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, adolescents and children aged 2 years and above.

4.2 Posology and method of administration

Posology

The potency of insulin analogues, including insulin detemir, is expressed in units (U), whereas the potency of human insulin is expressed in international units (IU). 1 unit (U) insulin detemir corresponds to 1 international unit (IU) of human insulin.

Levemir can be used alone as the basal insulin or in combination with bolus insulin. It can also be used in combination with oral antidiabetic medicinal products or as add-on therapy to liraglutide treatment.

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

Based on study results, the following titration guideline is recommended for adult diabetes patients:

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. Dose of Levemir should be adjusted individually.

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

Special populations

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

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

Paediatric population

The efficacy and safety of Levemir were demonstrated in adolescents and children aged 2 years and above in studies up to 12 months (see section 5.1).

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

Levemir has not been studied in children below the age of 2 years.

Transfer from other insulin medicinal products

When transferring from other intermediate or long-acting insulin medicinal products adjustment of the dose and timing of administration may be necessary (see section 4.4).

As with all insulin medicinal products, close glucose monitoring is recommended during the transfer and in the initial weeks thereafter (see section 4.4).

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

Method of administration

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

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

Levemir Penfill is designed to be used with Novo Nordisk insulin delivery systems and NovoFine or NovoTwist needles. The patient should be advised not to use any counterfeit needles.

Levemir Penfill is accompanied by a package leaflet with detailed instructions for use to be followed.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients (see section 6.1).

4.4 Special warnings and precautions for use

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

Hyperglycaemia

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

Hypoglycaemia

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

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

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

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

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

Transfer from other insulin medicinal 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 dose. Patients transferred to Levemir from another type of insulin may require a change in dose from that used with their usual insulin medicinal products. If an adjustment is needed, it may occur with the first dose or during the first few weeks or months.

Injection site reactions

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

Hypoalbuminaemia

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

Combination of Levemir with pioglitazone

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

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

Beta-blockers may mask the symptoms of hypoglycaemia.

Octreotide/lanreotide may either increase or decrease the insulin requirement.

Alcohol may intensify or reduce the hypoglycaemic effect of insulin.

4.6 Fertility, pregnancy and lactation

Pregnancy

Treatment with Levemir can be considered during pregnancy, but any potential benefit must be weighed against a possibly increased risk of an adverse pregnancy outcome.

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.

In an open-label randomised controlled clinical trial pregnant women with type 1 diabetes (n=310) were treated in a basal-bolus treatment regimen with Levemir (n=152) or NPH insulin (n=158) as basal insulin, both in combination with NovoRapid. Primary objective of this study was to assess the effect of Levemir on blood glucose regulation in pregnant women with diabetes (see section 5.1).

The overall rates of maternal adverse events were similar for Levemir and NPH insulin treatment groups; however, a numerically higher frequency of serious adverse events in the mothers (61 (40%) vs. 49 (31%)) and in the newborn children (36 (24%) vs. 32 (20%)) was seen for Levemir compared to NPH insulin. The number of live born children of women becoming pregnant after randomisation were 50 (83%) for Levemir and 55 (89%) for NPH. The frequency of congenital malformations was 4 (5%) for Levemir and 11 (7%) for NPH with 3 (4%) major malformations for Levemir and 3 (2%) for NPH.

Post-marketing data from an additional 250 outcomes from pregnant women exposed to Levemir indicate no adverse effects of insulin detemir on pregnancy and no malformative or feto/neonatal toxicity of insulin detemir.

Animal data do not indicate reproductive toxicity (see section 5.3).

Breast-feeding

It is unknown whether insulin detemir is excreted in human milk. No metabolic effects of ingested insulin detemir on the breast-fed newborn/infant are anticipated since insulin detemir, as a peptide, is digested into amino acids in the human gastrointestinal tract.

Breast-feeding women may require adjustments in insulin dose and diet.

Fertility

Animal studies do not indicate harmful effects with respect to fertility.

4.7 Effects on ability to drive and use machines

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

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

4.8 Undesirable effects

a. Summary of the safety profile

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

The most frequently reported adverse reaction during treatment is hypoglycaemia, please see section c below.
From clinical investigations, it is known that major hypoglycaemia, defined as requirement for third party intervention, occurs in approximately 6% of the patients treated with Levemir.

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

b. Tabulated list of adverse reactions

Adverse reactions listed below are based on clinical trial data and classified according to MedDRA 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).

Immune system disorders	Uncommon – Allergic reactions, potentially allergic reactions, urticaria, rash, eruptions*
	Very rare – Anaphylactic reactions*
Metabolism and nutrition disorders	Very common – Hypoglycaemia*
Nervous system disorders	Rare – Peripheral neuropathy
Eye disorders	Uncommon – Refraction disorders
	Uncommon – Diabetic retinopathy
Skin and subcutaneous tissue disorders	Uncommon – Lipodystrophy*
General disorders and administration site conditions	Common – Injection site reactions
	Uncommon – Oedema

* see section c

c. Description of selected adverse reactions

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

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

Hypoglycaemia
The most frequently reported adverse reaction is hypoglycaemia. It may occur if the insulin dose is too high in relation to the insulin requirement. Severe hypoglycaemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death. The symptoms of hypoglycaemia usually occur suddenly. They may include cold 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.

Lipodystrophy
Lipodystrophy (including lipohypertrophy, lipoatrophy) may occur at the injection site. Continuous rotation of the injection site within the particular injection area may help to reduce the risk of developing these reactions.

d. Paediatric population

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

e. Other special populations

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

4.9 Overdose

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

- Mild hypoglycaemic episodes can be treated by oral administration of glucose or sugary products. It is therefore recommended that the diabetic patient always carries sugar-containing products.
- Severe hypoglycaemic episodes, where the patient has become unconscious, can be treated with glucagon (0.5 to 1 mg) given intramuscularly or subcutaneously, by a trained person, or with glucose given intravenously by a healthcare professional. Glucose must 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: Drugs used in diabetes. Insulins and analogues for injection, long-acting: ATC code: A10AE05.

Mechanism of action

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

The blood glucose lowering effect of Levemir 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 Levemir 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 Levemir and NPH insulin

Pharmacodynamic Endpoint	Levemir 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 Levemir

The prolonged action of Levemir 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.

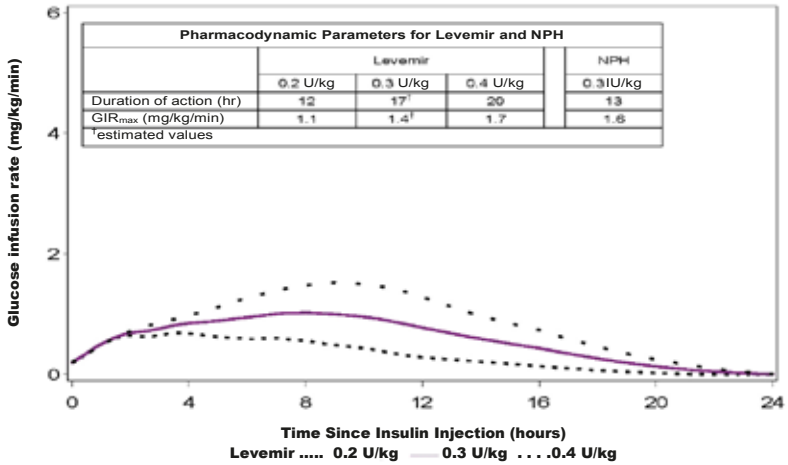

Figure 1. Activity profiles of Levemir in patients with type 1 diabetes.

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 medicinal products demonstrated that glycaemic control (HbA_{1c}) with Levemir is comparable to NPH insulin and insulin glargine and associated with less weight gain, see Table 2 below. In the study versus insulin glargine, Levemir was allowed to be administered once or twice daily whereas insulin glargine was to be administered once a day, 55% of the Levemir treated subjects completed the 52 weeks of treatment on the twice daily regimen.

Table 2. Change in body weight after insulin treatment

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

In trials investigating the use of oral antidiabetic medicinal products, combination therapy with Levemir resulted in a 61-65% lower risk of minor nocturnal hypoglycaemia compared to NPH insulin.

An open-label randomised clinical trial in patients with type 2 diabetes not reaching target with oral anti-diabetic medicinal products was conducted. The trial started with a 12 week run-in period with liraglutide+metformin, where 61% reached an HbA_{1c} <7%. The 39% of patients not achieving target were randomised to have Levemir once-daily added or continue on liraglutide+metformin for 52 weeks. Addition of Levemir provided a further reduction of HbA_{1c} from 7.6% to 7.1% after 52 weeks. There were no major hypoglycaemic episodes. A major hypoglycaemic episode is defined as an episode where the subject was not able to treat him/herself and if glucagon or i.v. glucose was needed. See table 3.

Table 3. Clinical trial data - Levemir add-on to liraglutide+metformin

	Study week	Randomised Levemir + liraglutide + metformin N = 160	Randomised Liraglutide + metformin N = 149	P-value
Mean change in HbA_{1c} from baseline (%)	0-26 weeks	-0.51	+0.02	<0.0001
	0-52 weeks	-0.50	0.01	<0.0001
Proportions of patients achieving HbA_{1c} <7% targets (%)	0-26 weeks	43.1	16.8	<0.0001
	0-52 weeks	51.9	21.5	<0.0001
Change in body weight from baseline (kg)	0-26 weeks	-0.16	-0.95	0.0283
	0-52 weeks	-0.05	-1.02	0.0416
Minor hypoglycaemic episodes (per patient year)	0-26 weeks	0.224	0.019	0.0075
	0-52 weeks	0.228	0.034	0.0011

In long-term trials in patients with type 1 diabetes receiving a basal-bolus insulin therapy, fasting plasma glucose was improved with Levemir compared with NPH insulin. Glycaemic control (HbA_{1c}) with Levemir was 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.

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

Pregnancy

Levemir was studied in an open-label randomised controlled clinical trial pregnant women with type 1 diabetes (n=310) were treated in a basal-bolus treatment regimen with Levemir (n=152) or NPH insulin (n=158) as basal insulin, both in combination with NovoRapid (see section 4.6).
Levemir was non-inferior to NPH insulin as measured by HbA_{1c} at gestational week (GW) 36, and the reduction in mean HbA_{1c} through pregnancy was similar, see table 4.

Table 4. Maternal glycaemic control

	Levemir	NPH	Difference/ Odds Ratio/ Rate Ratio 95% CI
Mean HbA_{1c} (%) at GW 36	6.27	6.33	Difference: -0.06 [-0.21; 0.08]
Mean FPG at GW 36 (mmol/l)	4.76	5.41	Difference: -0.65 [-1.19; -0.12]
Proportions of patients achieving HbA_{1c} ≤6% targets at both GW 24 and GW 36 (%)	41%	32%	Odds Ratio: 1.36 [0.78; 2.37]
Overall number of major hypoglycemia episodes during pregnancy (per patient year)	1.1	1.2	Rate Ratio: 0.82 [0.39; 1.75]

Paediatric population

The efficacy and safety of Levemir has been studied for up to 12 months, in two randomised controlled clinical trials in adolescents and children (n=694 in total); one of the studies included in total 82 children aged 2-5 years. Both trials demonstrated that glycaemic control (HbA_{1c}) with Levemir is comparable to NPH insulin when given as basal-bolus therapy, using a non-inferiority margin of 0.4%. In addition less weight gain (SD score, weight corrected for gender and age) was observed with Levemir than with NPH insulin.

The trial including children above 2 years was extended for an additional 12 months (total of 24 months treatment data) to assess antibody formation after long-term treatment with Levemir. After an increase in insulin antibodies during the first year, the insulin antibodies decreased during the second year to a level slightly higher than pre-trial level. Results indicate that antibody development had no negative effect on glycaemic control and Levemir dose.

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

Biotransformation

Degradation of insulin detemir is similar to that of human insulin; all metabolites formed are inactive.

Elimination

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

Linearity

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

No pharmacokinetic or pharmacodynamic interactions were observed between liraglutide and Levemir when administering a single dose of Levemir 0.5 U/kg with liraglutide 1.8 mg at steady state in patients with type 2 diabetes.

Special populations

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

Renal and hepatic impairment

There was no clinically relevant difference in pharmacokinetics of Levemir between subjects with renal or hepatic impairment and healthy subjects. As the pharmacokinetics of Levemir 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 Levemir.

Paediatric population

The pharmacokinetic properties of Levemir 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.

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 and development. 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 in 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

Needles and Levemir Penfill must not be shared. The cartridge must not be refilled.

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

Levemir which has been frozen must not be used.

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

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

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

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, adolescents and children aged 2 years and above.

4.2 Posology and method of administration

Posology

The potency of insulin analogues, including insulin detemir, is expressed in units (U), whereas the potency of human insulin is expressed in international units (IU). 1 unit (U) insulin detemir corresponds to 1 international unit (IU) of human insulin.

Levemir can be used alone as the basal insulin or in combination with bolus insulin. It can also be used in combination with oral antidiabetic medicinal products or as add-on therapy to liraglutide treatment.

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

Based on study results, the following titration guideline is recommended for adult diabetes patients:

Average pre-breakfast SMPG*	Levemir dose adjustment
> 10.0 mmol/l (180 mg/dl)	+ 8 U
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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. Dose of Levemir should be adjusted individually.

