levemir dose adjustment**
> 10.0 mmol /L (180 mg/ dL)	+ 8 U
9.1-10.0 mmol /L (163-180 mg/dL)	+ 6 U
8.1-9.0 mmol/L (145-162 mg/dL)	+ 4 U
7.1-8.0 mmol/L (127-144 mg/dL)	+ 2 U
6.1-7.0 mmol/L (109-126 mg/dL)	+ 2 U
If one SMPG measurement	
3.1-4.0 mmol/L (56-72 mg/ dL)	- 2 U
< 3.1 mmol/L (< 56 mg/ dL)	- 4 U

* Self Monitored Plasma Glucose

When **Levemir®** is used as part of a basal bolous insulin regimen **Levemir®** should be administered once or twice daily depending on patients' needs. Dosage of **Levemir®** should be adjusted individually.

Adjustment of dosage may be necessary if patients undertake increased physical activity, change their usual diet or during concomitant illness.

Special populations

Elderly (≥ 65 years old)
Levemir can be used in elderly patients. As with all insulin products, in elderly patients, glucose monitoring should be intensified and insulin detemir dosage adjusted on an individual basis.

Renal and hepatic impairment
Renal or hepatic impairment may reduce the patient's insulin requirements. As with all insulin medicinal products, in patients with renal or hepatic impairment, glucose monitoring should be intensified and the insulin detemir dose adjusted on an individual basis.

Paediatric use

The efficacy and safety of **Levemir®** were demonstrated in children and adolescents aged 6 to 17 years in studies up to 6 months (see section 5.1).

As with all insulin medicinal products, in children and adolescents, glucose monitoring should be intensified and the insulin detemir dose adjusted on an individual basis.

The efficacy and safety of **Levemir**® have not been studied in children below the age of 6 years. **Levemir®** should only be used in this age group under careful medical supervision.

Transfer from other insulin products

Transfer to **Levemir®** from other intermediate or long-acting insulin products may require adjustment of dose and timing of administration (see section 4.4).

As with all insulin products, close glucose monitoring is recommended during the transfer and in the initial weeks thereafter.

Concomitant antidiabetic treatment may need to be adjusted (dose and/or timing of oral antidiabetic medicines or concurrent short/rapid-acting insulin products).

Method of administration

Levemir is a long-acting insulin analogue used as a basal insulin .**Levemir®** is for subcutaneous administration **only**. **Levemir®** must not be administered intravenously, as it may result in severe hypoglycaemia. Intramuscular administration should also be avoided. **Levemir®** is not to be used in insulin infusion pumps**.**

Levemir® is administered subcutaneously by injection in the abdominal wall, the thigh, the upper arm, the deltoid region or the gluteal region. Injection sites should therefore always be rotated within the same region in order to avoid lipodystrophy. As with all insulin products the duration of action will vary according to the dose, injection site, blood flow, temperature and level of physical activity.
The injection can be given at any time during the day, but at the same time each day. For patients who require twice daily dosing to optimise blood glucose control, the evening dose can be administered in the evening or at bedtime

Levemir® FlexPen® are pre-filled pens designed to be used with NovoFine® needles up to a length of 8 mm. FlexPen® delivers 1-60 units in increments of 1 unit. The patient should be advised not to use any counterfeit needles.
Levemir® Penfill® is designed to be used with Novo Nordisk insulin delivery systems and NovoFine® needles.

Levemir® FlexPen® is colour coded and accompanied by a package leaflet with detailed instruction for use to be followed.
Levemir® Penfill® is accompanied by a package leaflet with detailed instruction for use to be followed.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

Before travelling between different time zones, the patient should seek the doctor’s advice since this may mean that the patient has to take the insulin and meals at different times.

Hyperglycaemia

Inadequate dosing or discontinuation of treatment, especially in type 1 diabetes, may lead to hyperglycaemia and diabetic ketoacidosis. Usually the first symptoms of hyperglycaemia develop gradually over a period of hours or days. They include thirst, increased frequency of urination, nausea, vomiting, drowsiness, flushed dry skin, dry mouth, loss of appetite as well as acetone odour of breath. In type 1 diabetes, untreated hyperglycaemic events eventually lead to diabetic ketoacidosis, which is potentially lethal.

