

PRODUCT MONOGRAPH

Levemir[®]

(insulin detemir)

Levemir[®] Penfill[®] 100 U/mL, Solution for Injection in a cartridge

Solution for Injection

House Standard

Antidiabetic Agent

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Levemir[®]

(insulin detemir)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

| Route of Administration | Dosage Form / Strength | Clinically Relevant Nonmedicinal Ingredients |
|-------------------------|-----------------------------------|--|
| subcutaneous | solution for injection / 100 U/mL | disodium phosphate dihydrate, glycerol, metacresol, phenol, sodium chloride, acetate and water for injection. Hydrochloric acid and/or sodium hydroxide may be added to adjust pH. |

DESCRIPTION

Levemir[®] (insulin detemir) is a sterile solution of insulin detemir for use as an injection. Insulin detemir is a long-acting basal insulin analogue, with up to 24 hours duration of action, produced by a process that includes expression of recombinant DNA in *Saccharomyces cerevisiae* followed by chemical modification.

INDICATIONS AND CLINICAL USE

Levemir[®] (insulin detemir) is indicated for:

- the treatment of adult patients with type 1 or type 2 diabetes mellitus who require a long-acting (basal) insulin for the control of hyperglycemia;
- the treatment of pediatric patients with type 1 diabetes mellitus who require a long-acting (basal) insulin for the control of hyperglycemia. The safety and efficacy of **Levemir[®]** has not been studied in children below the age of 6 years.
- the treatment of type 2 diabetes mellitus in combination with oral anti-diabetic agents (OADs) [metformin, sulfonylureas or a thiazolidinedione] in adult patients who are not in adequate metabolic control on OADs alone.

Levemir[®] is also recommended in combination with short- or rapid-acting meal time insulin

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.

Levemir[®] (insulin detemir) is contraindicated during episodes of hypoglycemia (see HYPOGLYCEMIA AND TREATMENT OF OVERDOSAGE).

WARNINGS AND PRECAUTIONS

General

Hypoglycemia is the most common adverse effect of insulin, including **Levemir**[®].

Inadequate dosing or discontinuation of treatment, especially in type 1 diabetes, may lead to hyperglycemia and diabetic ketoacidosis. Usually the first symptoms of hyperglycemia 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 hyperglycemic events eventually lead to diabetic ketoacidosis, which is potentially lethal.

Concomitant illness, especially infections and feverish conditions, usually increases the patient's insulin requirement.

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

Levemir[®] should not be administered intravenously as it may result in severe hypoglycemia.

Levemir[®] is not to be used in insulin infusion pumps.

Absorption after intramuscular administration is faster and greater than absorption after subcutaneous administration.

Insulin may cause sodium retention and edema particularly if previously poor metabolic control is improved by intensified insulin therapy.

When using **Levemir**[®] in combination with oral anti-diabetic agents (OADs) [metformin, sulfonylureas or a thiazolidinedione, please refer to the respective product monograph for OADs for their Warnings and Precautions Information.

Mixture with other Insulin

Levemir[®] should not be mixed with other insulin for injection.

If **Levemir**[®] is mixed with other insulin preparations the profile of action of one or both individual components will change. Mixing **Levemir**[®] with a rapid-acting insulin analogue like

NovoRapid® (insulin aspart), results in an action profile with a lower and delayed maximum effect compared to separate injections.

Hypoglycemia

As with other insulins, hypoglycemia is the most common adverse effect of insulin therapy, including *Levemir*®.

As with all insulin preparations, hypoglycemic reactions may be associated with the administration of *Levemir*®. Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as long duration of diabetes, diabetic nerve disease, use of medications such as beta-blockers, or intensified diabetes control.

Hypoglycemia may occur if the insulin dose is too high in relation to the insulin requirement (see ADVERSE REACTIONS and HYPOGLYCEMIA AND TREATMENT OF OVERDOSAGE).

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

Glucose monitoring is recommended for all patients with diabetes.

Carcinogenesis and Mutagenesis

See PART II: SCIENTIFIC INFORMATION – TOXICOLOGY.

Hepatic/Biliary/Pancreas

Hepatic Impairment: As with other insulins, the requirements for *Levemir*® may need to be adjusted in patients with hepatic impairment (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

Immune

Local Allergic Reaction: As with any insulin therapy, injection site reactions may occur and include pain; itching; hives; swelling and inflammation. 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*®.

Systemic Allergic Reaction: Systemic allergic reactions have rarely occurred with insulin treatment. These reactions may be characterized by a generalized rash (with pruritus); shortness of breath; wheezing and a drop in blood pressure. Severe cases of generalized allergy including anaphylactic reaction may be life threatening.

Insulin administration may cause formation of insulin antibodies. A positive correlation was observed in clinical trials between the dose of *Levemir*® (insulin detemir) and the formation of insulin detemir specific antibodies, but this did not appear to affect HbA1c. The long term

impact of insulin detemir antibodies on glycemic control is under investigation. (see PART II: CLINICAL TRIALS)

Renal

Renal Impairment: As with other insulins, the requirements for *Levemir*[®] may need to be adjusted in patients with renal impairment (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

Special Populations

Pregnant Women: There is no clinical experience with *Levemir*[®] during pregnancy or lactation. Animal reproduction studies have not revealed any differences between *Levemir*[®] and human insulin regarding embryotoxicity and teratogenicity.

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.

Nursing Women: It is unknown whether *Levemir*[®] is excreted in significant amounts in human milk. For this reason, caution should be exercised when *Levemir*[®] is administered to a nursing mother. Patients with diabetes who are lactating may require adjustments in insulin dose, meal plan or both.

Geriatrics:

There was no clinically relevant difference in pharmacokinetics of *Levemir*[®] between elderly and young subjects.

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

Pediatrics:

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. The pharmacokinetic properties were similar in the three groups. The efficacy and safety of *Levemir*[®] were demonstrated in children and adolescents aged 6 to 17 years. No evaluated pediatric efficacy and safety data are available to support pediatric dosing advice below the age of 6 years.

Monitoring and Laboratory Tests

As with all insulin therapy, the therapeutic response to **Levemir**[®] should be monitored by periodic blood glucose tests. Glycosylated hemoglobin should be measured every 3 to 4 months in all patients taking insulin.

Information for Patients

Patients should be informed about the potential advantages and disadvantages of **Levemir**[®] (insulin detemir) therapy including possible side effects. Patients should also be offered continued education and advice on insulin therapies, delivery device options, life-style management, self-monitoring, complications of insulin therapy, timing of dosage, instruction for use of injection devices and storage of insulin.

To obtain optimal glycemic control, the need for regular blood glucose self-monitoring should be considered when using **Levemir**[®].

Female patients should be advised to discuss with their physician if they are pregnant or if they intend to become pregnant.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The safety profile of **Levemir**[®] (insulin detemir) observed in clinical trials is similar to the safety profile reported for Novo Nordisk human insulin products.

Adverse drug reactions observed in patients using **Levemir**[®] are mainly dose-dependent and are due to the pharmacologic effect of insulin. Hypoglycemia is a common undesirable effect. It may occur if the insulin dose is too high in relation to the insulin requirement. From clinical investigations it is known that major hypoglycemia, defined as requirement for third party intervention, occurs in approximately 6% of adult patients treated with **Levemir**[®]. Severe hypoglycemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death.

Injection site reactions are seen more frequently during treatment with **Levemir**[®], than with human insulin. These reactions include redness, inflammation, bruising, swelling and itching at the injection site. Most of the injection site reactions are minor and of a transitory nature, i.e. they normally disappear during continued treatment in a few days to a few weeks.

Adverse Drug Reactions in Adult and Paediatric Patients

The overall percentage of adult patients treated with **Levemir**[®] expected to experience adverse drug reactions is estimated to be 12%. In the clinical study in pediatric subjects aged 6 to 17 years; adverse drug reactions were reported for 9.5% of patients treated with **Levemir**[®].

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Levemir[®] has been evaluated for safety in 3747 subjects treated for type 1 or type 2 diabetes: 518 in pharmacology trials, 195 in short-term trials and 3034 in the intermediate and long-term trials (including Trials 1385, 1372 and 1379). An additional 862 subjects were exposed to **Levemir**[®] during three (intermediate and long-term) phase 3 trials in which **Levemir**[®] was used as an add-on treatment to oral antidiabetic drugs (OADs) in subjects with type 2 diabetes (data summarized below).

In controlled clinical trials, discontinuation due to adverse events occurred in 1.7% of subjects with **Levemir**[®] and in 1.1% of subjects treated with comparators (mainly NPH insulin).

In controlled clinical trials, adverse drug reactions reported in children and adolescents with type 1 diabetes aged 6-17 years were similar to those observed in adult patients. The overall frequency, however, of major hypoglycemic episodes requiring third party assistance was higher in this age group (16% with **Levemir**[®], and 20% with NPH insulin). Only few of these episodes were reported as adverse drug reactions. Serious adverse events reported with **Levemir**[®], and NPH insulin in pediatric subjects (irrespective of correlation to trial products) included: gastroenteritis (2.2 vs. 0%), bone fractures (0.9 vs. 0%), ketosis (1.3 vs. 1.9%), accidental injury (0.4 vs. 1.7%) and convulsions (0.9% in both groups).

Serious Adverse Events with Possible or Probable Relationship to Trial Drug:

No serious adverse events with possible or probable relation to trial drug were reported with **Levemir**[®] or NPH insulin in $\geq 1\%$ of subjects.

The following serious adverse events with possible or probable relationship to trial drug were reported at an incidence of $< 1\%$ for **Levemir**[®] and NPH insulin in controlled clinical trials (in more than 1 subject, with higher frequency with **Levemir**[®] than with NPH insulin):

Metabolic and nutritional disorders: hyperglycemia.

