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Rx Only

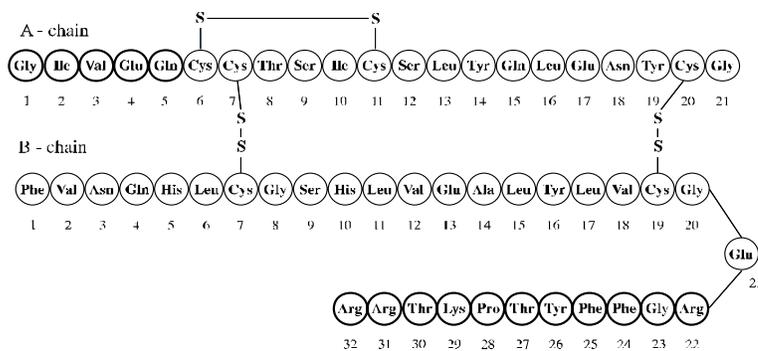
LANTUS[®]

(insulin glargine [rDNA origin] injection)

LANTUS[®] must NOT be diluted or mixed with any other insulin or solution.

DESCRIPTION

LANTUS[®] (insulin glargine [rDNA origin] injection) is a sterile solution of insulin glargine for use as an injection. Insulin glargine is a recombinant human insulin analog that is a long-acting (up to 24-hour duration of action), parenteral blood-glucose-lowering agent. (See CLINICAL PHARMACOLOGY). LANTUS is produced by recombinant DNA technology utilizing a non-pathogenic laboratory strain of *Escherichia coli* (K12) as the production organism. 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. Chemically, it is 21^A-Gly-30^Ba-L-Arg-30^Bb-L-Arg-human insulin and has the empirical formula C₂₆₇H₄₀₄N₇₂O₇₈S₆ and a molecular weight of 6063. It has the following structural formula:



LANTUS consists of insulin glargine dissolved in a clear aqueous fluid. Each milliliter of LANTUS (insulin glargine injection) contains 100 IU (3.6378 mg) insulin glargine, 30 mcg zinc, 2.7 mg m-cresol, 20 mg glycerol 85%, and water for injection. The pH is adjusted by addition of aqueous solutions of hydrochloric acid and sodium hydroxide. LANTUS has a pH of approximately 4.

CLINICAL PHARMACOLOGY

Mechanism of Action:

The primary activity of insulin, including insulin glargine, is regulation of glucose metabolism. Insulin and its analogs 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.

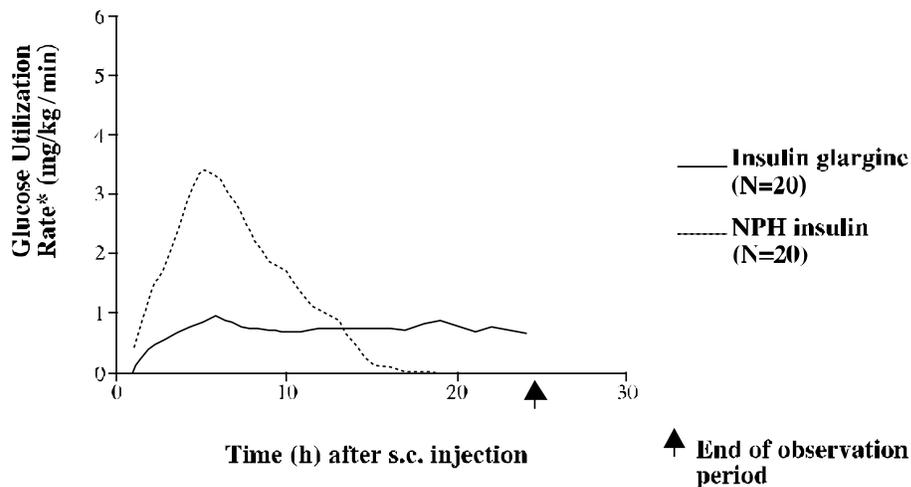
Pharmacodynamics:

Insulin glargine is a human insulin analog that has been designed to have low aqueous solubility at neutral pH. At pH 4, as in the LANTUS injection solution, it is completely soluble. After

injection into the subcutaneous tissue, the acidic solution is neutralized, leading to formation of microprecipitates from which small amounts of insulin glargine are slowly released, resulting in a relatively constant concentration/time profile over 24 hours with no pronounced peak. This profile allows once-daily dosing as a patient's basal insulin.

In clinical studies, the glucose-lowering effect on a molar basis (i.e., when given at the same doses) of intravenous insulin glargine is approximately the same as human insulin. In euglycemic 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 relatively constant with no pronounced peak 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 conducted for a maximum of 24 hours after the injection. The median time between injection and the end of pharmacological effect was 14.5 hours (range: 9.5 to 19.3 hours) for NPH human insulin, and 24 hours (range: 10.8 to >24.0 hours) (24 hours was the end of the observation period) for insulin glargine.

Figure 1. Activity Profile in Patients with Type 1 Diabetes[†]



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

[†] Between-patient variability (CV, coefficient of variation); insulin glargine, 84% and NPH, 78%.

The longer duration of action (up to 24 hours) of LANTUS is directly related to its slower rate of absorption and supports once-daily subcutaneous administration. The time course of action of insulins, including LANTUS, may vary between individuals and/or within the same individual.

Pharmacokinetics:

Absorption and Bioavailability. After subcutaneous injection of insulin glargine in healthy subjects and in patients with diabetes, the insulin serum concentrations indicated a slower, more

prolonged absorption and a relatively constant concentration/time profile over 24 hours with no pronounced peak in comparison to NPH human insulin. Serum insulin 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 relatively constant concentration/time profile has been demonstrated. The duration of action after abdominal, deltoid, or thigh subcutaneous administration was similar.

Metabolism. A metabolism study in humans indicates that insulin glargine is partly metabolized at the carboxyl terminus of the B chain in the subcutaneous depot to form two active metabolites with in vitro activity similar to that of insulin, M1 (21^A-Gly-insulin) and M2 (21^A-Gly-des-30^B-Thr-insulin). Unchanged drug and these degradation products are also present in the circulation.

Special Populations:

Age, Race, and Gender. Information on the effect of age, race, and gender on the pharmacokinetics of LANTUS is not available. However, in controlled clinical trials in adults (n=3890) and a controlled clinical trial in pediatric patients (n=349), subgroup analyses based on age, race, and gender did not show differences in safety and efficacy between insulin glargine and NPH human insulin.

Smoking. The effect of smoking on the pharmacokinetics/pharmacodynamics of LANTUS has not been studied.

Pregnancy. The effect of pregnancy on the pharmacokinetics and pharmacodynamics of LANTUS has not been studied (see PRECAUTIONS, Pregnancy).

