

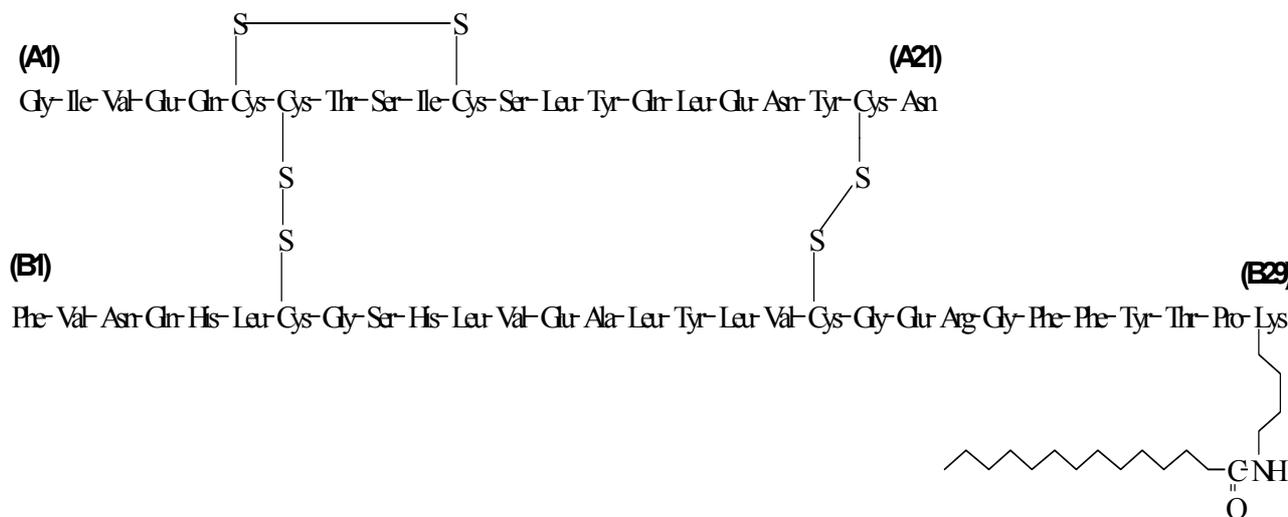
PRODUCT INFORMATION

Levemir[®] FlexPen[®]
Levemir[®] Penfill[®]

NAME OF THE MEDICINE

Insulin detemir

Insulin detemir (rys) has the empirical formula C₂₆₇H₄₀₂N₆₄O₇₆S₆ and a molecular weight of 5916.9.



CAS no. 169148-63-4

DESCRIPTION

Levemir is a soluble, basal insulin analogue with a prolonged duration of effect. Insulin detemir (rys) is produced by recombinant DNA technology using *Saccharomyces cerevisiae*. One unit of insulin detemir contains 0.142 mg salt-free anhydrous insulin detemir. One unit (U) of insulin detemir corresponds nominally to one IU (international unit) of human insulin.

Levemir is a clear, colourless, neutral solution of insulin detemir 100 U/mL. Levemir is a solution for injection.

Levemir also contains the following inactive ingredients: glycerol, phenol, meta-cresol, zinc acetate, dibasic sodium phosphate dihydrate, sodium chloride, hydrochloric acid, sodium hydroxide and water for injections.

PHARMACOLOGY

Pharmacodynamics

Levemir is a soluble, basal insulin analogue with a prolonged duration of effect (Figure 1).

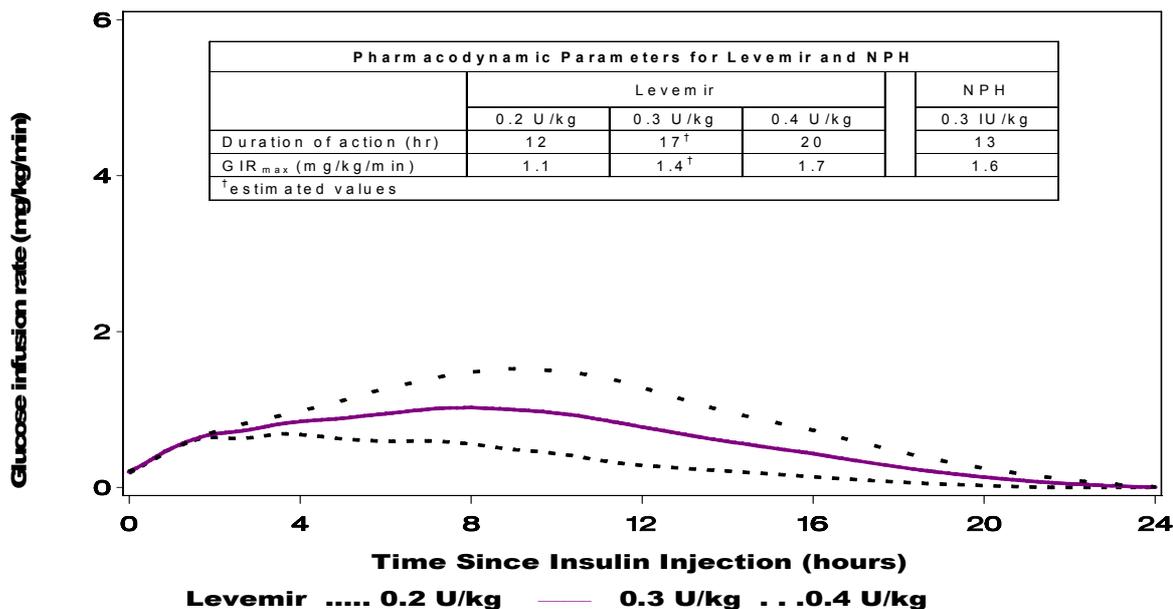


Figure 1: Activity profiles of Levemir in patients with type 1 diabetes.