Adverse Events Regardless of Relationship to Trial Drug:

Table 1 – Adverse events reported with *Levemir*[®] and NPH insulin occurring in $\geq 1\%$ of subjects regardless of drug relationship.

| System Organ Class | <i>Levemir</i> [®] n=3747 (%) | NPH insulin n=2084 (%) |
|--|--|------------------------------|
| Respiratory System Disorders | | |
| Upper Respiratory Tract Infection | 16.4 | 16.3 |
| Pharyngitis | 5.2 | 5.3 |
| Bronchitis | 2.4 | 2.1 |
| Rhinitis | 2.2 | 2.4 |
| Sinusitis | 2.0 | 2.1 |
| Coughing | 2.0 | 1.8 |
| Central and Peripheral Nervous System Disorders | | |
| Headache | 16.0 | 14.5 |
| Dizziness | 1.8 | 0.9 |
| Gastro-intestinal System disorders | | |
| Abdominal pain | 4.2 | 3.0 |
| Diarrhea | 3.2 | 4.2 |
| Nausea | 3.0 | 2.6 |
| Gastroenteritis | 3.4 | 3.1 |
| Vomiting | 1.9 | 2.1 |
| Toothache | 1.5 | 1.6 |
| Dyspepsia | 1.2 | 1.8 |
| Body as a Whole - General Disorders | | |
| Influenza-like Symptoms | 5.4 | 5.4 |
| Back Pain | 3.3 | 3.0 |
| Fatigue | 1.5 | 0.9 |
| Fever | 1.4 | 1.2 |
| Pain | 1.2 | 0.9 |
| Musculo-Skeletal System Disorders | | |
| Arthralgia | 1.9 | 1.9 |
| Skeletal Pain | 1.0 | 1.3 |
| Myalgia | 0.7 | 1.4 |
| Resistance Mechanism Disorders | | |
| Viral Infection | 2.0 | 2.2 |
| Infection | 1.2 | 1.4 |
| Vision Disorders | | |
| Retinal Disorder | 2.4 | 2.4 |
| Conjunctivitis | 0.7 | 1.1 |
| Secondary Terms | | |
| Accidental Injury | 3.0 | 3.2 |
| Other Events | 1.1 | 0.0 |
| Metabolic and Nutritional Disorders | | |
| Hypoglycemia | 1.4 | 0.8 |
| Application Site Disorders | | |
| Injection site reaction | 1.7 | 0.6 |
| Urinary System Disorders | | |
| Urinary tract infection | 1.5 | 1.3 |
| Cardiovascular Disorders, General | | |
| Hypertension | 0.8 | 1.0 |
| Reproductive Disorders, Female | | |
| Dysmenorrhea | 1.1 | 0.9 |

Adverse Events in Trials of *Levemir*[®] in Combination with Oral Antidiabetic Drugs (OADs)

Three intermediate and long-term phase 3 trials (NN304-1632, NN304-1373, NN304-1530) were conducted, in which *Levemir*[®] was used as an add-on treatment to oral antidiabetic drugs (OADs) in subjects with type 2 diabetes. The therapeutic response to *Levemir*[®] was compared to that of NPH insulin or insulin glargine. A total of 862 subjects with type 2 diabetes were exposed to *Levemir*[®] during these three studies. The percentage of subjects reporting adverse events with insulin detemir was 56%, NPH insulin was 49% and insulin glargine was 80%. The majority of the adverse events were mild in severity. A total of 3% subjects withdrew due to adverse events: 4% in the *Levemir*[®] group, 2% in the NPH insulin group and 4% in the insulin glargine group.

The most common adverse events with *Levemir*[®] were upper respiratory tract infection and headache. For adverse events reported in $\geq 1\%$ of subjects, the only events reported in higher frequency with *Levemir*[®] than with comparators were injection site disorders, cystitis and hyperhidrosis.

The only possibly or probably related adverse events that were reported in $\geq 1\%$ of subjects were: headache (all treatment groups), injection site disorders (insulin detemir and NPH insulin groups) and additionally peripheral edema, hypoglycemia and dizziness in the insulin glargine group.

No severe adverse events were reported in $\geq 1\%$ of subjects in the *Levemir*[®] or the NPH insulin groups. In the insulin glargine group, severe adverse events reported in $\geq 1\%$ of subjects were coronary artery disease, cholelithiasis, hypoglycaemia, cerebrovascular disorder and chest pain.

Less Common Clinical Trial Adverse Events (<1%):

In addition, the following adverse events were reported at an incidence of <1% for *Levemir*[®] and NPH insulin in controlled clinical trials (in more than 1 subject, with higher frequency with *Levemir*[®] than with NPH insulin), regardless of drug relationship.

Respiratory system disorders: pneumonia, laryngitis, asthma, tracheitis, respiratory disorder and pulmonary edema.

Central and peripheral nervous system disorder: migraine, tremor, hypertonia, neuralgia, dysphonia, hyperkinesia, hyporeflexia, carpal tunnel syndrome, hyperaesthesia and paralysis.

Gastro-intestinal System disorders: gastritis, constipation, tooth disorder, gingivitis, gastro-intestinal disorder (not otherwise specified), haemorrhoids, dry mouth, colitis, gastroesophageal reflux, tooth caries aggravated, dysphagia, rectum hemorrhage, irritable bowel syndrome and mucositis (not otherwise specified).

Body as a whole - general disorders: allergic reaction (anaphylactic shock), potentially allergic reaction, headache, asthenia, hot flushes, syncope, carpal tunnel syndrome, neck rigidity,

enlarged abdomen, substernal chest pain, aggravated condition, face edema, mouth edema and sudden death.

Musculo-skeletal system disorders: arthrosis, bone fracture, tendon disorder, back pain, ischias, osteoporosis, tenosynovitis, torticollis and muscle weakness.

Resistance mechanism disorders: abscess, rhinitis, otitis media and parasitic infection.

Vision disorders: abnormal vision, eye pain, eye infection, eye abnormality, keratitis, corneal ulceration, ocular hemorrhage and retinal hemorrhage.

Skin and appendages disorders: skin disorder, pruritus, increased sweating, eczema, skin ulceration, onychomycosis, skin hypertrophy, acne, photosensitivity reaction, dry skin, alopecia, bullous eruption, dermatitis contact, dermatitis, cold clammy skin, lichenoid dermatitis, pilonidal cyst, skin discoloration, otitis externa and verruca.

Secondary terms: other events, bite food poisoning, medication error, varicella and under assessment.

Metabolic and nutritional disorders: hyperglycemia, hypoglycemic coma, hyperlipemia, gout, thirst, weight decrease, aggravated diabetes mellitus, hyperkalaemia, xerophthalmia and diabetic coma.

Application site disorders: injection site hematoma, injection site inflammation, cellulitis and needle injury.

Psychiatric disorders: anxiety, somnolence, confusion, anorexia, emotional lability and thinking abnormally.

Urinary system disorders: renal pain, albuminuria, hematuria, polyuria, abnormal glomerular renal function and abnormal urine.

Cardiovascular disorders, general: cardiac failure, edema dependent, heart murmur, weak pulse, aneurysm, left cardiac failure and heart disorder.

Reproductive disorders, female: dysmenorrhea, vaginitis, menorrhagia, premenstrual tension, amenorrhoea, breast disorder (not otherwise specified) and mastitis.

Platelet, bleeding and clotting disorder: epistaxis, hematoma and arterial leg thrombosis.

Hearing and vestibular disorders: earache, ear disorder (not otherwise specified), motion sickness and vestibular disorder.

Vascular (extracardiac) disorders: phlebitis, flushing, vascular disorder, leg thrombophlebitis, vein disorder and purpura.

Heart rate and rhythm disorders: palpitation, bradycardia and heart block.

Myo-endo-pericardial and valve disorder: angina pectoris, cardiomyopathy and myocardial infarction.

Neoplasm: lipoma, ovarian cyst and lymphoma malignant.

Endocrine disorders: hypothyroidism, hyperthyroidism and goitre.

Red blood cell disorders: hypochromic anaemia.

Liver and biliary system disorders: biliary pain.

White cell and RES disorders: lymphadenopathy.

Special senses other, disorders: taste perversion.

Collagen disorders: rheumatoid arthritis.

Post-Market Adverse Drug Reactions

As of 31 October 2006, Novo Nordisk has received 115 adverse drug reaction reports in pediatric patients. Of these cases, 52 were serious (hereunder 8 unexpected). Most adverse reactions were reported in the following SOCs (System Organ Class): General disorders and administration site conditions, Metabolism and nutrition disorders, Investigations and Skin and subcutaneous tissue disorders (see table 2 below). The nature of the events reported is expected in relation to administration of an insulin product. Furthermore, the type of adverse events in pediatric population is similar to that seen in adults. A higher frequency of hypoglycemia was reported in children compared to adults; however this can be explained by underreporting of these events in adults.

In children aged 6-11 years, 39 cases of adverse drug reactions were reported spontaneously, of which 11 were serious (one of them was unlisted). In children aged 12-17 years, 64 cases of adverse drug reactions were reported, of which 35 were serious (four of them were unexpected).

Twelve (12) cases of spontaneously reported adverse drug reactions occurred in children below 6 years of age and were thus recorded in relation to off-label use – three of these cases were serious.

Table 2 – Distribution of Post-market Adverse Events in Children and Adults by System Organ Class

| SOC (System Organ Class)* | General disorders and administration site conditions (most frequent events – injection site reactions) | Metabolism and nutrition disorders (most frequent events – hypoglycemia) | Investigations (most frequent events – Blood Glucose increased) | Skin and subcutaneous tissue disorders (most frequent events – rash, pruritus and urticaria) |
|---------------------------|--|--|---|--|
| Children (<18 years) | 29% | 27% | 12% | 12% |
| Adults | 30% | 13% | 20% | 9% |

* System Organ Class are coded by use of MedDRA® (Medical Dictionary for Regulatory Affairs)

DRUG INTERACTIONS

Overview

Drug Interactions

As with insulins in general, concomitant use of other drugs may influence insulin requirements.

The following substances may reduce insulin requirements: Oral antidiabetic drugs, monoamine oxidase inhibitors (MAOI), non-selective beta-blocking agents, angiotensin converting enzyme (ACE) inhibitors, salicylates, and alcohol.

The following substances may increase insulin requirements: Oral contraceptives, thiazides, glucocorticoids, thyroid hormones, beta-sympathomimetics, growth hormone and danazol.

Beta-blocking agents may mask the symptoms of hypoglycemia and delay recovery from hypoglycemia.

Octreotide/lanreotide may both increase and decrease insulin requirement.

Alcohol may intensify and prolong the hypoglycemic effect of insulin.

Drug-Drug Interactions

Interactions with other drugs have not been established.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions

Hypoglycemia may occur as a result of an excess of insulin relative to food intake, energy expenditure, or both. Omission of a meal or unplanned strenuous physical exercise may lead to hypoglycemia. (Please see HYPOGLYCEMIA AND TREATMENT OF OVERDOSAGE)

DOSAGE AND ADMINISTRATION

Dosing Considerations

Levemir[®] (insulin detemir) is indicated for the treatment of both adult and pediatric patients with type 1 diabetes mellitus, and adult patients with type 2 diabetes mellitus.

Levemir[®] should be used once daily in combination with:

- Oral antidiabetic drugs (OADs); or
- Short- or rapid-acting meal time insulin.

When *Levemir*[®] is used as part of a basal-bolus insulin regimen, *Levemir*[®] has the option of being administered twice daily, depending on patients' needs.

For patients who require twice daily dosing to optimise blood glucose control, the evening dose can be administered either with the evening meal or at bedtime.

Dosage of *Levemir*[®] is individual and determined, based on the physician's advice, in accordance with the needs of the patient.