Hypoglycaemia

Omission of a meal or unplanned strenuous physical exercise may lead to hypoglycaemia.

Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement (see sections 4.8 and 4.9).

Patients whose blood glucose control is greatly improved, e.g. by intensified insulin therapy, may experience a change in their usual warning symptoms of hypoglycaemia, and should be advised accordingly. Usual warning symptoms may disappear in patients with longstanding diabetes.

Concomitant illness, especially infections and feverish conditions, usually increases the patient's insulin requirements. Concomitant diseases in the kidney, liver or affecting the adrenal, pituitary or thyroid gland can require changes in insulin dose.

When patients are transferred between different types of insulin medicinal products, the early warning symptoms of hypoglycaemia may change or become less pronounced than those experienced with their previous insulin

Transfer from other insulin products

Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type, origin (animal, human, human insulin analogue) and/or method of manufacture (recombinant DNA versus animal source insulin) may result in the need for a change in dosage. Patients transferred to **Levemir®** from another type of insulin may require a change in dosage from that used with their usual insulins. If an adjustment is needed, it may occur with the first dose or during the first few weeks or months.

Injection site reactions

As with any insulin therapy, injection site reactions may occur and include pain, redness, hives, inflammation, bruising, swelling and itching. 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®**.

Hypoalbuminaemia

There are limited data in patients with severe hypoalbuminaemia. Careful monitoring is recommended in these patients.

Combination of **Levemir** with pioglitazone

Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for development of cardiac heart failure. This should be kept in mind if treatment with the combination of pioglitazone and **Levemir** is considered. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs.

4.5 Interaction with other medicinal products and other forms of interaction

A number of medicinal products are known to interact with the glucose metabolism.

The following substances may reduce the patient's insulin requirements:
Oral antidiabetic medicinal products, monoamine oxidase inhibitors (MAOI), beta-blockers, angiotensin converting enzyme (ACE) inhibitors, salicylates, anabolic steroids and sulphonamides.

The following substances may increase the patient's insulin requirements:
Oral contraceptives, thiazides, glucocorticoids, thyroid hormones, sympathomimetics, growth hormone and danazol.

Beta-blocking agents may mask the symptoms of hypoglycaemia.

Octreotide/lanreotide may both increase or decrease insulin requirement.

Alcohol may intensify or reduce the hypoglycaemic effect of insulin.

4.6 Fertility, pregnancy and Lactation

Pregnancy
There is no clinical experience with insulin detemir during pregnancy.

Animal reproduction studies have not revealed any differences between insulin detemir and human insulin regarding embryotoxicity and teratogenicity. Caution should be exercised when prescribing to pregnant women.

In general, intensified blood glucose control and monitoring of pregnant women with diabetes are recommended throughout pregnancy and when contemplating pregnancy. Insulin requirements usually fall in the first trimester and increase subsequently during the second and third trimester. After delivery, insulin requirements normally return rapidly to pre-pregnancy values.

Breast-feeding
There is no clinical experience with insulin detemir during breast-feeding. Caution should be exercised when prescribing to breast-feeding women. Breast-feeding women may require adjustments in insulin dose and diet.

Fertility

Animal reproduction studies with insulin detemir have not revealed any adverse effects on fertility

4.7 Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery).

Patients should be advised to take precautions to avoid hypoglycaemia while driving. This is particularly important in those who have reduced or absent awareness of the warning signs of hypoglycaemia or have frequent episodes of hypoglycaemia. The advisability of driving should be considered in these circumstances.

4.8 Undesirable effects

a. Summary of the safety profile

Adverse reactions observed in patients using **Levemir®** are mainly due to the pharmacologic effect of insulin. The overall percentage of treated patients expected to experience adverse drug reactions is estimated to be 12%.

The most frequently reported adverse reaction during treatment is hypoglycaemia, please see section c below.

From clinical investigations it is known that major hypoglycemia, defined as requirement for third party intervention, occurs in approximately 6% of the patients treated with **Levemir®**.

