

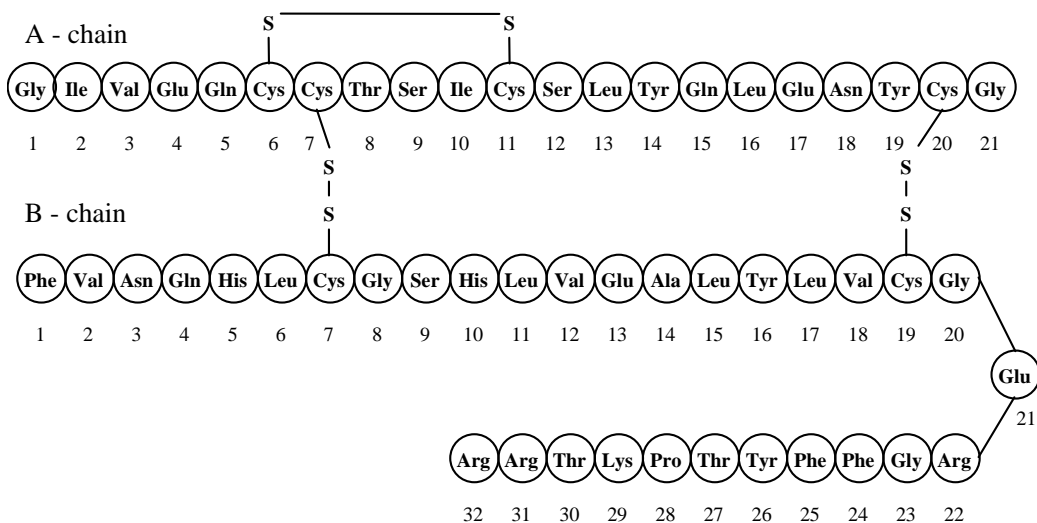
Data Sheet

Lantus[®] and Lantus[®] SoloStar[®]

Insulin glargine, 100IU in 10 mL vials, and 3 mL cartridges

Presentation

LANTUS [insulin glargine injection {rDNA origin}] is a recombinant human insulin analogue produced by DNA technology. Insulin glargine differs from human insulin in that the amino acid asparagine at position A21 is replaced by glycine and two arginines are added to the C-terminus of the B-chain. The chemical name is 21^A-Gly-30^Ba-L-Arg-30^Bb-L-Arg-human insulin. The empirical formula is C₂₆₇H₄₀₄N₇₂O₇₈S₆ and the molecular weight is 6063. The structural formula is shown below:



The CAS number is 160337-95-1.

LANTUS is a sterile solution of insulin glargine in vials and cartridges for use as an injection. The 3mL cartridges contain 100 IU/mL (3.6378 mg/mL) insulin glargine, zinc chloride, meta-cresol, glycerol, hydrochloric acid and sodium hydroxide for pH adjustment and water for injections. The 10mL vials contain 100 IU/mL (3.6378 mg/mL) insulin glargine, zinc chloride, meta-cresol, polysorbate 20, glycerol, hydrochloric acid and sodium hydroxide for pH adjustment and water for injections.

Uses

Pharmacodynamic Properties

Mode of Action

The primary activity of insulin, including insulin glargine, is regulation of glucose metabolism. Insulin and its analogues lower blood glucose levels by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin inhibits lipolysis in the adipocyte, inhibits proteolysis and enhances protein synthesis.

LANTUS differs from other insulins because its unique structure provides a smooth and peakless profile with a prolonged duration of action of 24 hours (end of observation period) compared to 14.5 hours for NPH human insulin.

Pharmacodynamics

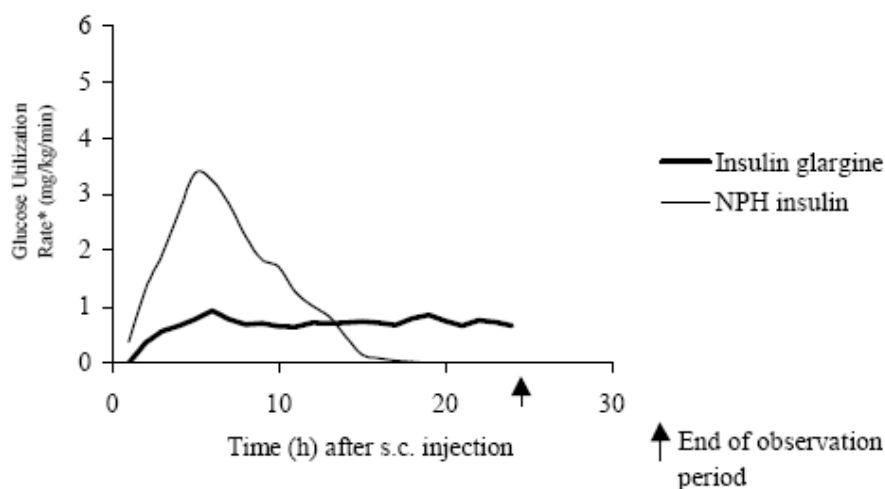
Insulin glargine is a human insulin analogue that has been designed to have low solubility at