Recommended Dose and Dosage Adjustment

New Patients: Patients being initiated on insulin for the first time can be started on *Levemir*[®] in the same manner as they would be on human insulin.

Type 2 patients adding *Levemir*[®] to OAD:

In combination with oral antidiabetic agents, it is recommended to initiate *Levemir*[®] treatment with once daily administration at a dose of 10U or 0.1- 0.2U/kg. The dose of *Levemir*[®] should be titrated on individual patients' needs.

The following titration guideline is recommended based on the average of three self-measured pre-breakfast plasma glucose concentrations:

| Average pre-breakfast self-measured plasma glucose (SMPG) | <i>Levemir</i> [®] dose adjustment |
|---|---|
| >10.0 mmol/L | +8 |

| | |
|-------------------------|--------------------|
| 9.1-10.0 mmol/L | +6 |
| 8.1-9.0 mmol/L | +4 |
| 7.1-8.0 mmol/L | +2 |
| 6.1-7.0 mmol/L | +2 |
| 4.1-6.0 mmol/L: | no change (target) |
| If one SMPG measurement | |
| 3.1-4.0 mmol/L | -2 |
| <3.1 mmol/L | -4 |

Transfer Patients: When patients are transferred from other insulin to *Levemir*[®], the change should be made as directed by the physician.

Patients transferring to *Levemir*[®] from intermediate or long-acting insulin may require adjustment of dose and timing of administration to achieve glycemic target.

Close glucose monitoring is recommended during the transition and in the initial weeks thereafter. Concomitant antidiabetic treatment may need to be adjusted (dose and timing of concurrent short-acting insulins or the dose of oral antidiabetic agents, see WARNINGS AND PRECAUTIONS, General).

Administration

Levemir[®] should not be mixed or diluted with any other insulin for injection (see WARNINGS AND PRECAUTIONS).

Levemir[®] (insulin detemir) is administered subcutaneously in the abdominal wall, the buttock, the thigh or the upper arm. Injection sites should be rotated within the same region. As with all insulins, the duration of action will vary according to the dose, injection site, blood flow, temperature and level of physical activity.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. *Levemir*[®] should never be used if it has become viscous (thickened) or cloudy; it should only be used if it is clear and colourless. *Levemir*[®] should not be used after its expiration date.

In patients with diabetes mellitus, optimized metabolic control effectively delays the onset and slows the progression of late diabetic complications. Optimized metabolic control, including glucose monitoring is therefore recommended.

As a precautionary measure, patients should carry a spare syringe and extra insulin in case the insulin delivery device is lost or damaged.

HYPOGLYCEMIA AND TREATMENT OF OVERDOSAGE

Hypoglycemia may occur as a result of an excessive dose of insulin relative to food intake, energy expenditure, or both. Omission of a meal or unplanned strenuous physical exercise may

lead to hypoglycemia. Symptoms of hypoglycemia may occur suddenly. They may include cold sweat, cool pale skin, fatigue, drowsiness, excessive hunger, vision changes, headache, nausea and palpitation. Severe hypoglycemia may lead to unconsciousness and/or convulsions and may be fatal.

Mild hypoglycemic episodes can be treated by oral administration of glucose or sugary products. It is therefore recommended that patients with diabetes carry sugar-containing products.

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

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Levemir[®] (insulin detemir) is a soluble, long-acting basal insulin analogue with a flat and predictable action profile with a prolonged duration of action. The nocturnal glucose profile is flatter and smoother with **Levemir**[®] than with NPH insulin. **Levemir**[®] has improved predictability of action compared to other basal preparations such as NPH (Neutral Protamine Hagedorn) insulin.

The prolonged action of **Levemir**[®] is mediated by the slower systemic absorption of insulin detemir molecules at the injection site due to strong self-association of the drug molecule and albumin binding via the fatty acid side-chain. More than 98% of insulin detemir in the bloodstream is albumin bound and insulin detemir is distributed more slowly to peripheral target tissues compared to NPH insulin. The absorption kinetics and action profile of **Levemir**[®] has less intra-patient variability compared to NPH insulin and insulin glargine in our studies.

Pharmacodynamics

Intra-patient variability of **Levemir**[®] actions was compared to NPH insulin and insulin glargine in a parallel group, randomized, double-blind, clinical pharmacology study of 52 patients Study NN304-1450 with type 1 diabetes each receiving 4 doses of assigned treatments. Variability in glucodynamic effects (intra-patient variability in average and maximum glucose infusion rates) from one injection to another, as expressed by the coefficient of variation, was 2- to 2.5-fold less for **Levemir**[®] than for NPH insulin, ($p < 0.001$) vs. insulin detemir, and 1.6- to 1.8-fold less than for insulin glargine ($p < 0.001$).

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

Figure 1 shows Glucose Infusion Rate results from an isoglycemic clamp study in patients with type 1 diabetes.

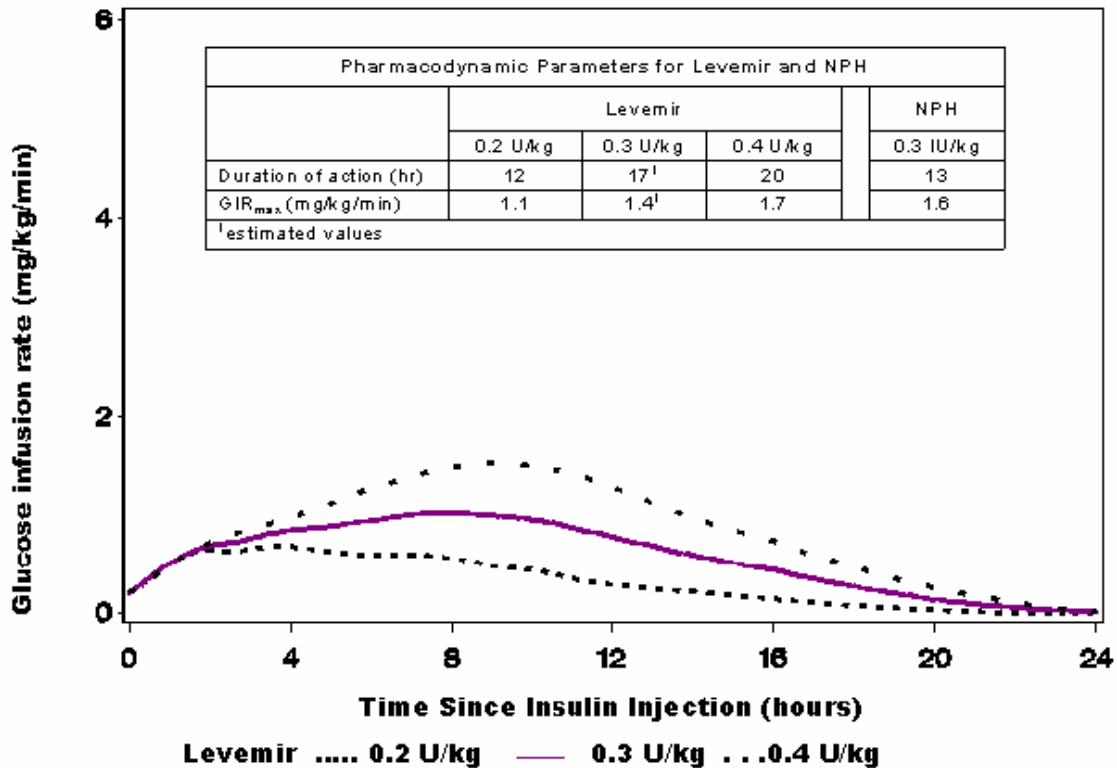


Figure 1 – Activity profiles for *Levemir*[®]

The duration of action is up to 24 hours (please see Figure 1), 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 (*range*: 6 - 24 hours), total effect] is observed after subcutaneous administration.

The time action profile of *Levemir*[®] shows significantly less intra-patient variability than other basal insulins. This reduced variability results in a more predictable glycemic response for an individual.

In long-term treatment trials (≥ 6 months) in patients with type 1 diabetes, fasting plasma glucose was improved with *Levemir*[®] compared with NPH insulin when given as basal-bolus therapy. Glycemic control, measured as glycosylated hemoglobin (HbA1c) with *Levemir*[®] is comparable to NPH insulin.

The overall risk of hypoglycemia did not differ between type 1 patients treated with **Levemir**[®], NPH or insulin glargine.

The risk of nocturnal hypoglycemia was reduced by 22% for **Levemir**[®] as compared to NPH.

The risk of severe hypoglycemia was 72% lower ($p < 0.047$) and nocturnal hypoglycaemia was 32% ($p < 0.046$) lower with insulin detemir when compared to insulin glargine, Study NN304-1372.

The risk of hypoglycemia is a major limiting factor in achieving targets for glycemic control in insulin-treated patients with diabetes. Therefore, risk of hypoglycemia is addressed in the context of clinical efficacy.

Our studies in patients with type 2 diabetes treated with basal insulin in combination with oral antidiabetic drugs demonstrated that glycaemic control (HbA1c) with **Levemir**[®] is comparable to NPH and insulin glargine and associated with less weight gain (see CLINICAL TRIALS section).

In trials with the use of OAD-insulin combination therapy **Levemir**[®] treatment resulted in a lower risk of minor nocturnal hypoglycemia compared to NPH.

Pharmacokinetics

Table 3 - Summary of insulin detemir's Pharmacokinetic Parameters in subjects with type 1 Diabetes

| Single dose (U/kg) | C _{max} (pmol/L) Mean (SD) | T _{max} (min) median (minimum;maximum) | AUC _{0-∞} (pmol·10 ³ ·min/L) mean (SD) |
|--------------------|--|---|--|
| 0.1 | 1434 (920) | 240 (119; 480) | 1232 (1119) |
| 0.2 | 2896 (1910) | 360 (119; 660) | 1681 (925) |
| 0.4 | 4422 (1774) | 420 (300; 540) | 3709 (1766) |
| 0.8 | 7278 (2809) | 420 (300; 600) | 6715 (2665) |
| 1.6 | 16535 (9344) | 420 (180; 480) | 14235 (6181) |

Absorption: In our studies, after subcutaneous injection of **Levemir**[®] in healthy subjects and in patients with diabetes, intra-subject variation in absorption is lower for **Levemir**[®] than NPH insulin and insulin glargine. Dose proportionality in serum concentrations was observed after subcutaneous administration.

Maximum serum concentration is reached between 6 and 8 hours after administration.

Bioavailability of insulin detemir is approximately 60%.

Distribution, Metabolism and Excretion: 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 dose.

An apparent volume of distribution for insulin detemir (approximately 0.1 L/kg) indicates that a high fraction of insulin detemir is circulating in the blood.

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

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.