Injection site reactions are seen more frequently during treatment with **Levemir®** than with human insulin. These reactions include pain, redness, hives, inflammation, bruising, swelling and itching at the injection site. Most of the injection site reactions are minor and of a transitory nature, i.e. they normally disappear during continued treatment in a few days to a few weeks.
At the beginning of the insulin treatment, refraction anomalies and oedema may occur; these reactions are usually of transitory nature. Fast improvement in blood glucose control may be associated with acute painful neuropathy, which is usually reversible. Intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy, while long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy.

b. Tabulated list of adverse reactions

Adverse reactions listed below are classified according to frequency and System Organ Class. Frequency categories are defined according to the following convention: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to ≤1/100); rare (≥1/10,000 to ≤1/1,000); very rare (≤1/10,000), not known (cannot be estimated from the available data).

Nervous system disorders	Rare - Peripheral neuropathy
Eye disorders	Uncommon - Refraction disorders
	Uncommon - Diabetic retinopathy

Metabolism and nutrition disorders	Very Common – Hypoglycaemia
General disorders and administration site conditions	Common - Injection site reactions
	Uncommon – Oedema
Immune system disorders*	Uncommon Allergic reactions, potentially allergic reactions, urticaria, rash and eruptions* Very rare – Anaphylactic reactions*
Skin and subcutaneous tissue disorders	Uncommon - Lipodystrophy

* see section c

c. Description of selected adverse reactions

Allergic reactions, potentially allergic reactions, urticaria, rash, eruptions:
Allergic reactions, potentially allergic reactions, urticaria, rash and eruptions are uncommon when **Levemir®** is used in basal-bolus regimen. However, when used in combination with oral antidiabetic medicinal products, three clinical studies have shown a frequency of common (2.2% of allergic reactions and potentially allergic reactions have been observed).

Anaphylactic reactions:
The occurrence of generalised hypersensitivity reactions (including generalised skin rash, itching, sweating, gastrointestinal upset, angioneurotic oedema, difficulties in breathing, palpitation and reduction in blood pressure) is very rare but can potentially be life threatening.

Hypoglycaemia:
The most frequently reported adverse reaction is hypoglycaemia. It may occur if the insulin dose is too high in relation to the insulin requirement. Severe

hypoglycaemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death. The symptoms of hypoglycaemia usually occur suddenly. They may include cold sweat, cool pale skin, fatigue, nervousness or tremor, anxiousness, unusual tiredness or weakness, confusion, difficulty in concentration, drowsiness, excessive hunger, vision changes, headache, nausea and palpitation.

Lipodystrophy
Lipodystrophy is reported as uncommon. It may occur at the injection site as a consequence of failure to rotate injection sites within an area.

d. Paediatric population

Based on post-marketing sources and clinical trials, the frequency, type and severity of adverse reactions observed in the paediatric population do not indicate any differences to the broader experience in the general population.

e. Other special populations

Based on post-marketing sources and clinical trials, the frequency, type and severity of adverse reactions observed in the elderly patients and in patients with renal or hepatic impairment do not indicate any differences to the broader experience in the general population.

4.9 Overdose

A specific overdose for insulin cannot be defined, however, hypoglycaemia may develop over sequential stages if too high doses relative to the patient's requirement are administered:

- Mild hypoglycaemic episodes can be treated by oral administration of glucose or sugary products. It is therefore recommended that the diabetic patient always carries sugar containing products

- Severe hypoglycaemic episodes, where the patient has become unconscious, can be treated by glucagon (0.5 to 1 mg) given intramuscularly or subcutaneously by a trained person, or by glucose given intravenously by a health care professional. Glucose must also be given intravenously, if the patient does not respond to glucagon within 10 to 15 minutes. Upon regaining consciousness, administration of oral carbohydrates is recommended for the patient in order to prevent a relapse.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Insulins and analogues for injection, long-acting:
ATC code: A10AE05.

Mechanism of action

Insulin detemir is a soluble, long-acting insulin analogue with a prolonged duration of effect used as a basal insulin.

The blood glucose lowering effect of insulin detemir is due to the facilitated uptake of glucose following binding of insulin to receptors on muscle and fat cells and to the simultaneous inhibition of glucose output from the liver.

The time action profile of insulin detemir is statistically significantly less variable and therefore more predictable than for NPH (Neutral Protamine Hagedorn) insulin as seen from the within-subject Coefficients of Variation (CV) for the total and maximum pharmacodynamic effect in Table 1.

