ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Levemir 100 U/ml 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 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 cartridge. Penfill.

Clear, colourless, neutral solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of diabetes mellitus in adults and adolescents and children aged 6 - 17 years.

4.2 Posology and method of administration

Levemir is a long-acting insulin analogue used as a basal insulin.

Posology

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 injection can be given at any time during the day, but at the same time each day. 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-bolus insulin regimen Levemir should be administered once or twice daily depending on patients' needs. Dosage of Levemir should be adjusted individually.

For patients who require twice daily dosing to optimise blood glucose control, the evening dose can be administered in the evening or at bedtime. Adjustment of dosage may be necessary if patients undertake increased physical activity, change their usual diet or during concomitant illness.

Special populations

As with all insulin products, in elderly patients and patients with renal or hepatic impairment, glucose monitoring should be intensified and insulin detemir dosage 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).

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 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. 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.

Levemir Penfill is designed to be used with Novo Nordisk insulin delivery systems and NovoFine needles. 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

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.

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.

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 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.

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

Adverse reactions observed in patients using Levemir are mainly dose-dependent and due to the pharmacologic effect of insulin. The overall percentage of treated patients expected to experience adverse drug reactions is estimated to be 12%.
Hypoglycaemia is a common undesirable effect. It may occur if the insulin dose is too high in relation to the insulin requirement. From clinical investigations it is known that major hypoglycaemia, defined as requirement for third party intervention, occurs in approximately 6% of the patients treated with Levemir. Severe hypoglycaemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death.

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.

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
	Fast improvement in blood glucose control may be associated with the condition "acute painful neuropathy", which is usually reversible
Eye disorders	Uncommon - Refraction disorders
	Refraction anomalies may occur upon initiation of insulin

	therapy. These symptoms are usually of transitory nature. Uncommon - Diabetic retinopathy Long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy. However, intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy.
Metabolism and nutrition disorders	Common – Hypoglycaemia Symptoms of hypoglycaemia usually occur suddenly. They may include cold sweats, 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. Severe hypoglycaemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death.
General disorders and administration site conditions	Common - Injection site reactions Injection site reactions (pain, redness, hives, inflammation, bruising, swelling and itching) at the injection site may occur during treatment with insulin. These reactions are usually transitory and normally they disappear during continued treatment. Uncommon - Lipodystrophy Lipodystrophy may occur at the injection site as a consequence of failure to rotate injection sites within an area. Uncommon - Oedema Oedema may occur upon initiation of insulin therapy. These symptoms are usually of transitory nature.
Immune system disorders*	Common In three clinical studies with subjects treated in combination with oral antidiabetic agents a frequency of 2.2% of allergic reactions and potentially allergic reactions have been observed.

	Uncommon Allergic reactions, potentially allergic reactions, urticaria, rash and eruptions: Such symptoms may be due to generalised hypersensitivity. Other signs of generalised hypersensitivity may be itching, sweating, gastrointestinal upset, angioneurotic oedema, difficulties in breathing, palpitation and reduction in blood pressure. Generalised hypersensitivity reactions are potentially life threatening (anaphylactic reactions).

* Frequencies are uncommon in basal-bolus regimen, but common in three clinical trials in combination with oral antidiabetic medicine.

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.

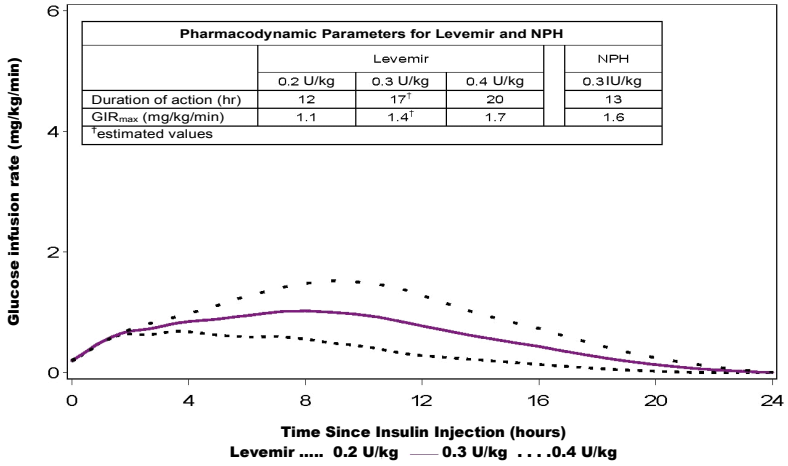

Figure 1: Activity profiles of Levemir in patients with type 1 diabetes.

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 daily	Insulin detemir twice daily	NPH insulin	Insulin glargine
20 week	+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 3.1 mmol/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.

Metabolism
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: 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

30 months.

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 cartridge in the outer carton 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

3 ml solution cartridge (type 1 glass) with a plunger (bromobutyl) and a stopper (bromobutyl/polyisoprene) in a carton. Pack sizes of 1, 5 and 10 cartridges. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Levemir Penfill is for use by one person only. 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.

7. MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/278/001
EU/1/04/278/002
EU/1/04/278/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01 June 2004
Date of last renewal: 16 April 2009

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

Levemir 100 U/ml solution for injection in pre-filled pen.

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.

*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.

Clear, colourless, neutral solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of diabetes mellitus in adults and adolescents and children aged 6 - 17 years.

4.2 Posology and method of administration

Levemir is a long-acting insulin analogue used as a basal insulin.

Posology

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 injection can be given at any time during the day, but at the same time each day. 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-bolus insulin regimen Levemir should be administered once or twice daily depending on patients' needs. Dosage of Levemir should be adjusted individually.

For patients who require twice daily dosing to optimise blood glucose control, the evening dose can be administered in the evening or at bedtime. Adjustment of dosage may be necessary if patients undertake increased physical activity, change their usual diet or during concomitant illness.

Special populations

As with all insulin products, in elderly patients and patients with renal or hepatic impairment, glucose monitoring should be intensified and insulin detemir dosage 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).

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 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. 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.

Levemir FlexPen are pre-filled pens designed to be used with NovoFine or NovoTwist needles. FlexPen delivers 1-60 units in increments of 1 unit.

Levemir FlexPen is colour coded and 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

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.

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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.

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The following substances may reduce the patient’s insulin requirements:
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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 Pregnancy and lactation

<u>Pregnancy</u>

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.

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

Adverse reactions observed in patients using Levemir are mainly dose-dependent and due to the pharmacologic effect of insulin. The overall percentage of treated patients expected to experience adverse drug reactions is estimated to be 12%.
Hypoglycaemia is a common undesirable effect. It may occur if the insulin dose is too high in relation to the insulin requirement. From clinical investigations it is known that major hypoglycaemia, defined as requirement for third party intervention, occurs in approximately 6% of the patients treated with Levemir. Severe hypoglycaemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death.

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.

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
	Fast improvement in blood glucose control may be associated with the condition "acute painful neuropathy", which is usually reversible
Eye disorders	Uncommon - Refraction disorders
	Refraction anomalies may occur upon initiation of insulin

	therapy. These symptoms are usually of transitory nature. Uncommon - Diabetic retinopathy Long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy. However, intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy.
Metabolism and nutrition disorders	Common – Hypoglycaemia Symptoms of hypoglycaemia usually occur suddenly. They may include cold sweats, 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. Severe hypoglycaemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death.
General disorders and administration site conditions	Common - Injection site reactions Injection site reactions (pain, redness, hives, inflammation, bruising, swelling and itching) at the injection site may occur during treatment with insulin. These reactions are usually transitory and normally they disappear during continued treatment. Uncommon – Lipodystrophy Lipodystrophy may occur at the injection site as a consequence of failure to rotate injection sites within an area. Uncommon – Oedema Oedema may occur upon initiation of insulin therapy. These symptoms are usually of transitory nature.
Immune system disorders*	Common In three clinical studies with subjects treated in combination with oral antidiabetic agents a frequency of 2.2% of allergic reactions and potentially allergic reactions have been observed.

	Uncommon
	Allergic reactions, potentially allergic reactions, urticaria, rash and eruptions:
	Such symptoms may be due to generalised hypersensitivity. Other signs of generalised hypersensitivity may be itching, sweating, gastrointestinal upset, angioneurotic oedema, difficulties in breathing, palpitation and reduction in blood pressure. Generalised hypersensitivity reactions are potentially life threatening (anaphylactic reactions).

* Frequencies are uncommon in basal-bolus regimen, but common in three clinical trials in combination with oral antidiabetic medicine.

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	NPH insulin

	CV (%)	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.

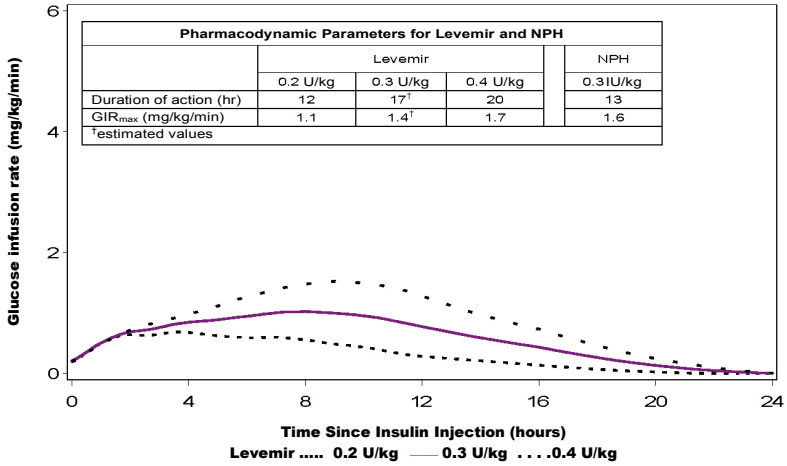

Figure 1: Activity profiles of Levemir in patients with type 1 diabetes.