Special Populations and Conditions

Pediatrics: 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. The pharmacokinetic properties were similar in the three groups. The efficacy and safety of *Levemir*[®] were demonstrated in children and adolescents aged 6 to 17 years. No pediatric efficacy and safety data are available to support pediatric dosing advice below the age of 6 years.

Geriatrics: There was no clinically relevant difference in pharmacokinetics of *Levemir*[®] between elderly and young subjects.

Gender: No clinically relevant difference between genders is seen in pharmacokinetic parameters.

Obesity: In controlled clinical trials, which included patients with Body Mass Index (BMI) up to 50 kg/m², subgroup analyses based on BMI did not show any differences in safety and efficacy between *Levemir*[®] and NPH insulin.

Ethnic Origin: In two trials in healthy Japanese and Caucasian subjects, there were no clinically relevant differences seen in pharmacokinetic parameters.

Hepatic Insufficiency: Individuals with severe hepatic dysfunction, without diabetes, were observed to have lower AUCs as compared to healthy volunteers.

Caution should be taken when making general dosing recommendations for subjects with liver impairment. As with other insulin preparations, titration with *Levemir*[®] and glucose monitoring should be intensified in patients with liver impairment.

Renal Insufficiency: There was no clinically relevant difference in pharmacokinetics of *Levemir*[®] between subjects with renal impairment and healthy subjects.

Pregnancy: The effect of pregnancy on the pharmacokinetics and pharmacodynamics of *Levemir*[®] has not been studied (see WARNINGS AND PRECAUTIONS, Pregnant Women).

Smoking: The effect of smoking on the pharmacokinetics and pharmacodynamics of *Levemir*[®] has not been studied.

STORAGE AND STABILITY

Levemir[®] (insulin detemir) should be stored between 2°C and 8°C (in a refrigerator) not near a freezing compartment. Do not freeze. In order to protect from light, *Levemir*[®] Penfill[®] cartridges should be kept in the outer carton.

Levemir[®] Penfill[®] in use or carried as a spare can be kept at temperatures not above 30°C for up to 42 days. *Levemir*[®] is not to be kept in the refrigerator.

Levemir[®] should not be used after the expiry date printed on the package.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Levemir[®] Penfill[®] (insulin detemir) cartridges are designed for use with Novo Nordisk Insulin Delivery Devices and NovoFine[®] needles.

Each presentation is in a strength of 100 Units of insulin detemir per mL.

Pack sizes for all presentations include 1 x 3 mL, 5 x 3 mL, and 10 x 3 mL.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Insulin Detemir

Chemical Name: Lys^{B29}-(N^ε-tetradecanoyl) des (B30) human insulin

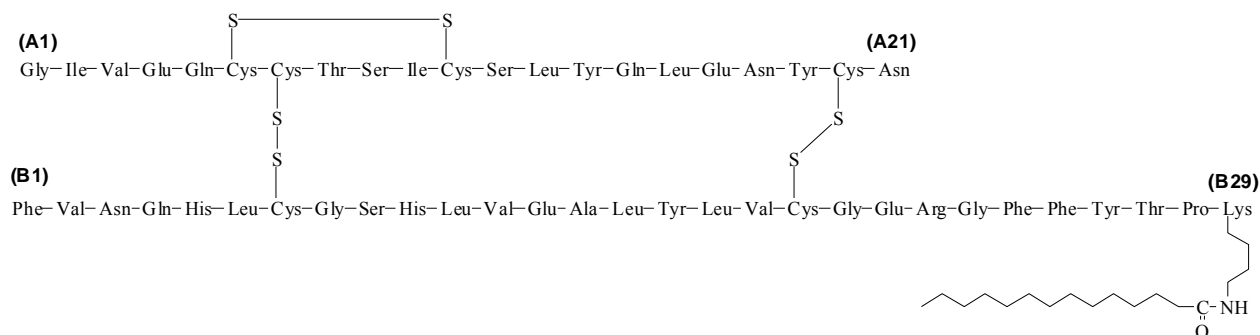
Structural Formula: C₂₆₇H₄₀₂O₇₆N₆₄S₆

Molecular Weight: 5916.9

Insulin detemir differs from human insulin in that the amino acid molecule in position B30 has been omitted and a 14-C fatty acid chain has been attached to position B29.

Structural formula:

Figure 2 – Structural formula of insulin detemir



Product Characteristics

Levemir[®] (insulin detemir) is a sterile, aqueous, clear, colourless and neutral solution. One unit (U) of **Levemir**[®] corresponds to one IU of human insulin. One unit of **Levemir**[®] contains 0.142 mg salt-free anhydrous insulin detemir. Each milliliter of **Levemir**[®] contains 100 U (14.2 mg/ml) insulin detemir, 0.89 mg disodium phosphate dihydrate, 30.0 mg mannitol, 2.06 mg metacresol, 1.80 mg phenol, 1.17 mg sodium chloride, 65.4 µg zinc acetate and water for injection. Hydrochloric acid and/or sodium hydroxide may be added to adjust pH. **Levemir**[®] has a pH of approximately 7.4.

Viral Inactivation

Levemir[®] (insulin detemir) is considered to be virologically safe.

CLINICAL TRIALS

Study demographics and trial design

The efficacy and safety of **Levemir**[®] given once-daily at bedtime or twice-daily (before breakfast and at bedtime, or at 12-hour intervals) was compared to that of once-daily or twice-daily NPH insulin or once-daily glargine in open-label, randomized, active control, parallel studies of efficacy.

In general, **Levemir**[®] achieved a level of glycemic control similar to NPH insulin and insulin glargine, as measured by glycosylated hemoglobin (HbA1c). The overall rate of hypoglycemia did not differ between patients with diabetes treated with **Levemir**[®] and those treated with NPH insulin or insulin glargine.

Within-subject variation in glycemic excursions, and fluctuations throughout the day were generally reduced with use of **Levemir**[®] as compared to NPH insulin. In combination with a short or rapid-acting insulin, variability of fasting blood glucose was consistently and significantly lower with **Levemir**[®] in both type 1 and type 2 patients compared to NPH insulin. In type 1 and type 2 diabetes trials, in contrast to comparator treatments, **Levemir**[®] was not associated with significant weight gain.

Type 1 Diabetes:

In three large randomized, controlled clinical studies, adult patients with type 1 diabetes (NN304-1335, n = 747; NN304-1447, n = 400; NN304-1448, n = 408) were randomized to basal-bolus treatment with once- or twice-daily **Levemir**[®] or with NPH insulin once- or twice-daily for 4 to 6 months. The bolus (mealtime) treatment was regular human insulin or insulin aspart. In these studies, **Levemir**[®] and NPH insulin had a similar effect on glycosylated hemoglobin, with a similar overall rate of hypoglycemia. Nocturnal glucose profiles were flatter and smoother, and the risk for nocturnal hypoglycemia was reduced (by 22%) for **Levemir**[®] as compared to NPH insulin. **Levemir**[®], in contrast to comparator treatment, was associated with weight loss or smaller weight increase. In the secondary outcomes, **Levemir**[®] demonstrated significantly improved fasting plasma glucose (FPG) (Table 5) and within-subject variation with similar overall rates of hypoglycemia and safety profiles including adverse events, laboratory safety parameters, physical examination, and vital signs, compared with NPH insulin.

A 6 month, open-labelled, randomized, parallel efficacy and safety study (NN304-1379, n=347) compared **Levemir**[®] and NPH in children and adolescents with type 1 diabetes on a once or twice daily basal-bolus regimen. Glycemic control with **Levemir**[®], as measured by HbA1c, was demonstrated to be similar to NPH insulin in children and adolescents, with a decrease in mean HbA1c of approximately 0.8%-point with both treatments. The **Levemir**[®] group had lower mean FPG [8.4 vs. 9.6 mmol/L, $p=0.022$] and less day-to-day variation in home-measured FPG [SD 3.3 vs. 4.3, $p < 0.001$]. The relative risk of experiencing any hypoglycemic episode was similar between the two treatment groups [$p=0.351$], while the risk of experiencing a nocturnal hypoglycemic episode was 26% lower with **Levemir**[®] [$p=0.041$]. **Levemir**[®] resulted in a smaller increase in mean BMI at the end of treatment, compared to NPH insulin. On average, the BMI

in the insulin detemir group increased by 0.2 kg/m² during the trial, while the BMI in the NPH insulin group increased by 0.7 kg/m² [$p < 0.001$].

Overall, the efficacy and safety results obtained in study NN304-1379 in children and adolescents are similar to those obtained in adults.

Type 2 Diabetes: Basal-Bolus regimen

In two large, randomized, controlled clinical studies (NN304-1336 = 505 and NN304-1385 = 394) in adults with type 2 diabetes, *Levemir*[®] was evaluated up to 6 months as part of a regimen of *Levemir*[®] once-or-twice daily plus bolus insulin aspart. The comparator basal insulin in both trials was NPH insulin plus either insulin aspart or human soluble insulin. As measured by values of glycosylated hemoglobin or fasting plasma glucose, *Levemir*[®] had efficacy similar to the corresponding once-or twice-daily NPH insulin. The overall incidence of hypoglycemia (which was lower for type 2 diabetes than type 1 diabetes) was generally similar for *Levemir*[®] and NPH insulin. *Levemir*[®], in contrast to comparator treatment, was associated with significantly less weight gain.

Type 2 Diabetes: Combination Therapy with Oral Anti-Diabetic Agents (OADs)

Three (intermediate and long-term) phase 3 trials (NN304-1632, NN304-1373, and NN304-1530) were conducted to study the safety and efficacy of insulin detemir when used in combination with OADs in subjects with type 2 diabetes, who are inadequately treated on oral agents alone. All three trials were randomized, parallel, open-labelled multi-centre trials, in which the therapeutic response to *Levemir*[®] was compared to that of NPH insulin or insulin glargine. Subjects were titrated individually according to predetermined targets for glycaemic control (“treat-to-target”) with continuous dose titration throughout the trials based on self-measured plasma glucose (SMPG) recordings.

Target-driven titration led to clinically relevant reductions in HbA1c and FPG. HbA1c decreased similarly with *Levemir*[®] as with NPH insulin or insulin glargine. Treatment with *Levemir*[®] was confirmed to be well within the predefined limit of noninferiority to treatment with NPH insulin or insulin glargine with respect to HbA1c at the end of treatment in all three trials (Table 9). FPG decreased considerably from baseline to end of treatment in all treatment groups in all three trials. The average decrease in FPG was similar with insulin detemir compared to NPH insulin and insulin glargine. In trial NN304-1632, morning administration of *Levemir*[®] resulted in statistically significantly higher FPG levels compared to evening administration of NPH insulin. This could be expected considering that the basis for titration of *Levemir*[®] morning doses were pre-dinner plasma glucose concentrations rather than pre-breakfast values as used for the evening doses.