neutral pH. At pH 4, the pH of the LANTUS injection solution, it is completely soluble. After injection into the subcutaneous tissue, the acidic solution is neutralised, leading to formation of microprecipitates from which small amounts of insulin glargine are continuously released, providing a smooth, peakless, predictable time/concentration profile and a prolonged duration of action. This allows once daily dosing to meet a patient's basal insulin needs.

In clinical studies, intravenous insulin glargine and human insulin have been shown to be equipotent when given at the same doses.

In euglycaemic clamp studies in healthy subjects or in patients with type 1 diabetes, the onset of action of subcutaneous insulin glargine was slower than NPH human insulin. The effect profile of insulin glargine was smooth and peakless, and the duration of its effect was prolonged compared to NPH human insulin. Figure 1 shows results from a study in patients with type 1 diabetes. The median time between injection and the end of pharmacological effect was 14.5 hours for NPH human insulin and 24 hours (the end of the observation period) for insulin glargine.

Figure 1. Activity Profile in Type 1 Diabetic Patients



Mean GIR in subjects with type 1 diabetes mellitus after a single sc injection of 0.3 IU/kg insulin glargine or NPH (n=20).

* Determined as amount of glucose infused to maintain constant plasma glucose levels (hourly mean values).

The longer duration of LANTUS is directly related to its slower rate of absorption and supports once daily subcutaneous administration. The time course of action of insulin and insulin analogues such as LANTUS may vary considerably in different individuals or within the same individual but is, due to the lack of a peak, less variable with insulin glargine than with NPH insulin.

Pharmacokinetic Properties

After subcutaneous injection of insulin glargine in healthy subjects and patients with diabetes, the insulin serum concentrations indicated a slower, more prolonged absorption and a lack of a peak in comparison to NPH human insulin. However, the assay was unable to differentiate between the two forms of insulin (native human insulin and insulin glargine). Concentrations were thus consistent with the time profile of the pharmacodynamic activity of insulin glargine.

After subcutaneous injection of 0.3 IU/kg insulin glargine in patients with type 1 diabetes, a flat concentration-time profile has been demonstrated; this is also reflected in the wide range of T_{max} values (1.5 to 22.5 h) compared to 0.3 IU/kg NPH human insulin (2.5 to 10.0 h).

There were no relevant differences in serum insulin glargine levels and the duration of action after abdominal, deltoid or thigh subcutaneous administration.

In a randomised, controlled, double-blind, four-way crossover trial in healthy male volunteers, LANTUS with polysorbate 20 was found to be bioequivalent to LANTUS.

Metabolism

A metabolism study in man indicates that insulin glargine is partly degraded in the subcutaneous depot at the carboxyl terminus of the B chain to form the active metabolites, with similar in vitro activity to insulin, M1 (21^A-Gly-insulin) and M2 (21^A-Gly-des-30^B-Thr-insulin).

Special Populations

Age and Gender

There were no phase 1 studies to evaluate the effects of age and race. In clinical trials, subgroup analysis based on age and gender did not indicate any difference in safety and efficacy in insulin glargine treated patients compared to the total study population.

Obesity

In clinical trials, subgroup analysis based on BMI showed no differences in safety and efficacy in insulin glargine treated patients compared to the total study population. The same was true for NPH insulin.

Renal and Hepatic Impairment

No studies were performed in patients with renal or hepatic impairment. Careful glucose monitoring and dose adjustments of insulin or insulin analogues including insulin glargine may be necessary.

Clinical Trials

Efficacy Studies

The overall efficacy of once-daily insulin glargine on metabolic control was compared to that of once-daily and twice-daily NPH human insulin in open-label, randomised, active-control, parallel studies of 2327 adult patients and 349 paediatric patients with type 1 diabetes mellitus and 1563 patients with Type 2 diabetes mellitus. In general, insulin glargine maintained or improved the level of glycaemic control as measured by glycohaemoglobin and fasting glucose. In addition, fewer patients using insulin glargine reported hypoglycaemic episodes compared to patients using NPH human insulin.