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 daily	Insulin detemir twice daily	NPH insulin	Insulin glargine
20 week	+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 3.1 mmol/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.

Metabolism
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: 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

30 months.

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

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. Pack sizes of 1 (with or without needles), 5 (without needles) and 10 (without needles) pre-filled pens. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Levemir FlexPen is for use by one person only. 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.

7. MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/278/004
EU/1/04/278/005
EU/1/04/278/006
EU/1/04/278/010
EU/1/04/278/011

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01 June 2004
Date of last renewal: 16 April 2009

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

Levemir 100 U/ml solution for injection in pre-filled pen.

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.

*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. InnoLet.

Clear, colourless, neutral solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of diabetes mellitus in adults and adolescents and children aged 6 - 17 years.

4.2 Posology and method of administration

Levemir is a long-acting insulin analogue used as a basal insulin.

Posology

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 injection can be given at any time during the day, but at the same time each day. 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-bolus insulin regimen Levemir should be administered once or twice daily depending on patients' needs. Dosage of Levemir should be adjusted individually.

For patients who require twice daily dosing to optimise blood glucose control, the evening dose can be administered in the evening or at bedtime. Adjustment of dosage may be necessary if patients undertake increased physical activity, change their usual diet or during concomitant illness.

Special populations

As with all insulin products, in elderly patients and patients with renal or hepatic impairment, glucose monitoring should be intensified and insulin detemir dosage 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).

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 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 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.

Levemir InnoLet are pre-filled pens designed to be used with NovoFine needles. InnoLet delivers 1-50 units in increments of 1 unit.

Levemir InnoLet 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

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.

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.

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 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.

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

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

Hypoglycaemia is a common undesirable effect. It may occur if the insulin dose is too high in relation to the insulin requirement. From clinical investigations it is known that major hypoglycaemia, defined as requirement for third party intervention, occurs in approximately 6% of the patients treated with Levemir. Severe hypoglycaemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death.

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.

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
	Fast improvement in blood glucose control may be associated with the condition "acute painful neuropathy", which is usually reversible
Eye disorders	Uncommon - Refraction disorders
	Refraction anomalies may occur upon initiation of insulin

	therapy. These symptoms are usually of transitory nature. Uncommon - Diabetic retinopathy Long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy. However, intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy.
Metabolism and nutrition disorders	Common – Hypoglycaemia Symptoms of hypoglycaemia usually occur suddenly. They may include cold sweats, 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. Severe hypoglycaemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death.
General disorders and administration site conditions	Common - Injection site reactions Injection site reactions (pain, redness, hives, inflammation, bruising, swelling and itching) at the injection site may occur during treatment with insulin. These reactions are usually transitory and normally they disappear during continued treatment. Uncommon – Lipodystrophy Lipodystrophy may occur at the injection site as a consequence of failure to rotate injection sites within an area. Uncommon – Oedema Oedema may occur upon initiation of insulin therapy. These symptoms are usually of transitory nature.
Immune system disorders*	Common In three clinical studies with subjects treated in combination with oral antidiabetic agents a frequency of 2.2% of allergic reactions and potentially allergic reactions have been observed.

	Uncommon
	Allergic reactions, potentially allergic reactions, urticaria, rash and eruptions:
	Such symptoms may be due to generalised hypersensitivity. Other signs of generalised hypersensitivity may be itching, sweating, gastrointestinal upset, angioneurotic oedema, difficulties in breathing, palpitation and reduction in blood pressure. Generalised hypersensitivity reactions are potentially life threatening (anaphylactic reactions).

* Frequencies are uncommon in basal-bolus regimen, but common in three clinical trials in combination with oral antidiabetic medicine.

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	NPH insulin

	CV (%)	CV (%)
$AUC_{GIR,0-24h}$*	27	68
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*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.

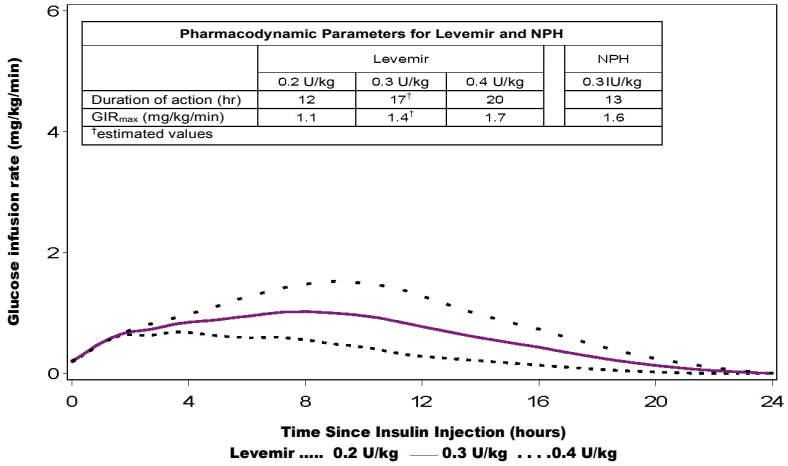

Figure 1: Activity profiles of Levemir in patients with type 1 diabetes.

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 daily	Insulin detemir twice daily	NPH insulin	Insulin glargine
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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 3.1 mmol/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.

Metabolism
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: 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

30 months.

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 InnoLet 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

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. Pack sizes of 1, 5 and 10 pre-filled pens. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Levemir InnoLet is for use by one person only. 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.

7. MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/278/007
EU/1/04/278/008
EU/1/04/278/009

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01 June 2004
Date of last renewal: 16 April 2009

10. DATE OF REVISION OF THE TEXT

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark

Novo Nordisk A/S
Hallas Allé
DK-4400 Kalundborg
Denmark

Name and address of the manufacturer responsible for batch release

Levemir InnoLet

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark

Levemir Penfill and FlexPen

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark

Novo Nordisk Production SAS
45, Avenue d'Orléans
F-28002 Chartres
France

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to medical prescription

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable

- **OTHER CONDITIONS**

Not applicable

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (CARTRIDGE. Penfill)

1. NAME OF THE MEDICINAL PRODUCT

Levemir 100 U/ml
Solution for injection in cartridge
Insulin detemir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 100 U (14.2 mg) of insulin detemir,

3. LIST OF EXCIPIENTS

glycerol, phenol, metacresol, zinc acetate, disodium phosphate dihydrate, sodium chloride, hydrochloric acid, sodium hydroxide for pH adjustment and water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in cartridge. Penfill

1 x 3 ml
5 x 3 ml
10 x 3 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Use only clear, colourless solution.
Levemir Penfill is for use by one person only

8. EXPIRY DATE

EXP/
After first opening: Use within 6 weeks

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C - 8°C)
Do not freeze
Keep the cartridge in the outer carton in order to protect from light
After first opening: Do not refrigerate. Store below 30°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard the needle after each injection

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/278/001 1 cartridge of 3 ml
EU/1/04/278/002 5 cartridges of 3 ml
EU/1/04/278/003 10 cartridges of 3 ml

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Levemir Penfill

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL (CARTRIDGE. Penfill)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Levemir 100 U/ml
Solution for injection in cartridge
Insulin detemir
SC use

2. METHOD OF ADMINISTRATION

Penfill

3. EXPIRY DATE

EXP/

4. BATCH NUMBER

Batch:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (PRE-FILLED PEN. FlexPen)

1. NAME OF THE MEDICINAL PRODUCT

Levemir 100 U/ml
Solution for injection in pre-filled pen.
Insulin detemir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 100 U (14.2 mg) of insulin detemir,

3. LIST OF EXCIPIENTS

glycerol, phenol, metacresol, zinc acetate, disodium phosphate dihydrate, sodium chloride, hydrochloric acid, sodium hydroxide for pH adjustment and water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled pen. FlexPen

1 x 3 ml
5 x 3 ml
10 x 3 ml
1 x 3 ml + 7 NovoFine needles
1 x 3 ml + 7 NovoTwist needles

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Needles are not included.
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Use only clear, colourless solution.
Levemir FlexPen is for use by one person only
Designed to be used with NovoFine or NovoTwist disposable needles up to a length of 8 mm

8. EXPIRY DATE

EXP/
After first opening: Use within 6 weeks.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C - 8°C)
Do not freeze
Keep the cap on in order to protect from light
After first opening: Do not refrigerate. Store below 30°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard the needle after each injection

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/278/004 1 pen of 3 ml
EU/1/04/278/005 5 pens of 3 ml
EU/1/04/278/006 10 pens of 3 ml
EU/1/04/278/010 1 pen of 3 ml and 7 NovoFine needles
EU/1/04/278/011 1 pen of 3 ml and 7 NovoTwist needles