The proportion of subjects who reported one or more hypoglycemic episodes during the treatment period in the confirmatory trials was consistently lower with *Levemir*[®] than with NPH insulin throughout the treatment period and lower with *Levemir*[®] compared to insulin glargine during the initiation period, but thereafter similar in the two treatment groups.

There is a lower risk of nocturnal hypoglycemic episodes with insulin detemir compared with NPH insulin when used as add-on treatment to OADs in subjects with type 2. There is a slightly lower risk of nocturnal hypoglycemic episodes with insulin detemir compared to insulin glargine in our studies when HbA1c levels were taken into account (NN304-1373).

Significantly lower weight gain was observed in clinical studies in Trial NN304-1632, NN304-1373 and NN304-1530 in subjects with type 2 diabetes using OADs. Subjects on NPH insulin experienced a significantly larger weight increase compared to insulin detemir. A significantly lower increase in body weight was also seen with insulin detemir compared with insulin glargine after 52 weeks of treatment $p < 0.001$ once daily detemir vs. glargine; $p < 0.012$ twice daily detemir vs. glargine.

Exploratory analyses with covariate adjustments for HbA1c, gave similar results, indicating that changes in body weight were independent of individual differences in HbA1c.

Table 4 - Change in body weight after insulin treatment

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

Table 5 - Summary of patient demographics for clinical trials in type 1 diabetes

| Study | Trial design | Dosage, route of administration and duration | | | | Study subjects (n)* | Mean age (Range) | Gender | |
|--|--|--|---------------------------------|-------------------|---------------------------------|---------------------|------------------|-----------------|-------------------|
| NN304-1335 | Randomized, controlled, once daily (bedtime) Levemir or NPH in combination with soluble insulin before each meal in patients with type 1 diabetes. | Treatment Group | Daily basal insulin dose (U/kg) | | Daily bolus insulin dose (U/kg) | | 747 | 40.5 (18-77) | Males and Females |
| | | | Pre-study mean | End of study mean | Pre-study mean | End of study mean | | | |
| | | Levemir | 0.31 | 0.27 | 0.44 | 0.47 | | | |
| | | NPH | 0.31 | 0.33 | 0.44 | 0.44 | | | |
| Administered subcutaneously, once daily (bed time), 6 months | | | | | | | | | |
| NN304-1447 | Randomized, controlled, Levemir/NovoRapid compared to NPH/NovoRapid treatment in adult patients with type 1 diabetes | Treatment Group | Daily basal insulin dose (U/kg) | | Daily bolus insulin dose (U/kg) | | 400 | 40.2 (18-77) | Males and Females |
| | | | Pre-study mean | End of study mean | Pre-study mean | End of study mean | | | |
| | | Levemir | 0.35 | 0.43 | 0.39 | 0.39 | | | |
| | | NPH | 0.32 | 0.38 | 0.37 | 0.34 | | | |
| Administered subcutaneously, twice daily, 16 weeks | | | | | | | | | |

| Study | Trial design | Dosage, route of administration and duration | | | | Study subjects (n)* | Mean age (Range) | Gender | |
|--|--|--|---------------------------------|-------------------|---------------------------------|---------------------|------------------|------------------|-------------------|
| NN304-1448 | Randomized, controlled, Levemir/NovoRapid compared to NPH/NovoRapid treatment in adult patients with type 1 diabetes. | Treatment Group | Daily basal insulin dose (U/kg) | | Daily bolus insulin dose (U/kg) | | 408 | 40.2 (18 -76) | Males and Females |
| | | | Pre-study mean | End of study mean | Pre-study mean | End of study mean | | | |
| | | Levemir | 0.36 | 0.49 | 0.40 | 0.38 | | | |
| | | NPH | 0.39 | 0.45 | 0.40 | 0.38 | | | |
| Administered subcutaneously, twice daily, 16 weeks | | | | | | | | | |
| NN304-1379 | Randomized, open, parallel, active controlled (NPH insulin), basal/bolus human soluble insulin (HIS) regimen in children and adolescents with type 1 diabetes. | | Daily basal insulin dose (U/kg) | | Daily bolus insulin dose (U/kg) | | 347 | 11.9 (6 – 17) | Males and Females |
| | | | Pre-study mean** | End of study mean | Pre-study mean** | End of study mean | | | |
| | | Levemir | NA | 0.66 | NA | 0.52 | | | |
| | | NPH | NA | 0.64 | NA | 0.51 | | | |
| Administered subcutaneous, twice daily, 16 weeks | | | | | | | | | |

* Number of exposed patients

** A large variety of insulin preparations (including human insulin and insulin analogues as separate injections and pre-mixed preparations) and injection regimens were used before the start of the trial. The overall distribution of regimens was similar in the two treatment groups. The mean pre-trial daily dose of basal insulin per kg body weight prior to randomization was similar in the two treatment groups. The mean daily bolus insulin dose per kg body weight remained unchanged during the trial in both treatment groups.

Table 6 - Study results – type 1 Adults: Combined ANOVA of HbA1c (%) at End of Trial in type 1 Diabetes Mellitus (Studies 1335, 1447, 1448)

| Primary Endpoints | Levemir | | NPH | | Difference (detemir – NPH) | |
|-------------------|---------|-------------|-----|-------------|----------------------------|----------------|
| | N | Mean (SE) | N | Mean (SE) | Mean | 95% CI |
| HbA1c (16 weeks) | 983 | 8.30 (0.10) | 485 | 8.41 (0.10) | -0.11 | [-0.20; -0.01] |

Table 7 - Summary of patient demographics for clinical trials in type 2 diabetes

| Study | Trial design | Dosage, route of administration and duration | | | | Study subjects (n)* | Mean age (Range) | Gender | |
|--|--|--|---------------------------------|-------------------|---------------------------------|---------------------|------------------|-----------------|-------------------|
| NN304-1336 | Open, randomised, parallel study comparing Levemir and NPH in patients with type 2 diabetes, using NovoRapid as bolus insulin. | Treatment Group | Daily basal insulin dose (U/kg) | | Daily bolus insulin dose (U/kg) | | 505 | 60.4 (35-91) | Males and Females |
| | | | Pre-study mean | End of study mean | Pre-study mean | End of study mean | | | |
| | | Levemir | 0.32 | 0.42 | 0.40 | 0.46 | | | |
| | | NPH | 0.31 | 0.39 | 0.40 | 0.40 | | | |
| Administered subcutaneously, once or twice daily, 6 months | | | | | | | | | |

| Study | Trial design | Dosage, route of administration and duration | | | | Study subjects (n)* | Mean age (Range) | Gender | | | | | | | | | | | | | | | | | | | |
|------------------------|---|---|---------------------------------|-------------------|--|---------------------|---------------------------------|--------|---------------------------------|-------------------|-----------------------|-------------------|----------------|------------------------|---------|------|-----------------------|-----------------|-------------------|-----|-----------------|-------------------|------|------|-----|-----------------|-------------------|
| NN304-1385 | Open, randomized, parallel study comparing Levemir/NovoRapid and NPH/HSI in type 2 patients. | <table border="1"> <thead> <tr> <th rowspan="2">Treatment Group</th> <th colspan="2">Daily basal insulin dose (U/kg)</th> <th colspan="2">Daily bolus insulin dose (U/kg)</th> </tr> <tr> <th>Pre-study mean</th> <th>End of study mean</th> <th>Pre-study mean</th> <th>End of study mean</th> </tr> </thead> <tbody> <tr> <td>Levemir</td> <td>0.42</td> <td>0.58</td> <td>0.20</td> <td>0.37</td> </tr> <tr> <td>NPH</td> <td>0.39</td> <td>0.46</td> <td>0.20</td> <td>0.33</td> </tr> </tbody> </table> <p>Administered subcutaneously, once or twice daily, 4 months</p> | | | | Treatment Group | Daily basal insulin dose (U/kg) | | Daily bolus insulin dose (U/kg) | | Pre-study mean | End of study mean | Pre-study mean | End of study mean | Levemir | 0.42 | 0.58 | 0.20 | 0.37 | NPH | 0.39 | 0.46 | 0.20 | 0.33 | 394 | 58.2 (29-80) | Males and Females |
| Treatment Group | Daily basal insulin dose (U/kg) | | Daily bolus insulin dose (U/kg) | | | | | | | | | | | | | | | | | | | | | | | | |
| | Pre-study mean | End of study mean | Pre-study mean | End of study mean | | | | | | | | | | | | | | | | | | | | | | | |
| Levemir | 0.42 | 0.58 | 0.20 | 0.37 | | | | | | | | | | | | | | | | | | | | | | | |
| NPH | 0.39 | 0.46 | 0.20 | 0.33 | | | | | | | | | | | | | | | | | | | | | | | |
| NN304-1632 | Open-label, randomized, parallel-group trial with once daily Levemir (morning or evening) or NPH (evening) as add-on to current OAD therapy in insulin naïve adult subjects with type 2 diabetes inadequately controlled on current OAD therapy | <table border="1"> <thead> <tr> <th rowspan="2">Treatment Group</th> <th colspan="2">Daily basal insulin dose (U/kg)</th> </tr> <tr> <th>Start of study mean</th> <th>End of study mean</th> </tr> </thead> <tbody> <tr> <td>Levemir (morning)</td> <td>0.13</td> <td>0.50</td> </tr> <tr> <td>Levemir (evening)</td> <td>0.13</td> <td>0.43</td> </tr> <tr> <td>NPH (evening)</td> <td>0.12</td> <td>0.38</td> </tr> </tbody> </table> <p>Administered subcutaneously, once daily, 20 weeks</p> | | | | Treatment Group | Daily basal insulin dose (U/kg) | | Start of study mean | End of study mean | Levemir (morning) | 0.13 | 0.50 | Levemir (evening) | 0.13 | 0.43 | NPH (evening) | 0.12 | 0.38 | 498 | 58.5 (29-89) | Males and Females | | | | | |
| Treatment Group | Daily basal insulin dose (U/kg) | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Start of study mean | End of study mean | | | | | | | | | | | | | | | | | | | | | | | | | |
| Levemir (morning) | 0.13 | 0.50 | | | | | | | | | | | | | | | | | | | | | | | | | |
| Levemir (evening) | 0.13 | 0.43 | | | | | | | | | | | | | | | | | | | | | | | | | |
| NPH (evening) | 0.12 | 0.38 | | | | | | | | | | | | | | | | | | | | | | | | | |
| NN304-1373 | Open-label, randomised, parallel-group trial with Levemir (once or twice daily) or glargine (once daily) as add-on to current OAD therapy in insulin naïve adult subjects with type 2 diabetes inadequately controlled on current OAD therapy | <table border="1"> <thead> <tr> <th rowspan="2">Treatment Group</th> <th colspan="2">Daily basal insulin dose (U/kg)</th> </tr> <tr> <th>Mean at 1 week</th> <th>Mean at 52 weeks</th> </tr> </thead> <tbody> <tr> <td>Levemir (once-daily)</td> <td>0.14</td> <td>0.52</td> </tr> <tr> <td>Levemir (twice-daily)*</td> <td>N/A</td> <td>1.00</td> </tr> <tr> <td>Glargine (once-daily)</td> <td>0.14</td> <td>0.44</td> </tr> </tbody> </table> <p>Administered subcutaneously, once or twice daily, 52 weeks</p> <p>* Between group dose differences cannot be interpreted since different dosing regimens were used.</p> | | | | Treatment Group | Daily basal insulin dose (U/kg) | | Mean at 1 week | Mean at 52 weeks | Levemir (once-daily) | 0.14 | 0.52 | Levemir (twice-daily)* | N/A | 1.00 | Glargine (once-daily) | 0.14 | 0.44 | 582 | 58.9 (27-82) | Males and Females | | | | | |
| Treatment Group | Daily basal insulin dose (U/kg) | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Mean at 1 week | Mean at 52 weeks | | | | | | | | | | | | | | | | | | | | | | | | | |
| Levemir (once-daily) | 0.14 | 0.52 | | | | | | | | | | | | | | | | | | | | | | | | | |
| Levemir (twice-daily)* | N/A | 1.00 | | | | | | | | | | | | | | | | | | | | | | | | | |
| Glargine (once-daily) | 0.14 | 0.44 | | | | | | | | | | | | | | | | | | | | | | | | | |
| NN304-1530 | Open-label, randomized, parallel-group trial with Levemir (twice daily) or NPH (twice daily) as add-on to current OAD therapy in insulin naïve adult subjects with type 2 diabetes inadequately controlled on current OAD therapy | <table border="1"> <thead> <tr> <th rowspan="2">Treatment Group</th> <th colspan="2">Daily basal insulin dose (U/kg)</th> </tr> <tr> <th>Mean at 1 week</th> <th>Mean at 24 weeks</th> </tr> </thead> <tbody> <tr> <td>Levemir (twice-daily)</td> <td>0.21</td> <td>0.77</td> </tr> <tr> <td>NPH (twice-daily)</td> <td>0.21</td> <td>0.52</td> </tr> </tbody> </table> <p>Administered subcutaneously, once or twice daily, 24 weeks</p> | | | | Treatment Group | Daily basal insulin dose (U/kg) | | Mean at 1 week | Mean at 24 weeks | Levemir (twice-daily) | 0.21 | 0.77 | NPH (twice-daily) | 0.21 | 0.52 | 475 | 60.8 (27-80) | Males and Females | | | | | | | | |
| Treatment Group | Daily basal insulin dose (U/kg) | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Mean at 1 week | Mean at 24 weeks | | | | | | | | | | | | | | | | | | | | | | | | | |
| Levemir (twice-daily) | 0.21 | 0.77 | | | | | | | | | | | | | | | | | | | | | | | | | |
| NPH (twice-daily) | 0.21 | 0.52 | | | | | | | | | | | | | | | | | | | | | | | | | |