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

Special populations

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Levemir can be used in elderly patients. As with all insulin medicinal products, in elderly patients, glucose monitoring should be intensified and the Levemir dose adjusted on an individual basis.

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

Paediatric population

The efficacy and safety of Levemir were demonstrated in adolescents and children aged 2 years and above in studies up to 12 months (see section 5.1).

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

Levemir has not been studied in children below the age of 2 years.

Transfer from other insulin medicinal products

When transferring from other intermediate or long-acting insulin medicinal products adjustment of the dose and timing of administration may be necessary (see section 4.4).

As with all insulin medicinal products, close glucose monitoring is recommended during the transfer and in the initial weeks thereafter (see section 4.4).

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

Method of administration

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

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

Levemir FlexPen are pre-filled pens designed to be used with NovoFine or NovoTwist disposable needles up to a length of 8 mm. FlexPen delivers 1-60 units in increments of 1 unit. The patient should be advised not to use any counterfeit needles.

Levemir FlexPen is colour-coded and accompanied by a package leaflet with detailed instructions for use to be followed.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients (see section 6.1).

4.4 Special warnings and precautions for use

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

Hyperglycaemia

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

Hypoglycaemia

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

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

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

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

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

Transfer from other insulin medicinal 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 dose. Patients transferred to Levemir from another type of insulin may require a change in dose from that used with their usual insulin medicinal products. If an adjustment is needed, it may occur with the first dose or during the first few weeks or months.

Injection site reactions

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

Hypoalbuminaemia

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

Combination of Levemir with pioglitazone

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

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

Beta-blockers may mask the symptoms of hypoglycaemia.

Octreotide/lanreotide may either increase or decrease the insulin requirement.

Alcohol may intensify or reduce the hypoglycaemic effect of insulin.

4.6 Fertility, pregnancy and lactation

Pregnancy

Treatment with Levemir can be considered during pregnancy, but any potential benefit must be weighed against a possibly increased risk of an adverse pregnancy outcome.

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.

In an open-label randomised controlled clinical trial pregnant women with type 1 diabetes (n=310) were treated in a basal-bolus treatment regimen with Levemir (n=152) or NPH insulin (n=158) as basal insulin, both in combination with NovoRapid. Primary objective of this study was to assess the effect of Levemir on blood glucose regulation in pregnant women with diabetes (see section 5.1).

The overall rates of maternal adverse events were similar for Levemir and NPH insulin treatment groups; however, a numerically higher frequency of serious adverse events in the mothers (61 (40%) vs. 49 (31%)) and in the newborn children (36 (24%) vs. 32 (20%)) was seen for Levemir compared to NPH insulin. The number of live born children of women becoming pregnant after randomisation were 50 (83%) for Levemir and 55 (89%) for NPH. The frequency of congenital malformations was 4 (5%) for Levemir and 11 (7%) for NPH with 3 (4%) major malformations for Levemir and 3 (2%) for NPH.

Post-marketing data from an additional 250 outcomes from pregnant women exposed to Levemir indicate no adverse effects of insulin detemir on pregnancy and no malformative or feto/neonatal toxicity of insulin detemir.

Animal data do not indicate reproductive toxicity (see section 5.3).

Breast-feeding

It is unknown whether insulin detemir is excreted in human milk. No metabolic effects of ingested insulin detemir on the breast-fed newborn/infant are anticipated since insulin detemir, as a peptide, is digested into amino acids in the human gastrointestinal tract.

Breast-feeding women may require adjustments in insulin dose and diet.

Fertility

Animal studies do not indicate harmful effects with respect to fertility.

4.7 Effects on ability to drive and use machines

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

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

4.8 Undesirable effects

a. Summary of the safety profile

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

The most frequently reported adverse reaction during treatment is hypoglycaemia, please see section c below.
From clinical investigations, it is known that major hypoglycaemia, defined as requirement for third party intervention, occurs in approximately 6% of the patients treated with Levemir.

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

b. Tabulated list of adverse reactions

Adverse reactions listed below are based on clinical trial data and classified according to MedDRA 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).

Immune system disorders	Uncommon – Allergic reactions, potentially allergic reactions, urticaria, rash, eruptions*
	Very rare – Anaphylactic reactions*
Metabolism and nutrition disorders	Very common – Hypoglycaemia*
Nervous system disorders	Rare – Peripheral neuropathy
Eye disorders	Uncommon – Refraction disorders
	Uncommon – Diabetic retinopathy
Skin and subcutaneous tissue disorders	Uncommon – Lipodystrophy*
General disorders and administration site conditions	Common – Injection site reactions
	Uncommon – Oedema

* see section c

c. Description of selected adverse reactions

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

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

Hypoglycaemia
The most frequently reported adverse reaction is hypoglycaemia. It may occur if the insulin dose is too high in relation to the insulin requirement. Severe hypoglycaemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death. The symptoms of hypoglycaemia usually occur suddenly. They may include cold 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.

Lipodystrophy
Lipodystrophy (including lipohypertrophy, lipoatrophy) may occur at the injection site. Continuous rotation of the injection site within the particular injection area may help to reduce the risk of developing these reactions.

d. Paediatric population

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

e. Other special populations

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

4.9 Overdose

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

- Mild hypoglycaemic episodes can be treated by oral administration of glucose or sugary products. It is therefore recommended that the diabetic patient always carries sugar-containing products.
- Severe hypoglycaemic episodes, where the patient has become unconscious, can be treated with glucagon (0.5 to 1 mg) given intramuscularly or subcutaneously, by a trained person, or with glucose given intravenously by a healthcare professional. Glucose must 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: Drugs used in diabetes. Insulins and analogues for injection, long-acting: ATC code: A10AE05.

Mechanism of action

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

The blood glucose lowering effect of Levemir 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 Levemir 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 Levemir and NPH insulin

Pharmacodynamic Endpoint	Levemir 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 Levemir

The prolonged action of Levemir 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.

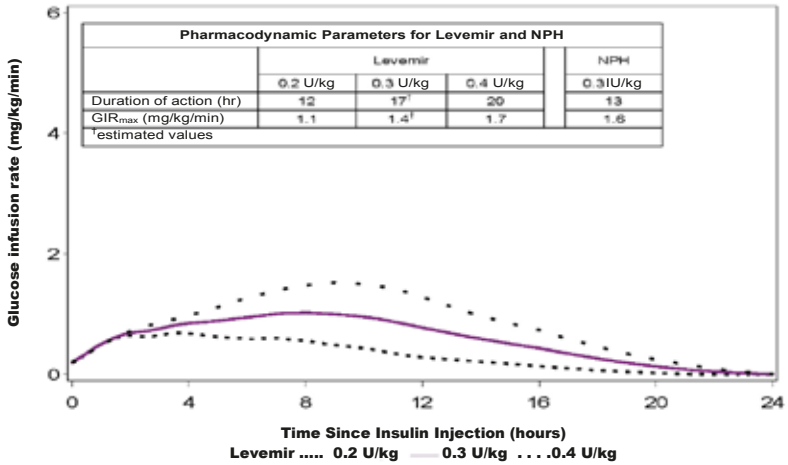


Figure 1. Activity profiles of Levemir in patients with type 1 diabetes.

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 medicinal products demonstrated that glycaemic control (HbA_{1c}) with Levemir is comparable to NPH insulin and insulin glargine and associated with less weight gain, see Table 2 below. In the study versus insulin glargine, Levemir was allowed to be administered once or twice daily whereas insulin glargine was to be administered once a day, 55% of the Levemir treated subjects completed the 52 weeks of treatment on the twice daily regimen.

Table 2. Change in body weight after insulin treatment

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

In trials investigating the use of oral antidiabetic medicinal products, combination therapy with Levemir resulted in a 61-65% lower risk of minor nocturnal hypoglycaemia compared to NPH insulin.

An open-label randomised clinical trial in patients with type 2 diabetes not reaching target with oral anti-diabetic medicinal products was conducted. The trial started with a 12 week run-in period with liraglutide+metformin, where 61% reached an HbA_{1c} <7%. The 39% of patients not achieving target were randomised to have Levemir once-daily added or continue on liraglutide+metformin for 52 weeks. Addition of Levemir provided a further reduction of HbA_{1c} from 7.6% to 7.1% after 52 weeks. There were no major hypoglycaemic episodes. A major hypoglycaemic episode is defined as an episode where the subject was not able to treat him/herself and if glucagon or i.v. glucose was needed. See table 3.

Table 3. Clinical trial data - Levemir add-on to liraglutide+metformin

	Study week	Randomised Levemir + liraglutide + metformin N = 160	Randomised Liraglutide + metformin N = 149	P-value
Mean change in HbA_{1c} from baseline (%)	0-26 weeks	-0.51	+0.02	<0.0001
	0-52 weeks	-0.50	0.01	<0.0001
Proportions of patients achieving HbA_{1c} <7% targets (%)	0-26 weeks	43.1	16.8	<0.0001
	0-52 weeks	51.9	21.5	<0.0001
Change in body weight from baseline (kg)	0-26 weeks	-0.16	-0.95	0.0283
	0-52 weeks	-0.05	-1.02	0.0416
Minor hypoglycaemic episodes (per patient year)	0-26 weeks	0.224	0.019	0.0075
	0-52 weeks	0.228	0.034	0.0011

In long-term trials in patients with type 1 diabetes receiving a basal-bolus insulin therapy, fasting plasma glucose was improved with Levemir compared with NPH insulin. Glycaemic control (HbA_{1c}) with Levemir was 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.

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

Pregnancy

Levemir was studied in an open-label randomised controlled clinical trial pregnant women with type 1 diabetes (n=310) were treated in a basal-bolus treatment regimen with Levemir (n=152) or NPH insulin (n=158) as basal insulin, both in combination with NovoRapid (see section 4.6).
Levemir was non-inferior to NPH insulin as measured by HbA_{1c} at gestational week (GW) 36, and the reduction in mean HbA_{1c} through pregnancy was similar, see table 4.

Table 4. Maternal glycaemic control

	Levemir	NPH	Difference/ Odds Ratio/ Rate Ratio 95% CI
Mean HbA_{1c} (%) at GW 36	6.27	6.33	Difference: -0.06 [-0.21; 0.08]
Mean FPG at GW 36 (mmol/l)	4.76	5.41	Difference: -0.65 [-1.19; -0.12]
Proportions of patients achieving HbA_{1c} ≤6% targets at both GW 24 and GW 36 (%)	41%	32%	Odds Ratio: 1.36 [0.78; 2.37]
Overall number of major hypoglycemia episodes during pregnancy (per patient year)	1.1	1.2	Rate Ratio: 0.82 [0.39; 1.75]

Paediatric population

The efficacy and safety of Levemir has been studied for up to 12 months, in two randomised controlled clinical trials in adolescents and children (n=694 in total); one of the studies included in total 82 children aged 2-5 years. Both trials demonstrated that glycaemic control (HbA_{1c}) with Levemir is comparable to NPH insulin when given as basal-bolus therapy, using a non-inferiority margin of 0.4%. In addition less weight gain (SD score, weight corrected for gender and age) was observed with Levemir than with NPH insulin.

The trial including children above 2 years was extended for an additional 12 months (total of 24 months treatment data) to assess antibody formation after long-term treatment with Levemir. After an increase in insulin antibodies during the first year, the insulin antibodies decreased during the second year to a level slightly higher than pre-trial level. Results indicate that antibody development had no negative effect on glycaemic control and Levemir dose.

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

Biotransformation

Degradation of insulin detemir is similar to that of human insulin; all metabolites formed are inactive.

Elimination

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

Linearity

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

No pharmacokinetic or pharmacodynamic interactions were observed between liraglutide and Levemir when administering a single dose of Levemir 0.5 U/kg with liraglutide 1.8 mg at steady state in patients with type 2 diabetes.

Special populations

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

Renal and hepatic impairment

There was no clinically relevant difference in pharmacokinetics of Levemir between subjects with renal or hepatic impairment and healthy subjects. As the pharmacokinetics of Levemir 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 Levemir.

Paediatric population

The pharmacokinetic properties of Levemir 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.

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 and development. 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 in a carton.

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

Needles and Levemir FlexPen must not be shared. The cartridge must not be refilled.

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

Levemir which has been frozen must not be used.

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

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

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

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, adolescents and children aged 2 years and above.

4.2 Posology and method of administration

Posology

The potency of insulin analogues, including insulin detemir, is expressed in units (U), whereas the potency of human insulin is expressed in international units (IU). 1 unit (U) insulin detemir corresponds to 1 international unit (IU) of human insulin.

Levemir can be used alone as the basal insulin or in combination with bolus insulin. It can also be used in combination with oral antidiabetic medicinal products or as add-on therapy to liraglutide treatment.

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

Based on study results, the following titration guideline is recommended for adult diabetes patients:

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. Dose of Levemir should be adjusted individually.

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

Special populations

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

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

Paediatric population

The efficacy and safety of Levemir were demonstrated in adolescents and children aged 2 years and above in studies up to 12 months (see section 5.1).

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

Levemir has not been studied in children below the age of 2 years.

Transfer from other insulin medicinal products

When transferring from other intermediate or long-acting insulin medicinal products adjustment of the dose and timing of administration may be necessary (see section 4.4).

As with all insulin medicinal products, close glucose monitoring is recommended during the transfer and in the initial weeks thereafter (see section 4.4).

