Levemir®
FlexPen®

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

Qualitative and quantitative composition
1 ml of the solution contains 100 U of 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*.
1 unit (U) of insulin detemir corresponds to 1 international unit (IU) of human insulin.

Pharmaceutical form
Clear, colourless, neutral solution for injection in pre-filled pen. FlexPen®.

Therapeutic indications
Treatment of diabetes mellitus in adults, adolescents and children aged 1 year and above.

Posology
Levemir® is a soluble, basal insulin analogue with a prolonged duration of effect (up to 24 hours). Compared to other insulin products, basal-bolus therapy with Levemir® is not associated with weight gain.
The lower risk of nocturnal hypoglycaemia compared to NPH (Neutral Protamine Hagedorn) insulin allows a more intensive titration towards target blood glucose levels for basal-bolus therapy. Levemir® provides better glycaemic control as measured by Fasting Plasma Glucose (FPG) compared to NPH insulin treatment.
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 and/or GLP-1 receptor agonists.

Dosage
When Levemir® is used in combination with oral antidiabetic medicinal products or when added to GLP-1 receptor agonists, it is recommended to use Levemir® once daily, initially at a dose of 0.1–0.2 U/kg, or of 10 U **in adult patients.** The dose of Levemir® should be titrated based on the individual patient's needs.

When a GLP-1 receptor agonist is added to Levemir®, it is recommended to reduce the dose of Levemir® by 20% to minimise the risk of hypoglycaemia. Subsequently, dosage should be adjusted individually.

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For individual dose adjustments, the following two titration guidelines are recommended **for adults:**

Adult type 2 diabetes titration guideline:

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
4.1–6.0 mmol/l (73–108 mg/dl)	no change (target)
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

Adult type 2 diabetes simple self-titration guideline:

Average pre-breakfast SMPG*	Levemir® dose adjustment
> 6.1 mmol/l (> 110 mg/dl)	+3 U
4.4–6.1 mmol/l (80–110 mg/dl)	no change (target)
< 4.4 mmol/l (< 80 mg/dl)	-3 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 the patient's needs. The dose of Levemir® should be adjusted individually.
For patients who require twice-daily dosing to optimise blood glucose control, the evening dose can be administered in the evening or at bedtime. Adjustment of dose may be necessary if patients undertake increased physical activity, change their usual diet or during concomitant illness.

Special populations
As with all insulin products, in elderly patients and patients with renal or hepatic impairment, glucose monitoring should be intensified and the Levemir® dosage adjusted on an individual basis.

Paediatric population
Levemir® can be used in adolescents and children from the age of 1 year (see *Pharmacodynamic properties*). When changing basal insulin to Levemir®, dose reduction of basal and bolus insulin needs to be considered on an individual basis, in order to minimise the risk of hypoglycaemia (see *Special warnings and precautions for use*).

In children and adolescents, glucose monitoring should be intensified and the Levemir® dose adjusted on an individual basis.

The safety and efficacy of Levemir® in children below the age of 1 year has not been established. No data are available.

Transfer from other insulin products
Transfer to Levemir® from intermediate or long-acting insulin products may require adjustment of dose and timing of administration (see *Special warnings and precautions for use*).
As with all insulin products, close glucose monitoring is recommended during the transfer and in the initial weeks thereafter.
Concomitant antidiabetic treatment may need to be adjusted (dose and/or timing of oral antidiabetic medicines or concurrent short-acting insulin products).

Method of administration
Levemir® is for subcutaneous administration **only.**
Levemir® must not be administered intravenously, as it may result in severe hypoglycaemia. Intramuscular administration should also be avoided. Levemir® is not to be used in insulin infusion pumps.
Levemir® is administered subcutaneously by injection in the abdominal wall, the thigh, the upper arm, the deltoid region or the gluteal region. Injection sites should always be rotated within the same region in order to reduce the risk of lipodystrophy. As with all insulin products, the duration of action will vary according to the dose, injection site, blood flow, temperature and level of physical activity.
Levemir® FlexPen® is a pre-filled pen 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.
Levemir® FlexPen® is colour-coded and accompanied by a package leaflet with detailed instructions for use to be followed.