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Levemir FlexPen

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PEN LABEL (PRE-FILLED PEN. FlexPen)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Levemir 100 U/ml
Solution for injection in pre-filled pen. FlexPen
Insulin detemir
SC use

2. METHOD OF ADMINISTRATION

FlexPen

3. EXPIRY DATE

EXP/

4. BATCH NUMBER

Batch:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (PRE-FILLED PEN. InnoLet)

1. NAME OF THE MEDICINAL PRODUCT

Levemir 100 U/ml
Solution for injection in pre-filled pen.
Insulin detemir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 100 U (14.2 mg) of insulin detemir,

3. LIST OF EXCIPIENTS

glycerol, phenol, metacresol, zinc acetate, disodium phosphate dihydrate, sodium chloride, hydrochloric acid, sodium hydroxide for pH adjustment and water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled pen. InnoLet

1 x 3 ml
5 x 3 ml
10 x 3 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Needles are not included.
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Use only clear, colourless solution.
Levemir InnoLet is for use by one person only
Designed to be used with NovoFine disposable needles up to a length of 8 mm

8. EXPIRY DATE

EXP/
After first opening: Use within 6 weeks.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C - 8°C)
Do not freeze
Keep the cap on in order to protect from light
After first opening: Do not refrigerate. Store below 30°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard the needle after each injection

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/278/007 1 pen of 3 ml
EU/1/04/278/008 5 pens of 3 ml
EU/1/04/278/009 10 pens of 3 ml

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Levemir InnoLet

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PEN LABEL (PRE-FILLED PEN. InnoLet)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Levemir 100 U/ml
Solution for injection in pre-filled pen. InnoLet
Insulin detemir
SC use

2. METHOD OF ADMINISTRATION

InnoLet

3. EXPIRY DATE

EXP/

4. BATCH NUMBER

Batch:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml

6. OTHER

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Levemir 100 U/ml solution for injection in cartridge
Insulin detemir

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again
- If you have any further questions, ask your doctor, nurse or pharmacist
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor, nurse or pharmacist.

In this leaflet:

1. What Levemir is and what it is used for
2. Before you use Levemir
3. How to use Levemir
4. Possible side effects
5. How to store Levemir
6. Further information

1. WHAT LEVEMIR IS AND WHAT IT IS USED FOR

Levemir is a modern insulin (insulin analogue) with a long-acting effect (up to 24 hours). Modern insulins are improved versions of human insulin.

Levemir is used to treat diabetes mellitus in adults, children and adolescents aged 6-17 years. It may be used in combination with oral antidiabetic medicines or with meal-related rapid acting insulin products.

2. BEFORE YOU USE LEVEMIR

Do not use Levemir

- ► If you are allergic (hypersensitive) to insulin detemir or any of the other ingredients of Levemir (see *6 Further information*)
- ► If you suspect hypoglycaemia (low blood sugar) is starting (see *4 Possible side effects*)
- ► In insulin infusion pumps
- ► If the cartridge or the device containing the cartridge is dropped, damaged or crushed
- ► If it hasn't been stored correctly or if it has been frozen (see *5 How to store Levemir*)
- ► If the insulin does not appear water clear and colourless.

Before using Levemir

- ► Check the label to make sure it is the right type of insulin
- ► Always check the cartridge, including the rubber plunger (stopper). Do not use it if any damage is seen or if there is a gap between the rubber plunger and the white label band. Take it back to your supplier. See your delivery system manual for further instructions
- ► Disinfect the rubber membrane with a medicinal swab
- ► Always use a new needle for each injection to prevent contamination.

Take special care with Levemir

- ► If you have trouble with your kidneys or liver, or with your adrenal, pituitary or thyroid glands

► If you are exercising more than usual or if you want to change your usual diet, as this may affect your blood sugar level
► If you are ill: carry on taking your insulin and consult your doctor
► If you are going abroad: travelling over time zones may affect your insulin needs and the timing of the injections. Consult your doctor if you are planning such travelling.

There is no experience with the use of Levemir in children below the age of 6 years. Therefore, only use Levemir in children below this age, if your doctor have specifically told you to.

As with all insulin products, in elderly patients and patients with renal or heparic impairment, glucose monitoring should be intensified and insulin detemir dosage adjusted on a individual basis.

Using other medicines

Some medicines affect the way glucose works in your body and this may influence your insulin dose. Listed below are the most common medicines, which may affect your insulin treatment. Tell your doctor, nurse or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. In particular, you should tell your doctor if you are using any medicine as mentioned below that affects your blood sugar level.

If you take any of the below medicine your blood sugar level may fall (hypoglycaemia):
- Other medicines for the treatment of diabetes
- Monoamine oxidase inhibitors (MAOI) (used to treat depression)
- Beta-blockers (used to treat high blood pressure)
- Angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure)
- Salicylates (used to relieve pain and lower fever)
- Anabolic steroids (such as testosterone)
- Sulphonamides (used to treat infections).

If you take any of the below medicine your blood sugar level may rise (hyperglycaemia):
- Oral contraceptives (birth control pills)
- Thiazides (used to treat high blood pressure or excessive fluid retention)
- Glucocorticoids (such as "cortisone" used to treat inflammation)
- Thyroid hormones (use to treat thyroid gland disorders)
- Sympathomimetics (such as epinephrine [adrenaline], or salbutamol, terbutaline used to treat asthma)
- Growth hormone (medicine for stimulation of skeletal and somatic growth and pronounced influence on the body’s metabolic processes)
- Danazol (medicine acting on ovulation).

Octreotide and lanreotide (used for treatment of acromegaly) may both increase or decrease your sugar level.

Beta-blockers (used to treat high blood pressure) may weaken or suppress entirely the first warning symptoms which help you to recognise a hypoglycaemia.

Taking Levemir with food and drink

► If you are drinking alcohol your need for insulin may change, as your blood sugar level may either rise or fall. Carefull monitoring is recommended.

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.
► If you are pregnant, planning a pregnancy or breast-feeding please contact your doctor for advice. Your insulin dosage may need to be changed during pregnancy particulary after

delivery. Careful control of your diabetes, and prevention of hypoglycaemia, is important, for the health of your baby.

Driving and using machines

If your blood sugar is low or high your concentration and ability to react might be affected and therefore also your ability to drive or operate a machine. Bear in mind that you could endanger yourself or others. Please ask your doctor whether you can drive a car:
► If you have frequent hypoglycaemias
► If you find it hard to recognise hypoglycaemia.

3. HOW TO USE LEVEMIR

Dosage

Talk about your insulin dose with your doctor and nurse. Do not change your insulin unless your doctor tells you to. Make sure you get the Levemir Penfill that your doctor and nurse have told you to use and follow their advice carefully**.** This leaflet is a general guide.
If your doctor has switched you from one type or brand of insulin to another, your dose may have to be adjusted by your doctor.

Frequency of administration

When Levemir is used in combination with an oral antidiabetic medicine, Levemir should be administered once a day. When Levemir is used as part of a basal-bolus insulin regimen Levemir should be administered once or twice daily depending on patients' needs. Dosage of Levemir should be adjusted individually. For patients who require twice daily dosing to optimise blood glucose control, the evening dose can be administered in the evening or at bedtime.

Method of administration

Levemir is for injection under the skin (subcutaneously). Never inject your insulin directly into a vein (intravenously) or muscle (intramuscular). Always vary the sites you inject within the same region to avoid lumps (see *4 Possible side effects*). The best places to give yourself an injection are: the front of your thighs, the front of your waist (abdomen), or the upper arm. You should always measure your blood glucose regularly.

- Inject the insulin under the skin. Use the injection technique advised by your doctor or nurse and described in your delivery system manual
- Keep the needle under your skin for at least 6 seconds to make sure that the full dose has been delivered
- After each injection be sure to remove and discard the needle and store Levemir without the needle attached. Otherwise, the liquid may leak out, which can cause inaccurate dosing.

Do not refill the cartridge.
Levemir Penfill cartridges are designed to be used with Novo Nordisk insulin delivery systems and NovoFine needles.
If you are treated with Levemir Penfill and another insulin Penfill cartridge, you should use two insulin delivery systems, one for each type of insulin.

If you take more insulin than you should

If you take too much insulin your blood sugar gets too low (this is called hypoglycaemia or hypo). This may also happen:
- If you eat too little or miss a meal
- If you exercise more than usual.

The warning signs of a hypo may come on suddenly and can include: cold sweat; cool pale skin; headache; rapid heart beat; feeling sick; feeling very hungry; temporary changes in vision; drowsiness; unusual tiredness and weakness; nervousness or tremor; feeling anxious; feeling confused; difficulty in concentrating.

If you feel a hypo coming on: take a high sugar snack and then measure your blood sugar.
If your blood sugar is too low: eat glucose tablets or another high sugar snack (sweets, biscuits, fruit juice), then rest.
Always carry glucose tablets, sweets, biscuits or fruit juice with you, just in case.