Obesity. In controlled clinical trials, which included patients with Body Mass Index (BMI) up to and including 49.6 kg/m², subgroup analyses based on BMI did not show any differences in safety and efficacy between insulin glargine and NPH human insulin.

Renal Impairment. The effect of renal impairment on the pharmacokinetics of LANTUS has not been studied. However, some studies with human insulin have shown increased circulating levels of insulin in patients with renal failure. Careful glucose monitoring and dose adjustments of insulin, including LANTUS, may be necessary in patients with renal dysfunction (see PRECAUTIONS, Renal Impairment).

Hepatic Impairment. The effect of hepatic impairment on the pharmacokinetics of LANTUS has not been studied. However, some studies with human insulin have shown increased circulating levels of insulin in patients with liver failure. Careful glucose monitoring and dose adjustments of insulin, including LANTUS, may be necessary in patients with hepatic dysfunction (see PRECAUTIONS, Hepatic Impairment).

CLINICAL STUDIES

The safety and effectiveness of insulin glargine given once-daily at bedtime was compared to that of once-daily and twice-daily NPH human insulin in open-label, randomized, active-control, parallel studies of 2327 adult patients and 349 pediatric patients with type 1 diabetes mellitus and 1563 adult patients with type 2 diabetes mellitus (see Tables 1-3). In general, the reduction in

glycated hemoglobin (HbA1c) with LANTUS was similar to that with NPH human insulin. The overall rates of hypoglycemia did not differ between patients with diabetes treated to LANTUS compared with NPH human insulin.

Type 1 Diabetes–Adult (see Table 1). In two large, randomized, controlled clinical studies (Studies A and B), patients with type 1 diabetes (Study A; n=585, Study B; n=534) were randomized to basal-bolus treatment with LANTUS once daily at bedtime 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. In one large, randomized, controlled clinical study (Study C), 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. In these studies, LANTUS and NPH human insulin had a similar effect on glycohemoglobin with a similar overall rate of hypoglycemia.

Table 1: Type 1 Diabetes Mellitus–Adult

	<u>Study A</u>		<u>Study B</u>		<u>Study C</u>	
	28 weeks		28 weeks		16 weeks	
Treatment duration	Regular insulin		Regular insulin		Insulin lispro	
Treatment in combination with	<u>LANTUS</u>	<u>NPH</u>	<u>LANTUS</u>	<u>NPH</u>	<u>LANTUS</u>	<u>NPH</u>
Number of subjects treated	292	293	264	270	310	309
HbA1c						
Endstudy mean	8.13	8.07	7.55	7.49	7.53	7.60
Adj. mean change from baseline	+0.21	+0.10	-0.16	-0.21	-0.07	-0.08
LANTUS – NPH	+0.11		+0.05		+0.01	
95% CI for Treatment difference	(-0.03; +0.24)		(-0.08; +0.19)		(-0.11; +0.13)	
Basal insulin dose						
Endstudy mean	19.2	22.8	24.8	31.3	23.9	29.2
Mean change from baseline	-1.7	-0.3	-4.1	+1.8	-4.5	+0.9
Total insulin dose						
Endstudy mean	46.7	51.7	50.3	54.8	47.4	50.7
Mean change from baseline	-1.1	-0.1	+0.3	+3.7	-2.9	+0.3
Fasting blood glucose (mg/dL)						
Endstudy mean	146.3	150.8	147.8	154.4	144.4	161.3
Adj. mean change from baseline	-21.1	-16.0	-20.2	-16.9	-29.3	-11.9

Type 1 Diabetes–Pediatric (see Table 2). In a randomized, controlled clinical study (Study D), pediatric patients (age range 6 to 15 years) with type 1 diabetes (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 glycohemoglobin and the incidence of hypoglycemia were observed in both treatment groups.

Table 2: Type 1 Diabetes Mellitus–Pediatric

	<u>Study D</u> 28 weeks Regular insulin	
	<u>LANTUS</u>	<u>NPH</u>
Treatment duration		
Treatment in combination with		
Number of subjects treated	174	175
HbA1c		
Endstudy mean	8.91	9.18
Adj. mean change from baseline	+0.28	+0.27
LANTUS – NPH	+0.01	
95% CI for Treatment difference	(-0.24; +0.26)	
Basal insulin dose		
Endstudy mean	18.2	21.1
Mean change from baseline	-1.3	+2.4
Total insulin dose		
Endstudy mean	45.0	46.0
Mean change from baseline	+1.9	+3.4
Fasting blood glucose (mg/dL)		
Endstudy mean	171.9	182.7
Adj. mean change from baseline	-23.2	-12.2

Type 2 Diabetes–Adult (see Table 3). In a large, randomized, controlled clinical study (Study E) (n=570), LANTUS was evaluated for 52 weeks as part of a regimen of combination therapy with insulin and oral antidiabetes 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 glycohemoglobin and fasting glucose. There was a low rate of hypoglycemia that was similar in LANTUS and NPH human insulin treated patients. In a large, randomized, controlled clinical study (Study F), in patients with type 2 diabetes not using oral antidiabetes agents (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 glycohemoglobin and fasting glucose with a similar incidence of hypoglycemia.

Table 3: Type 2 Diabetes Mellitus–Adult

	<u>Study E</u> 52 weeks Oral agents		<u>Study F</u> 28 weeks Regular insulin	
	<u>LANTUS</u>	<u>NPH</u>	<u>LANTUS</u>	<u>NPH</u>
Treatment duration				
Treatment in combination with				
Number of subjects treated	289	281	259	259
HbA1c				
Endstudy mean	8.51	8.47	8.14	7.96
Adj. mean change from baseline	-0.46	-0.38	-0.41	-0.59
LANTUS – NPH	-0.08		+0.17	
95% CI for Treatment difference	(-0.28; +0.12)		(-0.00; +0.35)	
Basal insulin dose				
Endstudy mean	25.9	23.6	42.9	52.5
Mean change from baseline	+11.5	+9.0	-1.2	+7.0
Total insulin dose				
Endstudy mean	25.9	23.6	74.3	80.0
Mean change from baseline	+11.5	+9.0	+10.0	+13.1
Fasting blood glucose (mg/dL)				

Endstudy mean	126.9	129.4	141.5	144.5
Adj. mean change from baseline	-49.0	-46.3	-23.8	-21.6

LANTUS Flexible Daily Dosing

The safety and efficacy of LANTUS administered pre-breakfast, pre-dinner, or at bedtime were evaluated in a large, randomized, controlled clinical study, in patients with type 1 diabetes (study G, n=378). Patients were also treated with insulin lispro at mealtime. LANTUS administered at different times of the day resulted in similar reductions in glycated hemoglobin compared to that with bedtime administration (see Table 4). In these patients, data are available from 8-point home glucose monitoring. The maximum mean blood glucose level was observed just prior to injection of LANTUS regardless of time of administration, i.e. pre-breakfast, pre-dinner, or bedtime.