Contraindications
Hypersensitivity to the active substance or to any of the excipients (see *List of excipients*).

Special warnings and precautions for use
Before travelling between different time zones, the patient should seek the doctor's advice since this means 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.
In children, care should be taken to match insulin doses (especially in basal-bolus regimens) with food intake and physical activities in order to minimise the risk of hypoglycaemia.

Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement (see *Undesirable effects* and *Overdose*).
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 requirement. Concomitant diseases in the kidney, liver or affecting the adrenal, pituitary or thyroid gland can require changes in the insulin dose.

Transfer from other insulin products
Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type, origin (human insulin, insulin analogue) and/or method of manufacture may result in the need for a change in dosage. Patients transferred to Levemir® from another type of insulin may require a change in dosage from that used with their usual insulin 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®.

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

Avoidance of accidental mix-ups/medication errors
Patients must be instructed to always check the insulin label before each injection to avoid accidental mix-ups between Levemir® and other insulin products.

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, GLP-1 receptor agonists, monoamine oxidase inhibitors (MAOIs), beta-blockers, angiotensin converting enzyme (ACE) inhibitors, salicylates, anabolic steroids and sulfonamides.

The following substances may increase the patient's insulin requirements:
Oral contraceptives, thiazides, glucocorticoids, thyroid hormones, sympathomimetics, growth hormone and danazol.
Beta-blocking agents may mask the symptoms of hypoglycaemia.
Octreotide/lanreotide may either increase or decrease the insulin requirement.
Alcohol may intensify or reduce the hypoglycaemic effect of insulin.

Pregnancy and lactation
Pregnancy
Treatment with Levemir® can be considered during pregnancy if the benefit justifies possible risks.
One randomised controlled clinical trial in pregnant women with type 1 diabetes compared Levemir® (n = 152) to NPH insulin (n = 158), both in combination with insulin aspart. The results showed similar efficacy of insulin detemir and NPH insulin and a similar overall safety profile during pregnancy, on pregnancy outcomes as well as on the foetus and the newborn (see *Pharmacodynamic properties*).
Post-marketing data from an additional approximately 300 outcomes from pregnant women exposed to Levemir® indicate no adverse effects of insulin detemir on pregnancy and no malformative or foeto/neonatal toxicity of insulin detemir.
Animal data do not indicate reproductive toxicity (see *Preclinical safety data*).
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.

Lactation
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.

Effects on ability to drive and use machines
The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery).
Patients should be advised to take precautions to avoid hypoglycaemia while driving. This is particularly important in those who have reduced or absent awareness of the warning signs of hypoglycaemia or have frequent episodes of hypoglycaemia. The advisability of driving should be considered in these circumstances.

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

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

From clinical investigations it is known that major 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 a 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 (painful 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 reduces the risk of developing these reactions.

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.

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 basal insulin analogue with a prolonged duration of effect used as a basal insulin.
The time action profile of Levemir® is significantly less variable than NPH insulin and insulin glargine.

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 Levemir® compared to NPH insulin.
The duration of action is up to 24 hours depending on dose providing an opportunity for once- or twice-daily administration. If administered twice daily, steady state will occur after 2–3 dose administrations. For doses in the interval of 0.2–0.4 U/kg, Levemir® exerts more than 50% of its maximum effect from 3–4 hours and up to approximately 14 hours after dose administration. Dose proportionality in pharmacodynamic response (maximum effect, duration of action, total effect) is observed after subcutaneous administration.
Lower day-to-day variability in FPG was demonstrated during treatment with Levemir® compared to NPH in long-term clinical trials.
Studies in patients with type 2 diabetes treated with basal insulin in combination with oral antidiabetic medicines demonstrated that glycaemic control (HbA_{1c}) with Levemir® is comparable to NPH insulin and insulin glargine and associated with less weight gain, see Table 1.