When symptoms of hypoglycaemia have disappeared or when blood glucose level is stabilised continue insulin treatment.
Tell relevant people you have diabetes and what may be the consequences, including the risk of passing out due to a hypo.
Tell relevant people that if you pass out (become unconscious), they must turn you on your side and get medical help straight away. They must not give you any food or drink. It could choke you.

You may recover more quickly from unconsciousness with an injection of the hormone glucagon by someone who knows how to use it. If you are given glucagon you will need glucose or a sugary snack as soon as you are conscious. If you do not respond to glucagon treatment, you will have to be treated in a hospital. Contact your doctor or an emergency ward after an injection of glucagon: you need to find the reason for your hypo to avoid getting more.

- ► If prolonged severe hypoglycaemia is not treated, it can cause brain damage (temporary or permanent) and even death
- ► If you have a hypo that makes you pass out, or a lot of hypos, talk to your doctor. The amount or timing of insulin, food or exercise may need to be adjusted.

If you forget to take your insulin

If you forget to take your insulin **y**our blood sugar may get too high (this is called hyperglycaemia). This may also happen:

- If you repeatedly take less insulin than you need
- If you get an infection or a fever
- If you eat more than usual
- If you exercise less than usual.

The warning signs appear gradually. They include: increased urination; feeling thirsty; losing your appetite; feeling sick (nausea or vomiting); feeling drowsy or tired; flushed, dry skin; dry mouth and a fruity (acetone) smell of the breath.
If you get any of these signs: test your blood sugar level, test your urine for ketones if you can, then seek medical advice immediately.
These may be signs of a very serious condition called diabetic ketoacidosis. If you do not treat it, this could lead to diabetic coma and eventually death.

If you stop taking your insulin

This could lead to severe hyperglycaemia (very high blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). Do not stop taking your insulin without speaking to a doctor, who will tell you what needs to be done.
If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Levemir can cause side effects, although not everybody gets them.

Side effects may occur with certain frequencies, which are defined as follows:
- Very common: affects more than 1 user in 10
- Common: affects 1 to 10 users in 100
- Uncommon: affects 1 to 10 users in 1,000
- Rare: affects 1 to 10 users in 10,000
- Very rare: affects less than 1 user in 10,000
- Not known: frequency cannot be estimated from the available data.

Uncommon side effects

Signs of allergy. Hives and rash may occur.
Seek medical advice immediately:
- ► If the above signs of allergy appear, or
- ► If you suddenly feel unwell, and you: start sweating; start being sick (vomiting); have difficulty in breathing; have a rapid heart beat; feel dizzy.

Vision problems. When you first start your insulin treatment, it may disturb your vision, but the disturbance is usually temporary.

Changes at the injection site (lipodystrophy). If you inject yourself too often at the same site, fatty tissue under the skin at this site may shrink (lipoatrophy) or thicken (lipohypertrophy). Changing the site with each injection may help to prevent such skin changes. If you notice your skin pitting or thickening at the injection site, tell your doctor or nurse because these reactions can become more severe, or they may change the absorption of your insulin if you inject in such a site.

Swollen joints. When you start taking insulin, water retention may cause swelling around your ankles and other joints. Normally this soon disappears.

Common side effects

Low blood sugar (hypoglycaemia).

Injection site reactions (pain, redness, hives, inflammation, bruising, swelling and itching). These usually disappear after a few weeks of taking your insulin. If they do not disappear see your doctor. If you have serious or continuing reactions, you may need to stop using Levemir and use another insulin.

Rare side effects

Disturbed sensation. Fast improvement in blood glucose control may cause disturbed sensation (numbness, weakness or pain) in legs or arms. These symptoms normally disappear.

Very rare side effects

Serious allergic reaction to Levemir or one of its ingredients (called a generalised allergic reaction). See also the warning in *2 Before using Levemir*.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor, nurse or pharmacist.

5. HOW TO STORE LEVEMIR

Keep out of the reach and sight of children.
Do not use Levemir after the expiry date which is stated on the cartridge label and carton, after EXP. The expiry date refers to the last day of that month.
Levemir Penfill that is not being used is to be stored in the refrigerator at 2°C - 8°C, away from the cooling element. Do not freeze.

Levemir Penfill that is being used or carried as a spare is not to be kept in the refrigerator. You can carry it with you and keep it at room temperature (below 30°C) for up to 6 weeks.
Always keep the cartridge in the outer carton when you are not using it in order to protect it from light.
Levemir must be protected from excessive heat and light.

Medicines should not be disposed of via waste water or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Levemir contains

- The active substance is insulin detemir. Each ml contains 100 U of insulin detemir. Each cartridge contains 300 U of insulin detemir in 3 ml solution for injection. 1 unit (U) insulin detemir corresponds to 1 international unit (IU) of human insulin
- The other ingredients are: glycerol, phenol, metacresol, zinc acetate, disodium phosphate dihydrate, sodium chloride, hydrochloric acid, sodium hydroxide and water for injections.

What Levemir looks like and contents of the pack

Levemir comes as a clear, colourless, aqueous solution.
Pack sizes of 1, 5 and 10 cartridges of 3 ml.
Not all packs may be marketed.

Marketing authorisation holder

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd, Denmark

Manufacturer

The manufacturer can be identified by the batch number printed on the slip of the carton and on the label:

- If the second and third characters are W5, S6, P5, K7, or ZF Novo Nordisk A/S, Novo Allé, DK-2880 Bagsværd, Denmark is the manufacturer

- If the second and third characters are H7 or T6 Novo Nordisk Production SAS, 45 Avenue d'Orléans F-28002 Chartres, France is the manufacturer.

This leaflet was last approved in

PACKAGE LEAFLET: INFORMATION FOR THE USER

Levemir 100 U/ml solution for injection in pre-filled pen
Insulin detemir

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again
- If you have any further questions, ask your doctor, nurse or pharmacist
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor, nurse or pharmacist.

In this leaflet:

1. What Levemir is and what it is used for
2. Before you use Levemir
3. How to use Levemir
4. Possible side effects
5. How to store Levemir
6. Further information

1. WHAT LEVEMIR IS AND WHAT IT IS USED FOR

Levemir is a modern insulin (insulin analogue) with a long-acting effect (up to 24 hours). Modern insulins are improved versions of human insulin.

Levemir is used to treat diabetes mellitus in adults, children and adolescents aged 6 -17 years. It may be used in combination with oral antidiabetic medicines or with meal-related rapid acting insulin products.

2. BEFORE YOU USE LEVEMIR

Do not use Levemir

- ► If you are allergic (hypersensitive) to insulin detemir or any of the other ingredients of Levemir (see *6 Further information*)
- ► If you suspect hypoglycaemia (low blood sugar) is starting (see *4 Possible side effects*)
- ► In insulin infusion pumps
- ► If FlexPen is dropped, damaged or crushed
- ► If it hasn't been stored correctly or if it has been frozen (see *5 How to store Levemir*)
- ► If the insulin does not appear water clear and colourless.

Before using Levemir

- ► Check the label to make sure it is the right type of insulin
- ► Always use a new needle for each injection to prevent contamination.

Take special care with Levemir

- ► If you have trouble with your kidneys or liver, or with your adrenal, pituitary or thyroid glands
- ► If you are exercising more than usual or if you want to change your usual diet, as this may affect your blood sugar level
- ► If you are ill: carry on taking your insulin and consult your doctor

► If you are going abroad: travelling over time zones may affect your insulin needs and the timing of the injections. Consult your doctor if you are planning such travelling.

There is no experience with the use of Levemir in children below the age of 6 years. Therefore, only use Levemir in children below this age, if your doctor have specifically told you to.

As with all insulin products, in elderly patients and patients with renal or heparic impairment, glucose monitoring should be intensified and insulin detemir dosage adjusted on a individual basis.

Using other medicines

Some medicines affect the way glucose works in your body and this may influence your insulin dose. Listed below are the most common medicines, which may affect your insulin treatment. Tell your doctor, nurse or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. In particular, you should tell your doctor if you are using any medicine as mentioned below that affects your blood sugar level.

If you take any of the below medicine your blood sugar level may fall (hypoglycaemia):
- Other medicines for the treatment of diabetes
- Monoamine oxidase inhibitors (MAOI) (used to treat depression)
- Beta-blockers (used to treat high blood pressure)
- Angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure)
- Salicylates (used to relieve pain and lower fever)
- Anabolic steroids (such as testosterone)
- Sulphonamides (used to treat infections).

If you take any of the below medicine your blood sugar level may rise (hyperglycaemia):
- Oral contraceptives (birth control pills)
- Thiazides (used to treat high blood pressure or excessive fluid retention)
- Glucocorticoids (such as "cortisone" used to treat inflammation)
- Thyroid hormones (use to treat thyroid gland disorders)
- Sympathomimetics (such as epinephrine [adrenaline], or salbutamol, terbutaline used to treat asthma)
- Growth hormone (medicine for stimulation of skeletal and somatic growth and pronounced influence on the body’s metabolic processes)
- Danazol (medicine acting on ovulation).

Octreotide and lanreotide (used for treatment of acromegaly) may both increase or decrease your sugar level.

Beta-blockers (used to treat high blood pressure) may weaken or suppress entirely the first warning symptoms which help you to recognise a hypoglycaemia.