In this study, 5% of patients in the LANTUS-breakfast arm discontinued treatment because of lack of efficacy. No patients in the other two arms discontinued for this reason. Routine monitoring during this trial revealed the following mean changes in systolic blood pressure: pre-breakfast group, 1.9 mm Hg; pre-dinner group, 0.7 mm Hg; pre-bedtime group, -2.0 mm Hg.

The safety and efficacy of LANTUS administered pre-breakfast or at bedtime were also evaluated in a large, randomized, active-controlled clinical study (Study H, n=697) in type 2 diabetes patients no longer adequately controlled on oral agent therapy. All patients in this study also received AMARYL® (glimepiride) 3 mg daily. LANTUS given before breakfast was at least as effective in lowering glycated hemoglobin A1c (HbA1c) as LANTUS given at bedtime or NPH human insulin given at bedtime (see Table 4).

Table 4: Flexible LANTUS Daily Dosing in Type 1 (Study G) and Type 2 (Study H) Diabetes Mellitus

Treatment duration Treatment in combination with:	Study G 24 weeks			Study H 24 weeks		
	Insulin lispro			AMARYL® (glimepiride)		
	LANTUS Breakfast	LANTUS Dinner	LANTUS Bedtime	LANTUS Breakfast	LANTUS Bedtime	NPH Bedtime
Number of subjects treated*	112	124	128	234	226	227
HbA1c						
Baseline mean	7.56	7.53	7.61	9.13	9.07	9.09
Endstudy mean	7.39	7.42	7.57	7.87	8.12	8.27
Mean change from baseline	-0.17	-0.11	-0.04	-1.26	-0.95	-0.83
Basal insulin dose (IU)						
Endstudy mean	27.3	24.6	22.8	40.4	38.5	36.8
Mean change from baseline	5.0	1.8	1.5			
Total insulin dose (IU)						
Endstudy mean	53.3	54.7	51.5	NA**	NA	NA
Mean change from baseline	1.6	3.0	2.3			

*Intent to treat **Not applicable

INDICATIONS AND USAGE

LANTUS is indicated for once-daily subcutaneous administration for the treatment of adult and pediatric patients with type 1 diabetes mellitus or adult patients with type 2 diabetes mellitus who require basal (long-acting) insulin for the control of hyperglycemia.

CONTRAINDICATIONS

LANTUS is contraindicated in patients hypersensitive to insulin glargine or the excipients.

WARNINGS

Hypoglycemia is the most common adverse effect of insulin, including LANTUS. As with all insulins, the timing of hypoglycemia may differ among various insulin formulations.

Glucose monitoring is recommended for all patients with diabetes.

Any change of insulin should be made cautiously and only under medical supervision.

Changes in insulin strength, timing of dosing, manufacturer, type (e.g., regular, NPH, or insulin analogs), species (animal, human), or method of manufacture (recombinant DNA versus animal-source insulin) may result in the need for a change in dosage. Concomitant oral antidiabetes treatment may need to be adjusted.

PRECAUTIONS

General:

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

LANTUS must NOT be diluted or mixed with any other insulin or solution. If LANTUS is diluted or mixed, the solution may become cloudy, and the pharmacokinetic/pharmacodynamic profile (e.g., onset of action, time to peak effect) of LANTUS and/or the mixed insulin may be altered in an unpredictable manner. When LANTUS and regular human insulin were mixed immediately before injection in dogs, a delayed onset of action and time to maximum effect for regular human insulin was observed. The total bioavailability of the mixture was also slightly decreased compared to separate injections of LANTUS and regular human insulin. The relevance of these observations in dogs to humans is not known.

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

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

Hypoglycemia:

As with all insulin preparations, hypoglycemic reactions may be associated with the administration of LANTUS. Hypoglycemia is the most common adverse effect of insulins. Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as long duration of diabetes, diabetes nerve disease, use of medications such as beta-blockers, or intensified diabetes control (see PRECAUTIONS, Drug Interactions). Such situations may result in severe hypoglycemia (and, possibly, loss of consciousness) prior to patients' awareness of hypoglycemia.

The time of occurrence of hypoglycemia depends on the action profile of the insulins used and may, therefore, change when the treatment regimen or timing of dosing is changed. Patients being switched from twice daily NPH insulin to once-daily LANTUS should have their initial LANTUS dose reduced by 20% from the previous total daily NPH dose to reduce the risk of hypoglycemia (see DOSAGE AND ADMINISTRATION, Changeover to LANTUS). The prolonged effect of subcutaneous LANTUS may delay recovery from hypoglycemia. In a clinical study, symptoms of hypoglycemia or counterregulatory hormone responses were similar after intravenous insulin glargine and regular human insulin both in healthy subjects and patients with type 1 diabetes.

Renal Impairment:

Although studies have not been performed in patients with diabetes and renal impairment, LANTUS requirements may be diminished because of reduced insulin metabolism, similar to observations found with other insulins (see CLINICAL PHARMACOLOGY, Special Populations).

Hepatic Impairment:

Although studies have not been performed in patients with diabetes and hepatic impairment, LANTUS requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism, similar to observations found with other insulins (see CLINICAL PHARMACOLOGY, Special Populations).

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. Continuous rotation of the injection site within a given area may help to reduce or prevent these reactions. Most minor reactions to insulins usually resolve in a few days to a few weeks.

Reports of injection site pain were more frequent with LANTUS than NPH human insulin (2.7% insulin glargine versus 0.7% NPH). The reports of pain at the injection site were usually mild and did not result in discontinuation of therapy.

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

Intercurrent Conditions:

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

Information for Patients:

LANTUS must only be used if the solution is clear and colorless with no particles visible (see DOSAGE AND ADMINISTRATION, Preparation and Handling).

Patients must be advised that LANTUS must NOT be diluted or mixed with any other insulin or solution (see PRECAUTIONS, General).

Patients should be instructed on self-management procedures including glucose monitoring, proper injection technique, and hypoglycemia and hyperglycemia management. Patients must be

instructed on handling of special situations such as intercurrent conditions (illness, stress, or emotional disturbances), an inadequate or skipped insulin dose, inadvertent administration of an increased insulin dose, inadequate food intake, or skipped meals. Refer patients to the LANTUS “Patient Information” circular for additional information.

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

Patients with diabetes should be advised to inform their health care professional if they are pregnant or are contemplating pregnancy.

Drug Interactions:

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

The following are examples of substances that may increase the blood-glucose-lowering effect and susceptibility to hypoglycemia: oral antidiabetes products, ACE inhibitors, disopyramide, fibrates, fluoxetine, MAO inhibitors, propoxyphene, salicylates, somatostatin analog (e.g., octreotide), sulfonamide antibiotics.