Table 1. 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 with the use of OAD-insulin combination therapy, Levemir® treatment resulted in a 61–65% lower risk of minor nocturnal hypoglycaemia compared to NPH insulin.
An open-label randomised clinical trial in patients with type 2 diabetes not reaching target with oral antidiabetic 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 (n = 160) or continue on liraglutide+metformin (n = 149) for 52 weeks. Addition of Levemir® provided a further reduction of HbA_{1c} of 0.51% and 0.50% (from 7.6% to 7.1%) after 26 and 52 weeks, whereas no changes were seen for liraglutide+metformin (0.02% and 0.01% after 26 and 52 weeks); the changes were significant with addition of Levemir® after 26 and 52 weeks ($p < 0.0001$). The proportions of patients achieving the HbA_{1c} < 7% target were higher with addition of Levemir® compared to liraglutide+metformin after 26 weeks (43.1% vs 16.8%; $p < 0.0001$) and 52 weeks (51.9% vs 21.5%; $p < 0.0001$). There were no major hypoglycaemic episodes. Minor hypoglycaemic episodes (per patient year) were higher with addition of Levemir® compared to liraglutide+metformin after 26 weeks (0.286 vs 0.029; $p = 0.0037$) and after 52 weeks (0.228 vs 0.034; $p = 0.0011$). When adding Levemir® to liraglutide, the weight benefit of liraglutide was sustained; after 26 weeks weight changes with addition of Levemir® and liraglutide+metformin were -0.16 kg vs -0.95 kg ($p = 0.0283$) and after 52 weeks -0.05 kg vs -1.02 kg ($p = 0.0416$).

A 26-week, double blind, randomised clinical trial was conducted to investigate the efficacy and safety of adding liraglutide (1.8 mg) vs placebo in patients with type 2 diabetes inadequately controlled on basal insulin with or without metformin. The insulin dose was reduced by 20% for patients with baseline $HbA_{1c} \leq 8.0\%$ in order to minimise the risk of hypoglycaemia. Subsequently, patients were allowed to up-titrate their insulin dose to no higher than the pre-randomisation dose. Levemir® was the basal insulin product for 33% (n = 147) of the patients (97.3% using metformin). In these patients, addition of liraglutide resulted in a greater decline in HbA_{1c} compared to addition of placebo (to 6.93% vs to 8.24%), a greater decline in fasting plasma glucose (to 7.20 mmol/l vs to 8.13 mmol/l), and a greater decline in body weight (-3.47 kg vs -0.43 kg). Baseline values for these parameters were similar in the two groups. Observed rates of minor hypoglycaemic episodes were similar and no severe hypoglycaemic episodes were observed in either group.

In long-term trials (≥ 6 months) 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. The nocturnal glucose profile is flatter and smoother with Levemir® than with NPH insulin, resulting in a lower risk of nocturnal hypoglycaemia.
Antibody development has been observed with the use of Levemir®. However, this does not appear to have any impact on glycaemic control.

Pregnancy
In a randomised controlled clinical trial, pregnant women with type 1 diabetes (n = 310) were treated in a basal-bolus regimen where Levemir® (n = 152) was compared to NPH insulin (n = 158) with insulin aspart as mealtime insulin. Levemir® was shown to be non-inferior to NPH insulin measured by HbA_{1c} at gestational week 36. The development in mean HbA_{1c} through pregnancy was similar for subjects in the Levemir® and NPH insulin groups. The target of $HbA_{1c} \leq 6.0\%$ at both gestational week 24 and 36 was reached by 41% of the subjects in the Levemir® group and by 32% in the NPH insulin group. At gestational week 24 and 36, mean FPG was statistically significantly lower in the Levemir® group than in the NPH insulin group. There was no statistically significant difference between Levemir® and NPH insulin treatment groups in the rate of hypoglycaemic episodes during pregnancy. The overall frequencies of maternal adverse events during pregnancy were similar for Levemir® and NPH insulin treatment groups; however, a numerically higher frequency of serious adverse events during pregnancy in the mothers (61 (40%) vs 49 (31%)) and in the offspring during pregnancy and after birth (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 insulin. The frequency of children with congenital malformations was 4 (5%) in the Levemir® group and 11 (7%) in the NPH insulin group. Thereof, 3 (4%) children in the Levemir® group and 3 (2%) children in the NPH insulin group had major malformations.