**Data from Trial NN304-1338, a randomised, double-blind, cross-over trial involving 12 subjects.*

The duration of action is up to 24 hours depending on dose, providing an opportunity for once daily administration. Levemir can also be administered twice daily - when administered twice daily, steady state serum concentrations are reached after 2 to 3 dose administrations. For doses of 0.2 to 0.4 U/kg, Levemir exerts more than 50% of its total pharmacodynamic effect within the approximate period of 3 – 14 hours after dose administration.

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

The time action profile of Levemir was significantly less variable than NPH (Neutral Protamine Hagedorn) insulin and insulin glargine in a study that enrolled 54 (N = 18 per arm) subjects with type 1 diabetes (Table 1).

Table 1. Within-subject variability of the time action profile of Levemir, NPH insulin and insulin glargine in type 1 diabetes mellitus

Pharmacodynamic Endpoint	Variance - Levemir	Variance - NPH insulin	Variance - insulin glargine
AUC _{GIR,0-24h}	0.074	0.466	0.231
GIR _{max}	0.053	0.209	0.130

Pharmacodynamic variability: within-subject statistical variance (Trial 1450). Reproduced with modification.

Variance was derived from log transformed endpoints.

GIR_{max} – maximum glucose infusion rate

N = no. subjects randomised

Lower day-to-day variability in fasting plasma glucose (FPG), a secondary endpoint, was demonstrated during treatment with Levemir compared to NPH in long-term clinical trials in type 1 diabetes, including one in children and adolescents aged 6 to 17 years. The clinical benefit of this has not been demonstrated. Reduced variability in FPG for Levemir versus NPH was not able to be demonstrated consistently in subjects with type 2 diabetes.

Studies in patients with type 2 diabetes treated with basal insulin in combination with oral antidiabetic drugs (OADs) demonstrated that glycaemic control (HbA_{1c}) with Levemir is equivalent to NPH and to insulin glargine. Treatment with Levemir was associated with less weight gain (Table 2), however the trials were not specifically designed to test for this outcome and the clinical benefit has not been demonstrated. In the study

versus insulin glargine, Levemir was administered once or twice daily based on patients' needs, whereas insulin glargine was administered once a day.

Table 2. Change in body weight after insulin treatment – type 2 diabetes

Study duration	Insulin detemir once daily	Insulin detemir twice daily	NPH	Insulin glargine	
20 weeks	+ 0.7 kg (a.m) + 1.1 kg (p.m)		+ 1.6 kg		p = 0.005 not significant
26 weeks		+ 1.2 kg	+ 2.8 kg		p < 0.001
52 weeks	+ 2.3 kg	+ 3.7 kg		+ 4.0 kg	p < 0.001 not significant

In a trial investigating add-on insulin detemir with liraglutide and metformin (see 'Clinical Trials'), weight reduction of 3.5 kg was observed during the initial 12 week run-in period on liraglutide and metformin alone. Adding insulin detemir did not result in any further clinically significant loss of weight but the initial loss was sustained.

In clinical trials in adults using basal bolus insulin therapy, the overall rates of hypoglycaemia with Levemir and NPH insulin were similar. Analyses of nocturnal hypoglycaemia in patients with type 1 diabetes showed a significantly lower risk of minor nocturnal hypoglycaemia (able to self-treat and confirmed by capillary blood glucose less than 2.8 mmol/L or 3.1 mmol/L if expressed as plasma glucose) than with NPH insulin, whereas no difference was seen in type 2 diabetes. Furthermore, the overall risk of nocturnal hypoglycaemia in children and adolescents aged 2 to 17 years with type 1 diabetes was significantly lower with Levemir compared to NPH insulin. In trials with the use of OAD-insulin combination therapy in adults with type 2 diabetes, Levemir treatment resulted in a 61-65% lower risk of minor nocturnal hypoglycaemia compared to NPH.

The prolonged action of Levemir is thought to be mediated by the strong self-association of insulin detemir molecules at the injection site, and binding to plasma proteins, most likely albumin, via the fatty acyl side-chain. Insulin detemir is distributed more slowly to peripheral target tissues compared to isophane insulin.

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 decreased glucose output from the liver. *In vitro* testing of insulin detemir's binding to the insulin and IGF-1 receptors has shown that Levemir has reduced affinity to both receptors. The clinical correlates of this have not been established. The molar dose of insulin detemir is approximately fourfold higher compared with human insulin. One unit of Levemir is approximately equipotent to one international unit of human insulin. See 'Clinical Trials' section for dose data observed in randomised clinical trials in types 1 and 2 diabetes.

Pharmacokinetics

Absorption

Maximum serum concentration is reached 6 to 8 hours after administration. When administered twice daily, steady state serum concentrations are reached after 2 to 3 dose administrations. Intra-subject variation in absorption is lower for Levemir in type 1 diabetes 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 Levemir and fatty acids or other protein bound drugs.

Metabolism

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

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.

Linearity

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

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

Special populations

Elderly, renal and hepatic impairment

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

Gender

There was no clinically relevant difference between genders in pharmacokinetic parameters of Levemir.

Paediatrics

The pharmacokinetic properties of Levemir were investigated in children (6–12 years) and adolescents (13–17 years) with type 1 diabetes, and compared to adults with type 1 diabetes. A total of 16 males and 18 females were studied. No difference in pharmacokinetics was observed between the three age groups.