The following are examples of substances that may reduce the blood-glucose-lowering effect of insulin: corticosteroids, danazol, diuretics, sympathomimetic agents (e.g., epinephrine, albuterol, terbutaline), isoniazid, phenothiazine derivatives, somatropin, thyroid hormones, estrogens, progestogens (e.g., in oral contraceptives).

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

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

Carcinogenesis, Mutagenesis, Impairment of Fertility:

In mice and rats, standard two-year carcinogenicity studies with insulin glargine were performed at doses up to 0.455 mg/kg, which is for the rat approximately 10 times and for the mouse approximately 5 times the recommended human subcutaneous starting dose of 10 IU (0.008 mg/kg/day), based on mg/m². The findings in female mice were not conclusive due to excessive mortality in all dose groups during the study. Histiocytomas were found at injection sites in male rats (statistically significant) and male mice (not statistically significant) in acid vehicle containing groups. These tumors were not found in female animals, in saline control, or insulin comparator groups using a different vehicle. The relevance of these findings to humans is unknown.

Insulin glargine was not mutagenic in tests for detection of gene mutations in bacteria and mammalian cells (Ames- and HGPRT-test) and in tests for detection of chromosomal aberrations (cytogenetics in vitro in V79 cells and in vivo in Chinese hamsters).

In a combined fertility and prenatal and postnatal study in male and female rats at subcutaneous doses up to 0.36 mg/kg/day, which is approximately 7 times the recommended human subcutaneous starting dose of 10 IU (0.008 mg/kg/day), based on mg/m², maternal toxicity due to dose-dependent hypoglycemia, including some deaths, was observed. Consequently, a reduction of the rearing rate occurred in the high-dose group only. Similar effects were observed with NPH human insulin.

Pregnancy:

Teratogenic Effects: Pregnancy Category C. Subcutaneous reproduction and teratology studies have been performed with insulin glargine and regular human insulin in rats and Himalayan rabbits. The drug was given to female rats before mating, during mating, and throughout pregnancy at doses up to 0.36 mg/kg/day, which is approximately 7 times the recommended human subcutaneous starting dose of 10 IU (0.008 mg/kg/day), based on mg/m². In rabbits, doses of 0.072 mg/kg/day, which is approximately 2 times the recommended human subcutaneous starting dose of 10 IU (0.008 mg/kg/day), based on mg/m², were administered during organogenesis. The effects of insulin glargine did not generally differ from those observed with regular human insulin in rats or rabbits. However, in rabbits, five fetuses from two litters of the high-dose group exhibited dilation of the cerebral ventricles. Fertility and early embryonic development appeared normal.

There are no well-controlled clinical studies of the use of insulin glargine in pregnant women. It is essential for patients with diabetes or a history of gestational diabetes to maintain good metabolic control before conception and throughout pregnancy. Insulin requirements may decrease during the first trimester, generally increase during the second and third trimesters, and rapidly decline after delivery. Careful monitoring of glucose control is essential in such patients. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers:

It is unknown whether insulin glargine is excreted in significant amounts in human milk. Many drugs, including human insulin, are excreted in human milk. For this reason, caution should be exercised when LANTUS is administered to a nursing woman. Lactating women may require adjustments in insulin dose and diet.

Pediatric Use:

Safety and effectiveness of LANTUS have been established in the age group 6 to 15 years with type 1 diabetes.

Geriatric Use:

In controlled clinical studies comparing insulin glargine to NPH human insulin, 593 of 3890 patients with type 1 and type 2 diabetes were 65 years and older. The only difference in safety or effectiveness in this subpopulation compared to the entire study population was an expected higher incidence of cardiovascular events in both insulin glargine and NPH human insulin-treated patients.

In elderly patients with diabetes, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemic reactions. Hypoglycemia may be difficult to recognize in the elderly (see PRECAUTIONS, Hypoglycemia).

ADVERSE REACTIONS

The adverse events commonly associated with LANTUS include the following:

Body as a whole: allergic reactions (see PRECAUTIONS).

Skin and appendages: injection site reaction, lipodystrophy, pruritus, rash (see PRECAUTIONS).

Other: hypoglycemia (see WARNINGS and PRECAUTIONS).

In clinical studies in adult patients, there was a higher incidence of treatment-emergent injection site pain in LANTUS-treated patients (2.7%) compared to NPH insulin-treated patients (0.7%). The reports of pain at the injection site were usually mild and did not result in discontinuation of therapy. Other treatment-emergent injection site reactions occurred at similar incidences with both insulin glargine and NPH human insulin.

Retinopathy was evaluated in the 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 one clinical study involving patients with type 2 diabetes, a difference in the number of subjects with ≥ 3 -step progression in ETDRS scale over a 6-month period was noted by fundus photography (7.5% in LANTUS group versus 2.7% in NPH treated group). The overall relevance of this isolated finding cannot be determined due to the small number of patients involved, the short follow-up period, and the fact that this finding was not observed in other clinical studies.

OVERDOSAGE

An excess of insulin relative to food intake, energy expenditure, or both may lead to severe and sometimes long-term and life-threatening hypoglycemia. Mild episodes of hypoglycemia 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 hypoglycemia, continued observation and additional carbohydrate intake may be necessary to avoid reoccurrence of hypoglycemia.

DOSAGE AND ADMINISTRATION

LANTUS is a recombinant human insulin analog. Its potency is approximately the same as human insulin. It exhibits a relatively constant glucose-lowering profile over 24 hours that permits once-daily dosing.

LANTUS may be administered at any time during the day. LANTUS should be administered subcutaneously once a day at the same time every day. For patients adjusting timing of dosing with LANTUS, see **WARNINGS** and **PRECAUTIONS, Hypoglycemia**. LANTUS is not intended for intravenous administration (see **PRECAUTIONS**). Intravenous administration of the usual subcutaneous dose could result in severe hypoglycemia. The desired blood glucose levels as well as the doses and timing of antidiabetes medications must be determined individually. Blood glucose monitoring is recommended for all patients with diabetes. The prolonged duration of activity of LANTUS is dependent on injection into subcutaneous space.

As with all insulins, injection sites within an injection area (abdomen, thigh, or deltoid) must be rotated from one injection to the next.

In clinical studies, there was no relevant difference in insulin glargine absorption after abdominal, deltoid, or thigh subcutaneous administration. As for all insulins, the rate of absorption, and consequently the onset and duration of action, may be affected by exercise and other variables.

LANTUS is not the insulin of choice for the treatment of diabetes ketoacidosis. Intravenous short-acting insulin is the preferred treatment.

Pediatric Use:

LANTUS can be safely administered to pediatric patients ≥ 6 years of age. Administration to pediatric patients < 6 years has not been studied. Based on the results of a study in pediatric patients, the dose recommendation for changeover to LANTUS is the same as described for adults in DOSAGE AND ADMINISTRATION, Changeover to LANTUS.