Taking Levemir with food and drink

► If you are drinking alcohol your need for insulin may change, as your blood sugar level may either rise or fall. Carefull monitoring is recommended.

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.
► If you are pregnant, planning a pregnancy or breast-feeding please contact your doctor for advice. Your insulin dosage may need to be changed during pregnancy particularly after delivery. Careful control of your diabetes, and prevention of hypoglycaemia, is important, for the health of your baby.

Driving and using machines

If your blood sugar is low or high your concentration and ability to react might be affected and therefore also your ability to drive or operate a machine. Bear in mind that you could endanger yourself or others. Please ask your doctor whether you can drive a car:
► If you have frequent hypoglycaemias
► If you find it hard to recognise hypoglycaemia.

3. HOW TO USE LEVEMIR

Dosage

Talk about your insulin dose with your doctor and nurse. Do not change your insulin unless your doctor tells you to. Make sure you get the colour coded Levemir FlexPen that your doctor and nurse have told you to use and follow their advice carefully**.** This leaflet is a general guide.
If your doctor has switched you from one type or brand of insulin to another, your dose may have to be adjusted by your doctor.

Frequency of administration

When Levemir is used in combination with an oral antidiabetic medicine, Levemir should be administered once a day. When Levemir is used as part of a basal-bolus insulin regimen Levemir should be administered once or twice daily depending on patients' needs. Dosage of Levemir should be adjusted individually. For patients who require twice daily dosing to optimise blood glucose control, the evening dose can be administered in the evening or at bedtime.

Method of administration

Levemir is for injection under the skin (subcutaneously). Never inject your insulin directly into a vein (intravenously) or muscle (intramuscular). Always vary the sites you inject within the same region to avoid lumps (see *4 Possible side effects*). The best places to give yourself an injection are: the front of your thighs, the front of your waist (abdomen), or the upper arm. You should always measure your blood glucose regularly.

If you take more insulin than you should

If you take too much insulin your blood sugar gets too low (this is called hypoglycaemia or hypo). This may also happen:
• If you eat too little or miss a meal
• If you exercise more than usual.

The warning signs of a hypo may come on suddenly and can include: cold sweat; cool pale skin; headache; rapid heart beat; feeling sick; feeling very hungry; temporary changes in vision; drowsiness; unusual tiredness and weakness; nervousness or tremor; feeling anxious; feeling confused; difficulty in concentrating.

If you feel a hypo coming on: take a high sugar snack and then measure your blood sugar.
If your blood sugar is too low: eat glucose tablets or another high sugar snack (sweets, biscuits, fruit juice), then rest.
Always carry glucose tablets, sweets, biscuits or fruit juice with you, just in case.

When symptoms of hypoglycaemia have disappeared or when blood glucose level is stabilised continue insulin treatment.
Tell relevant people you have diabetes and what may be the consequences, including the risk of passing out due to a hypo.

Tell relevant people that if you pass out (become unconscious), they must turn you on your side and get medical help straight away. They must not give you any food or drink. It could choke you.

You may recover more quickly from unconsciousness with an injection of the hormone glucagon by someone who knows how to use it. If you are given glucagon you will need glucose or a sugary snack as soon as you are conscious. If you do not respond to glucagon treatment, you will have to be treated in a hospital. Contact your doctor or an emergency ward after an injection of glucagon: you need to find the reason for your hypo to avoid getting more.

► If prolonged severe hypoglycaemia is not treated, it can cause brain damage (temporary or permanent) and even death
► If you have a hypo that makes you pass out, or a lot of hypos, talk to your doctor. The amount or timing of insulin, food or exercise may need to be adjusted.

If you forget to take your insulin

If you forget to take your insulin your blood sugar may get too high (this is called hyperglycaemia). This may also happen:

- If you repeatedly take less insulin than you need
- If you get an infection or a fever
- If you eat more than usual
- If you exercise less than usual.

The warning signs appear gradually. They include: increased urination; feeling thirsty; losing your appetite; feeling sick (nausea or vomiting); feeling drowsy or tired; flushed, dry skin; dry mouth and a fruity (acetone) smell of the breath.
If you get any of these signs: test your blood sugar level, test your urine for ketones if you can, then seek medical advice immediately.
These may be signs of a very serious condition called diabetic ketoacidosis. If you do not treat it, this could lead to diabetic coma and eventually death.

If you stop taking your insulin

This could lead to severe hyperglycaemia (very high blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). Do not stop taking your insulin without speaking to a doctor, who will tell you what needs to be done.
If you have any further questions on the use of this product, ask your doctor or pharmacist.

How to handle Levemir FlexPen.

Levemir FlexPen is a pre-filled disposable pen containing insulin detemir.

Read carefully the Levemir FlexPen instructions for use included in this package leaflet. You must use the pen as described in the Instructions for Use

4. POSSIBLE SIDE EFFECTS

Like all medicines, Levemir can cause side effects, although not everybody gets them.

Side effects may occur with certain frequencies, which are defined as follows:

- Very common: affects more than 1 user in 10
- Common: affects 1 to 10 users in 100
- Uncommon: affects 1 to 10 users in 1,000
- Rare: affects 1 to 10 users in 10,000
- Very rare: affects less than 1 user in 10,000
- Not known: frequency cannot be estimated from the available data.

Uncommon side effects

Signs of allergy. Hives and rash may occur.
Seek medical advice immediately:
- ► If the above signs of allergy appear, or
- ► If you suddenly feel unwell, and you: start sweating; start being sick (vomiting); have difficulty in breathing; have a rapid heart beat; feel dizzy.

Vision problems**.** When you first start your insulin treatment, it may disturb your vision, but the disturbance is usually temporary.

Changes at the injection site (lipodystrophy). If you inject yourself too often at the same site, fatty tissue under the skin at this site may shrink (lipoatrophy) or thicken (lipohypertrophy). Changing the site with each injection may help to prevent such skin changes. If you notice your skin pitting or thickening at the injection site, tell your doctor or nurse because these reactions can become more severe, or they may change the absorption of your insulin if you inject in such a site.

Swollen joints. When you start taking insulin, water retention may cause swelling around your ankles and other joints. Normally this soon disappears.

Common side effects

Low blood sugar (hypoglycaemia).

Injection site reactions (pain, redness, hives, inflammation, bruising, swelling and itching). These usually disappear after a few weeks of taking your insulin. If they do not disappear see your doctor. If you have serious or continuing reactions, you may need to stop using Levemir and use another insulin.

Rare side effects

Disturbed sensation. Fast improvement in blood glucose control may cause disturbed sensation (numbness, weakness or pain) in legs or arms. These symptoms normally disappear.

Very rare side effects

Serious allergic reaction to Levemir or one of its ingredients (called a generalised allergic reaction). See also the warning in *2 Before using Levemir.*

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor, nurse or pharmacist.

5. HOW TO STORE LEVEMIR

Keep out of the reach and sight of children.
Do not use Levemir after the expiry date which is stated on the FlexPen label and carton, after EXP. The expiry date refers to the last day of that month.
Levemir FlexPen that is not being used is to be stored in the refrigerator at 2°C - 8°C, away from the cooling element. Do not freeze.
Levemir FlexPen that is being used or carried as a spare is not to be kept in the refrigerator. You can carry it with you and keep it at room temperature (below 30°C) for up to 6 weeks.
Always keep the cap on your FlexPen when you are not using it in order to protect it from light.
Levemir must be protected from excessive heat and light.

Medicines should not be disposed of via waste water or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Levemir contains

- The active substance is insulin detemir. Each ml contains 100 U of insulin detemir. Each pre-filled pen contains 300 U of insulin detemir in 3 ml solution for injection. 1 unit (U) insulin detemir corresponds to 1 international unit (IU) of human insulin
- The other ingredients are: glycerol, phenol, metacresol, zinc acetate, disodium phosphate dihydrate, sodium chloride, hydrochloric acid, sodium hydroxide and water for injections.

What Levemir looks like and contents of the pack

Levemir comes as a clear, colourless, aqueous solution.
Pack sizes of 1 (with or without needles), 5 (without needles) and 10 (without needles) pre-filled pens of 3 ml. Not all packs may be marketed.

Marketing authorisation holder

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd, Denmark

Manufacturer

The manufacturer can be identified by the batch number printed on the slip of the carton and on the label:

- If the second and third characters are W5, S6, P5, K7, or ZF Novo Nordisk A/S, Novo Allé, DK-2880 Bagsværd, Denmark is the manufacturer

- If the second and third characters are H7 or T6 Novo Nordisk Production SAS, 45 Avenue d'Orléans F-28002 Chartres, France is the manufacturer.

Now turn over for information on how to use your FlexPen.