Table 1. Within-Subject Variability of the time action profile of insulin detemir and NPH insulin

Pharmacodynamic Endpoint	Insulin detemir CV (%)	NPH insulin CV (%)
$AUC_{GIR,0-24h}$*	27	68
GIR_{max}**	23	46

*Area under the curve ** Glucose Infusion Rate p-value < 0.001 for all comparisons with insulin detemir

The prolonged action of insulin detemir is mediated by the strong self-association of insulin detemir molecules at the injection site and albumin binding via the fatty acid side-chain. Insulin detemir is distributed more slowly to peripheral target tissues compared to NPH insulin. These combined mechanisms of protraction provide a more reproducible absorption and action profile of insulin detemir compared to NPH insulin.

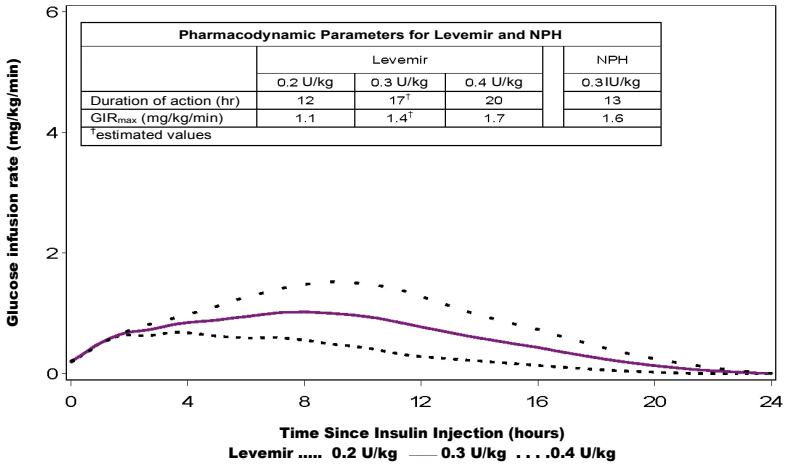

Figure 1: Activity profiles of Levemir® in patients with type 1 diabetes.

The duration of action is up to 24 hours depending on dose providing an opportunity for once or twice daily administration. If administered twice daily, steady state will occur after 2-3 dose administrations. For doses in the interval of 0.2 – 0.4 U/kg, **Levemir®** exerts more than 50% of its maximum effect from 3-4 hours and up to approximately 14 hours after dose administration.

Dose proportionality in pharmacodynamic response (maximum effect, duration of action, total effect) is observed after subcutaneous administration.

Lower day-to-day variability in FPG was demonstrated during treatment with **Levemir®** compared to NPH in long-term clinical trials.

Studies in patients with type 2 diabetes treated with basal insulin in combination with oral antidiabetic medicines demonstrated that glycaemic control (HbA_{1c}) with

Levemir® is comparable to NPH insulin and insulin glargine and associated with less weight gain, please see Table 2 below. In the study versus insulin glargine, insulin detemir was allowed to be administered once or twice daily whereas insulin glargine was to be administered once a day, 55% of the insulin detemir-treated subjects completed the 52 weeks of treatment on the twice daily regimen.

Table 2. Change in body weight after insulin treatment

Study duration	Insulin detemir once	Insulin detemir twice	NPH insulin	Insulin glargine
20 weeks	+0.7 kg		+1.6 kg	
26 weeks		+1.2 kg	+2.8 kg	
52 weeks	+2.3 kg	+3.7 kg		+4.0 kg

In trials with the use of OAD-insulin combination therapy **Levemir®** treatment resulted in a 61-65% lower risk of minor nocturnal hypoglycaemia compared to NPH insulin.

In long-term treatment trials in patients with type 1 diabetes, fasting plasma glucose was improved with **Levemir®** compared with NPH insulin when given as basal/bolus therapy including in children and adolescents aged 6 to 17 years. Glycaemic control (HbA_{1c}) with **Levemir®** is comparable to NPH insulin, with a lower risk of nocturnal hypoglycaemia and no associated weight gain.