* Number of exposed patients

Table 8 - Study results – type 2, Basal-Bolus: ANOVA of HbA1c (%) at End of Trial in type 2 Diabetes Mellitus

| Primary Endpoints | Levemir | | NPH | | Difference (detemir – NPH) | |
|-----------------------|---------|-------------|-----|-------------|----------------------------|---------------|
| | N* | Mean (SE) | N* | Mean (SE) | Mean | 95% CI |
| Missing 1337 HbA | | | | | | |
| 1336 HbA1c (6 months) | 315 | 7.63 (0.07) | 155 | 7.48 (0.08) | 0.16 | [0.00; 0.31] |
| 1385 HbA1c (22 weeks) | 182 | 7.46 (0.07) | 192 | 7.52 (0.07) | -0.062 | [-0.25; 0.13] |

* Number of (modified) intent to treat (ITT) subjects

Table 9 - Study results - ANOVA of HbA1c (%) at End of Treatment in Combination with OADs in type 2 Diabetes Mellitus

| Detemir vs NPH or Glargine | | | | | | |
|----------------------------|-----------------|--------------|------------------|--------------|--------------|---------------|
| Trial ID Dose regimen | Detemir | | NPH or Glargine* | | Difference** | |
| | N | Mean (SE) | N | Mean (SE) | Mean | 95% C.I. |
| 1632 evening Once | 163 | 7.43 (0.088) | 157 | 7.33 (0.087) | 0.104 | -0.081; 0.289 |
| 1632 morning Once | 156 | 7.48 (0.088) | 157 | 7.36 (0.090) | 0.127 | -0.071; 0.324 |
| 1373 Once or twice | 268 | 7.16 (0.078) | 275 | 7.12 (0.078) | 0.045 | -0.114, 0.205 |
| 1530 Twice | 230 | 6.58 (0.064) | 232 | 6.46 (0.063) | 0.126 | -0.002; 0.254 |
| Detemir vs Detemir | | | | | | |
| 1632*** Once | Detemir evening | | Detemir morning | | Difference** | |
| | N | Mean (SE) | N | Mean (SE) | Mean | 95% C.I. |
| | 163 | 7.32 (0.083) | 156 | 7.35 (0.079) | -0.031 | -0.002; 0.145 |

* Comparator was NPH insulin in Trials NN304-1632 (once daily) and NN304-1530 (twice daily) and insulin glargine (once daily) in Trial NN304-1373.

** Difference is insulin detemir – comparator.

*** NPH insulin was only administered in the evening in Trial NN304-1632, but is compared to both insulin detemir dosed in the evening and in the morning.

Observed Antibody Formation:

Antibody development has been observed with the use of *Levemir*[®] in adult and pediatric patients. A positive correlation was observed between the dose of insulin detemir at end of trial and the formation of insulin detemir specific antibodies in adults and pediatric subjects. No correlation was observed between formation of insulin detemir specific antibodies and change in HbA1c, while a positive correlation was observed between formation of insulin detemir specific antibodies and hypoglycemic episodes in pediatric subjects.

The long term impact of insulin detemir antibodies on glycemic control is under investigation.

DETAILED PHARMACOLOGY

Insulin detemir is derived from human insulin by the omission of residue B30 and acylation of the side-chain amino group LysB29 by the naturally occurring fatty acid tetradecanoic acid.

A protracted pharmacodynamic action of insulin detemir can be attributed to increased self-association and albumin binding compared to human insulin which delays absorption from subcutaneous sites into the bloodstream and leads to slower distribution to target tissues (98 - 99 % bound to albumin in plasma).

The pharmacology of insulin detemir has been extensively examined *in vitro* and *in vivo* pre-clinical studies. Insulin detemir was less potent than human insulin in binding and activating the insulin receptor and in stimulating cellular glucose utilisation. This reduction was in the order of 4 - 5 fold as compared to human insulin (varying between 4 and 10 fold in various assays). The explanation for this reduction is linked to the fatty acid side chain at position B29 of the insulin molecule. The marketed version of **Levemir**[®] (insulin detemir) is equipotent on a unit to unit basis with human insulin.

Insulin detemir was also shown to have lower binding affinity than human insulin in binding to the IGF-I receptor and to dissociate faster from the insulin receptor than human insulin. These data, together with the reduced insulin receptor binding affinity, explain why insulin detemir is less potent than human insulin in stimulating mitogenesis (see TOXICITY).

The insulin and IGF-I receptor affinities and the metabolic and mitogenic potencies of insulin detemir are all reduced by approximately the same extent as compared to human insulin. Analogues showing a disproportionate increase in IGF-I receptor affinity over insulin receptor affinity have a greater mitogenic potential than human insulin. Thus, the balance between metabolic and mitogenic properties is similar for insulin detemir as for human insulin, which is beneficial from a safety perspective.

The low receptor binding affinity of insulin detemir combined with the high binding to serum albumin could give rise to a larger fraction of insulin detemir to undergo non-receptor mediated elimination compared to human insulin. This is thought to result in a low potency of insulin detemir in animal species like rabbits, mice and rats. Similarly, clinical trials have consistently shown that insulin detemir must be dosed at a higher molar dose than human insulin to provide comparable metabolic effect.

Insulin detemir is equipotent with human insulin in some species, e.g. in pig and dog (Table 10).

Table 10 – *In vivo* potency of insulin detemir in various species.

| Species | Relative potency of insulin detemir compared to NPH insulin (molar basis) | Relative potency of insulin detemir normalized to the potency estimated in humans (unit basis) |
|---------------|---|--|
| <i>Mouse</i> | 0.06 | 0.24 |
| <i>Rat</i> | 0.15 | 0.6 |
| <i>Rabbit</i> | 0.05 | < 0.2 |
| <i>Dog</i> | ~ 1 | 4 |
| <i>Pig</i> | ~1 | 4 |
| <i>Human</i> | Approx. 0.25 | 1 |

The pharmacological data for receptor binding, cellular metabolic activity and hypoglycemic activity in non-diabetic and diabetic animal models show that insulin detemir has the molecular pharmacology typical of insulin. Experiments in pigs furthermore indicate that insulin detemir has a flat and prolonged action profile compared to NPH insulin.

Cardiovascular studies plus a relevant range of standard behavioural and organ function tests and interaction studies have been conducted in rats and dogs. When initiating the safety pharmacology programme, the tentative human therapeutic dose was expected to be 1.8 nmol/kg. Dose level was selected to be 100 times the human therapeutic dose, but because of the lower potency shown in subsequent clinical trials the actual doses were only 15 - 25 times higher.

Dose levels used in rodents were up to 180 nmol/kg. In dogs, the highest dose administered was 18 nmol/kg (Table 11) due to the high sensitivity of this species to insulin treatment. No unanticipated findings were observed. In anaesthetised rats, increased blood pressure was observed at 180 nmol/kg. This finding was believed to be a stress-related reaction to the induced hypoglycemia. In anaesthetised dogs, a reduction in blood pressure was induced at 18 nmol/kg (Table 11) probably due to hypoglycemia. Other expected effects most likely related to hypoglycemia were decreased spontaneous diuresis (Table 11) at dose levels above the expected human therapeutic dose. The doses tested were above the doses used in the clinical development programme and therefore considered sufficient.

In conclusion, the safety pharmacology programme raised no safety issues.