Paediatric population
The efficacy and safety of Levemir® has been studied for up to 12 months in three randomised controlled clinical trials in adolescents and children with type 1 diabetes aged 1 year and above (n = 1,045 in total); the trials included in total 167 children aged 1–5 years. The trials demonstrated that glycaemic control (HbA_{1c}) with Levemir® is comparable to NPH insulin and insulin degludec when given as basal-bolus therapy. In the trial comparing Levemir® vs insulin degludec, the rate of hyperglycaemic episodes with ketosis was significantly higher for Levemir®, 1.09 and 0.68 episodes per patient-year of exposure, respectively. A lower rate of nocturnal hypoglycaemia (based on SMPG (Self Monitoring Plasma Glucose) measurements) and less weight gain (SD score, weight corrected for gender and age) were observed with insulin detemir than with NPH insulin. One trial 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 insulin detemir dose.

Efficacy and safety data for adolescent patients with type 2 diabetes mellitus have been extrapolated from data for children, adolescent and adult patients with type 1 diabetes mellitus and adult patients with type 2 diabetes mellitus. Results support the use of Levemir® in adolescent patients with type 2 diabetes mellitus.

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.

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 demonstrate that there is no clinically relevant interaction between insulin detemir and fatty acids or other protein bound drugs.

Metabolism
Degradation of Levemir® 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. There are no clinically relevant differences between genders in pharmacokinetic properties of Levemir®. 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
The pharmacokinetic properties of Levemir® were investigated in young children (1 to 5 years), children (6 to 12 years) and adolescents (13 to 17 years) and compared to adults with type 1 diabetes. There were no clinical differences in pharmacokinetic properties between young children, children, adolescents and adults. There were no clinically relevant differences in the pharmacokinetics of Levemir® between elderly and young patients, or between patients with renal or hepatic impairment and healthy subjects.

Preclinical safety data
In vitro tests in human cell lines investigating binding to the insulin and IGF-1 receptor sites have shown that insulin detemir has a reduced affinity to both receptors as well as a reduced effect on cell growth compared to human insulin. Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential or toxicity to reproduction.

Pharmaceutical particulars
List of excipients
Glycerol, phenol, metacresol, zinc acetate, disodium phosphate dihydrate, sodium chloride, hydrochloric acid/sodium hydroxide (for pH adjustment) and water for injections.

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

Special precautions for storage
Before opening: Store in a refrigerator (2°C–8°C). Keep away from the cooling element. Do not freeze. Keep the pen cap on Levemir® FlexPen® in order to protect from light. Levemir® must be protected from excessive heat and light.
During use or when carried as a spare: Store below 30°C. Can be stored in a refrigerator (2°C–8°C). Use within 6 weeks. Do not freeze.

Nature and contents of container
3 ml solution in cartridge (type 1 glass) with a plunger (bromobutyl) and a rubber closure (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.

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.

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

INSTRUCTIONS FOR USE FOR THE PATIENT

Do not use Levemir®
- ▶ **If you are allergic (hypersensitive)** to insulin detemir or any of the other ingredients in Levemir®.
- ▶ **If you suspect hypoglycaemia (low blood sugar)** is starting.
- ▶ **In insulin infusion pumps.**
- ▶ **If FlexPen® is dropped, damaged or crushed.**
- ▶ **If it has not been stored correctly** or if it has been frozen.
- ▶ **If the insulin does not appear water clear and colourless.**
- ▶ **After the expiry date which is stated on the FlexPen® label and carton after 'Expiry'.**

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.**

Method of administration
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. 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.

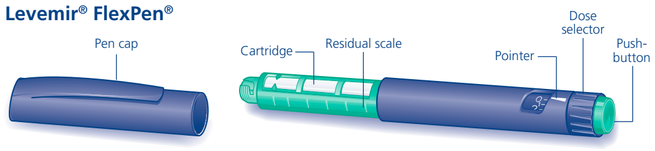
How to handle Levemir® FlexPen®
Read and follow the included Levemir® FlexPen® instructions for use carefully.