Initiation of LANTUS Therapy:

In a clinical study with insulin naïve patients with type 2 diabetes already treated with oral antidiabetes drugs, LANTUS was started at an average dose of 10 IU once daily, and subsequently adjusted according to the patient's need to a total daily dose ranging from 2 to 100 IU.

Changeover to LANTUS:

If changing from a treatment regimen with an intermediate- or long-acting insulin to a regimen with LANTUS, the amount and timing of short-acting insulin or fast-acting insulin analog or the dose of any oral antidiabetes drug may need to be adjusted. In clinical studies, when patients were transferred from once-daily NPH human insulin or ultralente human insulin to once-daily LANTUS, the initial dose was usually not changed. However, when patients were transferred from twice-daily NPH human insulin to LANTUS once daily, to reduce the risk of hypoglycemia, the initial dose (IU) was usually reduced by approximately 20% (compared to total daily IU of NPH human insulin) and then adjusted based on patient response (see PRECAUTIONS, Hypoglycemia).

A program of close metabolic monitoring under medical supervision is recommended during transfer and in the initial weeks thereafter. The amount and timing of short-acting insulin or fast-acting insulin analog may need to be adjusted. This is particularly true for patients with acquired antibodies to human insulin needing high-insulin doses and occurs with all insulin analogs. Dose adjustment of LANTUS and other insulins or oral antidiabetes drugs may be required; for example, if the patient's timing of dosing, weight or lifestyle changes, or other circumstances arise that increase susceptibility to hypoglycemia or hyperglycemia (see PRECAUTIONS, Hypoglycemia).

The dose may also have to be adjusted during intercurrent illness (see PRECAUTIONS, Intercurrent Conditions).

Preparation and Handling:

Parenteral drug products should be inspected visually prior to administration whenever the solution and the container permit. LANTUS must only be used if the solution is clear and colorless with no particles visible.

Mixing and diluting: LANTUS must NOT be diluted or mixed with any other insulin or solution (see PRECAUTIONS, General).

Vial: The syringes must not contain any other medicinal product or residue.

Cartridge system: If OptiClik™, the Insulin Delivery Device for LANTUS, malfunctions, LANTUS may be drawn from the cartridge system into a U-100 syringe and injected.

HOW SUPPLIED

LANTUS 100 units per mL (U-100) is available in the following package size:

10 mL vials (NDC 0088-2220-33)

3 mL cartridge system*, package of 5 (NDC 0088-2220-52)

*Cartridge systems are for use only in OptiClik™ (Insulin Delivery Device)

Storage:

Unopened Vial/Cartridge system:

Unopened LANTUS vials and cartridge systems should be stored in a refrigerator, 36°F - 46°F (2°C - 8°C). LANTUS should not be stored in the freezer and it should not be allowed to freeze. Discard if it has been frozen.

Open (In-Use) Vial/Cartridge system:

Opened vials, whether or not refrigerated, must be used within 28 days after the first use. They must be discarded if not used within 28 days. If refrigeration is not possible, the open vial can be kept unrefrigerated for up to 28 days away from direct heat and light, as long as the temperature is not greater than 86°F (30°C).

The opened (in-use) cartridge system in OptiClik™ should **NOT** be refrigerated but should be kept at room temperature (below 86°F [30°C]) away from direct heat and light. The opened (in-use) cartridge system in OptiClik™ kept at room temperature must be discarded after 28 days. Do not store OptiClik™, with or without cartridge system, in a refrigerator at any time.

LANTUS should not be stored in the freezer and it should not be allowed to freeze. Discard if it has been frozen.

These storage conditions are summarized in the following table:

	Not in-use (unopened) Refrigerated	Not in-use (unopened) Room Temperature	In-use (opened) (See Temperature Below)
10 mL Vial	Until expiration date	28 days	28 days Refrigerated or room temperature
3 mL Cartridge system	Until expiration date	28 days	28 days Refrigerated or room temperature
3 mL Cartridge system inserted into OptiClik™			28 days Room temperature only (Do not refrigerate)

Rev. August 2004

Manufactured by:

Aventis Pharma Deutschland GmbH

D-65926 Frankfurt am Main

Frankfurt, Germany

Manufactured for:

Aventis Pharmaceuticals Inc.

Kansas City, MO 64137 USA

US Patents 5,656,722, 5,370,629, and 5,509,905

Made in Germany

www.lantus.com

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Patient Information
LANTUS® 3 mL cartridge system (300 units per cartridge system)
100 units per mL (U-100)
(insulin glargine [recombinant DNA origin] injection)

- What is the most important information I should know about LANTUS?
- What is LANTUS?
- Who should NOT take LANTUS?
- How should I use LANTUS?
- What kind of insulin Pen should I use?
- Mixing with LANTUS
- Instructions for Use
- What can affect how much insulin I need?
- What are the possible side effects of LANTUS and other insulins?
- How should I store LANTUS?
- What are the ingredients in LANTUS?
- General Information about LANTUS

Read this “Patient Information” that comes with LANTUS (LAN-tus) before you start using it and each time you get a refill because there may be new information. This leaflet does not take the place of talking with your healthcare provider about your condition or treatment. If you have questions about LANTUS or about diabetes, talk with your healthcare provider.

What is the most important information I should know about LANTUS?

- **Do not change the insulin you are using without talking to your healthcare provider.** Any change of insulin should be made cautiously and only under medical supervision. Changes in insulin strength, manufacturer, type (for example: Regular, NPH, analogs), species (beef, pork, beef-pork, human) or method of manufacture (recombinant DNA versus animal-source insulin) may need a change in the dose. This dose change may be needed right away or later on during the first several weeks or months on the new insulin. Doses of oral anti-diabetic medicines may also need to change, if your insulin is changed.
- **You must test your blood sugar levels while using an insulin, such as LANTUS.** Your healthcare provider will tell you how often you should test your blood sugar level, and what to do if it is high or low.
- **Do NOT dilute or mix LANTUS with any other insulin or solution.** It will not work and you may lose blood sugar control, which could be serious.
- **LANTUS** comes as U-100 insulin and contains 100 units of LANTUS per milliliter (mL). One milliliter of U-100 insulin contains 100 units of insulin. (1 mL = 1 cc).