Table 11 – Safety Pharmacology

| Test | Doses ¹ (nmol/kg) | Results |
|--|--------------------------------------|---|
| Irwin test, mouse | 0, 1.8, 18, 180 | 18 and 180 nmol/kg - minor and short-lasting effects seen in some animals: decreased reactivity, spontaneous activity and exploration with some visual placing loss. |
| Locomotor, mouse | 0, 1.8, 18, 180 | 18 and 180 nmol/kg – statistical significant dose-dependent inhibition of static movements and active time. Marked reduction in rearing activity. |
| Hexobarbitone, mouse | 0, 1.8, 18, 180 | No significant effects on time to onset of sleep or duration of sleep induced by hexobarbitone. |
| Alcohol, mouse | 0, 1.8, 18, 180 | No significant effects on time to onset of sleep or duration of sleep induced by alcohol. 180 nmol/kg – mortality rate similar to positive control. |
| Anti-convulsant activity, mouse | 0, 1.8, 18, 180 | No inhibitory effects on pentylenetetrazol-induced convulsant activity. |
| Pro-convulsant activity, mouse | 0, 1.8, 18, 180 | No enhancing effect on pentylenetetrazol-induced convulsant activity. |
| Analgesic effect, mouse | 0, 1.8, 18, 180 | No effect on acetic acid-induced writhing in mice. |
| Body temperature, rat | 0, 1.8, 18, 180 | No significant effect on body temperature over a period of 24 hours. |
| Cardiovascular and respiratory, rat | 0, 1.8, 18, 180 | No effects in low doses (1.8 and 18 nmol/kg). Marginal but significant increase in mean and diastolic blood pressure most pronounced 45 minutes after dosing (180 nmol/kg). No ECG abnormalities detected. No effects on respiratory system. |
| Plasma levels, anaesthetized rat | 0, 1.8, 18, 180 | Dose dependent plasma concentration was attained. Maximum concentration was reached 45 minutes after dosing. |
| Cardiovascular and respiratory, dog | 0, 0.18, 1.8, 18 | No effect in low doses (0.18 and 1.8 nmol/kg). 18 nmol/kg – marginal decrease in diastolic blood pressure, significant at 3 - 4 hours after dosing. Significant increase in pO ₂ of arterial blood at 2 hours after dosing. No effects on respiratory system. |
| Water and electrolyte metabolism, rat | 0, 1.8, 18, 180 | Dose-dependent mild diuretic effect up to 4 hours after injection (18 and 180 nmol/kg). Slight and transient reduction in specific gravity of the urine (18 nmol/kg). Increase in urine volume and electrolyte excretion, decrease in specific gravity and osmolality (180 nmol/kg). The effects were apparent for 4 hours after dosing, but had disappeared by 24 hours. |
| Autonomic nervous system and smooth muscle, guinea pig ileum | 0.1 nM, 1nM, 10 nM, 100 nM, agonists | No effect on the baseline tension or the contractile response induced by the agonists histamine and acetylcholine. |
| Digestive System, mouse | 0, 1.8, 18, 180 | No significant effect on the gastrointestinal motility or irritation on the gastric mucosal surface. |

¹ single dose

TOXICOLOGY

The general toxicity (single-dose and repeat-dose toxicity) was assessed after intravenous and subcutaneous single-dose administration to mice and rats and after subcutaneous repeat-dose administration to rats and dogs for up to six and twelve months, respectively. These studies demonstrated no toxicity potential of insulin detemir other than effects directly or indirectly related to hypoglycemia. This is in agreement with published studies where a fast-acting formulation (Novolin[®] ge Toronto), a slow release formulation (Novolin[®] ge NPH) and a rapid-acting insulin analogue (insulin lispro) demonstrated very little effects other than those associated with hypoglycemia.

Table 12 – Single-dose Toxicity Overview

| Species (Strain, Route) | (M + F) Animals per Group | Doses (nmol/kg) | Observed Maximum Non-Lethal Dose (nmol/kg) |
|-------------------------|---------------------------|--------------------------------------|--|
| Rat (SD, s.c.) | 5 + 5 | 0, 375, 1500, 6000, 24000 | Highest non-lethal dose: 24000 nmol/kg in males and females. |
| Rat (SD, i.v.) | 5 + 5 | 0, 375, 1500, 6000, 12000, 24000 | Highest non-lethal dose: 6000 nmol/kg in males and females. |
| Mouse (NMRI, s.c.) | 5 + 5 | 0, 375, 1500, 6000, 24000 | Highest non-lethal dose: 1500 nmol/kg in males and females. |
| Mouse (NMRI, i.v.) | 5 + 5 | 0, 375, 750, 1500, 3000, 6000, 12000 | Highest non-lethal dose: 1500 nmol/kg in males and females. |

Table 13 – Repeat-dose Toxicity Overview

| Species (Strain, Route) | Daily Dose (nmol/kg/day) | Number of Animals (main & recovery) | Duration | Results |
|-------------------------|--------------------------|--|----------------------------|--|
| Rat (SPRD, s.c.) | 0 (Vehicle) | M: 12 (+ 6 kinetic); F: 12 (+ 6 kinetic) | 4 weeks | No observed Adverse Effects above 300 nmol/kg/day (apart from local effects) |
| | 30 | M: 12 (+ 6 kinetic); F: 12 (+ 6 kinetic) | | |
| | 96 | M: 12 (+ 6 kinetic); F: 12 (+ 6 kinetic) | | |
| | 300 | M: 12 (+ 6 kinetic); F: 12 (+ 6 kinetic) | | |
| Rat (SPRD, s.c.) | 0 (Vehicle) | M: 20+10; F: 20+10 | 3 months (4 week recovery) | No observed Adverse Effects above 300 nmol/kg/day (apart from local effects) |
| | 30 | M: 20; F: 20 | | |
| | 96 | M: 20+10; F: 20+10 | | |
| | 300 | M: 20+10; F: 20+10 | | |

| Species (Strain, Route) | Daily Dose (nmol/kg/day) | Number of Animals (main & recovery) | Duration | Results |
|-------------------------|--|-------------------------------------|----------------------------|--|
| | Positive Control (Novolin® NPH, 144 nmol/kg/day weeks 1-3; 72 nmol/kg/day from week 4) | M: 20; F: 20 | | |
| Rat (SPRD, s.c.) | 0 (Vehicle) | M: 25; F: 25 | 6 months | No observed Adverse Effects above 300 nmol/kg/day (apart from local effects) |
| | 30 | M: 25; F: 25 | | |
| | 96 | M: 25; F: 25 | | |
| | 300 | M: 25; F: 25 | | |
| | Positive Control (Novolin® NPH, 72 nmol/kg/day) | M: 25; F: 25 | | |
| Dog (Beagle, s.c.) | 0 (Vehicle) | M: 4; F: 4 | 4 weeks | No observed Adverse Effects above 9 nmol/kg/day (apart from local effects) |
| | 3 | M: 4; F: 4 | | |
| | 6 | M: 4; F: 4 | | |
| | 9 | M: 4; F: 4 | | |
| Dog (Beagle, s.c.) | 0 (Vehicle) | M: 6; F: 6 | 3 months (4 week recovery) | No observed Adverse Effects above 7.2 nmol/kg/day |
| | 1.8 | M: 4; F: 4 | | |
| | 3.6 | M: 6; F: 6 | | |
| | 7.2 | M: 6; F: 6 | | |
| | Positive Control (Novolin® NPH, 7.2 nmol/kg) | M: 4; F: 4 | | |
| Dog (Beagle, s.c.) | 0 (Vehicle) | M: 4; F: 4 | 6 months | No observed Adverse Effects above 1.8 nmol/kg/day |
| | 1.8 | M: 4; F: 4 | | |
| | 3.6 | M: 4; F: 4 | | |
| | 7.2 | M: 4; F: 4 | | |
| | Positive Control (Novolin® NPH, 7.2 nmol/kg) | M: 4; F: 4 | | |
| Dog (Beagle, s.c.) | 0 (Vehicle) | M: 4; F: 4 | 12 months | No observed Adverse Effects above 7.2 nmol/kg/day |
| | 1.8 | M: 4; F: 4 | | |
| | 3.6 | M: 4; F: 4 | | |
| | 7.2 | M: 4; F: 4 | | |
| | Positive Control (Novolin® NPH, 7.2 nmol/kg/day) | M: 4; F: 4 | | |

Mutagenicity

A standard set of experiments have been conducted involving the Ames Test, the mouse micronucleus test and the test for chromosome aberrations in human lymphocytes. All tests were negative. It was concluded that insulin detemir was not mutagenic under the conditions of these tests.

Mitogenicity

The mitogenic potency of insulin detemir was compared to human insulin in three different cell systems, Chinese Hamster Ovary Cells, K1 strain (CHO-K1), human mammary cancer fibroblasts (MCF-7 cells) and human osteosarcoma cells B10 (Saos/B10 cells).

It was concluded that mitogenic potency of insulin detemir is lower than that of human insulin and that the ratio between mitogenic and metabolic potencies of insulin detemir is similar to that of human insulin.

Carcinogenicity

Carcinogenicity trials have not been performed with insulin detemir. The analysis of mitogenic potential, receptor binding, genotoxicity and chronic rat studies conducted demonstrate that insulin detemir has a similar or reduced carcinogenic potential as compared to NPH insulin.

Immunogenicity

Immunogenicity was tested by comparing the antibody response to insulin detemir with the antibody response in parallel groups of rabbits treated with bovine or porcine insulin. There was no statistically significant difference between the groups receiving insulin detemir and porcine insulin, indicating that the immunogenicity of insulin detemir is either less than or equivalent to that of porcine insulin. There was a statistically significant difference with respect to antibody formation between the groups receiving insulin detemir and bovine insulin, indicating that insulin detemir was less immunogenic than bovine insulin.

In rat and dog toxicology studies, antibody development was either absent or low, indicating that antibody inhibition of the insulin was not an issue in the toxicological studies. Furthermore, the low antibody development in the toxicological studies may indicate a low antigenicity of insulin detemir in rats and dogs.

Pregnancy

In a fertility and embryonic development study, insulin detemir was administered to female rats before mating, during mating, and through pregnancy at doses up to 300 nmol/kg/day (3 times the recommended human dose, based on plasma Area Under the Curve (AUC) ratio). Doses of 150 and 300 nmol/kg/day produced numbers of litters with visceral anomalies. Doses up to 900 nmol/kg/day (approximately 135 times the recommended human dose based on AUC ratio) were given to rabbits during organogenesis. Drug-dose related increases in the incidence of fetuses

with gall bladder abnormalities such as small, bilobed, bifurcated and missing gall bladders were observed at doses of 900 nmol/kg/day. The rat and rabbit embryo-fetal development studies that included concurrent human insulin control groups indicated that insulin detemir and human insulin had similar effects regarding embryo-toxicity and teratogenicity.