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

Method of administration

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

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

Levemir InnoLet is a pre-filled pen designed to be used with NovoFine or NovoTwist disposable needles up to a length of 8 mm. InnoLet delivers 1-50 units in increments of 1 unit. The patient should be advised not to use any counterfeit needles.

Levemir InnoLet is accompanied by a package leaflet with detailed instructions for use to be followed.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients (see section 6.1).

4.4 Special warnings and precautions for use

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

Hyperglycaemia

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

Hypoglycaemia

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

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

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

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

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

Transfer from other insulin medicinal 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 dose. Patients transferred to Levemir from another type of insulin may require a change in dose from that used with their usual insulin medicinal products. If an adjustment is needed, it may occur with the first dose or during the first few weeks or months.

Injection site reactions

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

Hypoalbuminaemia

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

Combination of Levemir with pioglitazone

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

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

Beta-blockers may mask the symptoms of hypoglycaemia.

Octreotide/lanreotide may either increase or decrease the insulin requirement.

Alcohol may intensify or reduce the hypoglycaemic effect of insulin.

4.6 Fertility, pregnancy and lactation

Pregnancy

Treatment with Levemir can be considered during pregnancy, but any potential benefit must be weighed against a possibly increased risk of an adverse pregnancy outcome.

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-pregancy values.

In an open-label randomised controlled clinical trial pregnant women with type 1 diabetes (n=310) were treated in a basal-bolus treatment regimen with Levemir (n=152) or NPH insulin (n=158) as basal insulin, both in combination with NovoRapid. Primary objective of this study was to assess the effect of Levemir on blood glucose regulation in pregnant women with diabetes (see section 5.1).

The overall rates of maternal adverse events were similar for Levemir and NPH insulin treatment groups; however, a numerically higher frequency of serious adverse events in the mothers (61 (40%) vs. 49 (31%)) and in the newborn children (36 (24%) vs. 32 (20%)) was seen for Levemir compared to NPH insulin. The number of live born children of women becoming pregnant after randomisation were 50 (83%) for Levemir and 55 (89%) for NPH. The frequency of congenital malformations was 4 (5%) for Levemir and 11 (7%) for NPH with 3 (4%) major malformations for Levemir and 3 (2%) for NPH.

Post-marketing data from an additional 250 outcomes from pregnant women exposed to Levemir indicate no adverse effects of insulin detemir on pregnancy and no malformative or feto/neonatal toxicity of insulin detemir.

Animal data do not indicate reproductive toxicity (see section 5.3).

Breast-feeding

It is unknown whether insulin detemir is excreted in human milk. No metabolic effects of ingested insulin detemir on the breast-fed newborn/infant are anticipated since insulin detemir, as a peptide, is digested into amino acids in the human gastrointestinal tract.

Breast-feeding women may require adjustments in insulin dose and diet.

Fertility

Animal studies do not indicate harmful effects with respect to fertility.

4.7 Effects on ability to drive and use machines

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

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

4.8 Undesirable effects

a. Summary of the safety profile

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

The most frequently reported adverse reaction during treatment is hypoglycaemia, please see section c below.
From clinical investigations, it is known that major hypoglycaemia, defined as requirement for third party intervention, occurs in approximately 6% of the patients treated with Levemir.

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

b. Tabulated list of adverse reactions

Adverse reactions listed below are based on clinical trial data and classified according to MedDRA 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).

Immune system disorders	Uncommon – Allergic reactions, potentially allergic reactions, urticaria, rash, eruptions*
	Very rare – Anaphylactic reactions*
Metabolism and nutrition disorders	Very common – Hypoglycaemia*
Nervous system disorders	Rare – Peripheral neuropathy
Eye disorders	Uncommon – Refraction disorders
	Uncommon – Diabetic retinopathy
Skin and subcutaneous tissue disorders	Uncommon – Lipodystrophy*
General disorders and administration site conditions	Common – Injection site reactions
	Uncommon – Oedema

* see section c

c. Description of selected adverse reactions

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

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

Hypoglycaemia
The most frequently reported adverse reaction is hypoglycaemia. It may occur if the insulin dose is too high in relation to the insulin requirement. Severe hypoglycaemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death. The symptoms of hypoglycaemia usually occur suddenly. They may include cold 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.

Lipodystrophy
Lipodystrophy (including lipohypertrophy, lipoatrophy) may occur at the injection site. Continuous rotation of the injection site within the particular injection area may help to reduce the risk of developing these reactions.

d. Paediatric population

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

e. Other special populations

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

4.9 Overdose

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

- Mild hypoglycaemic episodes can be treated by oral administration of glucose or sugary products. It is therefore recommended that the diabetic patient always carries sugar-containing products.
- Severe hypoglycaemic episodes, where the patient has become unconscious, can be treated with glucagon (0.5 to 1 mg) given intramuscularly or subcutaneously by a trained person, or with glucose given intravenously, by a healthcare professional. Glucose must 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: Drugs used in diabetes. Insulins and analogues for injection, long-acting: ATC code: A10AE05.

Mechanism of action

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

The blood glucose lowering effect of Levemir 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 Levemir 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 Levemir and NPH insulin

Pharmacodynamic Endpoint	Levemir 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 Levemir

The prolonged action of Levemir 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.

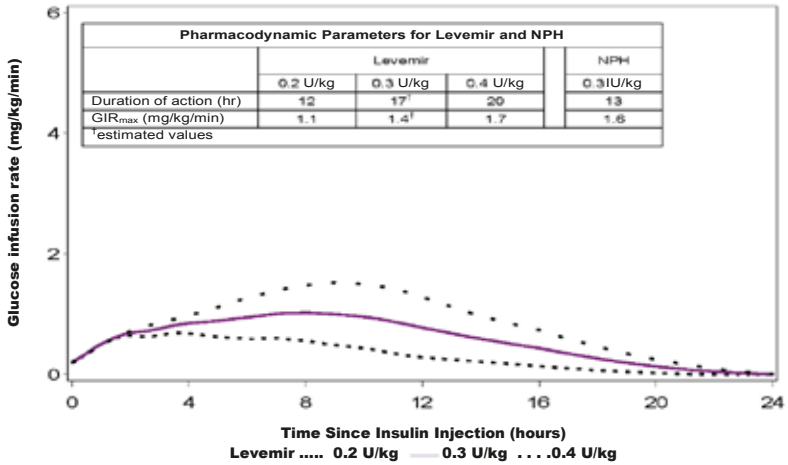


Figure 1. Activity profiles of Levemir in patients with type 1 diabetes.

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 medicinal products demonstrated that glycaemic control (HbA_{1c}) with Levemir is comparable to NPH insulin and insulin glargine and associated with less weight gain, see Table 2 below. In the study versus insulin glargine, Levemir was allowed to be administered once or twice daily whereas insulin glargine was to be administered once a day, 55% of the Levemir treated subjects completed the 52 weeks of treatment on the twice daily regimen.

Table 2. Change in body weight after insulin treatment

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

In trials investigating the use of oral antidiabetic medicinal products, combination therapy with Levemir resulted in a 61-65% lower risk of minor nocturnal hypoglycaemia compared to NPH insulin.

An open-label randomised clinical trial in patients with type 2 diabetes not reaching target with oral anti-diabetic medicinal products was conducted. The trial started with a 12 week run-in period with liraglutide+metformin, where 61% reached an HbA_{1c} <7%. The 39% of patients not achieving target were randomised to have Levemir once-daily added or continue on liraglutide+metformin for 52 weeks. Addition of Levemir provided a further reduction of HbA_{1c} from 7.6% to 7.1% after 52 weeks. There were no major hypoglycaemic episodes. A major hypoglycaemic episode is defined as an episode where the subject was not able to treat him/herself and if glucagon or i.v. glucose was needed. See table 3.

Table 3. Clinical trial data - Levemir add-on to liraglutide+metformin

	Study week	Randomised Levemir + liraglutide + metformin N = 160	Randomised Liraglutide + metformin N = 149	P-value
Mean change in HbA_{1c} from baseline (%)	0-26 weeks	-0.51	+0.02	<0.0001
	0-52 weeks	-0.50	0.01	<0.0001
Proportions of patients achieving HbA_{1c} <7% targets (%)	0-26 weeks	43.1	16.8	<0.0001
	0-52 weeks	51.9	21.5	<0.0001
Change in body weight from baseline (kg)	0-26 weeks	-0.16	-0.95	0.0283
	0-52 weeks	-0.05	-1.02	0.0416
Minor hypoglycaemic episodes (per patient year)	0-26 weeks	0.224	0.019	0.0075
	0-52 weeks	0.228	0.034	0.0011

In long-term trials in patients with type 1 diabetes receiving a basal-bolus insulin therapy, fasting plasma glucose was improved with Levemir compared with NPH insulin. Glycaemic control (HbA_{1c}) with Levemir was 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.

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

Pregnancy

Levemir was studied in an open-label randomised controlled clinical trial pregnant women with type 1 diabetes (n=310) were treated in a basal-bolus treatment regimen with Levemir (n=152) or NPH insulin (n=158) as basal insulin, both in combination with NovoRapid (see section 4.6).
Levemir was non-inferior to NPH insulin as measured by HbA_{1c} at gestational week (GW) 36, and the reduction in mean HbA_{1c} through pregnancy was similar, see table 4.

Table 4. Maternal glycaemic control

	Levemir	NPH	Difference/ Odds Ratio/ Rate Ratio 95% CI
Mean HbA_{1c} (%) at GW 36	6.27	6.33	Difference: -0.06 [-0.21; 0.08]
Mean FPG at GW 36 (mmol/l)	4.76	5.41	Difference: -0.65 [-1.19; -0.12]
Proportions of patients achieving HbA_{1c} ≤6% targets at both GW 24 and GW 36 (%)	41%	32%	Odds Ratio: 1.36 [0.78; 2.37]
Overall number of major hypoglycemia episodes during pregnancy (per patient year)	1.1	1.2	Rate Ratio: 0.82 [0.39; 1.75]

Paediatric population

The efficacy and safety of Levemir has been studied for up to 12 months, in two randomised controlled clinical trials in adolescents and children (n=694 in total); one of the studies included in total 82 children aged 2-5 years. Both trials demonstrated that glycaemic control (HbA_{1c}) with Levemir is comparable to NPH insulin when given as basal-bolus therapy, using a non-inferiority margin of 0.4%. In addition less weight gain (SD score, weight corrected for gender and age) was observed with Levemir than with NPH insulin.

The trial including children above 2 years was extended for an additional 12 months (total of 24 months treatment data) to assess antibody formation after long-term treatment with Levemir. After an increase in insulin antibodies during the first year, the insulin antibodies decreased during the second year to a level slightly higher than pre-trial level. Results indicate that antibody development had no negative effect on glycaemic control and Levemir dose.

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

Biotransformation

Degradation of insulin detemir is similar to that of human insulin; all metabolites formed are inactive.

Elimination

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

Linearity

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

No pharmacokinetic or pharmacodynamic interactions were observed between liraglutide and Levemir when administering a single dose of Levemir 0.5 U/kg with liraglutide 1.8 mg at steady state in patients with type 2 diabetes.

Special populations

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

Renal and hepatic impairment

There was no clinically relevant difference in pharmacokinetics of Levemir between subjects with renal or hepatic impairment and healthy subjects. As the pharmacokinetics of Levemir 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 Levemir.

Paediatric population

The pharmacokinetic properties of Levemir 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.

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 and development. 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 in a carton.

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

Needles and Levemir InnoLet must not be shared. The cartridge must not be refilled.

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

Levemir which has been frozen must not be used.

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

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

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

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. FlexTouch.

Clear, colourless, neutral solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of diabetes mellitus in adults, adolescents and children aged 2 years and above.

4.2 Posology and method of administration

Posology

The potency of insulin analogues, including insulin detemir, is expressed in units (U), whereas the potency of human insulin is expressed in international units (IU). 1 unit (U) insulin detemir corresponds to 1 international unit (IU) of human insulin.

Levemir can be used alone as the basal insulin or in combination with bolus insulin. It can also be used in combination with oral antidiabetic medicinal products or as add-on therapy to liraglutide treatment.

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

Based on study results, the following titration guideline is recommended for adult diabetes patients:

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. Dose of Levemir should be adjusted individually.

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

Special populations

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

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

Paediatric population

The efficacy and safety of Levemir were demonstrated in adolescents and children aged 2 years and above in studies up to 12 months (see section 5.1).

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

Levemir has not been studied in children below the age of 2 years.

Transfer from other insulin medicinal products

When transferring from other intermediate or long-acting insulin medicinal products adjustment of the dose and timing of administration may be necessary (see section 4.4).

As with all insulin medicinal products, close glucose monitoring is recommended during the transfer and in the initial weeks thereafter (see section 4.4).

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

Method of administration

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

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

Levemir FlexTouch are pre-filled pens designed to be used with NovoFine or NovoTwist disposable needles up to a length of 8 mm. FlexTouch delivers 1-80 units in increments of 1 unit. The patient should be advised not to use any counterfeit needles.

Levemir FlexTouch is colour-coded and accompanied by a package leaflet with detailed instructions for use to be followed.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients (see section 6.1).

4.4 Special warnings and precautions for use

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

Hyperglycaemia

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

Hypoglycaemia

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

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

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

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

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

Transfer from other insulin medicinal 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 dose. Patients transferred to Levemir from another type of insulin may require a change in dose from that used with their usual insulin medicinal products. If an adjustment is needed, it may occur with the first dose or during the first few weeks or months.