43 **What is Diabetes?**

- 44 • Your body needs insulin to turn sugar (glucose) into energy. If your body does not make
45 enough insulin, you need to take more insulin so you will not have too much sugar in
46 your blood.
- 47
- 48 • Insulin injections are important in keeping your diabetes under control. But the way you
49 live, your diet, careful checking of your blood sugar levels, exercise, and planned
50 physical activity, all work with your insulin to help you control your diabetes.
- 51

52 **What is LANTUS?**

- 53 • LANTUS (insulin glargine [recombinant DNA origin]) is a long-acting insulin. .
54 Because Lantus is made by recombinant DNA technology (rDNA) and is chemically
55 different from the insulin made by the human body, it is called an insulin analog.
56 LANTUS is used to treat patients with diabetes for the control of high blood sugar. It is
57 used once a day to lower blood glucose.
- 58
- 59 • LANTUS is a clear, colorless, sterile solution for injection under the skin
60 (subcutaneously).
- 61
- 62 • The active ingredient in LANTUS is insulin glargine. The concentration of insulin
63 glargine is 100 units per milliliter (mL), or U-100. LANTUS also contains zinc,
64 metacresol, glycerol, and water for injection as inactive ingredients. Hydrochloric acid
65 and/or sodium hydroxide may be added to adjust the pH.
- 66
- 67 • You need a prescription to get LANTUS. Always be sure you receive the right insulin
68 from the pharmacy. The carton and cartridge system should look like the ones in this
69 picture.
- 70
- 71



72
73
74

75

76 **Who should NOT take LANTUS?**

77 **Do not take lantus if you are allergic to insulin glargine** or any of the inactive ingredients in
78 LANTUS. Check with your healthcare provider if you are not sure.

79

- 80 • **Before starting LANTUS, tell your healthcare provider about all your medical**
81 **conditions including if you:**
- 82 • **have liver or kidney problems.** Your dose may need to be adjusted.
 - 83 • **are pregnant or plan to become pregnant.** It is not known if LANTUS may harm your
84 unborn baby. It is very important to maintain control of your blood sugar levels during
85 pregnancy. Your healthcare provider will decide which insulin is best for you during
86 your pregnancy.
 - 87 • **are breast-feeding or plan to breast-feed.** It is not known whether LANTUS passes
88 into your milk. Many medicines, including insulin, pass into human milk, and could
89 affect your baby. Talk to your healthcare provider about the best way to feed your baby.
- 90 • **about all the medicines you take including** prescription and non-prescription medicines,
91 vitamins and herbal supplements.

92

93 **How should I use LANTUS?**

94 See the "**Instructions for OptiClik™ Use**" section for additional information.

95

- 96 • Follow the instructions given by your healthcare provider about the type or types of
97 insulin you are using. Do not make any changes with your insulin unless you have talked
98 to your healthcare provider. Your insulin needs may change because of illness, stress,
99 other medicines, or changes in diet or activity level. Talk to your healthcare provider
100 about how to adjust your insulin dose.
- 101 • You may take LANTUS at any time during the day but you must take it at the same time
102 every day.
- 103 • Only use LANTUS that is clear and colorless. If your LANTUS is cloudy or slightly
104 colored, return it to your pharmacy for a replacement.
- 105 • Follow your healthcare provider's instructions for testing your blood sugar.
- 106 • Inject LANTUS under your skin (subcutaneously) in your upper arm, abdomen (stomach
107 area), or thigh (upper leg). Never inject it into a vein or muscle.
- 108 • Change (rotate) injection sites within the same body area.

109

110 **What kind of insulin Pen should I use?**

- 111 • Always use the OptiClik™ device distributed by Aventis Pharmaceuticals. If you use any
112 other device than OptiClik™ insulin Pen with this cartridge, you may get the wrong dose
113 of insulin causing serious problems for you, such as a blood sugar level that is too low or
114 too high. Always use a new needle each time you give LANTUS injection.

115

- 116 • **NEEDLES AND INSULIN PEN MUST NOT BE SHARED.**

117

- 118 • Disposable needle should be used only once. Used needle should be placed in sharps
119 containers (such as red biohazard containers), hard plastic containers (such as detergent
120 bottles), or metal containers (such as an empty coffee can). Such containers should be
121 sealed and disposed of properly.
122

123 **Mixing with LANTUS**

- 124 • **Do NOT dilute or mix LANTUS with any other insulin or solution.** It will not work as
125 intended and you may lose blood sugar control, which could be serious.
126

127 **Instructions for Opticlik™ Use**

128 **It is important to read, understand, and follow the step-by-step instructions in the**
129 **“OptiClik™ Instruction Leaflet” before using OptiClik™ insulin Pen. Failure to follow the**
130 **instructions may result in getting too much or too little insulin.** If you have lost your leaflet
131 or have a question, go to www.opticlik.com or call 1-800-633-1610.
132

133 The following general notes should be taken into consideration before injecting Lantus:
134

- 135 • Always wash your hands before handling the cartridge system and/or the OptiClik™ insulin
136 Pen.
137 • Always attach a new needle before use.
138 • Always perform the safety test before use.
139 • Check the insulin solution in the cartridge system to make sure it is clear, colorless, and free
140 of particles. If it is not, throw it away.
141 • Do NOT mix or dilute LANTUS with any other insulin or solution. LANTUS will not work
142 if it is mixed or diluted and you may lose blood sugar control, which could be serious.
143 • Decide on an injection area - either upper arm, thigh, or abdomen. Do not use the same
144 injection site as your last injection.
145 • After injecting LANTUS, leave the needle in the skin for an additional 10 seconds. Then pull
146 the needle straight out. Gently press on the spot where you injected yourself for a few
147 seconds. **Do not rub the area.**
148 • Do not drop the OptiClik™ insulin Pen.
149

150
151 If your blood glucose reading is high or low, tell your healthcare provider so the dose can be
152 adjusted.

153 **What can affect how much insulin I need?**

154 **Illness.** Illness may change how much insulin you need. It is a good idea to think ahead and
155 make a "sick day" plan with your healthcare provider in advance so you will be ready when this
156 happens. Be sure to test your blood sugar more often and call your healthcare provider if you are
157 sick.
158

159 **Medicines.** Many medicines can affect your insulin needs. Other medicines, including
160 prescription and non-prescription medicines, vitamins, and herbal supplements, can change the
161 way insulin works. You may need a different dose of insulin when you are taking certain other

162 medicines. **Know all the medicines you take**, including prescription and non-prescription
163 medicines, vitamins and herbal supplements. You may want to keep a list of the medicines you
164 take. You can show this list to your healthcare provider and pharmacists anytime you get a new
165 medicine or refill. Your healthcare provider will tell you if your insulin dose needs to be
166 changed.

167
168 **Meals.** The amount of food you eat can affect your insulin needs. If you eat less food, skip
169 meals, or eat more food than usual, you may need a different dose of insulin. Talk to your
170 healthcare provider if you change your diet so that you know how to adjust your LANTUS and
171 other insulin doses.

172
173 **Alcohol.** Alcohol, including beer and wine, may affect the way LANTUS works and affect your
174 blood sugar levels. Talk to your healthcare provider about drinking alcohol.

175
176 **Exercise or Activity level.** Exercise or activity level may change the way your body uses
177 insulin. Check with your healthcare provider before you start an exercise program because your
178 dose may need to be changed.