CLINICAL TRIALS

The confirmatory therapeutic clinical development programme to evaluate the efficacy and safety of Levemir consisted of 15 phase 3, randomised, parallel-group (versus isophane insulin and/or insulin glargine), open-label, multicentre clinical trials. The trial programme randomised a total of 1945 adult patients with type 1 diabetes and a total of 2433 adult patients with type 2 diabetes. Ten of the studies employed the marketed formulation, and the remaining five employed a less concentrated (but nevertheless bioequivalent) ‘early-development’ formulation. In addition, the efficacy and safety of Levemir were demonstrated in two studies in children and adolescents with type 1 diabetes. One of these studies, of 6 months’ duration, investigated children aged 6 to 17 years (N = 347). The second of these studies, of 12 months’ duration (N = 347) plus an extension phase to 24 months (N = 146), investigated children and adolescents aged from 2 to 17 years. The efficacy component of the clinical trials were designed primarily to test non-inferiority to the comparator, not equivalence.

In intermediate and long-term treatment trials intended to demonstrate the non-inferiority of the marketed formulation of Levemir to human insulin, the primary outcome was HbA_{1c}. Secondary outcomes included FPG levels, multi-point blood glucose profiles, within-subject variation for fasting blood/plasma glucose (FBG or FPG), hypoglycaemia, quality of life, antibody levels, daily doses and safety profiles as measured by adverse events, laboratory safety parameters, physical examination, weight and vital signs. Levemir provides equivalent glycaemic control as measured by HbA_{1c} and better glycaemic control as measured by FPG, although not at some other times as determined by 9 point blood glucose profiles, compared to human isophane insulin treatment in type 1 diabetes. Intensive therapy with Levemir is also associated with lower day-to-day FBG variation in type 1 diabetes, and equivalent safety profiles except for weight. Reduced variability in FPG for Levemir versus human isophane insulin was not able to be demonstrated consistently in subjects with type 2 diabetes.

Levemir is not associated with weight gain over 4 – 6 months in type 1 diabetes, however the trials were not designed to test for this outcome and the clinical benefit of this has not been demonstrated.

Clinical studies in type 1 diabetes

In three large randomised, controlled clinical studies, adult patients with type 1 diabetes (1335 study, N = 749; 1447 study, N = 400; 1448 study, N = 409) were randomised to basal/bolus treatment with once- or twice-daily Levemir (marketed formulation insulin detemir) or with NPH insulin once- or twice-daily, for 4 to 6 months. The bolus (mealtime) treatment was soluble human insulin (1335 study) or insulin aspart (1447 and 1448 studies). In these studies, Levemir and NPH had a similar effect on the primary outcome of HbA_{1c} (Table 3). In the secondary outcomes, Levemir demonstrated significantly improved FPG (Table 3) and within-subject variation (1335 study p<0.001, 1447 study p<0.001; 1448 study p<0.001), with similar overall rates of hypoglycaemia and safety profiles including adverse events, laboratory safety parameters,

physical examination, and vital signs, compared with NPH insulin. In a 9 point blood glucose profile (1335 study), the overall profiles were significantly different between Levemir and NPH insulin ($p=0.006$), with blood glucose concentrations being lower from before breakfast and throughout the day until after bedtime, in the Levemir group. In 10 point blood glucose profiles (1447 and 1448 studies), the overall profiles were similar during the day but tended to differ at night, with lower night-time blood glucose concentrations in some of the Levemir groups. In the 1335 study, antibody formation was increased with Levemir but did not compromise glycaemic control.

Two additional multicentre, open-label, randomised, confirmatory clinical trials were conducted in adult subjects with type 1 diabetes to assess HbA_{1c} response during treatment for up to 6 months. Twice-daily Levemir (early-development formulation insulin detemir) or NPH insulin were compared when combined with bolus insulin aspart (1205 study; N = 448) or with bolus soluble human insulin (1181 study; N = 461). At the end of 6 months of treatment, the primary outcomes of mean HbA_{1c} values were equivalent for Levemir and NPH in both studies. In the 1205 study, the secondary outcomes which were statistically different between treatment groups included lower within-subject variation in FBG with Levemir compared

Table 3. Results in type 1 diabetes (studies 1335, 1447, 1448)

Trial ID	Treatment (regimen)	N [#]	HbA _{1c} (%) - end of study mean	FPG (mmol/L) - end of study mean	Daily basal insulin dose (U/kg or IU/kg)		Daily bolus insulin dose (U/kg or IU/kg)	
			(Levemir - NPH [95% CI])	(Levemir - NPH [95% CI])	Pre-study mean	End of study mean	Pre-study mean	End of study mean
1335	Levemir [§] (nocte)	492	8.26	10.1	0.31	0.27	0.44	0.47
	NPH (nocte)*	257	8.38	11.2	0.31	0.33	0.44	0.44
			(-0.12 [-0.25, 0.02])	(-1.2 [-1.8, -0.5])				
1447	Levemir [§] (b.d.)	271	7.66	9.50 [∞]	0.35	0.43	0.39	0.39
	NPH (b.d.)	129	7.73	11.13	0.32	0.38	0.37	0.34
			(-0.07 [-0.22, 0.08])	(-1.64 [-2.45, -0.82])				
1448	Levemir [§] (b.d.)	276	7.76	9.34 [∞]	0.36	0.49	0.40	0.38
	NPH (b.d.)	133	7.94	11.24	0.39	0.45	0.40	0.38
			(-0.18 [-0.34, -0.02])	(-1.90 [-2.79, -1.02])				

#N = number of patients randomised. §Marketed formulation insulin detemir. *Once daily NPH insulin may be expected to favour Levemir. ∞Data from both arms pooled. Baseline values were included as covariates in an ANOVA analysis.

with NPH insulin ($p<0.001$), lower relative risk (0.78) of hypoglycaemia with Levemir compared with NPH insulin [95%CI: 0.62, 0.97], and a significant difference in the 9 point blood glucose profile, with blood glucose concentrations lower before breakfast and higher from lunch through 02:00 hours in the Levemir group compared with the NPH insulin group ($p=0.036$). The mean doses of both basal and bolus insulins were higher after 6 months in the Levemir group compared with the NPH group.