In clinical trials using basal bolus insulin therapy, the overall rates of hypoglycaemia with **Levemir®** and NPH insulin were similar. Analyses of nocturnal hypoglycaemia in patients with type 1 diabetes showed a significantly lower risk of minor nocturnal hypoglycaemia (able to self-treat and confirmed by capillary blood glucose less than 2.8 mmol/L or 3.1mmol/L if expressed as plasma glucose) than with NPH insulin, whereas no difference was seen in type 2 diabetes. Furthermore, the overall risk of nocturnal hypoglycaemia in children and adolescents aged 6 to 17 years with type 1 diabetes was significantly lower with **Levemir®** compared to NPH insulin.

Antibody development has been observed with the use of **Levemir®**. However, this does not appear to have any impact on glycaemic control.

5.2 Pharmacokinetic properties

Absorption:
Maximum serum concentration is reached between 6 and 8 hours after administration. When administered twice daily, steady state serum concentrations are reached after 2-3 dose administrations. Within-patient variation in absorption is lower for **Levemir®** than for other basal insulin preparations.
The absolute bioavailability of insulin detemir when administered subcutaneous is approximately 60%.

Distribution
An apparent volume of distribution for insulin detemir (approximately 0.1 l/kg) indicates that a high fraction of insulin detemir is circulating in the blood.
The results of the *in vitro* and *in vivo* protein binding studies suggest that there is no clinically relevant interaction between insulin detemir and fatty acids or other protein bound medicinal products.

Biotransformation
Degradation of insulin detemir is similar to that of human insulin; all metabolites

formed are inactive.

Elimination
The terminal half-life after subcutaneous administration is determined by the rate of absorption from the subcutaneous tissue. The terminal half-life is between 5 and 7 hours depending on the dose.

Linearity
Dose proportionality in serum concentrations (maximum concentration, extent of absorption) is observed after subcutaneous administration in the therapeutic dose range.

Special populations
Paediatric patients: The pharmacokinetic properties of insulin detemir were investigated in children (6–12 years) and adolescents (13–17 years) and compared to adults with type 1 diabetes. There was no clinically relevant difference in pharmacokinetic properties.

Elderly (≥ 65 years old)
There was no clinically relevant difference in pharmacokinetics of insulin detemir between elderly and young subjects.

Renal and hepatic impairment: There was no clinically relevant difference in pharmacokinetics of insulin detemir between subjects with renal or hepatic impairment and healthy subjects. As the pharmacokinetics of insulin detemir has not been studied extensively in these populations, it is advised to monitor plasma glucose closely in these populations.

Gender: There are no clinically relevant differences between genders in pharmacokinetic properties of insulin detemir.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and toxicity to reproduction. Receptor affinity data and *in vitro* mitogenicity tests revealed no evidence of an increased mitogenic potential compared to human insulin.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycerol
Phenol
Metacresol
Zinc (acetate)
Disodium phosphate dihydrate
Sodium chloride
Hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

Substances added to **Levemir®** may cause degradation of insulin detemir, e.g. if the medicinal product contains thiols or sulphites. **Levemir®** should not be added to infusion fluids.
This medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

After first opening: A maximum of 6 weeks when stored below 30°C.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C). Keep away from the cooling element. Do not freeze.

Keep the cap on FlexPen® in order to protect from light.

After first opening or carried as a spare: Do not refrigerate. Store below 30°C.

Levemir® must be protected from excessive heat and light.

6.5 Nature and contents of container

FlexPen- 3 ml solution in cartridge (type 1 glass) with a plunger (bromobutyl) and a stopper (bromobutyl/polyisoprene) contained in a pre-filled multidose disposable pen made of polypropylene.
Penfill - A cartridge (type 1 glass) with a plunger (bromobutyl) and a stopper (bromobutyl/polyisoprene) in a carton. Pack size : 5 cartridges.

6.6 Special precautions for disposal and other handling

Needles and **Levemir®** must not be shared. The cartridge must not be refilled.

Levemir® must not be used if it does not appear clear and colourless.

Levemir® which has been frozen must not be used.

The patient should be advised to discard the needle after each injection.

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7. REGISTRATION NUMBER(S)

132 40 31119

8. REGISTRATION HOLDER

Novo Nordisk Ltd.
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אסמכתא להחמרות –
עלון מאושר – EMA

נבדק מול תעודת איכות וטופס פרטי תכשיר חתומים

נבדק ע"י דפנה