Type 1 Diabetes in Adults (see Table 3)

In phase 3 studies, patients with type 1 diabetes (n=1119) were randomised to basal-bolus treatment with LANTUS once daily or to NPH human insulin once or twice daily and treated for 28 weeks. Regular human insulin was administered before each meal. LANTUS was administered at bedtime. NPH human insulin was administered once daily at bedtime or in the morning and at bedtime when used twice daily. LANTUS had a larger effect in reducing fasting glucose than NPH human insulin administered twice daily, but was comparable with NPH human insulin twice daily in its effect on glycohaemoglobin (GHb) and incidence of nocturnal and severe hypoglycaemia. Compared to once daily NPH human insulin, LANTUS had a similar effect on fasting glucose and GHb. However, fewer patients receiving LANTUS reported severe hypoglycaemic episodes after initial titration, from study month 2 onward, (0.9% vs 5.6%, p<0.05) and fewer patients reported nocturnal hypoglycaemic episodes (11.0% vs 21.3%, p<0.05). Hypoglycaemia was reported with similar frequency during the first month of the studies (during initial titration period) after starting treatment with LANTUS compared to NPH human insulin.

In another phase 3 study, patients with type 1 diabetes (n=619) were treated for 16 weeks with a basal-bolus insulin regimen where insulin lispro was used before each meal. LANTUS was administered once daily at bedtime and NPH human insulin was administered once or twice daily. LANTUS had a larger effect in reducing fasting glucose than NPH human insulin. LANTUS and NPH human insulin had a similar effect on GHb, with similar numbers of patients reporting a hypoglycaemic episode.

Type 1 Diabetes in Children (see Table 4)

In a randomized, controlled clinical study, paediatric patients (ranging in age from 6 to 15 years) with type 1 diabetes (Study 3003, n=349) were treated for 28 weeks with a basal-bolus insulin regimen where regular human insulin was used before each meal. LANTUS was administered

once daily at bedtime and NPH human insulin was administered once or twice daily. Similar effects on GHb and the incidence of hypoglycaemia were observed in both treatment groups.

Type 2 Diabetes (see Table 1)

In one phase 3 study (Study 3002, n=570), LANTUS was evaluated for 20 weeks as part of a regimen of combination therapy with insulin and oral antidiabetic agents (a sulfonylurea, metformin, acarbose, or combinations of these drugs). LANTUS administered once daily at bedtime was as effective as NPH human insulin administered once daily at bedtime in reducing GHb and fasting glucose. However, fewer patients treated with LANTUS reported a nocturnal hypoglycaemic episode after initial titration, from study month 2 to end of study (Table 1). This benefit of LANTUS was most pronounced in the subgroup of patients who had not previously been treated with insulin (LANTUS: 9.9%, NPH human insulin: 24.0%; p<0.05; see Table 3).

Table 1. Study report 3002: Patients with nocturnal hypoglycaemia

	LANTUS	NPH	p
Month 2 – Week 20	10.1%	16.9%	0.0195
Week 20 – end of study	5.7%	11.4%	0.0150
Entire treatment	12.1%	24.2%	0.0002

In another phase 3 study in patients with type 2 diabetes not using oral antidiabetic agents (Study 3006, n=518), a basal-bolus regimen of LANTUS once daily at bedtime or NPH human insulin administered once or twice daily was evaluated for 28 weeks. Regular human insulin was used before meals as needed. LANTUS had similar effectiveness as either once- or twice-daily NPH human insulin in reducing GHb and fasting glucose. However, fewer patients treated with LANTUS reported nocturnal hypoglycaemia from study month 2 to end of study (Table 2).

Table 2. Study report 3006: Patients with nocturnal hypoglycaemia

	LANTUS	NPH	p
Month 2 – end of study	26.5%	35.5%	0.0136
Entire treatment	31.3%	40.2%	0.0160

Type 1 and Type 2 Diabetes

Table 3 compares regimens of LANTUS once daily to NPH human insulin either once or twice daily in subgroups of patients from phase 3 studies based upon prior basal insulin regimens.