Both 1205 and 1181 clinical trials were extended for an additional 6 months (as trial IDs 1316 and 1243 respectively) to assess maintenance of Levemir efficacy up to a period of 1 year of treatment. At the end of extension trials 1316 and 1243, HbA_{1c} values for Levemir treatment were equivalent to those of the NPH parallel treatment group.

Clinical studies in children and adolescents with type 1 diabetes

Study 1379 was a multicentre, open-label, randomised, confirmatory clinical trial conducted in subjects (N = 347) with type 1 diabetes aged between 6 and 17 years. After 26 weeks of treatment with Levemir or NPH, both given once or twice daily in combination with bolus insulin aspart, the primary endpoint (HbA_{1c}) for Levemir was non-inferior to NPH (Table 4). Other secondary outcomes measured included within-subject variability in FPG, 8-point PG profiles, nocturnal PG, overall safety profiles as measured by adverse events

and laboratory measures including weight (in terms of change in body mass index (BMI)) and vital signs, rates of overall and (pre-defined) sub-categories of hypoglycaemia, incidences of diabetic ketoacidosis requiring hospitalisation, and antibody formation. The secondary outcomes which were statistically different between treatment groups included lower within-subject variation in FPG with Levemir compared with NPH insulin ($p < 0.001$), lesser increase in BMI with Levemir ($p < 0.001$), and lower overall risk of nocturnal hypoglycaemia with Levemir ($p = 0.011$) compared to NPH insulin, although hypoglycaemic episodes in general occurred with similar frequencies in both groups (see 'Adverse Effects'). The study had no subgroup analysis by once daily/twice daily Levemir. Levels of Levemir-specific and cross-reacting antibodies increased in the Levemir but not the NPH insulin group, and the levels of Levemir-specific antibodies correlated with dose per kg body weight. Doses of basal and bolus insulins were equivalent in both treatment groups.

Study 1689 was a 12-month, multinational, multi-centre, open- labelled, randomised, parallel, efficacy and safety clinical trial comparing Levemir and NPH Insulin in 348 children and adolescents 2-16 years with type 1 diabetes on a basal-bolus regimen with insulin aspart as bolus insulin. Glycaemic control (HbA_{1c}) with Levemir was similar to NPH insulin when given as basal-bolus therapy. A lower risk of 24h and nocturnal hypoglycaemia and a lower rate (number of events/1000 exposure years) of severe adverse events were observed with Levemir than with NPH. Furthermore, less weight gain was observed with Levemir than with NPH insulin. The change in mean weight at 52 weeks from baseline in the Levemir group was 3.2 kg and 4.1 kg in the NPH group. No severe nocturnal hypoglycaemic episodes were reported with Levemir in this trial.

Table 4. Results in type 1 diabetes - children and adolescents (studies 1379 & 1689)

Trial ID	Treatment	N [#]	HbA _{1c} (%) – end of study mean (Levemir-NPH [95% CI])
1379	Levemir + insulin aspart	232	8.02
	NPH + insulin aspart	115	7.93
			(0.09 [-0.12, 0.29]) [†]
1689	Levemir + insulin aspart	177	8.75
	NPH + insulin aspart	170 [‡]	8.64
			(0.12 [-0.12, 0.36]) [†]

#N = number of subjects randomised.

[†]Non-inferiority defined as upper limit of 95% CI for (HbA_{1c} (Levemir) - HbA_{1c} (NPH)) < 0.4%

[‡]One patient randomised to the NPH arm withdrew consent prior to the administration of insulin.

Study 1689 was extended for an additional 12 months (total of 24 months' treatment data; extension designated as 'study 1690') to assess antibody formation after long-term treatment with Levemir. After an increase in the levels of insulin antibodies during the first year, the levels decreased during the second year to those slightly higher than observed pre-trial. There was slight increase in HbA_{1c} during the extension period for all the age groups: mean% (SD) 0.10% (0.77) for the 2 to 5 year age group, 0.27% (1.08) for the 6 to 12 year, 0.11% (1.60) for the 13 to 16 year and 0.17% (1.22) for the overall population. Of the total population, 15 (10.3%) patients were within the target range for pre-prandial PG of ≥ 4 to ≤ 7 mmol/L.

Clinical studies in type 2 diabetes

Combination therapy with oral antidiabetic drugs (OADs) (studies 1337, 1373, 1530, 1632)

Four phase 3, multicentre, open, randomised studies of Levemir versus NPH and/or insulin glargine, all in combination with one or more OADs, have been conducted in patients with type 2 diabetes inadequately controlled on OADs (or, in the case of study 1337, inadequately controlled on basal monotherapy). The studies (N = 2029 total) were conducted with durations between 20 weeks and 1 year, and in all studies the primary efficacy measure was HbA_{1c} and secondary endpoints included FPG, multi-point blood glucose profiles, within-subject variability, hypoglycaemia, weight and safety profiles.