179
180 **Travel.** If you travel across time zones, talk with your healthcare provider about how to time
181 your injections. When you travel, wear your medical alert identification. Take extra insulin and
182 supplies with you.

183
184 **Pregnancy or nursing.** The effects of LANTUS on an unborn child or on a nursing baby are
185 unknown. Therefore, tell your healthcare provider if you planning to have a baby, are pregnant,
186 or nursing a baby. Good control of diabetes is especially important during pregnancy and
187 nursing.

188
189 **What are the possible side effects of LANTUS and other insulins?**

190
191 Insulins, including LANTUS, can cause hypoglycemia (low blood sugar), hyperglycemia (high
192 blood sugar), allergy, and skin reactions.

193
194 **Hypoglycemia (low blood sugar):**

195 Hypoglycemia is often called an "insulin reaction" or "low blood sugar". It may happen
196 when you do not have enough sugar in your blood. Common causes of hypoglycemia are
197 illness, emotional or physical stress, too much insulin, too little food or missed meals, and
198 too much exercise or activity.

199 Early warning signs of hypoglycemia may be different, less noticeable or not noticeable
200 at all in some people. That is why it is important to check your blood sugar as you have
201 been advised by your healthcare provider.

202
203 **Hypoglycemia can happen with:**

- 204
- **Taking too much insulin.** This can happen when too much insulin is injected.

- 205 • **Not enough carbohydrate (sugar or starch) intake.** This can happen if a meal or snack
206 is missed or delayed.
207
- 208 • **Vomiting or diarrhea** that decreases the amount of sugar absorbed by your body.
209
- 210 • **Intake of alcohol.**
211
- 212 • **Medicines that affect insulin.** Be sure to discuss all your medicines with your healthcare
213 provider. **Do not start any new medicines until you know how they may affect your**
214 **insulin dose.**
215
- 216 • **Medical conditions that can affect your blood sugar levels or insulin.** These
217 conditions include diseases of the adrenal glands, the pituitary, the thyroid gland, the
218 liver, and the kidney.
219
- 220 • **Too much glucose use by the body.** This can happen if you exercise too much or have a
221 fever.
222
- 223 • **Injecting insulin the wrong way or in the wrong injection area.**
224

225 Hypoglycemia can be mild to severe. Its onset may be rapid. . Some patients have few or no
226 warning symptoms, including:

- 227 • patients with diabetes for a long time
- 228 • patients with diabetic neuropathy (nerve problems)
- 229 • or patients using certain medicines for high blood pressure or heart problems.
230

231 Hypoglycemia may reduce your ability to drive a car or use mechanical equipment and you may
232 risk injury to yourself or others.
233

234 Severe hypoglycemia can be dangerous and can cause temporary or permanent harm to your
235 heart or brain. **It may cause unconsciousness, seizures, or death.**

236 Symptoms of hypoglycemia may include:

- 237 • anxiety, irritability, restlessness, trouble concentrating, personality changes, mood changes,
238 or other abnormal behavior
- 239 • tingling in your hands, feet, lips, or tongue
- 240 • dizziness, light-headedness, or drowsiness
- 241 • nightmares or trouble sleeping
- 242 • headache
- 243 • blurred vision
- 244 • slurred speech
- 245 • palpitations (fast heart beat)
- 246 • sweating
- 247 • tremor (shaking)
- 248 • unsteady gait (walking).

249

250 If you have hypoglycemia often or it is hard for you to know if you have the symptoms of
251 hypoglycemia, talk to your healthcare provider.

252

253 Mild to moderate hypoglycemia is treated by eating or drinking carbohydrates such as fruit juice,
254 raisins, sugar candies, milk or glucose tablets. Talk to your healthcare provider about the amount
255 of carbohydrates you should eat to treat mild to moderate hypoglycemia.

256

257 Severe hypoglycemia may require the help of another person or emergency medical people. A
258 person with hypoglycemia who is unable to take foods or liquids with sugar by mouth, or is
259 unconscious needs medical help fast and will need treatment with a glucagon injection or glucose
260 given intravenously (IV). Without medical help right away, serious reactions or even death could
261 happen.

262

263 **Hyperglycemia (high blood sugar):**

264 Hyperglycemia happens when you have too much sugar in your blood. Usually, it means
265 there is not enough insulin to break down the food you eat into energy your body can use.

266 Hyperglycemia can be caused by a fever, an infection, stress, eating more than you
267 should, taking less insulin than prescribed, or it can mean your diabetes is getting worse.

268

269 **Hyperglycemia can happen with:**

270 • **Insufficient (too little) insulin.** This can happen from:

271

- injecting too little or no insulin

272

- incorrect storage (freezing, excessive heat)

273

- use after the expiration date.

274

275 • **Too much carbohydrate intake.** This can happen if you eat larger meals, eat more
276 often, or increase the amount of carbohydrate in your meals.

277

278 • **Medicines that affect insulin.** Be sure to discuss all your medicines with your
279 healthcare provider. **Do not start any new medicines until you know how they may**
280 **affect your insulin dose.**

281

282 • **Medical conditions that affect insulin.** These medical conditions include fevers,
283 infections, heart attacks, and stress.

284

285 • **Injecting insulin the wrong way or in the wrong injection area.**

286

287 Testing your blood or urine often will let you know if you have hyperglycemia. If your tests are
288 often high, tell your healthcare provider so your dose of insulin can be changed.

289

290 Hyperglycemia can be mild or severe. It can **progress to diabetic ketoacidosis (DKA) or very**
291 **high glucose levels (hyperosmolar coma) and result in unconsciousness and death.**

292

293 Although diabetic ketoacidosis occurs most often in patients with type 1 diabetes, it can also
294 happen in patients with type 2 diabetes who become very sick. Because some patients get few
295 symptoms of hyperglycemia, it is important to check your blood sugar/urine sugar and ketones
296 regularly.

297

298 **Symptoms of hyperglycemia include:**

- 299 • confusion or drowsiness
- 300 • increased thirst
- 301 • decreased appetite, nausea, or vomiting
- 302 • rapid heart rate
- 303 • increased urination and dehydration (too little fluid in your body).

304

305 **Symptoms of DKA also include:**

- 306 • fruity smelling breath
- 307 • fast, deep breathing
- 308 • stomach area (abdominal) pain.

309

310 **Severe or continuing hyperglycemia or DKA needs evaluation and treatment right away by**
311 **your healthcare provider.**

312

313 **Do not use LANTUS to treat diabetic ketoacidosis.**

314

315 Other possible side effects of LANTUS include:

316

317 **Serious allergic reactions:**

318 Some times severe, life-threatening allergic reactions can happen with insulin. If you
319 think you are having a severe allergic reaction, get medical help right away. Signs of
320 insulin allergy include:

- 321 • rash all over your body
- 322 • shortness of breath
- 323 • wheezing (trouble breathing)
- 324 • fast pulse
- 325 • sweating
- 326 • low blood pressure.