Table 3. Summary of Main Therapeutic Outcome of the Clinical Studies

Type 1 Diabetes Mellitus

Diabetes population	Treatment	Endstudy mean (mean change from baseline)				% of patients with hypoglycaemia		
		n	Glycated haemoglobin (%)	n	Fasting blood glucose (mmol/L) ^a	n	Nocturnal ^b	Severe ^c
Previous use of once-daily basal injection regimen								
with regular human insulin	LANTUS	222	7.98 (0.01)	222	8.4 (-0.9)	222	11.0% ^h	0.9% ^h
	NPH human insulin (once daily)	218	7.95 (-0.05)	218	8.2 (-1.2)	218	21.3%	5.6%
with insulin lispro	LANTUS	73	7.11 (-0.25)	73	8.0 (-1.4)	73	6.8%	2.7%
	NPH human insulin (once daily)	69	7.46 (-0.23)	69	8.7 (-0.9)	69	9.0%	4.5%
Previous use of more than once-daily basal injection regimen								

Diabetes population	Treatment	Endstudy mean (mean change from baseline)				% of patients with hypoglycaemia		
		n	Glycated haemoglobin (%)	n	Fasting blood glucose (mmol/L) ^a	n	Nocturnal ^b	Severe ^c
with regular human insulin	LANTUS	334	7.77 (0.06)	334	7.9 (1.3) ^h	334	18.9%	3.4%
	NPH human insulin (twice daily)	345	7.69 (-0.05)	345	8.7 (-0.7)	345	21.6%	4.4%
with insulin lispro	LANTUS	237	7.66 (-0.03)	237	8.0 (-1.7) ^h	237	9.9%	0.9%
	NPH human insulin (twice daily)	240	7.64 (-0.05)	240	9.1 (-0.6)	240	10.0%	0.4%
Type 2 Diabetes Mellitus								
Diabetes population	Treatment	Endstudy mean (mean change from baseline)				% of patients with hypoglycaemia		
		n	Glycated haemoglobin (%)	n	Fasting blood glucose (mmol/L) ^a	n	Nocturnal ^d	Severe ^e
Insulin in combination with oral antidiabetic agents								
No previous insulin use	LANTUS	216	8.45 (-0.65)	214	7.1 (-3.3)	222	9.9% ^{d,h}	1.8% ^e
	NPH human insulin (once daily)	195	8.27 (-0.63)	195	7.4 (-3.1)	204	24.0% ^d	0.5% ^e
Previous insulin use	LANTUS	64	9.12 (0.31)	66	7.2 (-1.1)	67	19.4% ^d	1.5% ^e
	NPH human insulin (once daily)	71	9.15 (0.42)	73	7.4 (-1.1)	77	24.7% ^d	2.6% ^e
Insulin without oral antidiabetic agents								
Previous use of once-daily basal insulin	LANTUS	52	8.07 (-0.34)	52	8.5 (-0.8)	52	13.7% ^f	0.0% ^g
	NPH human insulin (once daily)	48	7.92 (-0.45)	48	7.9 (-1.2)	48	25.0% ^f	0.0% ^g
Previous use of more than once-daily basal insulin	LANTUS	207	8.15 (-0.44)	207	7.7 (-1.4)	207	29.8% ^f	0.5% ^g
	NPH human insulin (twice daily)	211	7.96 (-0.61)	211	8.1 (-1.1)	211	27.9% ^f	2.4% ^g
^a Fasting blood glucose conversion, mg/dL/18=mmol/L ^b Percent of patients with type 1 diabetes experiencing nocturnal hypoglycaemia; defined as events occurring while asleep between bedtime insulin administration and fasting blood glucose; with a blood glucose < 36 mg/dL (2.0 mmol/L); from month 2 to end of study ^c Percent of patients with type 1 diabetes experiencing severe hypoglycaemia; defined as events requiring assistance of another person; with a blood glucose < 36 mg/dL (2.0 mmol/L); from month 2 to end of study ^d Percent of patients with type 2 diabetes experiencing nocturnal hypoglycaemia; defined as events occurring while asleep between bedtime insulin administration and fasting blood glucose; entire treatment period ^e Percent of patients with type 2 diabetes experiencing severe hypoglycaemia; defined as events requiring assistance of another person; entire treatment period ^f Percent of patients with type 2 diabetes experiencing nocturnal hypoglycaemia; defined as events occurring while asleep between bedtime insulin administration and fasting blood glucose; from month 2 to end of study ^g Percent of patients with type 2 diabetes experiencing severe hypoglycaemia; defined as events requiring assistance of another person; from month 2 to end of study ^h p<0.05; LANTUS compared with NPH human insulin								

Type 1 Diabetes in Children

Table 4 compares regimens of LANTUS once daily to NPH human insulin either once or twice daily in subgroups of patients from Phase 3 studies based upon prior basal insulin regimens.