In study 1337 (N = 467), the earliest of the aforementioned combination-with-OAD studies, Levemir was inferior to NPH insulin for HbA_{1c} (mean difference (Levemir – NPH) [95% CI] was 0.56 [0.33, 0.78]). In the studies performed subsequently (N = 1562 total), Levemir was non-inferior to the NPH/insulin glargine comparator for HbA_{1c} (Table 5). Secondary endpoints were similar between Levemir and comparators with the exception of weight (see 'Pharmacodynamics').

In study 1373, a comparison with insulin glargine, the results of the primary efficacy endpoint was for the ITT group 0.045 (-0.114 to 0.205), indicating that the predefined non-inferiority criteria were met. In the ITT group, the mean (SE) HbA_{1c} at end of treatment was 7.16 (0.078) for the Levemir group and 7.12 (0.078) for the glargine group. For the once daily Levemir group, the difference was 0.061 (-0.142 to 0.263) and for the twice daily group, 0.003 (-0.189 to 0.195). There was no significant difference in fasting plasma glucose at 52 weeks. The ratio of final daily dose (U/kg Levemir/glargine) was 1.16 for the once daily Levemir group and 2.26 for the twice daily group, and 1.77 overall.

In study 1632, there was less risk of nocturnal hypoglycaemia with morning Levemir than evening Levemir.

Table 5. Results in type 2 diabetes - combination therapy with OADs (studies 1337, 1373, 1530, 1632)

Trial ID	Treatment (regimen)	N [#]	HbA _{1c} (%) – end of study mean (Levemir - comparator [95% CI])	FPG (mmol/L) – end of study mean (Levemir - comparator [95% CI])
1337	Levemir (o.d.) + metformin	309	8.5	8.6
	NPH (o.d.) + metformin	158	8.0	8.6
			(0.56 [0.33, 0.78])	(-0.1 [-0.71, -0.49])
1373	Levemir (o.d or b.d.) + OAD	291	7.16	7.14
	glargine (o.d.) + OAD	291	7.12	6.98
			(0.05 [-0.11, 0.21])	(0.16 [-0.26, 0.58])
1530	Levemir (b.d.) + OAD	237	6.58	6.62
	NPH (b.d.) + OAD	239	6.46	6.30
			(0.13 [0.00, 0.25])	(0.32 [-0.02, 0.66])
1632	Levemir (o.d. - morning) + OAD	168	7.48	8.32
	NPH (o.d. - evening) + OAD	166	7.36	7.44
			(0.13 [-0.07, 0.32])	(0.88 [0.31, 1.45])
	Levemir (o.d. - evening) + OAD	170	7.43	7.04
	NPH (o.d. - evening) + OAD	166	7.33	7.50
			(0.10 [-0.08, 0.29])	(-0.46 [-1.05, 0.13])

#N = number of subjects randomised. o.d. = once daily injection. b.d. = twice daily injection.

Add-on therapy to liraglutide plus OADs (studies 1842, 1842 ext.)

An open-label randomised study in patients with type 2 diabetes not reaching target with OADs was conducted. The trial started with a 12 week run-in period with liraglutide+metformin, where 61% reached an HbA_{1c} <7%. The 39% of patients not achieving target were randomised to have Levemir once-daily added or continue on liraglutide+metformin for 52 weeks. Addition of Levemir provided a further reduction of HbA_{1c} from 7.6% to 7.1% after 52 weeks, no major hypoglycaemic episodes were reported with Levemir (see Table 6). Adding Levemir did not result in any further clinically significant loss of weight but the initial loss obtained with liraglutide+metformin dual therapy during the run-in period was maintained.

Table 6. Results in type 2 diabetes - Levemir as add-on therapy to liraglutide+metformin (studies 1842, 1842 ext.)

	Study weeks	Randomised Levemir + liraglutide + metformin (N = 160)	Randomised liraglutide + metformin (N = 149)	Treatment difference/ratio [95% CI]	P-value
Mean change in HbA _{1c} from baseline (%)	26	-0.51	+0.02	-0.52 [-0.68 ; -0.36]	<0.0001
	52	-0.50	0.01	-0.51 [-0.70 ; -0.31]	<0.0001
Proportions of patients achieving HbA _{1c} <7% targets (%)	26	43.1	16.8	3.75 ^a [2.19 ; 6.45]	<0.0001
	52	51.9	21.5	3.94 ^a [2.37 ; 6.55]	<0.0001
Minor hypoglycaemic episodes (per patient year)	26	0.286	0.029	9.91 ^b [2.11 ; 46.62]	0.0037
	52	0.228	0.034	6.80 ^b [0.78 ; 8.97]	0.0011

^aOdds ratio; ^bRate ratio

Basal/bolus therapy (study 1336)

Study 1336 (N = 505) was a 6 month, phase 3, multicentre, open, randomised, parallel study of Levemir (marketed formulation insulin detemir) and NPH in patients with type 2 diabetes treated with a basal/bolus regimen. Insulin aspart was employed as the bolus insulin. The primary endpoint was HbA_{1c}, and after 6 months the reduction in HbA_{1c} was non-inferior for Levemir versus NPH (mean difference (Levemir – NPH) [95% CI] was 0.157 [0.003, 0.312]). Secondary endpoints such as FPG, 9 point blood glucose profiles, hypoglycaemia (total and nocturnal), quality of life and most of the safety profiles were all similar between the two treatment groups. The within-subject variation in FBG (p=0.021) was significantly lower for Levemir compared with NPH insulin. At end of study, the mean basal insulin doses were 36.4 units per day for Levemir, and 35.3 IU per day for NPH, and the mean bolus insulin doses were 40.2 U and 35.8 U per day respectively.