Injection site reactions

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

Hypoalbuminaemia

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

Combination of Levemir with pioglitazone

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

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

Beta-blockers may mask the symptoms of hypoglycaemia.

Octreotide/lanreotide may either increase or decrease the insulin requirement.

Alcohol may intensify or reduce the hypoglycaemic effect of insulin.

4.6 Fertility, pregnancy and lactation

Pregnancy

Treatment with Levemir can be considered during pregnancy, but any potential benefit must be weighed against a possibly increased risk of an adverse pregnancy outcome.

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-pregancy values.

In an open-label randomised controlled clinical trial pregnant women with type 1 diabetes (n=310) were treated in a basal-bolus treatment regimen with Levemir (n=152) or NPH insulin (n=158) as basal insulin, both in combination with NovoRapid. Primary objective of this study was to assess the effect of Levemir on blood glucose regulation in pregnant women with diabetes (see section 5.1).

The overall rates of maternal adverse events were similar for Levemir and NPH insulin treatment groups; however, a numerically higher frequency of serious adverse events in the mothers (61 (40%) vs. 49 (31%)) and in the newborn children (36 (24%) vs. 32 (20%)) was seen for Levemir compared to NPH insulin. The number of live born children of women becoming pregnant after randomisation were 50 (83%) for Levemir and 55 (89%) for NPH. The frequency of congenital malformations was 4 (5%) for Levemir and 11 (7%) for NPH with 3 (4%) major malformations for Levemir and 3 (2%) for NPH.

Post-marketing data from an additional 250 outcomes from pregnant women exposed to Levemir indicate no adverse effects of insulin detemir on pregnancy and no malformative or feto/neonatal toxicity of insulin detemir.

Animal data do not indicate reproductive toxicity (see section 5.3).

Breast-feeding

It is unknown whether insulin detemir is excreted in human milk. No metabolic effects of ingested insulin detemir on the breast-fed newborn/infant are anticipated since insulin detemir, as a peptide, is digested into amino acids in the human gastrointestinal tract.

Breast-feeding women may require adjustments in insulin dose and diet.

Fertility

Animal studies do not indicate harmful effects with respect to fertility.

4.7 Effects on ability to drive and use machines

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

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

4.8 Undesirable effects

a. Summary of the safety profile

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

The most frequently reported adverse reaction during treatment is hypoglycaemia, please see section c below.
From clinical investigations, it is known that major hypoglycaemia, defined as requirement for third party intervention, occurs in approximately 6% of the patients treated with Levemir.

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

b. Tabulated list of adverse reactions

Adverse reactions listed below are based on clinical trial data and classified according to MedDRA 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).

Immune system disorders	Uncommon – Allergic reactions, potentially allergic reactions, urticaria, rash, eruptions*
	Very rare – Anaphylactic reactions*
Metabolism and nutrition disorders	Very common – Hypoglycaemia*
Nervous system disorders	Rare – Peripheral neuropathy
Eye disorders	Uncommon – Refraction disorders
	Uncommon – Diabetic retinopathy
Skin and subcutaneous tissue disorders	Uncommon – Lipodystrophy*
General disorders and administration site conditions	Common – Injection site reactions
	Uncommon – Oedema

* see section c

c. Description of selected adverse reactions

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

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

Hypoglycaemia
The most frequently reported adverse reaction is hypoglycaemia. It may occur if the insulin dose is too high in relation to the insulin requirement. Severe hypoglycaemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death. The symptoms of hypoglycaemia usually occur suddenly. They may include cold 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.

Lipodystrophy
Lipodystrophy (including lipohypertrophy, lipoatrophy) may occur at the injection site. Continuous rotation of the injection site within the particular injection area may help to reduce the risk of developing these reactions.

d. Paediatric population

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

e. Other special populations

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

4.9 Overdose

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

- Mild hypoglycaemic episodes can be treated by oral administration of glucose or sugary products. It is therefore recommended that the diabetic patient always carries sugar-containing products.
- Severe hypoglycaemic episodes, where the patient has become unconscious, can be treated with glucagon (0.5 to 1 mg) given intramuscularly or subcutaneously, by a trained person, or with glucose given intravenously by a healthcare professional. Glucose must 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: Drugs used in diabetes. Insulins and analogues for injection, long-acting: ATC code: A10AE05.

Mechanism of action

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

The blood glucose lowering effect of Levemir 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 Levemir 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 2.

Table 2. Within-subject variability of the time action profile of Levemir and NPH insulin

Pharmacodynamic Endpoint	Levemir 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 Levemir

The prolonged action of Levemir 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.

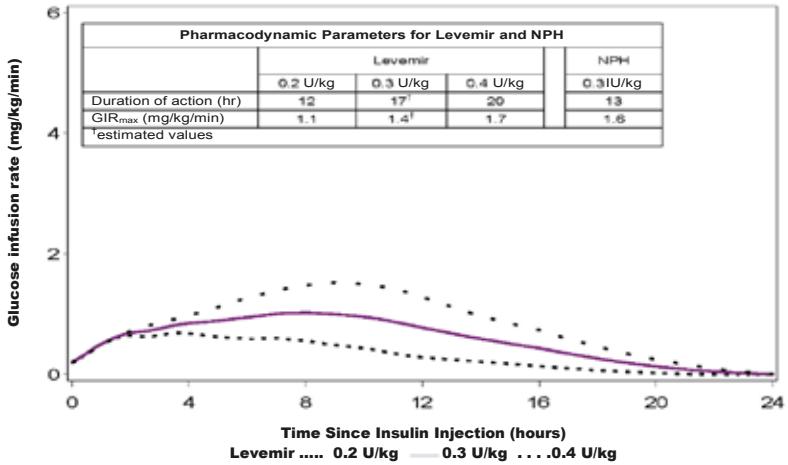


Figure 1. Activity profiles of Levemir in patients with type 1 diabetes.

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 medicinal products demonstrated that glycaemic control (HbA_{1c}) with Levemir is comparable to NPH insulin and insulin glargine and associated with less weight gain, see Table 2 below. In the study versus insulin glargine, Levemir was allowed to be administered once or twice daily whereas insulin glargine was to be administered once a day, 55% of the Levemir treated subjects completed the 52 weeks of treatment on the twice daily regimen.

Table 2. Change in body weight after insulin treatment

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

In trials investigating the use of oral antidiabetic medicinal products combination therapy with Levemir resulted in a 61-65% lower risk of minor nocturnal hypoglycaemia compared to NPH insulin.

An open-label randomised clinical trial in patients with type 2 diabetes not reaching target with oral anti-diabetic medicinal products was conducted. The trial started with a 12 week run-in period with liraglutide+metformin, where 61% reached an HbA_{1c} <7%. The 39% of patients not achieving target were randomised to have Levemir once-daily added or continue on liraglutide+metformin for 52 weeks. Addition of Levemir provided a further reduction of HbA_{1c} from 7.6% to 7.1% after 52 weeks. There were no major hypoglycaemic episodes. A major hypoglycaemic episode is defined as an episode where the subject was not able to treat him/herself and if glucagon or i.v. glucose was needed. See table 3.

Table 3. Clinical trial data - Levemir add-on to liraglutide+metformin

	Study week	Randomised Levemir + liraglutide + metformin N = 160	Randomised Liraglutide + metformin N = 149	P-value
Mean change in HbA_{1c} from baseline (%)	0-26 weeks	-0.51	+0.02	<0.0001
	0-52 weeks	-0.50	0.01	<0.0001
Proportions of patients achieving HbA_{1c} <7% targets (%)	0-26 weeks	43.1	16.8	<0.0001
	0-52 weeks	51.9	21.5	<0.0001
Change in body weight from baseline (kg)	0-26 weeks	-0.16	-0.95	0.0283
	0-52 weeks	-0.05	-1.02	0.0416
Minor hypoglycaemic episodes (per patient year)	0-26 weeks	0.224	0.019	0.0075
	0-52 weeks	0.228	0.034	0.0011

In long-term trials in patients with type 1 diabetes receiving a basal-bolus insulin therapy, fasting plasma glucose was improved with Levemir compared with NPH insulin. Glycaemic control (HbA_{1c}) with Levemir was 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.

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

Pregnancy

Levemir was studied in an open-label randomised controlled clinical trial pregnant women with type 1 diabetes (n=310) were treated in a basal-bolus treatment regimen with Levemir (n=152) or NPH insulin (n=158) as basal insulin, both in combination with NovoRapid (see section 4.6).
Levemir was non-inferior to NPH insulin as measured by HbA_{1c} at gestational week (GW) 36, and the reduction in mean HbA_{1c} through pregnancy was similar, see table 4.

Table 4. Maternal glycaemic control

	Levemir	NPH	Difference/ Odds Ratio/ Rate Ratio 95% CI
Mean HbA_{1c} (%) at GW 36	6.27	6.33	Difference: -0.06 [-0.21; 0.08]
Mean FPG at GW 36 (mmol/l)	4.76	5.41	Difference: -0.65 [-1.19; -0.12]
Proportions of patients achieving HbA_{1c} ≤6% targets at both GW 24 and GW 36 (%)	41%	32%	Odds Ratio: 1.36 [0.78; 2.37]
Overall number of major hypoglycemia episodes during pregnancy (per patient year)	1.1	1.2	Rate Ratio: 0.82 [0.39; 1.75]

Paediatric population

The efficacy and safety of Levemir has been studied for up to 12 months, in two randomised controlled clinical trials in adolescents and children (n=694 in total); one of the studies included in total 82 children aged 2-5 years. Both trials demonstrated that glycaemic control (HbA_{1c}) with Levemir is comparable to NPH insulin when given as basal-bolus therapy, using a non-inferiority margin of 0.4%. In addition less weight gain (SD score, weight corrected for gender and age) was observed with Levemir than with NPH insulin.

The trial including children above 2 years was extended for an additional 12 months (total of 24 months treatment data) to assess antibody formation after long-term treatment with Levemir. After an increase in insulin antibodies during the first year, the insulin antibodies decreased during the second year to a level slightly higher than pre-trial level. Results indicate that antibody development had no negative effect on glycaemic control and Levemir dose.

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

Biotransformation

Degradation of insulin detemir is similar to that of human insulin; all metabolites formed are inactive.

Elimination

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

Linearity

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

No pharmacokinetic or pharmacodynamic interactions were observed between liraglutide and Levemir when administering a single dose of Levemir 0.5 U/kg with liraglutide 1.8 mg at steady state in patients with type 2 diabetes.

Special populations

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

Renal and hepatic impairment

There was no clinically relevant difference in pharmacokinetics of Levemir between subjects with renal or hepatic impairment and healthy subjects. As the pharmacokinetics of Levemir 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 Levemir.

Paediatric population

The pharmacokinetic properties of Levemir 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.

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 and development. 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 FlexTouch pen 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 in a carton.

Pack sizes of 1 (with or without needles), 5 (without needles) and a multipack with 2 x 5 (without needles) pre-filled pens of 3 ml. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Needles and Levemir FlexTouch must not be shared. The cartridge must not be refilled.

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

Levemir which has been frozen must not be used.

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

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/278/012
EU/1/04/278/013
EU/1/04/278/014
EU/1/04/278/015
EU/1/04/278/016

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

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

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 and FlexTouch

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**

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the Marketing Authorisation, is in place and functioning before and whilst the product is on the market.

Risk Management Plan (RMP)

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the Risk Management Plan (RMP) presented in Module 1.8.2 of the Marketing Authorisation and any subsequent updates of the RMP agreed by the Committee for Medicinal Products for Human Use (CHMP).

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, any updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities.
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached.
- At the request of the European Medicines Agency.

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

1 cartridge of 3 ml contains 300 U
1 ml solution contains 100 U insulin detemir (equivalent to 14.2 mg),

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 OF ADMINISTRATION

Read the package leaflet before use
Subcutaneous 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 WARNINGS, IF NECESSARY

Use only clear, colourless solution.
Single patient use 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 NUMBERS

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 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

Novo Nordisk A/S

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

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

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 OF ADMINISTRATION

Needles are not included.
Read the package leaflet before use
Subcutaneous 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 WARNINGS, IF NECESSARY

Use only clear, colourless solution.
Single patient use 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 NUMBERS

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 OF ADMINISTRATION

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

Novo Nordisk A/S

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

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

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 OF ADMINISTRATION

Needles are not included.
Read the package leaflet before use
Subcutaneous 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 WARNINGS, IF NECESSARY

Use only clear, colourless solution.
Single patient use 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 NUMBERS

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 OF ADMINISTRATION

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

Novo Nordisk A/S

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (PRE-FILLED PEN FlexTouch)

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE

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

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. FlexTouch. (100 U/ml)

1 x 3 ml
5 x 3 ml
10 x 3 ml (2 x 5)
1 x 3 ml + 7 NovoFine needles
1 x 3 ml + 7 NovoTwist needles

5. METHOD AND ROUTE OF ADMINISTRATION

Needles are not included.
Read the package leaflet before use
Subcutaneous 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 WARNINGS, IF NECESSARY

Use only clear, colourless solution.
Single patient use 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 NUMBERS

EU/1/04/278/012 1 pen of 3 ml
EU/1/04/278/013 5 pens of 3 ml
EU/1/04/278/014 5 pens of 3 ml. This is part of a multipack of 10 pens and not for sale as individual pens
EU/1/04/278/015 1 pen of 3 ml and 7 NovoFine needles
EU/1/04/278/016 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 FlexTouch

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER WRAPPER LABEL ON MULTIPACKS (FlexTouch)

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

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. FlexTouch. (100 U/ml)

10 x 3 ml (2 x 5) This is a multipack and not for sale as individual pre-filled pens

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Needles are not included.
Read the package leaflet before use
Subcutaneous 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.
Single patient use 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/1/04/278/014

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Levemir FlexTouch

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PEN LABEL (PRE-FILLED PEN. FlexTouch)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

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

2. METHOD OF ADMINISTRATION

FlexTouch

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml

6. OTHER

Novo Nordisk A/S

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

Levemir is a modern insulin (insulin analogue) with a long-acting effect. Modern insulin products are improved versions of human insulin.