This leaflet was last approved in

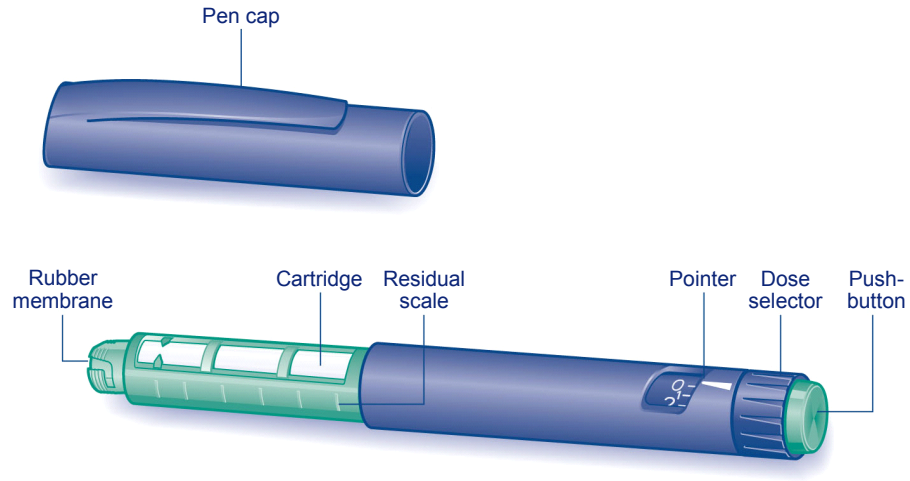
LEVEMIR solution for injection in a pre-filled pen. FlexPen. INSTRUCTIONS FOR USE

Please read the following instructions carefully before using your Levemir FlexPen.

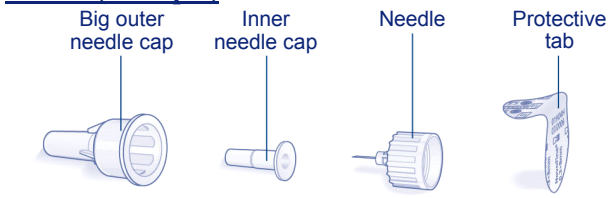
Your FlexPen is a unique dial-a-dose insulin pen. You can select doses from 1 to 60 units in increments of 1 unit. FlexPen is designed to be used with NovoFine or NovoTwist disposable needles up to a length of 8 mm. As a precautionary measure, always carry a spare insulin delivery device in case your FlexPen is lost or damaged.

The colour of the pen in the illustrations differs from your FlexPen.

Your Levemir FlexPen



Needle (example)



Maintenance

Your FlexPen is designed to work accurately and safely. It must be handled with care.
If it is dropped or crushed, there is a risk of damage and leakage of insulin.

You can clean the exterior of your FlexPen by wiping it with a medicinal swab. Do not soak it, wash or lubricate it as it may damage the pen.

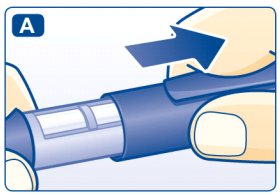
Do not refill your FlexPen.

Preparing your Levemir FlexPen

Check the label to make sure that your FlexPen contains the correct type of insulin.

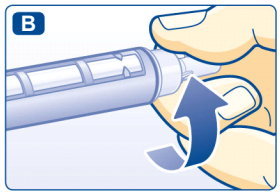
A
Pull off the cap.

Disinfect the rubber membrane with a medicinal swab.

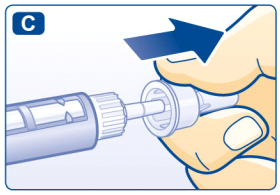


B
Remove the protective tab from a new disposable needle.

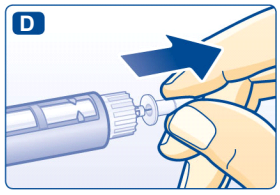
Screw the needle straight and tightly onto your FlexPen.



C
Pull off the big outer needle cap and keep it for later.



D
Pull off the inner needle cap and dispose of it.

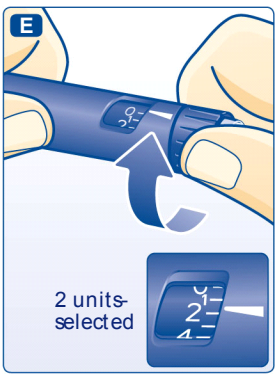


- Always use a new needle for each injection to prevent contamination.
- Be careful not to bend or damage the needle before use.
- To reduce the risk of unexpected needle sticks, never put the inner needle cap back on when you have removed it from the needle.

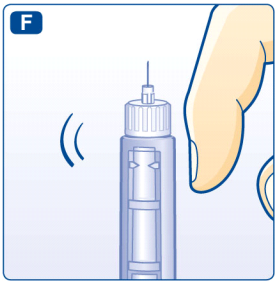
Checking the insulin flow

Prior to each injection small amounts of air may collect in the cartridge during normal use. To avoid injection of air and ensure proper dosing:

E
Turn the dose selector to select 2 units.



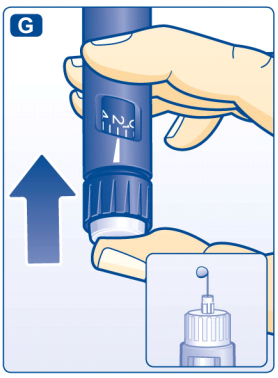
F
Hold your FlexPen with the needle pointing upwards and tap the cartridge gently with your finger a few times to make any air bubbles collect at the top of the cartridge.



G
Keeping the needle upwards, press the push-button all the way in. The dose selector returns to 0.

A drop of insulin should appear at the needle tip. If not, change the needle and repeat the procedure no more than six times.

If a drop of insulin still does not appear, the pen is defective, and you must use a new one.



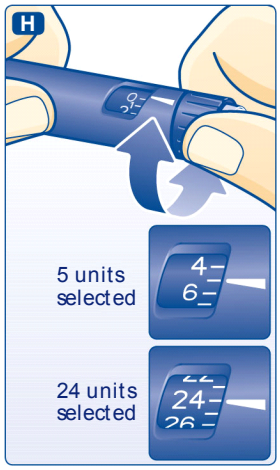
Selecting your dose

Check that the dose selector is set at 0.

H
Turn the dose selector to select the number of units you need to inject.

The dose can be corrected either up or down by turning the dose selector in either direction until the correct dose lines up with the pointer. When turning the dose selector be careful not to push the push-button as insulin will come out.

You cannot select a dose larger than the number of units left in the cartridge.



- Do not use the residual scale to measure your dose of insulin.

Making the injection

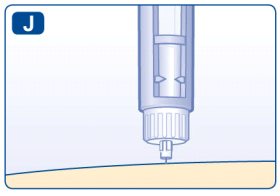
Insert the needle into your skin. Use the injection technique shown by your doctor or nurse.

I
Inject the dose by pressing the push-button all the way in until 0 lines up with the pointer. Be careful only to push the push-button when injecting.

Turning the dose selector will not inject insulin.

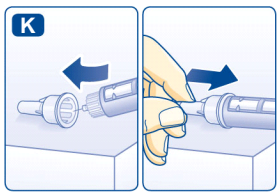
J
Keep the push-button fully depressed after the injection until the needle has been withdrawn from the skin.

The needle must remain under the skin for at least six seconds. This will ensure that the full dose has been injected.



K
Lead the needle into the big outer needle cap without touching the big outer needle cap. When the needle is covered, carefully push the big outer needle cap completely on and then unscrew the needle.

Dispose of it carefully and put the cap back on.



- Always remove the needle after each injection and store your FlexPen without the needle attached. Otherwise, the liquid may leak out which can cause inaccurate dosing.
- Caregivers should be most careful when handling used needles to avoid needle sticks.
- Dispose of the used FlexPen carefully without the needle attached.
- Do not share your FlexPen with anyone else.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Levemir 100 U/ml solution for injection in pre-filled pen
Insulin detemir

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again
- If you have any further questions, ask your doctor, nurse or pharmacist
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor, nurse or pharmacist.

In this leaflet:

1. What Levemir is and what it is used for
2. Before you use Levemir
3. How to use Levemir
4. Possible side effects
5. How to store Levemir
6. Further information

1. WHAT LEVEMIR IS AND WHAT IT IS USED FOR

Levemir is a modern insulin (insulin analogue) with a long-acting effect (up to 24 hours). Modern insulins are improved versions of human insulin.

Levemir is used to treat diabetes mellitus in adults, children and adolescents aged 6-17 years. It may be used in combination with oral antidiabetic medicines or with meal-related rapid acting insulin products.

2. BEFORE YOU USE LEVEMIR

Do not use Levemir

- ► If you are allergic (hypersensitive) to insulin detemir or any of the other ingredients of Levemir (see *6 Further informations*)
- ► If you suspect hypoglycaemia (low blood sugar) is starting (see *4 Possible side effects*)
- ► In insulin infusion pumps
- ► If InnoLet is dropped, damaged or crushed
- ► If it hasn't been stored correctly or if it has been frozen (see *5 How to store Levemir*)
- ► If the insulin does not appear water clear and colourless.

Before using Levemir

- ► Check the label to make sure it is the right type of insulin
- ► Always use a new needle for each injection to prevent contamination.

Take special care with Levemir

- ► If you have trouble with your kidneys or liver, or with your adrenal, pituitary or thyroid glands
- ► If you are exercising more than usual or if you want to change your usual diet, as this may affect your blood sugar level
- ► If you are ill: carry on taking your insulin and consult your doctor

► If you are going abroad: travelling over time zones may affect your insulin needs and the timing of the injections. Consult your doctor if you are planning such travelling.