Results of other ongoing studies supporting the basal/bolus use of Levemir in patients with type 2 diabetes mellitus are not yet available.

Basal monotherapy (study 1166)

Study 1166 (N = 439) was a 6 month, phase 3 basal monotherapy study of twice-daily Levemir (early-development formulation insulin detemir) versus NPH, in patients aged 35 years or more with type 2 diabetes receiving ≤ 120 IU total insulin per day. The primary endpoint was HbA_{1c}, and after 6 months Levemir was inferior to NPH insulin (mean difference (Levemir– NPH) [95% CI] was 0.660 [0.436, 0.885]). Secondary endpoints included FPG, 9 point blood glucose profiles, within-subject variability, hypoglycaemia and weight control. FPG and 9 point blood glucose profiles were inferior with Levemir compared with NPH. Within-subject variability and hypoglycaemia were similar between the two treatment arms. Withdrawals due to lack of efficacy were seen in 10.7% of Levemir subjects versus 0.7% of NPH subjects.

Clinical studies in pregnancy

In a randomised controlled clinical trial (study 1687), 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 meal time insulin. Levemir was shown to be non-inferior to NPH insulin measured by HbA_{1c} at gestational week 36 (treatment difference in the Full Analysis Set, -0.06% [95% CI -0.21 to 0.08]). The changes in mean HbA_{1c} through pregnancy were similar for subjects in the Levemir and NPH insulin groups. The target of HbA_{1c} ≤ 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 weeks 24 and 36, mean FPG was statistically significantly lower in the Levemir group than in the NPH insulin group. The estimated treatment difference was -0.94 mmol/L (95% CI: [-1.67 ; -0.21], p=0.012) at 24 gestational weeks and -0.65 mmol/L (95% CI: [-1.19 ; -0.12], P = 0.017) at 36 gestational weeks.

The rate of hypoglycaemic episodes during pregnancy was similar between the Levemir and NPH groups. 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 (see 'Use in Pregnancy').

INDICATIONS

Treatment of diabetes mellitus. (See 'Pharmacology' and 'Clinical Trials'.)

CONTRAINDICATIONS

Hypersensitivity to insulin detemir or any of the excipients.

PRECAUTIONS

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

Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement (see 'Adverse Effects' and 'Overdosage').

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 (for example, 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 who have frequent episodes of hypoglycaemia. The advisability of driving should be considered in these circumstances.

Omission of a meal or unplanned strenuous physical exercise may lead to hypoglycaemia (see 'Adverse Effects' and 'Overdosage').

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

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

Administration

Levemir is for subcutaneous administration only. Intramuscular administration should be avoided. Levemir is not to be administered intravenously as it may result in severe hypoglycaemia.

If Levemir is mixed with other insulin preparations the profile of action of one or both individual components may change. Mixing Levemir with a rapid-acting insulin analogue like insulin aspart will reduce and delay the maximum effect of the rapid-acting insulin compared to that observed following separate injections.

Levemir is not to be used in insulin infusion pumps.

Injection site reactions

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

Levemir contains metacresol, which may cause allergic reactions.

Transfer of patients between insulin types

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.

Combination of thiazolidinediones and insulin

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.

Incompatibilities

Substances added to Levemir may cause degradation of insulin detemir, for example if the medicinal product contains thiols or sulphites. Levemir should not be added to infusion fluids.

Carcinogenicity

The carcinogenic potential of insulin detemir has not been investigated in long-term animal studies.

Genotoxicity

Insulin detemir was not genotoxic in assays for reverse gene mutation in bacterial or chromosomal damage in cultured human lymphocytes. An *in vivo* micronucleus test in mice was also negative.

Effects on fertility

No adverse effects on male or female fertility were apparent in a study in rats dosed at levels up to 50 U/kg/day s.c.

Use in Pregnancy

Pregnancy Category: A

Treatment with Levemir can be considered during pregnancy, if the benefit justifies possible risks.

In a randomised controlled clinical trial (study 1687), pregnant women with type 1 diabetes were treated in a basal-bolus regimen where Levemir (N = 152) was compared to NPH insulin (N = 158), with insulin aspart as meal time insulin. A total of 470 women were randomised to two parallel treatment groups (233 and 237 subjects in Levemir and NPH groups, respectively). The Full Analysis Set consisted of 152 women in the Levemir group (79 pregnant (gestational age 8-12 weeks) at randomisation; 73 became pregnant post randomisation) and 158 women in the NPH group (83 pregnant (gestational age 8-12 weeks) at randomisation; 75 became pregnant post randomisation). Levemir was shown to be non-inferior to NPH insulin measured by HbA_{1c} at gestational week 36.

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. Pre-eclampsia is a syndrome defined by symptoms of hypertension and proteinuria. Pre-eclampsia was reported at an incidence of 10.5% with Levemir compared to 7% in NPH group.

The clinical trial results showed similar efficacy of Levemir and NPH insulin (see 'Clinical Trials' – 'Clinical studies in pregnancy').

Post-marketing data (approximately 300 outcomes from pregnant women exposed to Levemir) indicate no adverse effect of Levemir on pregnancy and no malformative or feto/neonatal toxicity of insulin detemir.

Animal reproduction studies showed increases in post-implantation loss and fetal anomalies in rats following treatment with insulin detemir at doses of 25-50 U/kg/day s.c. A teratology study in rabbits revealed increased in utero deaths and post-implantation losses following dosing with 37.5 U/kg/day s.c. Lower doses were not tested. Similar effects have also been reported for human insulin and other human insulin analogues. These effects are probably secondary to maternal hypoglycaemia.

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.