Table 4. Summary of Main Therapeutic Outcomes of the Clinical Studies in Children

Type 1 Diabetes Mellitus in Children

Treatment	Endstudy mean (mean change from baseline)			
	n	Glycated haemoglobin (%)	n	Fasting blood glucose (mmol/L)
Previous use of once-daily basal injection regimen				
LANTUS	92	9.15 (0.55)	105	9.99 (-1.34)
NPH human insulin (once daily)	80	9.26 (0.36)	93	10.51 (-0.74)
Previous use of more than once-daily basal injection regimen				
LANTUS	63	8.55 (0.12)	68	8.87 (-1.21)
NPH human insulin (twice daily)	54	8.86 (0.01)	57	9.50 (-0.40)

Indications

LANTUS is an insulin analogue indicated for once-daily subcutaneous administration in the treatment of type 1 or type 2 diabetes mellitus patients who require insulin for the control of hyperglycaemia.

Dosage and Administration

LANTUS is an insulin analogue, equipotent to human insulin, with a peakless glucose lowering profile and a prolonged duration of action that permits once daily dosing.

LANTUS is for individual patient use only.

LANTUS is given subcutaneously once a day. It may be administered at any time during the day, however, at the same time every day.

LANTUS is not intended for intravenous administration.

The desired blood glucose levels as well as the doses and timing of any antidiabetic medication, including LANTUS, must be determined and adjusted individually. In a clinical study in insulin-naïve patients with type 2 diabetes, LANTUS was started at a dose of 10.8 ± 4.9 IU (mean \pm SD; median dose 10 IU) LANTUS once daily and subsequently adjusted individually. Blood glucose monitoring is recommended for all individuals with diabetes.

Although absorption of LANTUS does not differ between abdominal, thigh or deltoid subcutaneous injection sites, as with all insulins, injection sites must be rotated from one injection to the next.

Dose adjustment may be required, for example, if the patient's weight or lifestyle change or other circumstances arise that increase susceptibility to hypo- or hyperglycaemia. Any change of insulin dose should be made cautiously and only under medical supervision.

LANTUS must not be mixed with any other insulin. Mixing can change the time/action profile of LANTUS and cause precipitation.

LANTUS must not be diluted. Diluting can change the time/action profile of LANTUS.

Changeover to LANTUS

The initial dose of LANTUS should be determined individually, depending on the desired blood glucose levels.

When changing from a treatment regimen with intermediate- or long-acting insulin to a regimen with LANTUS, the amount and timing of short-acting insulin or fast-acting insulin analogue or the dose of any oral antidiabetic drug may need to be adjusted.

In clinical studies, when adult patients were transferred from once daily NPH human insulin or ultralente human insulin to once daily LANTUS, the initial dose was usually not changed. In studies when patients were transferred from twice-daily NPH human insulin to LANTUS once daily at

bedtime, the initial dose (IU) was usually reduced by approximately 20% (compared to total daily IU of NPH human insulin) within the first week of treatment and then adjusted based on patient response. There was also a slightly higher rate of injection site pain seen with LANTUS, possibly related to the acidic nature of insulin glargine when compared with NPH insulin. The majority of injection site reactions were mild, with only one subject in each of the LANTUS and NPH treatment groups discontinuing study medication due to injection site adverse events.

A programme of close metabolic monitoring under medical supervision is recommended during changeover and in the initial weeks thereafter. As with all insulin analogues, this is particularly true for patients which, due to antibodies to human insulin, need high insulin doses and may experience markedly improved insulin response with insulin glargine.

With improved metabolic control and resultant increase in insulin sensitivity (reduced insulin requirements) further adjustment of the dose of LANTUS and other insulin or oral antidiabetic agents in the regimen may become necessary.

Paediatric Use

LANTUS can be administered to children aged 6 years and older. Administration to children less than 6 years of age has not been studied. Based on the result of a study in paediatric patients, the dose recommendation for changeover to LANTUS is the same as described for adults.

Contraindications

LANTUS must not be used in patients hypersensitive to insulin glargine or any of its excipients.

Precautions

LANTUS is not intended for intravenous administration. The prolonged duration of activity of insulin glargine is dependent on injection into subcutaneous space. Intravenous administration of the usual subcutaneous dose could result in severe hypoglycaemia.

LANTUS is not the insulin of choice for the treatment of diabetic ketoacidosis. Instead, intravenous regular insulin is recommended in such cases.

As with all insulins, the time course of LANTUS action may vary in different individuals or at different times in the same individual and the rate of absorption are dependent on blood supply, temperature and physical activity.

Patients, and if appropriate, their relatives must also be alert to the possibility of hyper- or hypoglycaemia, and know what actions to take.

In case of insufficient glucose control or a tendency to hyper- or hypoglycaemic episodes, the patient's compliance with all prescribed treatment regimen, injection sites and proper injection technique, the handling of the pen and all other relevant factors must be reviewed before dose adjustment is considered.