Levemir is used to reduce the high blood sugar level in adults, adolescents and children aged 2 years and above with diabetes mellitus (diabetes). Diabetes is a disease where your body does not produce enough insulin to control the level of your blood sugar. Levemir may be used in combination with tablets for diabetes or as add-on therapy to liraglutide (Victoza), which is used to treat type 2 diabetes in adults. Levemir can also be used with meal-related rapid acting insulin medicines.

Levemir has a long and steady blood-sugar-lowering action within 3 to 4 hours after injection. Levemir provides up to 24 hours of basal insulin coverage.

2. Before you use Levemir

Do not use Levemir

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

If any of these applies, do not use Levemir. Talk with your doctor, nurse or pharmacist for advice.

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) at the bottom of the cartridge. Do not use it if any damage is seen or if the rubber plunger has been drawn above the white label band at the bottom of the Penfill. This could be a result of leakage of insulin. If you suspect the cartridge to be damaged, take it back to your supplier. See your pen manual for further instructions.
► Always use a new needle for each injection to prevent contamination.
► Needles and Levemir Penfill must not be shared.

Take special care with Levemir

Some conditions and activities can affect your need for insulin. These include:
► If you have trouble with your kidneys or liver, or with your adrenal, pituitary or thyroid glands.
► If you exercise 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 your injections. Consult your doctor if you are planning such travelling.
► If you have very low albumin you need to carefully monitor your blood sugar level. Discuss this with your doctor.

Using other medicines

Tell your doctor, nurse or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. Some medicines affect the way blood sugar works in your body and this may influence your insulin dose. Listed below are the most common medicines which may affect your insulin treatment.

<u>Your blood sugar level may fall (hypoglycaemia) if you take:</u>
• 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).

<u>Your blood sugar level may rise (hyperglycaemia) if you take:</u>
• 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 (used 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, a rare hormonal disorder that usually occurs in middle-aged adults, caused by the pituitary gland producing excess growth hormone) may either increase or decrease your blood sugar level.

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

<u>Pioglitazone (tablets used for the treatment of type 2 diabetes)</u>

Some patients with long-standing type 2 diabetes and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

If you have taken any of the medicines listed here, tell your doctor, nurse or pharmacist.

Drinking alcohol and taking Levemir

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

Pregnancy and breast-feeding

► If you are pregnant or planning a pregnancy please contact your doctor for advice. Your insulin dose may need to be changed during pregnancy and after delivery. Careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby.
► If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses.

Ask your doctor or pharmacist for advice before taking any medicine while pregnant or breast-feeding.

Driving and using machines

► Please ask your doctor whether you can drive a car or operate a machine:
• If you have frequent hypoglycaemia.
• If you find it hard to recognise hypoglycaemia.

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.

Important information about some of the ingredients in Levemir

Levemir contains less than 1 mmol sodium (23 mg) per dose, i.e. Levemir is essentially 'sodium-free'.

3. How to use Levemir

Dose and when to take your insulin

Always use your insulin as prescribed by your doctor and follow the doctors advice carefully.

Levemir may be used in combination with tablets for diabetes or as add-on therapy to liraglutide (Victoza), which is used to treat type 2 diabetes in adults. Levemir can also be used with meal-related rapid acting insulin medicines.

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. Do not change your insulin unless your doctor tells you to.

Use in children

Levemir can be used in adolescents and children aged 2 years and above.

There is no experience with the use of Levemir in children below the age of 2 years.

Use in special patient groups

If you have reduced kidney or liver function, or if you are above 65 years of age, you need to check your blood sugar more regularly and discuss changes in your insulin dose with your doctor.

How often to inject

When Levemir is used in combination with tablets for diabetes or as add-on therapy to liraglutide, 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. Dose of Levemir should be adjusted individually. The injection can be given at any time during the day, but at the same time each day. For patients who require twice daily dosing to optimise blood sugar control, the evening dose can be administered in the evening or at bedtime.

How and where to inject

Levemir is for injection under the skin (subcutaneously). Never inject your insulin directly into a vein (intravenously) or muscle (intramuscularly).
With each injection, change the injection site within the particular area of skin that you use. This may reduce the risk of developing lumps or skin pitting (see section 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 sugar regularly.

- ► Do not refill the cartridge.
- ► Levemir Penfill cartridges are designed to be used with Novo Nordisk insulin delivery systems and NovoFine or NovoTwist 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.
- ► As a precautionary measure, always carry a spare Penfill cartridge in case your Penfill cartridge is lost or damaged.

How to inject Levemir

- ► Inject the insulin under the skin. Use the injection technique advised by your doctor or nurse and as described in your pen manual.
- ► Keep the needle under your skin for at least 6 seconds. Keep the push-button fully depressed until the needle has been withdrawn from the skin. This will ensure correct delivery and limit possible flow of blood into the needle or insulin reservoir.
- ► 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.

If you take more insulin than you should

If you take too much insulin your blood sugar gets too low this is called hypoglycaemia. See Other effects from diabetes in section 4.

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. See Other effects from diabetes in section 4.

If you stop taking your insulin

Do not stop taking your insulin without speaking with a doctor, who will tell you what needs to be done. This could lead to very high blood sugar (severe hyperglycaemia) and ketoacidosis. See Other effects from diabetes in section 4.
If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

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

Very common side effects
Affecting more than 1 in every 10 people.

Low blood sugar (hypoglycaemia): See details in Other effects from diabetes, below.

Common side effects
Affecting less than 1 in every 10 people.

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.

Uncommon side effects
Affecting less than 1 in every 100 people.

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.

► If you notice any of these, get medical advice immediately.

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): The fatty tissue under the skin at the injection site may shrink (lipoatrophy) or thicken (lipohypertrophy). Changing the site with each injection may help to reduce the risk of developing such skin changes. If you notice your skin pitting or thickening at the injection site, tell your doctor or nurse. 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.

Diabetic retinopathy (an eye disease related to diabetes which can lead to loss of vision): If you have diabetic retinopathy and your blood sugar level improves very fast, the retinopathy may get worse. Ask your doctor about this.

Rare side effects
Affecting less than 1 in every 1,000 people.

Painful neuropathy (pain due to nerve damage): If your blood sugar level improves very fast, you may get nerve related pain, this is called acute painful neuropathy and is usually transient.

Very rare side effects
Affecting less than 1 in every 10,000 people.

Serious allergic reaction to Levemir or one of its ingredients (called a systemic allergic reaction). See also the warning in section 2, Before you use Levemir.

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

Other effects from diabetes

► **Low blood sugar (hypoglycaemia)**

Low blood sugar may occur if you:
- Inject too much insulin.
- Eat too little or miss a meal.
- Exercise more than usual.
- Drink alcohol (See Drinking alcohol and taking Levemir in section 2).

Warning signs of low blood sugar:
The warning signs 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.

What to do if you experience low blood sugar:
► If you experience low blood sugar, eat glucose tablets or another high sugar snack (sweets, biscuits, fruit juice). Measure your blood sugar if possible and rest. Always carry glucose tablets, sweets, biscuits or fruit juice with you, just in case.

When symptoms of low blood sugar have disappeared or when your blood sugar level is stabilised, continue insulin treatment as usual.

► Tell relevant people that you have diabetes and what the consequences may be, including the risk of passing out (become unconscious) due to low blood sugar. Let them know that if you pass out, they must turn you on your side and get medical help straight away. They must not give you any food or drink due to risk of suffocation.

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.

► If prolonged severe low blood sugar is not treated, it can cause brain damage (temporary or permanent) and even death.
► If you have such a low blood sugar that you pass out, if you have had need for injection of glucagon, or if you have experienced many incidents of low blood sugar, talk with a doctor. The amount or timing of insulin, food or exercise may need to be adjusted.

► **High blood sugar (hyperglycaemia)**

High blood sugar may occur if you:
- Have not injected enough insulin.
- Forget to take your insulin or stop taking insulin.
- Repeatedly take less insulin than you need.
- Get an infection and/or a fever.
- Eat more than usual.
- Exercise less than usual.

Warning signs of high blood sugar:
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.

What to do if you experience high blood sugar:

► If you get any of above 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 (build-up of acid in the blood because the body is breaking down fat instead of sugar). If you do not treat it, this could lead to diabetic coma and eventually death.

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.

Before opening: Levemir Penfill that is not being used is to be stored in the refrigerator at 2°C to 8°C, away from the cooling element. Do not freeze.

During use or when carried as a spare: 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 wastewater 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 and Manufacturer

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 S6, P5, K7, R7, VG, FG 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

Detailed information on this medicine is available on the website of the European Medicines Agency http://www.ema.europa.eu.

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

Levemir is a modern insulin (insulin analogue) with a long-acting effect. Modern insulin products are improved versions of human insulin.

Levemir is used to reduce the high blood sugar level in adults, adolescents and children aged 2 years and above with diabetes mellitus (diabetes). Diabetes is a disease where your body does not produce enough insulin to control the level of your blood sugar. Levemir may be used in combination with tablets for diabetes or as add-on therapy to liraglutide (Victoza), which is used to treat type 2 diabetes in adults. Levemir can also be used with meal-related rapid acting insulin medicines.

Levemir has a long and steady blood-sugar-lowering action within 3 to 4 hours after injection. Levemir provides up to 24 hours of basal insulin coverage.

2. Before you use Levemir

Do not use Levemir

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

If any of these applies, do not use Levemir. Talk with your doctor, nurse or pharmacist for advice.

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.

► Needles and Levemir FlexPen must not be shared.

Take special care with Levemir

Some conditions and activities can affect your need for insulin. These include:
► If you have trouble with your kidneys or liver, or with your adrenal, pituitary or thyroid glands.
► If you exercise 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 your injections. Consult your doctor if you are planning such travelling.
► If you have very low albumin you need to carefully monitor your blood sugar level. Discuss this with your doctor.

Using other medicines

Tell your doctor, nurse or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. Some medicines affect the way blood sugar works in your body and this may influence your insulin dose. Listed below are the most common medicines which may affect your insulin treatment.

<u>Your blood sugar level may fall (hypoglycaemia) if you take:</u>
• 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).

<u>Your blood sugar level may rise (hyperglycaemia) if you take:</u>
• 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 (used 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, a rare hormonal disorder that usually occurs in middle-aged adults, caused by the pituitary gland producing excess growth hormone) may either increase or decrease your blood sugar level.

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

<u>Pioglitazone (tablets used for the treatment of type 2 diabetes)</u>
Some patients with long-standing type 2 diabetes and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

If you have taken any of the medicines listed here, tell your doctor, nurse or pharmacist.

Drinking alcohol and taking Levemir

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

Pregnancy and breast-feeding

► If you are pregnant or planning a pregnancy please contact your doctor for advice. Your insulin dose may need to be changed during pregnancy and after delivery. Careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby.
► If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses.

Ask your doctor or pharmacist for advice before taking any medicine while pregnant or breast-feeding.

Driving and using machines

► Please ask your doctor whether you can drive a car or operate a machine:
• If you have frequent hypoglycaemia.
• If you find it hard to recognise hypoglycaemia.

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.

Important information about some of the ingredients in Levemir

Levemir contains less than 1 mmol sodium (23 mg) per dose, i.e. Levemir is essentially 'sodium-free'.

3. How to use Levemir

Dose and when to take your insulin

Always use your insulin as prescribed by your doctor and follow the doctors advice carefully.

Levemir may be used in combination with tablets for diabetes or as add-on therapy to liraglutide (Victoza), which is used to treat type 2 diabetes in adults. Levemir can also be used with meal-related rapid acting insulin medicines.

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. Do not change your insulin unless your doctor tells you to.

Use in children

Levemir can be used in adolescents and children aged 2 years and above.

There is no experience with the use of Levemir in children below the age of 2 years.

Use in special patient groups

If you have reduced kidney or liver function, or if you are above 65 years of age, you need to check your blood sugar more regularly and discuss changes in your insulin dose with your doctor.

How often to inject

When Levemir is used in combination with tablets for diabetes or as add-on therapy to liraglutide, 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. Dose of Levemir should be adjusted individually. The injection can be given at any time during the day, but at the same time each day. For patients who require twice daily dosing to optimise blood sugar control, the evening dose can be administered in the evening or at bedtime.

How and where to inject

Levemir is for injection under the skin (subcutaneously). Never inject your insulin directly into a vein (intravenously) or muscle (intramuscularly).
With each injection, change the injection site within the particular area of skin that you use. This may reduce the risk of developing lumps or skin pitting (see section 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 sugar regularly.

How to handle Levemir FlexPen

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

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

Always ensure you use the correct pen before you inject your 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. See Other effects from diabetes in section 4.