Use in lactation

There is currently no clinical experience with insulin detemir during lactation. Lactating women may require adjustments in insulin dose and diet.

INTERACTIONS WITH OTHER MEDICINES

A number of medicinal products are known to interact with glucose metabolism. Possible interactions must therefore be taken into account by the physician.

The following substances may reduce the patient's insulin requirements:

Oral antidiabetic drugs (OADs), monoamine oxidase inhibitors (MAOIs), non-selective beta-adrenergic blocking agents, angiotensin converting enzyme (ACE) inhibitors, salicylates, anabolic steroids (except danazol and oxymetholone), alpha-adrenergic blocking agents, quinine, quinidine and sulphonamides.

The following substances may increase the patient's insulin requirements:

Oral contraceptives, thiazides, glucocorticoids, thyroid hormones, sympathomimetics, growth hormone, diazoxide, asparaginase, nicotinic acid, oxymetholone and danazol.

Insulin detemir is greater than 97% protein-bound in plasma, independent of gender. The results of *in vitro* studies do not suggest any clinically relevant albumin binding interactions between insulin detemir and fatty acids or other protein-bound drugs (such as warfarin, frusemide, tolbutamide, diazepam, glibenclamide, nifedipine, repaglinide, aspirin or valproic acid) or other drugs known to bind to domains IIA and IIIA of the albumin molecule. As there is a vast excess (about 400 000) of albumin binding sites available in plasma per insulin detemir molecule, there would be little risk that lower albumin concentrations resulting from some disease states like nephrotic syndrome might affect the ratio of bound to free insulin detemir or that acute displacement could occur. This is supported by *in vitro* studies as well as subgroup analyses from the clinical trial programme. Nevertheless, there are limited data in patients with severe hypoalbuminaemia.

Beta blockers may mask the symptoms of hypoglycaemia and delay recovery from hypoglycaemia.

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

Alcohol may intensify and prolong, or reduce, the hypoglycaemic effect of insulin.

ADVERSE EFFECTS

a. Summary of the safety profile

Adverse drug reactions observed in patients using Levemir are mainly dose-dependent and due to the pharmacologic effect of insulin. 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.

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

At the beginning of the insulin treatment, refraction anomalies and oedema may occur; these reactions are usually of transitory nature. Fast improvement in blood glucose control may be associated with acute painful neuropathy, which is usually reversible. Intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy, while long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy.

b. Tabulated list of adverse events and adverse reactions

Table 7. Comparative incidence of adverse events (% of patients) during intermediate and long term clinical trials

EVENT	Levemir N* = 3249	Isophane human insulin N* = 1944
Respiratory		
URTI	19.3	18.5
Pharyngitis	6.2	5.7
Bronchitis	3.1	2.7
Sinusitis	2.5	2.3
Coughing	2.4	2.3
Central and Peripheral Nervous System Disorders		
Headache	16.2	15.8
Migraine	1.1	0.9
Dizziness	1.1	0.8
Gastro-intestinal System Disorders		
Abdominal pain	4.9	3.4
Gastroenteritis	4.1	3.5
Toothache	1.9	1.7
Body as a Whole – General Disorders		
Back pain	4.0	3.3
Pain	1.4	0.9
Allergic reaction	1.2	1.0
Fatigue	1.1	1.0
Skin and Appendages Disorders		
Skin disorder	1.0	0.7
Urinary System Disorders		
Urinary tract infection	1.8	1.5
Application Site Disorders		
Injection site reaction	1.8	1.1

Treatment emergent adverse events; Levemir incidence $\geq 1.0\%$ and $>$ isophane human insulin group.

*N = number of patients exposed to each treatment arm

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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$); not known (cannot be estimated from the available data).

Table 8. Frequencies of adverse drug reactions from clinical trials, which by an overall judgement are considered related to Levemir.

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

* see section c

c. Description of selected adverse reactions

Allergic reactions, potentially allergic reactions, urticaria, rash and eruptions

Allergic reactions, potentially allergic reactions, urticaria, rash and eruptions are uncommon when Levemir is used in basal-bolus regimen. In three clinical studies with subjects treated in combination with OADs a higher frequency (2.2%) of allergic reactions and potentially allergic reactions has been observed compared with the frequency observed across all studies (0.1-1.0%; see below).

Anaphylactic reactions

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

Hypoglycaemia

The most frequently reported adverse reaction is hypoglycaemia. It may occur if the insulin dose is too high in relation to the insulin requirement. Severe hypoglycaemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death. The symptoms of hypoglycaemia usually occur suddenly. They may include cold sweats, cool pale skin, fatigue, nervousness or tremor, anxiousness, unusual tiredness or weakness, confusion, difficulty in concentration, drowsiness, excessive hunger, vision changes, headache, nausea and palpitation.

Lipodystrophy

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

Antibody development

Antibody development has been observed with the use of Levemir in adults and children, however no discernable impact on glycaemic control or dose has been noted. In a 12 month clinical trial in children and adolescents aged 6-17 years with type 1 diabetes (1689 study), rises in insulin detemir specific and cross-reacting antibodies were observed in the Levemir but not the NPH comparator groups. In the 1690 extension study to 24 months, insulin antibody levels decreased during the second year to those slightly higher than pre-trial levels (see 'Clinical Trials').

DOSAGE AND ADMINISTRATION

Levemir is a long-acting insulin analogue used alone as a basal insulin or in combination with bolus insulin. It can also be used in combination with OADs or as add-on therapy to liraglutide.

For patients with type 1 diabetes mellitus, Levemir must be used in combination with rapid- or short-acting insulin.