Medication errors have been reported in which other insulins, particularly short-acting insulins, have been accidentally administered instead of insulin glargine.

Hypoglycaemia

Hypoglycaemia is the most common adverse effect of insulins. The incidence of hypoglycaemia in regimens that include insulin glargine is significantly reduced compared with regimens containing NPH human insulin. The time of occurrence of hypoglycaemia depends on the action profile of the insulins and may, therefore, change when the treatment regimen is changed.

As with all insulins, particular caution (including intensified blood glucose monitoring) should be exercised in patients who are at greater risk of clinically significant sequelae from hypoglycaemic episodes.

The prolonged effect of subcutaneous insulin glargine may delay recovery from hypoglycaemia.

In clinical studies, symptoms of hypoglycaemia or counter-regulatory hormone responses were similar after intravenous insulin glargine and human insulin both in healthy volunteers and patients with type 1 diabetes. However, the warning symptoms of hypoglycaemia may be changed, be less pronounced, or be absent in certain risk groups, as for example, in patients whose glycaemic

control is markedly improved; in elderly patients; where an autonomic neuropathy is present; in patients with a long history of diabetes; in patients receiving concurrent treatment with certain other drugs.

Such situations may result in severe hypoglycaemia (and possibly loss of consciousness) prior to the patient's awareness of hypoglycaemia.

Renal Impairment

In patients with renal impairment, insulin requirements may be diminished because of reduced insulin metabolism. In the elderly, progressive deterioration of renal function may lead to a steady decrease in insulin requirements.

Hepatic Impairment

Although no studies have been performed in patients with diabetes and severe hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism.

Intercurrent Conditions

Insulin requirements may be altered during intercurrent conditions such as illness, emotional disturbances or stress.

Information for Patients

Patients should be instructed on self-management procedures including glucose monitoring, proper injection technique, and hypoglycaemia and hyperglycaemia management. Patients must be instructed on handling of special situations such as intercurrent conditions (illness, stress, or emotional disturbances), an inadequate food intake or skipped meals.

Patients must be advised that LANTUS must not be diluted or mixed with any other insulin or solution.

Accidental mix-ups between insulin glargine and other insulins, particularly short-acting insulins, have been reported. To avoid medication errors between insulin glargine and other insulins, patients should be instructed to always check the insulin label before each injection.

As with all patients who have diabetes, the ability to concentrate and/or react may be impaired as a result of hypoglycaemia or hyperglycaemia.

Patients with diabetes should be advised to inform their doctor if they are pregnant or are contemplating becoming pregnant.

Pens to be used with LANTUS cartridges

LANTUS cartridges should only be used with the following pens: ClikSTAR, Autopen 24, and should not be used with any other reusable pen as dosing accuracy has only been established with the listed pens.

Use in Pregnancy (Category B3)

There are no well-controlled clinical studies of the use of insulin glargine in pregnant women. A limited number of exposed pregnancies from Post Marketing Surveillance indicate no adverse effects of insulin glargine on pregnancy or on the health of the foetus and newborn child. To date, no other relevant epidemiological data are available.

It is essential for patients with pre-existing or gestational diabetes to maintain good metabolic control throughout pregnancy. Insulin requirements may decrease during the first trimester, increase during the second and third trimesters and rapidly decline after delivery. Careful blood glucose control is essential in such patients. Patients with diabetes should be advised to inform their doctor if they are pregnant or are contemplating pregnancy and insulin glargine should be used during pregnancy only if the potential benefits outweigh potential risk.

Embryofetal development studies in rats and rabbits have been performed at subcutaneous doses up to 20 IU/kg/day and 2 IU/kg/day, respectively (approximately 10 times and twice anticipated clinical exposure, respectively, based on BSA). The effects of insulin glargine generally did not

differ from those observed with NPH insulin in rats or rabbits. However, in rabbits dosed with 2 IU/kg/day there was an increased incidence of dilatation of the cerebral ventricles.

Use in Lactation

It is not known whether insulin glargine is excreted in significant amounts in human milk. Many drugs, including insulin, are excreted in human milk. For this reason, caution should be exercised when insulin glargine is administered to a nursing mother. Lactating women may require adjustments in insulin dose and diet.

Paediatric Use

In general, the safety profile for patients ≤ 18 years of age is similar to the safety profile for patients >18 years. The adverse events reports received from Post Marketing Surveillance included relatively more frequent injection site reactions (injection site pain, injection site reaction) and skin reactions (rash, urticaria) in patients ≤ 18 years of age than in patients >18 years.

Data from pooled clinical trials in adults and children aged 6 to 18 years did not show a greater incidence of either injection site reaction or skin reactions in the paediatric population compared to adults.