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. See Other effects from diabetes in section 4.

If you stop taking your insulin

Do not stop taking your insulin without speaking with a doctor, who will tell you what needs to be done. This could lead to very high blood sugar (severe hyperglycaemia) and ketoacidosis. See Other effects from diabetes in section 4.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

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

Very common side effects
Affecting more than 1 in every 10 people.

Low blood sugar (hypoglycaemia): See details in Other effects from diabetes, below.

Common side effects
Affecting less than 1 in every 10 people.

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.

Uncommon side effects
Affecting less than 1 in every 100 people.

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.

► If you notice any of these, get medical advice immediately.

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): The fatty tissue under the skin at the injection site may shrink (lipoatrophy) or thicken (lipohypertrophy). Changing the site with each injection may help to reduce the risk of developing such skin changes. If you notice your skin pitting or thickening at the injection site, tell your doctor or nurse. 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.

Diabetic retinopathy (an eye disease related to diabetes which can lead to loss of vision): If you have diabetic retinopathy and your blood sugar level improves very fast, the retinopathy may get worse. Ask your doctor about this.

Rare side effects
Affecting less than 1 in every 1,000 people.

Painful neuropathy (pain due to nerve damage): If your blood sugar level improves very fast, you may get nerve related pain, this is called acute painful neuropathy and is usually transient.

Very rare side effects
Affecting less than 1 in every 10,000 people.

Serious allergic reaction to Levemir or one of its ingredients (called a systemic allergic reaction). See also the warning in section 2, Before you use Levemir.

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

Other effects from diabetes

► **Low blood sugar (hypoglycaemia)**

Low blood sugar may occur if you:
- Inject too much insulin.
- Eat too little or miss a meal.
- Exercise more than usual.
- Drink alcohol (See Drinking alcohol and taking Levemir in section 2).

Warning signs of low blood sugar:
The warning signs 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.

What to do if you experience low blood sugar:

► If you experience low blood sugar, eat glucose tablets or another high sugar snack (sweets, biscuits, fruit juice). Measure your blood sugar if possible and rest. Always carry glucose tablets, sweets, biscuits or fruit juice with you, just in case.

When symptoms of low blood sugar have disappeared or when your blood sugar level is stabilised, continue insulin treatment as usual.

► Tell relevant people that you have diabetes and what the consequences may be, including the risk of passing out (become unconscious) due to low blood sugar. Let them know that if you pass out, they must turn you on your side and get medical help straight away. They must not give you any food or drink due to risk of suffocation.

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.

► If prolonged severe low blood sugar is not treated, it can cause brain damage (temporary or permanent) and even death.
► If you have such a low blood sugar that you pass out, if you have had need for injection of glucagon, or if you have experienced many incidents of low blood sugar, talk with a doctor. The amount or timing of insulin, food or exercise may need to be adjusted.

► **High blood sugar (hyperglycaemia)**

High blood sugar may occur if you:
- Have not injected enough insulin.
- Forget to take your insulin or stop taking insulin.
- Repeatedly take less insulin than you need.
- Get an infection and/or a fever.
- Eat more than usual.
- Exercise less than usual.

Warning signs of high blood sugar:
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.

What to do if you experience high blood sugar:
► If you get any of above 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 (build-up of acid in the blood because the body is breaking down fat instead of sugar). If you do not treat it, this could lead to diabetic coma and eventually death.

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.

Before opening: Levemir FlexPen that is not being used is to be stored in the refrigerator at 2°C to 8°C, away from the cooling element. Do not freeze.

During use or when carried as a spare: 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 pen 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 wastewater 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 and Manufacturer

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 S6, P5, K7, R7, VG, FG 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

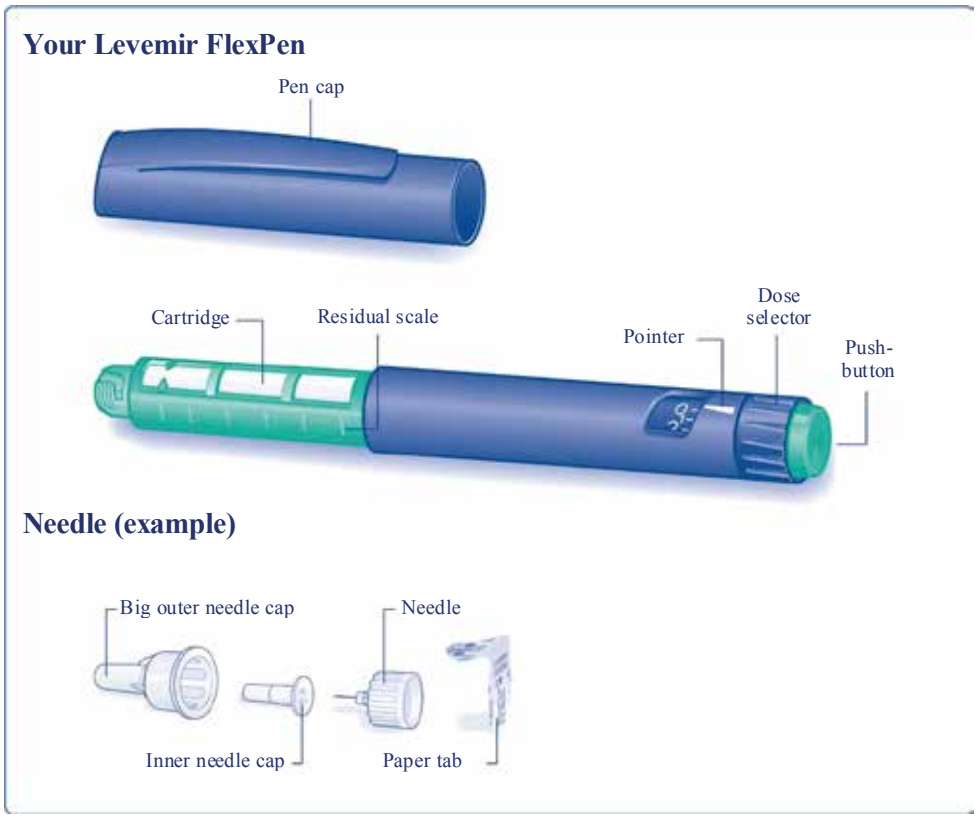
Detailed information on this medicine is available on the website of the European Medicines Agency http://www.ema.europa.eu.

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 precuationary measure, always carry a spare insulin delivery device in case your FlexPen is lost or damaged.



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 pen cap.

B
Take a new needle and tear off the paper tab.

Screw the needle straight and tightly onto your FlexPen.

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

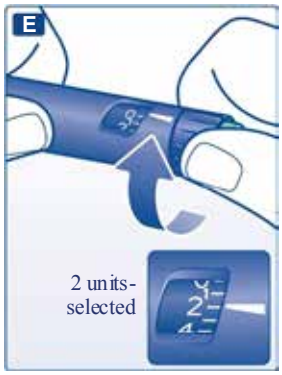
D
Pull off the inner needle cap and dispose of it.

- 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 6 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.

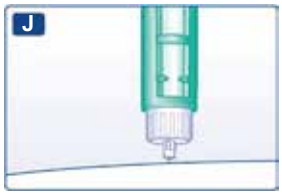
Making the injection

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.

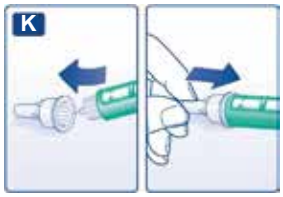
Turning the dose selector will not inject insulin.

J
► Keep the **push-button fully depressed** and let the needle remain under the skin for **at least 6 seconds**. This will make sure you get the full dose.
► Withdraw the needle from the skin then release the pressure on the push-button.



K
Lead the needle into the big outer needle cap without touching it. 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 pen 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.
- Needles and Levemir FlexPen must not be shared.

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

Levemir is a modern insulin (insulin analogue) with a long-acting effect. Modern insulin products are improved versions of human insulin.

Levemir is used to reduce the high blood sugar level in adults, adolescents and children aged 2 years and above with diabetes mellitus (diabetes). Diabetes is a disease where your body does not produce enough insulin to control the level of your blood sugar. Levemir may be used in combination with tablets for diabetes or as add-on therapy to liraglutide (Victoza), which is used to treat type 2 diabetes in adults. Levemir can also be used with meal-related rapid acting insulin medicines.

Levemir has a long and steady blood-sugar-lowering action within 3 to 4 hours after injection. Levemir provides up to 24 hours of basal insulin coverage.

2. Before you use Levemir

Do not use Levemir

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

If any of these applies, do not use Levemir. Talk with your doctor, nurse or pharmacist for advice.

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.

► Needles and Levemir InnoLet must not be shared.

Take special care with Levemir

Some conditions and activities can affect your need for insulin. These include:
► If you have trouble with your kidneys or liver, or with your adrenal, pituitary or thyroid glands.
► If you exercise 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 your injections. Consult your doctor if you are planning such travelling.
► If you have very low albumin you need to carefully monitor your blood sugar level. Discuss this with your doctor.

Using other medicines

Tell your doctor, nurse or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.
Some medicines affect the way blood sugar works in your body and this may influence your insulin dose. Listed below are the most common medicines which may affect your insulin treatment.

<u>Your blood sugar level may fall (hypoglycaemia) if you take:</u>
- 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).

<u>Your blood sugar level may rise (hyperglycaemia) if you take:</u>
- 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 (used 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, a rare hormonal disorder that usually occurs in middle-aged adults, caused by the pituitary gland producing excess growth hormone) may either increase or decrease your blood sugar level.

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

<u>Pioglitazone (tablets used for the treatment of type 2 diabetes)</u>
Some patients with long-standing type 2 diabetes and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

If you have taken any of the medicines listed here, tell your doctor, nurse or pharmacist.

Drinking alcohol and taking Levemir

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

Pregnancy and breast-feeding

► If you are pregnant or planning a pregnancy please contact your doctor for advice. Your insulin dose may need to be changed during pregnancy and after delivery. Careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby.
► If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses.

Ask your doctor or pharmacist for advice before taking any medicine while pregnant or breast-feeding.

Driving and using machines

► Please ask your doctor whether you can drive a car or operate a machine:
• If you have frequent hypoglycaemia.
• If you find it hard to recognise hypoglycaemia.

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.

Important information about some of the ingredients in Levemir

Levemir contains less than 1 mmol sodium (23 mg) per dose, i.e. Levemir is essentially 'sodium-free'.

3. How to use Levemir

Dose and when to take your insulin

Always use your insulin as prescribed by your doctor and follow the doctors advice carefully.

Levemir may be used in combination with tablets for diabetes or as add-on therapy to liraglutide (Victoza), which is used to treat type 2 diabetes in adults. Levemir can also be used with meal-related rapid acting insulin medicines.

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. Do not change your insulin unless your doctor tells you to.

Use in children

Levemir can be used in adolescents and children aged 2 years and above.

There is no experience with the use of Levemir in children below the age of 2 years.

Use in special patient groups

If you have reduced kidney or liver function, or if you are above 65 years of age, you need to check your blood sugar more regularly and discuss changes in your insulin dose with your doctor.

How often to inject

When Levemir is used in combination with tablets for diabetes or as add-on therapy to liraglutide, 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. Dose of Levemir should be adjusted individually. The injection can be given at any time during the day, but at the same time each day. For patients who require twice daily dosing to optimise blood sugar control, the evening dose can be administered in the evening or at bedtime.

How and where to inject

Levemir is for injection under the skin (subcutaneously). Never inject your insulin directly into a vein (intravenously) or muscle (intramuscularly).
With each injection, change the injection site within the particular area of skin that you use. This may reduce the risk of developing lumps or skin pitting (see section 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 sugar regularly.

How to handle Levemir InnoLet

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

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

Always ensure you use the correct pen before you inject your 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. See Other effects from diabetes in section 4.

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. See Other effects from diabetes in section 4.

If you stop taking your insulin

Do not stop taking your insulin without speaking with a doctor, who will tell you what needs to be done. This could lead to very high blood sugar (severe hyperglycaemia) and ketoacidosis. See Other effects from diabetes in section 4.
If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

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

Very common side effects
Affecting more than 1 in every 10 people.

Low blood sugar (hypoglycaemia): See details in Other effects from diabetes, below.

Common side effects
Affecting less than 1 in every 10 people.

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.

Uncommon side effects
Affecting less than 1 in every 100 people.

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.

► If you notice any of these, get medical advice immediately.

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): The fatty tissue under the skin at the injection site may shrink (lipoatrophy) or thicken (lipohypertrophy). Changing the site with each injection may help to reduce the risk of developing such skin changes. If you notice your skin pitting or thickening at the injection site, tell your doctor or nurse. 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.

Diabetic retinopathy (an eye disease related to diabetes which can lead to loss of vision): If you have diabetic retinopathy and your blood sugar level improves very fast, the retinopathy may get worse. Ask your doctor about this.

Rare side effects
Affecting less than 1 in every 1,000 people.

Painful neuropathy (pain due to nerve damage): If your blood sugar level improves very fast, you may get nerve related pain, this is called acute painful neuropathy and is usually transient.

Very rare side effects
Affecting less than 1 in every 10,000 people.

Serious allergic reaction to Levemir or one of its ingredients (called a systemic allergic reaction). See also the warning in section 2, Before you use Levemir.