When Levemir is used as part of a basal-bolus insulin regimen Levemir should be administered once or twice daily depending on patients' needs. Dosage of Levemir should be adjusted individually. For patients who require twice daily dosing to optimise blood glucose control, the evening dose can be administered either with the evening meal, at bedtime, or 12 hours after the morning dose.

In combination with OADs or as add on therapy to liraglutide in type 2 diabetes it is recommended to initiate Levemir treatment with once daily administration at a dose of 10 U or 0.1-0.2 U/kg. The dose of Levemir should be titrated based on individual patients' needs. Based on study results, the following titration guideline is recommended (Table 9):

Table 9. Dosage titration algorithm – Levemir with OADs in type 2 diabetes

Average pre-breakfast self-monitored plasma glucose (SMPG)	Levemir dose adjustment (U)
> 10 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
If one SMPG measurement	
3.1 – 4.0 mmol/L	- 2
< 3.1 mmol/L	- 4

In combination with OADs in type 2 diabetes, where optimisation of blood glucose control is not achieved with once daily injection, consideration should be given to adding a mealtime bolus injection of short-/rapid-acting insulin, or to transferring the patient to a pre-mixed insulin.

As with all insulins, adjustment of dosage may also be necessary if patients undertake increased physical activity, change their usual diet or during concomitant illness.

Special populations

Elderly, renal and hepatic impairment

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.

Paediatrics

Specific nonclinical studies in juvenile animals have not been conducted.

The efficacy and safety of Levemir were demonstrated in adolescents and children aged 2 years' and above in studies up to 24 months in duration (see 'Clinical Trials').

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

Pregnancy

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.

Hypoalbuminaemia

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

Transfer from other insulins

Transfer to Levemir from intermediate or long-acting insulins may require adjustment of dose and timing of administration (see 'Precautions'). As with all insulins, close glucose monitoring is recommended during the transition and in the initial weeks thereafter.

Concomitant antidiabetic treatment may need to be adjusted (dose and/or timing of concurrent short/rapid-acting insulins or OADs). An increase in soluble insulin requirements has been demonstrated in some individuals who have been transferred from human insulin to Levemir.

Method of Administration

Levemir is for subcutaneous administration only by injection in the thigh, abdominal wall, the upper arm, or the gluteal region. As with human insulin, the rate and extent of absorption of insulin detemir may be higher when administered subcutaneously in the abdomen or upper arm as opposed to the thigh. Injection sites should be rotated within the same region in order to reduce the risk of lipodystrophy. Formal studies with administration in the gluteal region have not been conducted. 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.

Instructions for use and handling

Levemir FlexPen and Levemir Penfill are for use by one person only. Levemir must not be used if it has been frozen. Levemir must not be used if the solution does not appear clear and colourless.

Levemir FlexPen

The carton contains a Consumer Medicine Information package leaflet with instructions for use and handling. Please note that insulin is not delivered if the patient reverse dials the insulin pen by returning the dose selector to zero after inserting the needle. Patients should be instructed that insulin injection only occurs when the pushbutton is depressed.

The cartridge inside Levemir FlexPen must not be refilled. NovoFine[®] or NovoTwist[®] needles up to a length of 8 mm are designed to be used with Levemir FlexPen. The patient should be advised to discard the needle after each injection.

Levemir Penfill

The carton contains a Consumer Medicine Information package leaflet with instructions for use and handling. The leaflet refers to the instructions for using the accompanying Novo Nordisk insulin delivery system (durable device for repeated use).

Levemir Penfill cartridges must not be refilled. Levemir Penfill cartridges are designed to be used with Novo Nordisk insulin delivery systems and NovoFine or NovoTwist disposable needles. The patient should be advised to discard the needle after each injection.

OVERDOSAGE

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

- Mild hypoglycaemic episodes can be treated by oral administration of glucose or sugary products. It is therefore recommended that the person with diabetes always carry products containing sugar with them. Adjustments in drug dosage or meal patterns may be needed.
- Severe hypoglycaemic episodes, where the patient is not able to treat themselves, 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 medical professional. Glucose must be given intravenously if the patient does not respond to glucagon within 10 to 15 minutes. After apparent clinical recovery from hypoglycaemia, continued observation and additional carbohydrate intake may be necessary to avoid recurrence of hypoglycaemia.

PRESENTATION AND STORAGE CONDITIONS

Presentations

Levemir contains insulin detemir 100 U/mL. The following presentations are available:

Levemir FlexPen

Levemir FlexPen is a pre-filled, multidose, disposable syringe consisting of a pen injector and a 3mL cartridge. The cartridge is made of glass, contains a bromobutyl rubber piston and is closed with a latex-free bromobutyl/polyisoprene rubber disc. The pen injector is made of plastic (polypropylene, POM). Five Levemir FlexPen are packed in a carton.

Levemir Penfill

Levemir Penfill is a 3mL cartridge made of glass, containing a bromobutyl rubber piston and closed with a latex-free bromobutyl/polyisoprene rubber disc. Five Levemir Penfill cartridges are packed in a carton.

Storage conditions

Before use:

Levemir products should be stored in a refrigerator between 2°C and 8°C. Keep away from the cooling element. Do not freeze.

In use or carried as a spare:

Levemir products in use or carried as spares should be kept at ambient temperature (at or below 30°C) for up to 4 weeks, but any remainder must then be discarded. They should not be exposed to excessive heat or light.

Levemir FlexPen: Keep the pen cap on when not in use in order to protect from light.

Levemir Penfill: Keep the cartridges in the outer carton in order to protect from light.

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

S4

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (the ARTG)

9 September 2011

DATE OF MOST RECENT AMENDMENT

16 October 2013