There is no experience with the use of Levemir in children below the age of 6 years. Therefore, only use Levemir in children below this age, if your doctor have specifically told you to.

As with all insulin products, in elderly patients and patients with renal or heparic impairment, glucose monitoring should be intensified and insulin detemir dosage adjusted on a individual basis.

Using other medicines

Some medicines affect the way glucose works in your body and this may influence your insulin dose. Listed below are the most common medicines, which may affect your insulin treatment. Tell your doctor, nurse or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. In particular, you should tell your doctor if you are using any medicine as mentioned below that affects your blood sugar level.

If you take any of the below medicine your blood sugar level may fall (hypoglycaemia):
- Other medicines for the treatment of diabetes
- Monoamine oxidase inhibitors (MAOI) (used to treat depression)
- Beta-blockers (used to treat high blood pressure)
- Angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure)
- Salicylates (used to relieve pain and lower fever)
- Anabolic steroids (such as testosterone)
- Sulphonamides (used to treat infections).

If you take any of the below medicine your blood sugar level may rise (hyperglycaemia):
- Oral contraceptives (birth control pills)
- Thiazides (used to treat high blood pressure or excessive fluid retention)
- Glucocorticoids (such as "cortisone" used to treat inflammation)
- Thyroid hormones (use to treat thyroid gland disorders)
- Sympathomimetics (such as epinephrine [adrenaline], or salbutamol, terbutaline used to treat asthma)
- Growth hormone (medicine for stimulation of skeletal and somatic growth and pronounced influence on the body’s metabolic processes)
- Danazol (medicine acting on ovulation).

Octreotide and lanreotide (used for treatment of acromegaly) may both increase or decrease your sugar level.

Beta-blockers (used to treat high blood pressure) may weaken or suppress entirely the first warning symptoms which help you to recognise a hypoglycaemia.

Taking Levemir with food and drink

► If you are drinking alcohol your need for insulin may change, as your blood sugar level may either rise or fall. Carefull monitoring is recommended.

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.
► If you are pregnant, planning a pregnancy or breast-feeding please contact your doctor for advice. Your insulin dosage may need to be changed during pregnancy particularly after delivery. Careful control of your diabetes, and prevention of hypoglycaemia, is important, for the health of your baby.

Driving and using machines

If your blood sugar is low or high your concentration and ability to react might be affected and therefore also your ability to drive or operate a machine. Bear in mind that you could endanger yourself or others. Please ask your doctor whether you can drive a car:
► If you have frequent hypoglycaemias
► If you find it hard to recognise hypoglycaemia.

3. HOW TO USE LEVEMIR

Dosage

Talk about your insulin dose with your doctor and nurse. Do not change your insulin unless your doctor tells you to. Make sure you get the Levemir InnoLet that your doctor and nurse have told you to use and follow their advice carefully**.** This leaflet is a general guide.
If your doctor has switched you from one type or brand of insulin to another, your dose may have to be adjusted by your doctor.

Frequency of administration

When Levemir is used in combination with an oral antidiabetic medicine, Levemir should be administered once a day. When Levemir is used as part of a basal-bolus insulin regimen Levemir should be administered once or twice daily depending on patients' needs. Dosage of Levemir should be adjusted individually. For patients who require twice daily dosing to optimise blood glucose control, the evening dose can be administered in the evening or at bedtime.

Method of administration

Levemir is for injection under the skin (subcutaneously). Never inject your insulin directly into a vein (intravenously) or muscle (intramuscular). Always vary the sites you inject within the same region, to avoid lumps (see *4 Possible side effects*). The best places to give yourself an injection are: the front of your thighs, the front of your waist (abdomen), or the upper arm. You should always measure your blood glucose regularly.

How to handle Levemir InnoLet

Levemir InnoLet is a pre-filled disposable pen containing insulin detemir.

Read carefully the Levemir InnoLet instructions for use included in this package leaflet. You must use the pen as described in the Instructions for Use

If you take more insulin than you should

If you take too much insulin your blood sugar gets too low (this is called hypoglycaemia or hypo). This may also happen:
- If you eat too little or miss a meal
- If you exercise more than usual.

The warning signs of a hypo may come on suddenly and can include: cold sweat; cool pale skin; headache; rapid heart beat; feeling sick; feeling very hungry; temporary changes in vision; drowsiness; unusual tiredness and weakness; nervousness or tremor; feeling anxious; feeling confused; difficulty in concentrating.

If you feel a hypo coming on: take a high sugar snack and then measure your blood sugar.
If your blood sugar is too low: eat glucose tablets or another high sugar snack (sweets, biscuits, fruit juice), then rest.

Always carry glucose tablets, sweets, biscuits or fruit juice with you, just in case.

When symptoms of hypoglycaemia have disappeared or when blood glucose level is stabilised continue insulin treatment.
Tell relevant people you have diabetes and what may be the consequences, including the risk of passing out due to a hypo.
Tell relevant people that if you pass out (become unconscious), they must turn you on your side and get medical help straight away. They must not give you any food or drink. It could choke you.

You may recover more quickly from unconsciousness with an injection of the hormone glucagon by someone who knows how to use it. If you are given glucagon you will need glucose or a sugary snack as soon as you are conscious. If you do not respond to glucagon treatment, you will have to be treated in a hospital. Contact your doctor or an emergency ward after an injection of glucagon: you need to find the reason for your hypo to avoid getting more.

► If prolonged severe hypoglycaemia is not treated, it can cause brain damage (temporary or permanent) and even death
► If you have a hypo that makes you pass out, or a lot of hypos, talk to your doctor. The amount or timing of insulin, food or exercise may need to be adjusted.

If you forget to take your insulin

If you forget to take your insulin **y**our blood sugar may get too high (this is called hyperglycaemia). This may also happen:

- If you repeatedly take less insulin than you need
- If you get an infection or a fever
- If you eat more than usual
- If you exercise less than usual.

The warning signs appear gradually. They include: increased urination; feeling thirsty; losing your appetite; feeling sick (nausea or vomiting); feeling drowsy or tired; flushed, dry skin; dry mouth and a fruity (acetone) smell of the breath.
If you get any of these signs: test your blood sugar level, test your urine for ketones if you can, then seek medical advice immediately.
These may be signs of a very serious condition called diabetic ketoacidosis. If you do not treat it, this could lead to diabetic coma and eventually death.

If you stop taking your insulin

This could lead to severe hyperglycaemia (very high blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). Do not stop taking your insulin without speaking to a doctor, who will tell you what needs to be done.
If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Levemir can cause side effects, although not everybody gets them.

Side effects may occur with certain frequencies, which are defined as follows:

- Very common: affects more than 1 user in 10
- Common: affects 1 to 10 users in 100
- Uncommon: affects 1 to 10 users in 1,000
- Rare: affects 1 to 10 users in 10,000
- Very rare: affects less than 1 user in 10,000
- Not known: frequency cannot be estimated from the available data.

Uncommon side effects

Signs of allergy. Hives and rash may occur.
Seek medical advice immediately:
- ► If the above signs of allergy appear, or
- ► If you suddenly feel unwell, and you: start sweating; start being sick (vomiting); have difficulty in breathing; have a rapid heart beat; feel dizzy.

Vision problems. When you first start your insulin treatment, it may disturb your vision, but the disturbance is usually temporary.

Changes at the injection site (lipodystrophy). If you inject yourself too often at the same site, fatty tissue under the skin at this site may shrink (lipoatrophy) or thicken (lipohypertrophy). Changing the site with each injection may help to prevent such skin changes. If you notice your skin pitting or thickening at the injection site, tell your doctor or nurse because these reactions can become more severe, or they may change the absorption of your insulin if you inject in such a site.

Swollen joints. When you start taking insulin, water retention may cause swelling around your ankles and other joints. Normally this soon disappears.

Common side effects

Low blood sugar (hypoglycaemia).

Injection site reactions (pain, redness, hives, inflammation, bruising, swelling and itching). These usually disappear after a few weeks of taking your insulin. If they do not disappear see your doctor. If you have serious or continuing reactions, you may need to stop using Levemir and use another insulin.

Rare side effects

Disturbed sensation. Fast improvement in blood glucose control may cause disturbed sensation (numbness, weakness or pain) in legs or arms. These symptoms normally disappear.

Very rare side effects

Serious allergic reaction to Levemir or one of its ingredients (called a generalised allergic reaction). See also the warning in *2 Before using Levemir.*

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor, nurse or pharmacist.

5. HOW TO STORE LEVEMIR

Keep out of the reach and sight of children.
Do not use Levemir after the expiry date which is stated on the InnoLet label and carton, after EXP. The expiry date refers to the last day of that month.
Levemir InnoLet that is not being used is to be stored in the refrigerator at 2°C - 8°C, away from the cooling element. Do not freeze.
Levemir InnoLet that is being used or carried as a spare is not to be kept in the refrigerator. You can carry it with you and keep it at room temperature (below 30°C) for up to 6 weeks.
Always keep the cap on your InnoLet when you are not using it in order to protect it from light.
Levemir must be protected from excessive heat and light.