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

Other effects from diabetes

► **Low blood sugar (hypoglycaemia)**

<u>Low blood sugar may occur if you:</u>
- Inject too much insulin.
- Eat too little or miss a meal.
- Exercise more than usual.
- Drink alcohol (See Drinking alcohol and taking Levemir in section 2).

<u>Warning signs of low blood sugar:</u>
The warning signs 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.

What to do if you experience low blood sugar:

► If you experience low blood sugar, eat glucose tablets or another high sugar snack (sweets, biscuits, fruit juice). Measure your blood sugar if possible and rest. Always carry glucose tablets, sweets, biscuits or fruit juice with you, just in case.

When symptoms of low blood sugar have disappeared or when your blood sugar level is stabilised, continue insulin treatment as usual.

► Tell relevant people that you have diabetes and what the consequences may be, including the risk of passing out (become unconscious) due to low blood sugar. Let them know that if you pass out, they must turn you on your side and get medical help straight away. They must not give you any food or drink due to risk of suffocation.

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.

► If prolonged severe low blood sugar is not treated, it can cause brain damage (temporary or permanent) and even death.
► If you have such a low blood sugar that you pass out, if you have had need for injection of glucagon, or if you have experienced many incidents of low blood sugar, talk with a doctor. The amount or timing of insulin, food or exercise may need to be adjusted.

► **High blood sugar (hyperglycaemia)**

High blood sugar may occur if you:
- Have not injected enough insulin.
- Forget to take your insulin or stop taking insulin.
- Repeatedly take less insulin than you need.
- Get an infection and/or a fever.
- Eat more than usual.
- Exercise less than usual.

Warning signs of high blood sugar:
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.

What to do if you experience high blood sugar:
► If you get any of above 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 (build-up of acid in the blood because the body is breaking down fat instead of sugar). If you do not treat it, this could lead to diabetic coma and eventually death.

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.

Before opening: Levemir InnoLet that is not being used is to be stored in the refrigerator at 2°C to 8°C, away from the cooling element. Do not freeze.

During use or when carried as a spare: 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 pen 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 wastewater 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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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, 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.

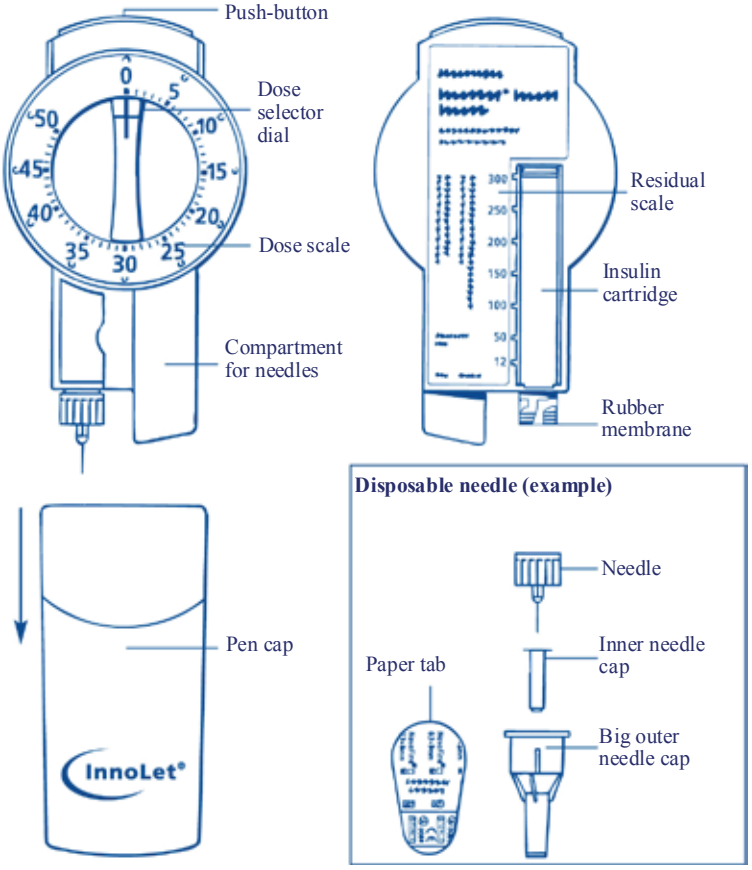
This leaflet was last approved in

Detailed information on this medicine is available on the website of the European Medicines Agency http://www.ema.europa.eu.

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

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

- ► Your InnoLet is a simple, compact pre-filled pen able to deliver 1 to 50 units in increments of 1 unit.
- ► InnoLet is designed to be used with NovoFine or NovoTwist disposable needles up to a length of 8 mm.
- ► Always carry a spare insulin delivery device in case your InnoLet is lost or damaged.

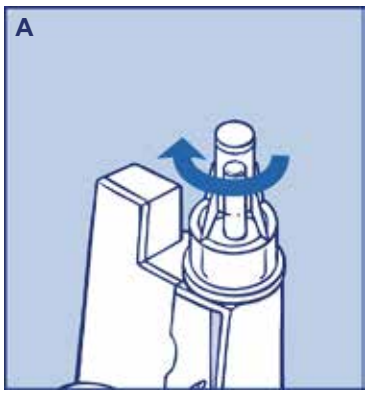


Preparing for injection

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

Attaching the needle

- Always use a new needle for each injection to prevent contamination.
- Take a new needle and tear off the paper tab.
- Screw the needle straight and tightly onto your InnoLet (picture **A**).
- Always use a new 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.

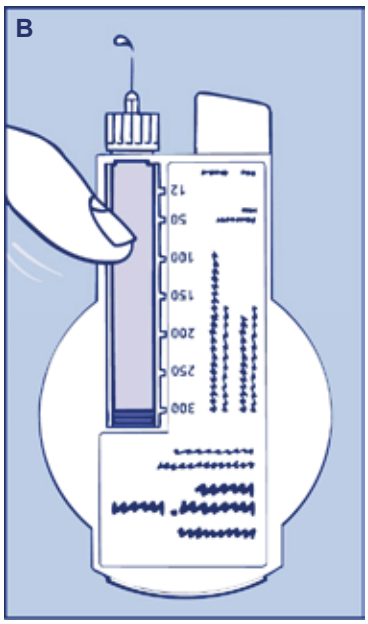


Priming to expel air prior to each injection

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 your 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 0.
- A drop of insulin should appear at the needle tip. If not, change the needle and repeat the procedure no more than 6 times.

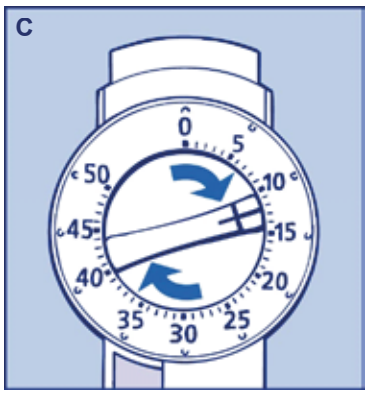
If a drop of insulin still does not appear, the device is defective and must not be used.



Setting the dose

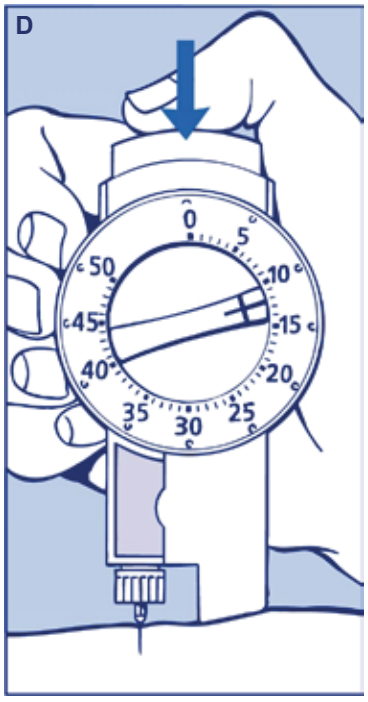
- Always check that the push-button is fully depressed and the dose selector is set to 0.
- Dial the number of units required by turning the dose selector clockwise (picture **C**). Do not use the residual scale to measure your dose of insulin.
- You will hear a click for every single unit dialled. The dose can be corrected by turning the dial either way. Do not turn the dial to correct the dose when the needle is inserted in the skin.

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



Injecting the insulin

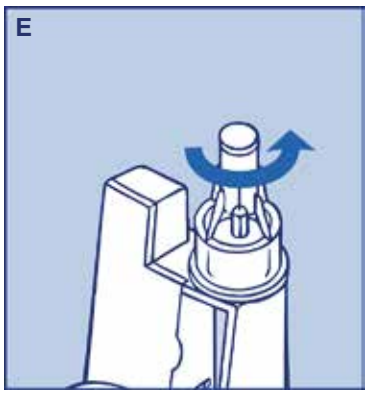
- Insert the needle into your skin. Use the injection technique advised by your doctor.
- Deliver the dose by pressing the push-button fully down (picture **D**). You will hear clicks as the dose selector returns to 0.
- After the injection, the needle should remain under the skin for **at least 6 seconds** 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 0 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 your InnoLet without the needle attached. Otherwise the liquid may leak out which can cause inaccurate dosing.
Healthcare professionals, relatives and other carers should follow general precautionary measures for removal and disposal of needles to eliminate the risk of unintended needlesticks.
Dispose of your used InnoLet carefully without the needle attached.
Needles and Levemir InnoLet must not be shared.



Maintenance

Your 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.

Do not refill your InnoLet.
You can clean your 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.

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

Levemir is a modern insulin (insulin analogue) with a long-acting effect. Modern insulin products are improved versions of human insulin.

Levemir is used to reduce the high blood sugar level in adults, adolescents and children aged 2 years and above with diabetes mellitus (diabetes). Diabetes is a disease where your body does not produce enough insulin to control the level of your blood sugar. Levemir may be used in combination with tablets for diabetes or as add-on therapy to liraglutide (Victoza), which is used to treat type 2 diabetes in adults. Levemir can also be used with meal-related rapid acting insulin medicines.

Levemir has a long and steady blood-sugar-lowering action within 3 to 4 hours after injection. Levemir provides up to 24 hours of basal insulin coverage.

2. Before you use Levemir

Do not use Levemir

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

If any of these applies, do not use Levemir. Talk with your doctor, nurse or pharmacist for advice.

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.

► Needles and Levemir FlexTouch must not be shared.

Take special care with Levemir
Some conditions and activities can affect your need for insulin. These include:
► If you have trouble with your kidneys or liver, or with your adrenal, pituitary or thyroid glands.
► If you exercise 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 your injections. Consult your doctor if you are planning such travelling.
► If you have very low albumin you need to carefully monitor your blood sugar level. Discuss this with your doctor.

Using other medicines
Tell your doctor, nurse or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. Some medicines affect the way blood sugar works in your body and this may influence your insulin dose. Listed below are the most common medicines which may affect your insulin treatment.

Your blood sugar level may fall (hypoglycaemia) if you take:
- 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).

Your blood sugar level may rise (hyperglycaemia) if you take:
- 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 (used 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, a rare hormonal disorder that usually occurs in middle-aged adults, caused by the pituitary gland producing excess growth hormone) may either increase or decrease your blood sugar level.

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

Pioglitazone (tablets used for the treatment of type 2 diabetes)
Some patients with long-standing type 2 diabetes and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

If you have taken any of the medicines listed here, tell your doctor, nurse or pharmacist.

Drinking alcohol and taking Levemir

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

Pregnancy and breast-feeding

► If you are pregnant or planning a pregnancy please contact your doctor for advice. Your insulin dose may need to be changed during pregnancy and after delivery. Careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby.
► If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses.

Ask your doctor or pharmacist for advice before taking any medicine while pregnant or breast-feeding.

Driving and using machines

► Please ask your doctor whether you can drive a car or operate a machine:
• If you have frequent hypoglycaemia.
• If you find it hard to recognise hypoglycaemia.

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.

Important information about some of the ingredients in Levemir

Levemir contains less than 1 mmol sodium (23 mg) per dose, i.e. Levemir is essentially 'sodium-free'.

3. How to use Levemir

Dose and when to take your insulin

Always use your insulin as prescribed by your doctor and follow the doctors advice carefully.

Levemir may be used in combination with tablets for diabetes or as add-on therapy to liraglutide (Victoza), which is used to treat type 2 diabetes in adults. Levemir can also be used with meal-related rapid acting insulin medicines.

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. Do not change your insulin unless your doctor tells you to.

Use in children

Levemir can be used in adolescents and children aged 2 years and above.

There is no experience with the use of Levemir in children below the age of 2 years.

Use in special patient groups

If you have reduced kidney or liver function, or if you are above 65 years of age, you need to check your blood sugar more regularly and discuss changes in your insulin dose with your doctor.

How often to inject

When Levemir is used in combination with tablets for diabetes or as add-on therapy to liraglutide, 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. Dose of

Levemir should be adjusted individually. The injection can be given at any time during the day, but at the same time each day. For patients who require twice daily dosing to optimise blood sugar control, the evening dose can be administered in the evening or at bedtime.

How and where to inject

Levemir is for injection under the skin (subcutaneously). Never inject your insulin directly into a vein (intravenously) or muscle (intramuscularly).
With each injection, change the injection site within the particular area of skin that you use. This may reduce the risk of developing lumps or skin pitting (see section 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 sugar regularly.