No clinical study safety data are available in patients below 6 years of age.

Interactions

A number of substances affect glucose metabolism and may require insulin dose adjustment.

Substances that may enhance the blood glucose lowering effect and susceptibility to hypoglycaemia include: oral antidiabetic agents, ACE inhibitors, pentoxifylline, perhexiline, disopyramide, fibrates, fluoxetine, MAO inhibitors, dextropropoxyphene, salicylates, sulfonamide antibiotics.

Substances that may reduce the blood glucose lowering effect and susceptibility to hypoglycaemia include: corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, oral contraceptives, phenothiazine derivatives, somatotrophin, sympathomimetic agents (eg epinephrine [adrenaline], salbutamol, terbutaline), thyroid hormones, protease inhibitors and atypical antipsychotic medications (eg olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts or alcohol may either potentiate or weaken the blood glucose lowering effect of insulin. Pentamidine may cause hypoglycaemia, which may be sometimes be followed by hyperglycaemia.

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation may be reduced or absent.

Adverse Effects

The adverse events most commonly associated with human insulin therapy include the following:

Clinical Trial Data

Table 5. Adverse Events in Phase 2/3 Trials (>2%)

	NPH (n= 1784)	Insulin glargine (n= 2106)
Upper respiratory infection	330 (18.5%)	367 (17.4%)
Infection	178 (10.0%)	182 (8.6%)
Accidental injury	97 (5.4%)	101 (4.8%)
Headache	74 (4.1%)	103 (4.9%)
Injection site haemorrhage	81 (4.5%)	89 (4.2%)
Retinal vascular disorder	81 (4.5%)	82 (3.9%)
Gastroenteritis	64 (3.6%)	68 (3.2%)
Sinusitis	62 (3.5%)	68 (3.2%)

	NPH (n= 1784)	Insulin glargine (n= 2106)
Rhinitis	63 (3.5%)	61 (2.9%)
Back pain	48 (2.7%)	57 (2.7%)
Injection site pain	13 (0.7%)	55 (2.6%)
Hypoglycaemic reaction	61 (3.4%)	54 (2.6%)
Neuropathy	45 (2.5%)	53 (2.5%)
Peripheral oedema	32 (1.8%)	42 (2.0%)
Urinary tract infection	35 (2.0%)	41 (1.9%)

Hypoglycaemia

Hypoglycaemia, in general the most frequent adverse reaction of insulin therapy, may occur if the insulin dose is too high in relation to the insulin requirement.

As with all insulins, severe hypoglycaemic attacks, especially if recurrent, may lead to neurological damage. Prolonged or severe hypoglycaemic episodes may be life-threatening.

In many patients, the signs and symptoms of neuroglycopenia are preceded by signs of adrenergic counter-regulation. Generally, the greater and more rapid the decline in blood glucose, the more marked is the phenomenon of counter-regulation and its symptoms.

Eyes

A marked change in glycaemic control may cause temporary visual impairment, due to temporary alteration in the turgidity and refractive index of the lens.

As with all insulin regimens, intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary visual impairment or worsening of diabetic retinopathy. However, long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy.

In patients with proliferative retinopathy, particularly if not treated with photocoagulation, severe hypoglycaemic episodes may result in transient partial or complete blindness.

Retinopathy was evaluated in Phase 3 clinical studies by means of retinal adverse events reported and fundus photography. The numbers of retinal adverse events reported for LANTUS and NPH treatment groups were similar for patients with type 1 and type 2 diabetes. Progression of retinopathy was investigated by fundus photography using a grading protocol derived from the Early Treatment Diabetic Retinopathy Study (ETDRS). In a 5-year NPH-controlled study, the primary outcome was progression by 3 or more steps on the ETDRS scale at study endpoint. The results of this analysis are shown in Table 6 for both the per-protocol (primary) and Intent-to-Treat (ITT) populations, and indicate non-inferiority of LANTUS to NPH in the progression of diabetic retinopathy as assessed by this outcome.

Table 6. Number (%) of Patients with 3 or More Step Progression on ETDRS Scale at Endpoint

	LANTUS (%)	NPH (%)	Difference^{a,b} (SE)	95% CI for difference
Per-protocol	53/374 (14.2%)	57/363 (15.7%)	-1.98% (2.57%)	-7.02% to 3.06%
Intent-to Treat	63/502 (12.5%)	71/487 (14.6%)	-2.10% (2.14%)	-6.29% to 2.09%

a Difference = LANTUS - NPH
b Using a generalised linear model (SAS GENMOD) with treatment and baseline HbA1c strata as the classified independent variables, and with binomial distribution and identity link function

Injection Site and Allergic Reactions

As with any insulin therapy, lipodystrophy may occur at the injection site and delay insulin absorption. Other injection site reactions with insulin therapy include redness, pain, itching, hives, swelling and inflammation. Most minor reactions to insulins usually resolve in a few days to a few weeks.