Instructions on how to use LEVEMIR® solution for injection in a FlexPen®

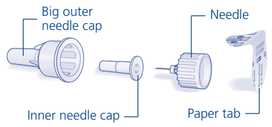
Read the following instructions carefully before using your FlexPen®. If you do not follow the instructions carefully, you may get too little or too much insulin, which can lead to too high or too low blood sugar level.

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

Levemir® FlexPen®



Needle (example)



Caring for your pen

Your FlexPen® must be handled with care.
If it is dropped, damaged or crushed, there is a risk of insulin leakage. This may cause inaccurate dosing, which can lead to too high or too low blood sugar level.

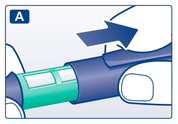
You can clean the exterior of your FlexPen® by wiping it with a medicinal swab. Do not soak it, wash or lubricate it as it may damage the pen.

Do not refill your FlexPen®.

Preparing your Levemir® FlexPen®

Check the name and coloured label of your pen to make sure that it contains the correct type of insulin. This is especially important if you take more than one type of insulin. If you take the wrong type of insulin, your blood sugar level may get too high or too low.

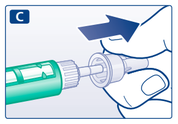
A Pull off the pen cap.



B Remove the paper tab from a new disposable needle.

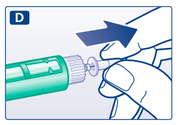
Screw the needle straight and tightly onto your FlexPen®.

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



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

Never try to put the inner needle cap back on the needle. You may stick yourself with the needle.

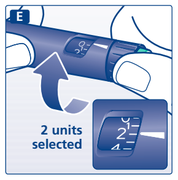


⚠ Always use a new needle for each injection. This reduces the risk of contamination, infection, leakage of insulin, blocked needles and inaccurate dosing.
⚠ Be careful not to bend or damage the needle before use.

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.

⚠ Always make sure that a drop appears at the needle tip before you inject. This makes sure that the insulin flows. If no drop appears, you will not inject any insulin, even though the dose selector may move. This may indicate a blocked or damaged needle.
⚠ Always check the flow before you inject. If you do not check the flow, you may get too little insulin or no insulin at all. This may lead to too high blood sugar level.

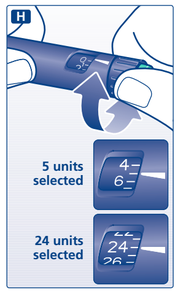
Selecting your dose

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.



⚠ Always use the dose selector and the pointer to see how many units you have selected before injecting the insulin.
⚠ Do not count the pen clicks. If you select and inject the wrong dose, your blood sugar level may get too high or too low. Do not use the residual scale, it only shows approximately how much insulin is left in your pen.

Further important information

⚠ Caregivers must be very careful when handling used needles – to reduce the risk of needle sticks and cross-infection.
⚠ Dispose of your used FlexPen® carefully without the needle attached.
⚠ Never share your pen or your needles with other people. It might lead to cross-infection.
⚠ Never share your pen with other people. Your medicine might be harmful to their health.
⚠ Always keep your pen and needles out of sight and reach of others, especially children.

Making the injection

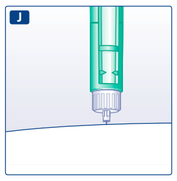
Insert the needle into your skin. Use the injection technique shown by your doctor or nurse.

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.

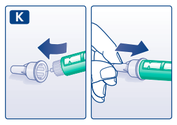
J Keep the push-button fully depressed and let the needle remain under the skin for at least 6 seconds. This will make sure you get the full dose. Withdraw the needle from the skin then release the pressure on the push-button.

Always make sure that the dose selector returns to 0 after the injection. If the dose selector stops before it returns to 0, the full dose has not been delivered, which may result in too high blood sugar level.



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 your FlexPen®.



⚠ Always remove the needle after each injection and store your FlexPen® without the needle attached. This reduces the risk of contamination, infection, leakage of insulin, blocked needles and inaccurate dosing.

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