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PART III: CONSUMER INFORMATION

Levemir[®] (insulin detemir)

This leaflet is part III of a three-part “Product Monograph” published when **Levemir[®]** was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about **Levemir[®]**.

Contact your doctor or pharmacist if you have any questions about this drug.

Read all of this leaflet carefully before you start using your insulin. Keep this leaflet. You may need to read it again.

If you have further questions, please ask your doctor, Diabetes Nurse Educator or pharmacist.

This medicine is prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

ABOUT THIS MEDICATION

A direction leaflet containing information for the patient is included in each package.

What is *Levemir[®]*

Levemir[®] (insulin detemir) is a human insulin analogue used to treat diabetes. **Levemir[®]** is a long-acting human insulin analogue which lowers your blood glucose. **Levemir[®]** has a flat and predictable profile for blood glucose control. The effect will last for up to 24 hours depending on the dose. It may be used in combination with oral antidiabetic agents or with meal-related short- or rapid-acting insulins. Compared to other insulins, therapy with **Levemir[®]** is associated with less weight gain.

Levemir[®] (insulin detemir) is indicated for:

- The treatment of adult patients with type 1 or type 2 diabetes mellitus who require a long-acting (basal) insulin for the control of hyperglycemia.
- The treatment of pediatric patients with type 1 diabetes mellitus who require a long-acting (basal) insulin for the control of hyperglycemia. The safety and efficacy of **Levemir[®]** has not been studied in children below the age of 6 years.
- the treatment of type 2 diabetes mellitus in combination with oral anti-diabetic agents (OADs) in adult patients who are not in adequate metabolic control on OADs alone.

Levemir[®] is also recommended in combination with short or rapid-acting meal-time insulin.

When *Levemir*[®] should not be used.

Do not use *Levemir*[®]:

- If you feel a hypo coming on (a hypo is short for a hypoglycemic reaction or low blood sugar). See *What to do in an emergency*, for more about hypos.
- If you are allergic (hypersensitive) to insulin detemir, metacresol or any of the other ingredients in this insulin. Look out for the signs of an allergic reaction (see *Possible side effects*).

What the medicinal ingredient is

The active ingredient in *Levemir*[®] is a human insulin analogue called *insulin detemir*.

What the nonmedicinal ingredients are:

Disodium phosphate dihydrate, glycerol, metacresol, phenol, sodium chloride, acetate and water for injection. Hydrochloric acid and/or sodium hydroxide may be added to adjust pH.

For a full listing of nonmedicinal ingredients see Part I of the product monograph.

Dosage forms

Levemir[®] is available from Novo Nordisk Canada in the following format:

- *Levemir*[®] Penfill[®] 3 mL cartridge (designed for use with Novo Nordisk Insulin Delivery Devices)

Levemir[®] Penfill[®] cartridges are designed for use with Novo Nordisk Insulin Delivery Systems and NovoFine[®] needles. Novo Nordisk cannot be held responsible for malfunctions occurring as a consequence of using *Levemir*[®] Penfill[®] cartridges in combination with products that do not meet the same specifications or quality standards as NovoFine[®] needles.

WARNINGS AND PRECAUTIONS

Before you use *Levemir*[®] talk to your doctor or pharmacist:

- If you have trouble with your kidneys or liver, or with your adrenal, pituitary or thyroid glands.
- If you drink alcohol: watch for signs of a hypo.
- If you exercise more than usual or if you want to change your usual diet.
- If you are ill: continue taking your insulin.
- If you go abroad: travelling over time zones may affect your insulin needs.
- If you are pregnant, or planning a pregnancy or are breastfeeding please contact your doctor for advice.

- If you drive or use tools or machines: watch for signs of a hypo. Your ability to concentrate or to react will be less during a hypo. Never drive or use machinery if you feel a hypo coming on.

Discuss with your doctor whether you should drive or use machines at all, if you have a lot of hypos or if you find it hard to recognize hypos.

Before you travel, check with your physician or pharmacist on the availability of **Levemir**[®] in other countries. If possible, bring enough **Levemir**[®] with you on your trip.

INTERACTIONS WITH THIS MEDICATION

When you use other medicines

Many medicines affect the way glucose works in your body and this may influence your insulin dose. Listed below are the most common medicines, which may affect your insulin treatment. Talk to your doctor or pharmacist if you take, or change any other medicines, even those not prescribed.

Your need for insulin may change if you also take: oral antidiabetic products; monoamine oxidase inhibitors; (MAOI); beta-blockers; ACE-inhibitors; acetylsalicylic acid (aspirin); thiazides; glucocorticoids (except topical administration); thyroid hormone therapy; beta-sympathomimetics; growth hormone; danazol; octreotide and lanreotide.

PROPER USE OF THIS MEDICATION

How to use **Levemir**[®]

Talk about your insulin needs with your doctor and Diabetes Nurse Educator. Follow their advice carefully. This leaflet is a general guide only.

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.

Before using **Levemir**[®]:

- Check the label to make sure you have the right type of insulin.
- Always check the Penfill[®] cartridge, including the rubber stopper (plunger). Don't use it if any damage is seen or if there is a gap between the rubber stopper and the white barcode label. Take it back to your supplier or call Novo Nordisk Canada at 1 800 465-4334 for assistance. See your Novo Nordisk Insulin Delivery Device manual for further instructions.
- Disinfect the rubber membrane with an alcohol swab.

Do not use *Levemir*[®]:

- In insulin infusion pumps.
- If the Penfill[®] cartridge or Novo Nordisk Insulin Delivery Device containing the cartridge is dropped, damaged or crushed; there is a risk of leakage of insulin.
- If the insulin has not been stored correctly or if it has been frozen (see *How to Store Levemir*[®]).
- If the insulin does not appear water-clear and colourless.

Do not refill a *Levemir*[®] Penfill[®] cartridge.

Levemir[®] Penfill[®] cartridges are designed to be used with Novo Nordisk Insulin Delivery Devices and NovoFine[®] needles as part of **The All In-One System**[®].

If you are treated with *Levemir*[®] Penfill[®] and another insulin in Penfill[®] cartridge, you should use two Novo Nordisk Insulin Delivery Devices, one for each type of insulin.

As a precautionary measure, you should carry a spare syringe and extra insulin in case the insulin delivery device is lost or damaged.

How to use this insulin

Levemir[®] is for injection under the skin (subcutaneously). Never inject your insulin directly into a vein or muscle. Always vary the sites you inject within the same region, to avoid lumps (see *Possible side effects*). The best places to give yourself an injection are: the front of your thighs; the front of your waist (abdomen); or the upper arm.

You should always measure your blood glucose regularly.

How to inject this insulin

- Inject the insulin under the skin. Use the injection technique advised by your doctor or Diabetes Nurse Educator and described in your Novo Nordisk Insulin Delivery Device manual.
- Keep the needle under your skin for at least 6 seconds to make sure that the full dose has been delivered.
- After each injection be sure to remove the needle. Otherwise, insulin may leak out when the temperature changes.

Overdose

Causes of a hypo

You get a hypo if your blood sugar gets too low. This might happen:

- If you take too much insulin.
- If you eat too little or miss a meal.
- If you exercise more than usual.

If your blood sugar gets too high

Your blood sugar may get too high (this is called hyperglycemia).

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; a dry mouth and a fruity (acetone) smelling breath.

If you get any of these signs: test your blood sugar level; test your urine for ketones if you can; then seek medical advice right away.

These may be signs of a very serious condition called diabetic ketoacidosis. If you don't treat it, this could lead to diabetic coma and death.

Causes of hyperglycemia:

- Forgetting to take your insulin.
- Repeatedly taking less insulin than you need.
- An infection or fever.
- Eating more than usual.
- Exercising less than usual.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

What to do in an emergency

If you get a hypo (hypoglycemia):

A hypo means your blood sugar level is too low.

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

If you get any of these signs: eat glucose tablets or a high sugar snack (sweets, biscuits, fruit juice), then rest.

Don't take any insulin if you feel a hypo coming on.

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

Tell your relatives, friends and close colleagues that if you pass out (become unconscious), they must turn you on your side and get medical help right away.

They must not give you anything to eat or drink as it could choke you.

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

Using glucagon

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

Possible side effects

Like all medicines, **Levemir**[®] can cause side effects, although not everybody gets them. Taking too much **Levemir**[®] may cause low blood sugar (hypoglycemia). Hypoglycemia is the most common side effect of insulin, including **Levemir**[®]. See the advice in *What to do in an emergency*.

Commonly reported side effects (less than 1 in 10):

Changes at the injection site. Reactions (redness, swelling, inflammation, itching and bruising) at the injection site may occur. 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.

Less commonly reported side effects (less than 1 in 100):

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 breathing; have a rapid heart beat; feel dizzy.

You may have a very rare serious allergic reaction to **Levemir**[®] or one of its ingredients (called a generalized allergic reaction). See also the warning in *Before you use Levemir*[®].

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

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

Rarely reported side effects (less than 1 in 1,000):

Disturbing sensations: Fast improvement in blood glucose control may cause disturbing sensations (numbness, weakness or pain) in the legs or arms. These symptoms normally disappear. If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor, Diabetes Nurse Educator or your pharmacist.

HOW TO STORE IT

How to store Levemir[®]

Keep out of the reach and sight of children.

Levemir[®] that is not being used should be stored in the fridge between 2°C - 8°C, away from the freezer compartment. Do not freeze.

Levemir[®] that is being used or is carried as a spare should not to be kept in the fridge. You can carry it with you and keep it at room temperature (not above 30°C) for up to 42 days.

Penfill[®]: Always keep your Penfill[®] cartridge in the outer carton when you are not using it, in order to protect it from light.

Levemir[®] should be protected from excessive heat and sunlight.

Do not use **Levemir**[®] after the expiry date printed on the label and carton.

Levemir[®] should not be disposed of in waste water or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help protect the environment.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected side effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance:

By toll-free telephone: 1-866-234-2345

By toll-free fax: 1-866-678-6789

Online: www.healthcanada.gc.ca/medeffect

By email: CanadaVigilance@hc-sc.gc.ca

By regular mail:

Canada Vigilance National Office
Marketed Health Products Safety and Effectiveness
Information Bureau
Marketed Health Products Directorate
Health Products and Food Branch
Health Canada
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

Note: Should you require information related to the management of the side effect, please contact your healthcare provider before notifying Canada Vigilance. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

What **Levemir**[®] looks like and package content

Levemir[®] Penfill[®] comes as a clear, colourless, aqueous solution of 5 cartridges of 3 mL per carton.

1 mL contains 100 U (units) of insulin detemir.

1 Penfill[®] cartridge contains 3 mL equivalent to 300 U.

This document plus the full Product Monograph, prepared for health professionals can be obtained by contacting the sponsor, Novo Nordisk Canada, at 1-800-465-4334

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