Immediate-type allergic reactions are rare. Such reactions to insulin (including insulin glargine) or the excipients may, for example, be associated with generalised skin reactions, angioedema, bronchospasm, hypotension, or shock and may be life threatening.

Animal studies with insulin glargine have identified significant local tolerance toxicity at the injection site following repeat subcutaneous administration. Care should be taken to rotate the site of injection.

Antibody production

Insulin administration may cause the formation of antibodies to insulin. In clinical studies, antibodies that cross-react with human insulin and insulin glargine were observed in both NPH human insulin and insulin glargine treatment groups with similar incidences. In rare cases, the presence of such insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyperglycaemia or hypoglycaemia.

Other reactions

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

Overdosage

Symptoms

An excess of insulin relative to food intake, energy expenditure or both may lead to severe and sometimes long-term and life-threatening hypoglycaemia.

Management

Mild episodes of hypoglycaemia can usually be treated with oral carbohydrates. Adjustments in drug dosage, meal patterns, or exercise may be needed.

More severe episodes with coma, seizure or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. After apparent clinical recovery from hypoglycaemia, continued observation and additional carbohydrate intake may be necessary to avoid recurrence of hypoglycaemia.

Pharmaceutical Precautions

Unopened vials, cartridges and pre-filled pens

Unopened vials, cartridges and pre-filled pens (such as Lantus SoloStar) should be stored in a refrigerator where the temperature is between +2°C and +8°C. Do not freeze. Discard if frozen. Keep in the outer carton in order to protect from light. Do not store next to the freezer compartment or freezer packs.

Before first use, LANTUS must be kept at room temperature for 1 to 2 hours.

LANTUS must only be used if the solution is clear, colourless with no particles visible, and if it is of water-like consistency.

Open (in use) or unrefrigerated vials, cartridges and pre-filled pens

LANTUS vials, cartridges or pre-filled pens, whether or not refrigerated, must be discarded after 28 days from first use.

Unrefrigerated vials, cartridges or pre-filled pens, whether in use or not, must be discarded after 28 days. This applies irrespective of whether the vial or cartridge is used immediately or is first carried as a spare for a while.

An empty vial, cartridge or pre-filled pen must never be reused and must be properly discarded.

Vials

Before withdrawing LANTUS from the vial for the first time, remove the plastic protective cap. Do not shake the vial vigorously as this may cause frothing. Froth may interfere with the correct measurement of dose.

Once in use, vials of LANTUS should be stored away from direct light between +2°C and +8°C. Do not freeze. Discard if frozen. If refrigeration is impossible, the vial of LANTUS in use may be kept unrefrigerated for up to 28 days, as long as the temperature is not greater than 25°C and it is kept away from direct heat and light. Whether or not it is refrigerated, the vial that is in use must be used within a 28 day period. Any unused contents must be discarded 28 days after opening.

Cartridges and pre-filled pens

Once in use, pre-filled pens (such as Lantus SoloStar) or a reusable injection pen containing a cartridge of LANTUS must not be stored in the refrigerator. LANTUS that is in use in injection pens may be kept unrefrigerated for up to 28 days, as long as the temperature is not greater than 25°C and it is kept away from direct heat and light. It must be used within a 28 day period or must be discarded 28 days after commencement of use.

Manufacturer instructions for using LANTUS in reusable or pre-filled disposable injection devices must be followed carefully for loading the cartridge into a reusable pen, and for attaching the needle, performing the safety test and administering the insulin injection. If the injection device is damaged, it should be discarded and a new injection device should be used.

If the reusable injection device malfunctions (see instructions for using the pen), or no pen is available, LANTUS may be withdrawn from the cartridge into a U100 syringe and injected subcutaneously. The syringe must not contain any other medicinal product or residue.

LANTUS must not be mixed with any other insulin nor be diluted. Mixing or diluting can change its time/action profile and mixing can cause precipitation.

Medicine Classification

Prescription Medicine

Package Quantities

LANTUS [insulin glargine injection] 100 units per mL (U 100) is available in packs of 10 mL vials, 3 mL cartridges for reusable insulin injection devices and 3mL cartridges in SoloStar pre-filled disposable devices.

Further Information

None

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Date of Preparation

26 August 2010