Medicines should not be disposed of via waste water or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

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- The other ingredients are: glycerol, phenol, metacresol, zinc acetate, disodium phosphate dihydrate, sodium chloride, hydrochloric acid, sodium hydroxide and water for injections.

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Levemir comes as a clear, colourless, aqueous solution.
Pack sizes of 1, 5 and 10 pre-filled pens of 3 ml. Not all packs may be marketed.

Marketing authorisation holder and manufacturer:

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd, Denmark

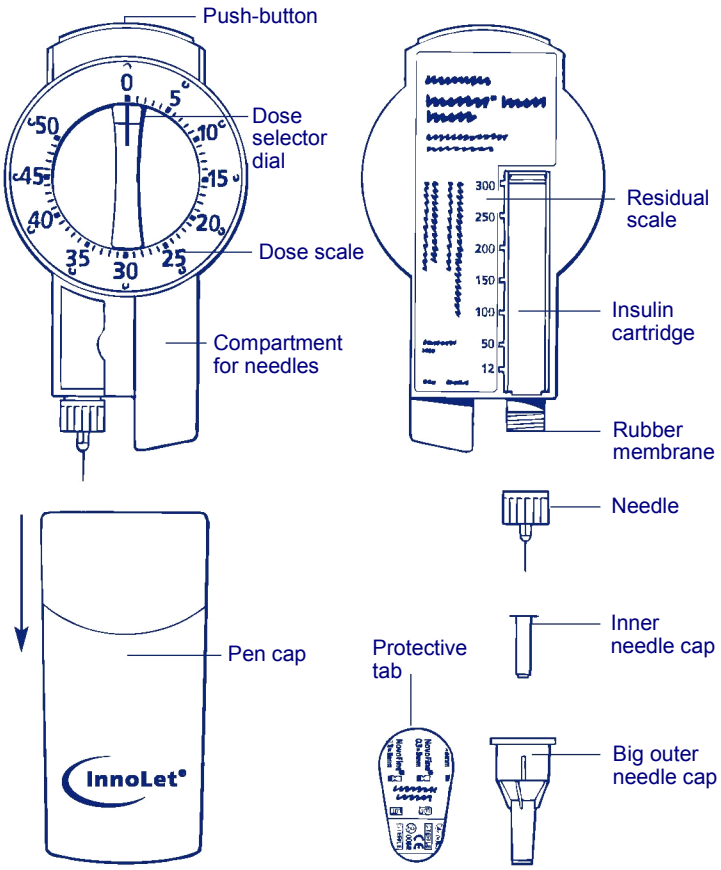
Now turn over for information on how to use your InnoLet.

This leaflet was last approved in

LEVEMIR solution for injection in a pre-filled pen. InnoLet. INSTRUCTIONS FOR USE

Please read the following instructions carefully before using your Levemir InnoLet.

Levemir InnoLet is a simple, compact pre-filled pen able to deliver 1 to 50 units in increments of 1 unit. Levemir InnoLet is designed to be used with NovoFine needles of 8 mm or shorter in length. As a precautionary measure, always carry a spare insulin delivery device in case your InnoLet is lost or damaged.

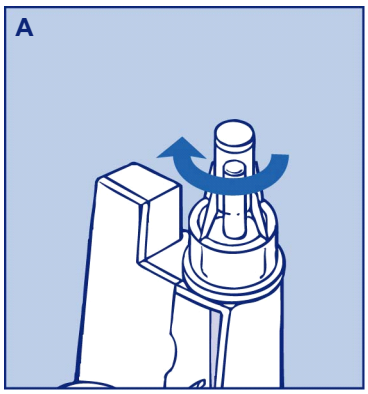


Preparing for injection

Check the label to be sure that your Levemir InnoLet contains the correct type of insulin. Take off the cap (as shown by the arrow).

Attaching the needle

- Disinfect the rubber membrane with a medicinal swab
- Always use a new needle for each injection to prevent contamination
- Remove the protective tab from a NovoFine needle
- Screw the needle straight and tightly onto Levemir InnoLet (picture **A**).
- Always use a new NovoFine disposable needle for each injection. Do not bend or damage the needle before use
- Pull off the big outer needle cap and the inner needle cap. You may want to store the big outer needle cap in the compartment.

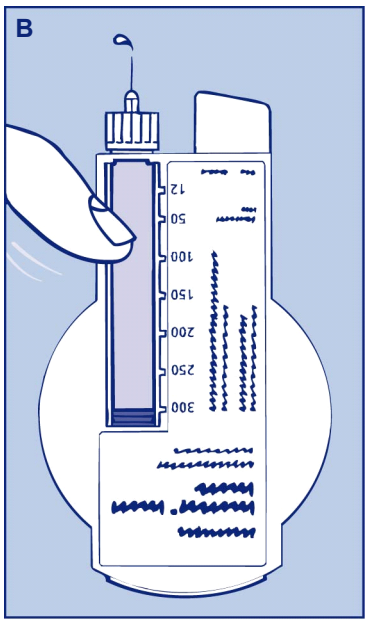


Priming to expel air prior to each injection

Small amounts of air may collect in the needle and cartridge during normal use.
To avoid injection of air and ensure proper dosing:

- Dial 2 units by turning the dose selector clockwise
- Hold Levemir InnoLet with the needle upwards and tap the cartridge gently with your finger a few times (picture **B**) to make any air bubbles collect at the top of the cartridge
- Keeping the needle upwards, press the push-button and the dose selector returns to zero
- A drop of insulin should appear at the needle tip. If not, change the needle and repeat the procedure no more than 6 times.

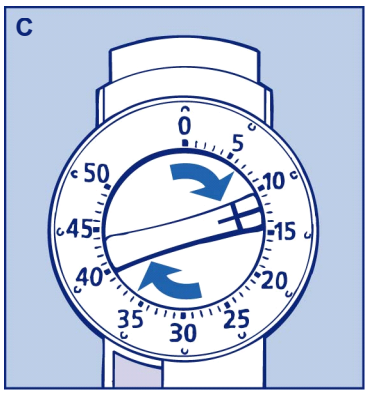
If a drop of insulin still does not appear, the device is defective and must not be used.



Setting the dose

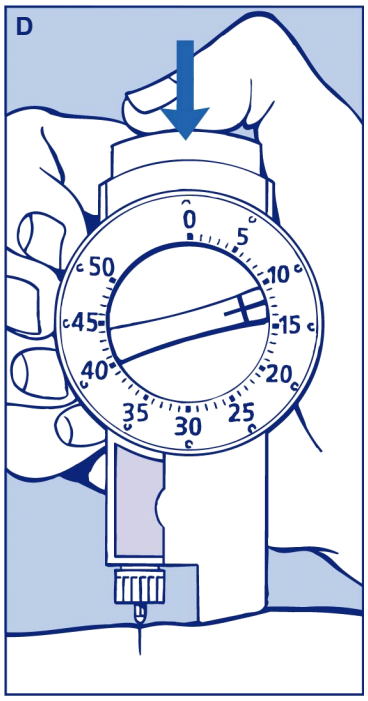
- Always check that the push-button is fully depressed and the dose selector is set to zero
- Dial the number of units required by turning the dose selector clockwise (picture **C**). Do not use the residual scale to measure your dose of insulin
- You will hear a click for every single unit dialled. The dose can be corrected by turning the dial either way.

You cannot set a dose larger than the number of units remaining in the cartridge.



Injecting the insulin

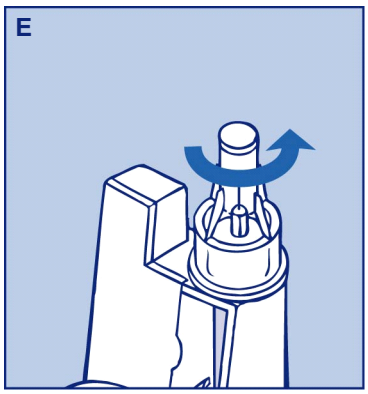
- Insert the needle into your skin. Use the injection technique advised by your doctor
- Deliver the dose by pressing the push-button fully down (picture **D**). You will hear clicks as the dose selector returns to zero
- After the injection, the needle should remain under the skin for at least 6 seconds to ensure that the full dose has been delivered
- Make sure not to block the dose selector while injecting, as the dose selector must be allowed to return to zero when you press the push-button
- Discard the needle after each injection.



Removing the needle

- Replace the big outer needle cap and unscrew the needle (picture **E**). Dispose of it carefully.

Use a new needle for each injection.
Be sure to remove and discard the needle after each injection and store Levemir InnoLet without the needle attached. Otherwise, the liquid may leak out which can cause inaccurate dosing.
Health care professionals, relatives and other carers should follow general precautionary measures for removal and disposal of needles to eliminate the risk of unintended needle penetration.
Dispose of your used Levemir InnoLet carefully without the needle attached.



Maintenance

Your Levemir InnoLet is designed to work accurately and safely. It should be handled with care. If it is dropped, damaged or crushed, there is a risk of leakage of insulin.
As a precautionary measure, always carry a spare insulin delivery device in case your InnoLet is lost or damaged.
Do not refill Levemir InnoLet.
You can clean your Levemir InnoLet by wiping it with a medicinal swab. Do not soak it in surgical spirit or wash or lubricate it. This may damage the mechanism.