How to handle Levemir FlexTouch

Levemir FlexTouch is a pre-filled, colour-coded, disposable pen containing insulin detemir.

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

Always ensure you use the correct pen before you inject your 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. See Other effects from diabetes in section 4.

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. See Other effects from diabetes in section 4.

If you stop taking your insulin

Do not stop taking your insulin without speaking with a doctor, who will tell you what needs to be done.This could lead to very high blood sugar (severe hyperglycaemia) and ketoacidosis. See Other effects from diabetes in section 4.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

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

Very common side effects
Affecting more than 1 in every 10 people.

Low blood sugar (hypoglycaemia): See details in Other effects from diabetes, below.

Common side effects
Affecting less than 1 in every 10 people.

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.

Uncommon side effects
Affecting less than 1 in every 100 people.

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.

► If you notice any of these, get medical advice immediately.

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): The fatty tissue under the skin at the injection site may shrink (lipoatrophy) or thicken (lipohypertrophy). Changing the site with each injection may help to reduce the risk of developing such skin changes. If you notice your skin pitting or thickening at the injection site, tell your doctor or nurse. 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.

Diabetic retinopathy (an eye disease related to diabetes which can lead to loss of vision): If you have diabetic retinopathy and your blood sugar level improves very fast, the retinopathy may get worse. Ask your doctor about this.

Rare side effects
Affecting less than 1 in every 1,000 people.

Painful neuropathy (pain due to nerve damage): If your blood sugar level improves very fast, you may get nerve related pain, this is called acute painful neuropathy and is usually transient.

Very rare side effects
Affecting less than 1 in every 10,000 people.

Serious allergic reaction to Levemir or one of its ingredients (called a systemic allergic reaction). See also the warning in section 2, Before you use Levemir.

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

Other effects from diabetes

► **Low blood sugar (hypoglycaemia)**

Low blood sugar may occur if you:
- Inject too much insulin.
- Eat too little or miss a meal.
- Exercise more than usual.
- Drink alcohol (See Drinking alcohol and taking Levemir in section 2).

Warning signs of low blood sugar:
The warning signs 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.

What to do if you experience low blood sugar:

► If you experience low blood sugar, eat glucose tablets or another high sugar snack (sweets, biscuits, fruit juice). Measure your blood sugar if possible and rest. Always carry glucose tablets, sweets, biscuits or fruit juice with you, just in case.

When symptoms of low blood sugar have disappeared or when your blood sugar level is stabilised, continue insulin treatment as usual.

► Tell relevant people that you have diabetes and what the consequences may be, including the risk of passing out (become unconscious) due to low blood sugar. Let them know that if you pass out, they must turn you on your side and get medical help straight away. They must not give you any food or drink due to risk of suffocation.

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.

► If prolonged severe low blood sugar is not treated, it can cause brain damage (temporary or permanent) and even death.
► If you have such a low blood sugar that you pass out, if you have had need for injection of glucagon, or if you have experienced many incidents of low blood sugar, talk with a doctor. The amount or timing of insulin, food or exercise may need to be adjusted.

► **High blood sugar (hyperglycaemia)**

High blood sugar may occur if you:
- Have not injected enough insulin.
- Forget to take your insulin or stop taking insulin.
- Repeatedly take less insulin than you need.
- Get an infection and/or a fever.
- Eat more than usual.
- Exercise less than usual.

Warning signs of high blood sugar:
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.

What to do if you experience high blood sugar:
► If you get any of above 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 (build-up of acid in the blood because the body is breaking down fat instead of sugar). If you do not treat it, this could lead to diabetic coma and eventually death.

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 FlexTouch label and carton after 'EXP.' The expiry date refers to the last day of that month.

Before opening: Levemir FlexTouch that is not being used is to be stored in the refrigerator at 2°C to 8°C, away from the cooling element. Do not freeze.

During use or when carried as a spare: Levemir FlexTouch 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 pen cap on your FlexTouch 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 wastewater 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 a multipack with 2 x 5 (without needles) pre-filled pens of 3 ml. Not all pack sizes 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 FlexTouch.

This leaflet was last approved in

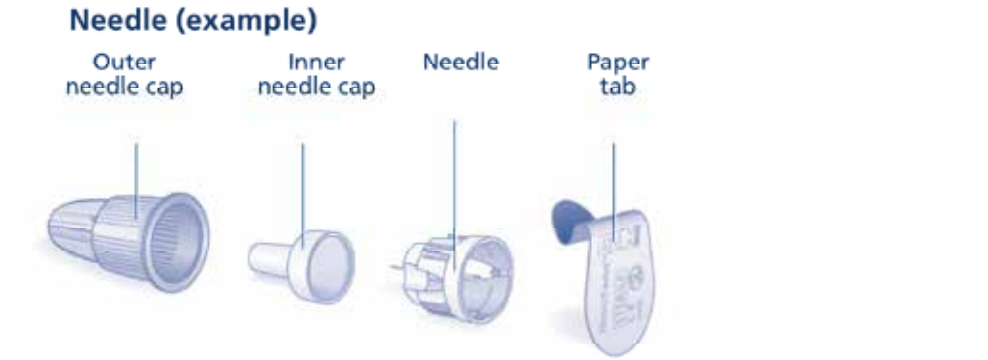
Detailed information on this medicine is available on the website of the European Medicines Agency http://www.ema.europa.eu.

Instructions on how to use Levemir FlexTouch

Please read these instructions carefully before using your Levemir FlexTouch pen. Use the coloured label to make sure that your FlexTouch pen contains the type of insulin you need.

Your Levemir FlexTouch pen is an easy-to-use pre-filled insulin pen with a light-touch dose button.

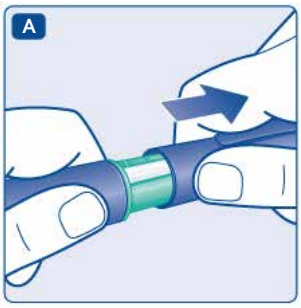
Levemir FlexTouch contains 300 units of insulin and delivers doses from 1 to 80 units, in increments of 1 unit. Levemir FlexTouch is designed to be used with NovoFine or NovoTwist disposable needles up to a length of 8 mm.



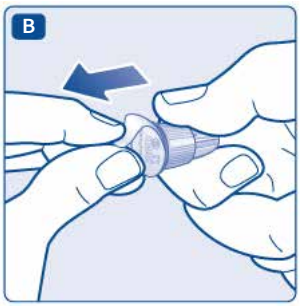
Preparing your Levemir FlexTouch pen

Check the coloured label on your Levemir FlexTouch pen to make sure that it contains the type of insulin you need.

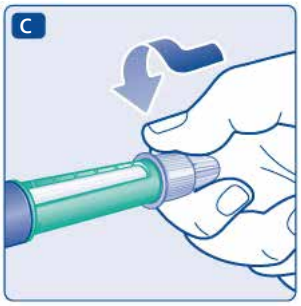
A Pull off the pen cap.



B Take a new disposable needle and tear off the paper tab.



C Screw the needle straight onto the pen. Make sure the needle is on tight.

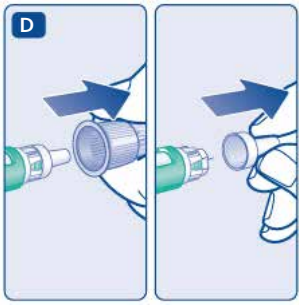


D Pull off the outer needle cap and save it.
You will need it after the injection, to safely remove the needle from the pen.

Pull off the inner needle cap and throw it away.

If you try to put it back on, you may accidentally hurt yourself with the needle.

A drop of insulin may appear at the needle tip. This is normal.



- Always use a new needle for each injection as this will prevent contamination and blocked needles.
- Never bend or damage the needle.

Checking the insulin flow

Make sure that you receive your full dose by always checking the insulin flow before you select and inject your dose.

E Turn the dose selector to select 2 units.

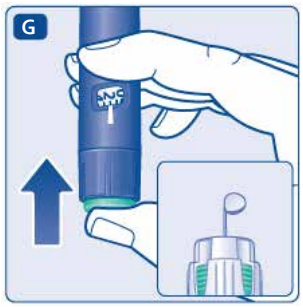
F Hold the pen with the needle pointing up.

Tap the top of the pen a few times to let any air bubbles rise to the top.

G Press the dose button with your thumb until the display returns to zero. The figure 0 lines up with the pointer. A drop of insulin will appear at the needle tip.

If no drop appears, repeat steps **E** to **G** up up to 6 times. If no drop appears after these new attempts, change the needle and repeat steps **E** to **G** once more.

Do not use the pen if a drop of insulin still does not appear.



- Always make sure that a drop appears at the needle tip before you inject.

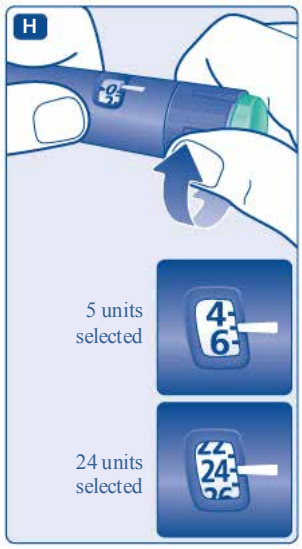
Selecting your dose

Use the dose selector on your Levemir FlexTouch pen to ensure exact and easy dose selection. You can select up to 80 units per dose.

H Select the dose you need. You can turn the dose selector forwards or backwards. Stop when the right number of units lines up with the pointer.

The dose selector clicks differently when turned forwards, backwards or past the number of units left.

When the pen contains less than 80 units, the display stops at the number of units left.



- How much insulin is left?

  You can use the insulin scale to see approximately how much insulin is left in the pen.

  You can use the display to see exactly how much insulin is left – if the pen contains less than 80 units: Turn the dose selector until the display stops. The figure that lines up with the pointer shows how many units are left.

- Never use the pen clicks to count the number of units you **select**. Only the display and pointer will indicate the exact number of units.

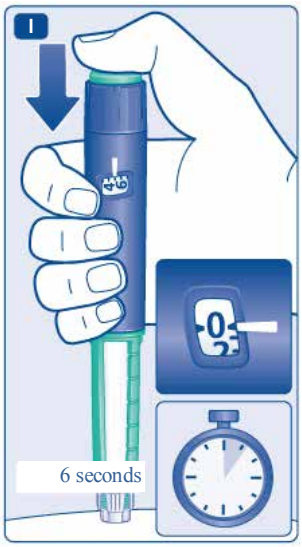
- Never use the insulin scale to measure how much insulin to inject. Only the display and pointer will indicate the exact number of units.

Injecting your dose

Make sure that you receive your full dose by using the right injection technique.

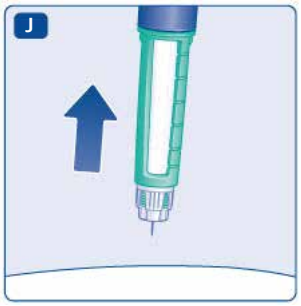
I Insert the needle into your skin as your doctor or nurse has shown you. Make sure you can see the display. Press the dose button until the display returns to zero. The figure 0 lines up with the pointer, and you may hear or feel a click.

- After the display has returned to zero, leave the needle under the skin for **at least 6 seconds** to make sure that you get your full dose.



J Remove the needle from the skin.

After that, you may see a drop of insulin at the needle tip. This is normal and has no effect on the dose you just received.

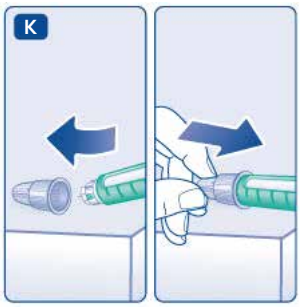


- Always remove and dispose of the needle after each injection to prevent blocked needles. If the needle is blocked, you will **not** receive your full dose.

K Lead the needle tip into the outer needle cap on a flat surface. Do not touch the needle or the cap.

Once the needle is covered, carefully push the outer needle cap completely on and then unscrew the needle. Dispose of it carefully, and put the pen cap back on after every use.

When the pen is empty, throw it away without a needle on as instructed by your doctor, nurse, pharmacist or local authorities.



- Never use the pen clicks to count the number of units you **inject**. Only the display and pointer will indicate the exact number of units.

- Never touch the display when you inject, as this can block the injection.
- Never put the inner needle cap back on once you have removed it from the needle. This reduces the risk of hurting yourself with the needle.
- Always store the pen without a needle attached. This prevents contamination, infection and leakage of insulin and ensures accurate dosing.

Caring for your Levemir FlexTouch pen

Your Levemir FlexTouch pen is accurate and safe to use. However, you must take care of it:

- Do not drop your pen or knock it against hard surfaces. If you do drop it or suspect that something is wrong with it, always screw on a new disposable needle and check the insulin flow before you inject.
- Do not try to refill your pen – it is pre-filled.
- Do not try to repair your pen or pull it apart.
- Do not expose your pen to dust, dirt or any kind of liquid.
- Do not try to wash, soak or lubricate your pen. If necessary, clean it with a mild detergent on a moistened cloth.
- See section 5, How to store Levemir in this leaflet for information on how to store your pen.
- **Important information**
- Always carry an extra Levemir FlexTouch in case you lose or damage your current pen. Also carry new disposable needles.
- Always keep your pen and needles out of reach of others, especially children.
- Needles and Levemir FlexTouch must not be shared.
- Caregivers should be most careful when handling used needles to avoid hurting themselves.