327

328 **Reactions at the injection site:**

329 Injecting insulin can cause the following reactions on the skin at the injection site:

- 330 • little depression in the skin (lipoatrophy)
- 331 • skin thickening (lipohypertrophy)
- 332 • red, swelling, itchy skin (injection site reaction).

333

334 You can reduce the chance of getting an injection site reaction if you change (rotate) the
335 injection site each time. An injection site reaction should clear up in a few days or a few weeks.
336 If injection site reactions do not go away or keep happening call your healthcare provider.

337

338 Tell your healthcare provider if you have any side effects that bother you.

339

340 These are not all the side effects of LANTUS. Ask your healthcare provider or pharmacist for
341 more information.

342

343 **How should I store LANTUS?**344 • **Unopened cartridge system:**

345 Store new unopened LANTUS cartridge systems in a refrigerator (not the freezer)
 346 between 36°F to 46°F (2°C to 8°C). Do not freeze LANTUS. Keep LANTUS out of
 347 direct heat and light. If a cartridge system has been frozen or overheated, throw it away.

348 • **Open (In-Use) cartridge system:**

349 Once a cartridge system is opened, you can keep it at room temperature (below 86°F
 350 [30°C]) but away from direct heat and light for 28 days. Cartridge system in OptiClik™
 351 insulin Pen must be discarded 28 days after the first use even if it still contains LANTUS.
 352 The opened cartridge system in OptiClik™ insulin Pen should be kept at room
 353 temperature (below 86°F [30°C]) and away from direct heat and light for up to 28 days
 354 For example, do not leave it in a car on a summer day. Do not store OptiClik, with or
 355 without cartridge system, in a refrigerator at any time.

357 These storage conditions are summarized in the following table:

	Not in-use (unopened)	Not in-use (unopened)	In-use (opened)
	Refrigerated	Room Temperature	(See Temperature Below)
3 mL Cartridge system	Until expiration date	28 days	28 days Refrigerated or room temperature
3 mL Cartridge system inserted into OptiClik™			28 days Room temperature only (Do not refrigerate)

358

359

360 • Do not use a cartridge system of LANTUS after the expiration date stamped on the label.

361 • Do not use LANTUS if it is cloudy, colored, or if you see particles.

362

363 **General Information about LANTUS**

364 • Use LANTUS only to treat your diabetes. **Do not** give or share LANTUS with another
 365 person, even if they have diabetes also. It may harm them.

366

367 • This leaflet summarizes the most important information about LANTUS. If you would
 368 like more information, talk with your healthcare provider. You can ask your healthcare
 369 provider or pharmacist for information about LANTUS that is written for healthcare
 370 professionals. For more information about LANTUS call 1-800-633-1610 or go to
 371 website www.lantus.com.

372

373

374 **ADDITIONAL INFORMATION**

375 **DIABETES FORECAST** is a national magazine designed especially for patients with diabetes
 376 and their families and is available by subscription from the American Diabetes Association

377 (ADA), P.O. Box 363, Mt. Morris, IL 61054-0363, 1-800-DIABETES (1-800-342-2383). You
378 may also visit the ADA website at www.diabetes.org.

379 Another publication, **COUNTDOWN**, is available from the Juvenile Diabetes Research
380 Foundation International (JDRF), 120 Wall Street, 19th Floor, New York, New York 10005, 1-
381 800-JDF-CURE (1-800-533-2873). You may also visit the JDRF website at www.jdf.org.

382
383 To get more information about diabetes, check with your healthcare professional or diabetes
384 educator or visit www.DiabetesWatch.com.

385
386 Additional information about LANTUS can be obtained by calling 1-800-633-1610 or by visiting
387 www.lantus.com.

388
389 Rev. xxxxx
390 Aventis Pharmaceuticals Inc.
391 Kansas City, MO 64137 USA
392 ©2004 Aventis Pharmaceuticals Inc.

393
394 † Lantus[®] is a registered trademark of Aventis Pharmaceuticals Inc.
395

Patient Information

LANTUS® 10 mL vial (1000 units per vial) 100 units per mL (U-100) (insulin glargine [recombinant DNA origin] injection)

- What is the most important information I should know about LANTUS?
- What is LANTUS?
- Who should NOT take LANTUS?
- How should I use LANTUS?
- What kind of syringe should I use?
- Mixing with LANTUS
- Instructions for Use
 - How do I draw the insulin into the syringe?
 - How do I inject LANTUS?
- What can affect how much insulin I need?
- What are the possible side effects of LANTUS and other insulins?
- How should I store LANTUS?
- General Information about LANTUS

Read this “Patient Information” that comes with LANTUS (LAN-tus) before you start using it and each time you get a refill because there may be new information. This leaflet does not take the place of talking with your healthcare provider about your condition or treatment. If you have questions about LANTUS or about diabetes, talk with your healthcare provider.

What is the most important information I should know about LANTUS?

- **Do not change the insulin you are using without talking to your healthcare provider.** Any change of insulin should be made cautiously and only under medical supervision. Changes in insulin strength, manufacturer, type (for example: Regular, NPH, analogs), species (beef, pork, beef-pork, human) or method of manufacture (recombinant DNA versus animal source insulin) may need a change in the dose. This dose change may be needed right away or later on during the first several weeks or months on the new insulin. Doses of oral anti-diabetic medicines may also need to change, if your insulin is changed.
- **You must test your blood sugar levels while using an insulin, such as LANTUS.** Your healthcare provider will tell you how often you should test your blood sugar level, and what to do if it is high or low.
- **Do NOT dilute or mix LANTUS with any other insulin or solution.** It will not work and you may lose blood sugar control, which could be serious.
- **LANTUS** comes as U-100 insulin and contains 100 units of LANTUS per milliliter (mL). One milliliter of U-100 insulin contains 100 units of insulin. (1 mL = 1 cc).

What is Diabetes?

- Your body needs insulin to turn sugar (glucose) into energy. If your body does not make enough insulin, you need to take more insulin so you will not have too much sugar in your blood.
- Insulin injections are important in keeping your diabetes under control. But the way you live, your diet, careful checking of your blood sugar levels, exercise, and planned physical activity, all work with your insulin to help you control your diabetes.

What is LANTUS?

- LANTUS (insulin glargine [recombinant DNA origin]) is a long-acting insulin. Because Lantus is made by recombinant DNA technology (rDNA) and is chemically different from the insulin made by the human body, it is called an insulin analog. LANTUS is used to treat patients with diabetes for the control of high blood sugar. It is used once a day to lower blood sugar.
- LANTUS is a clear, colorless, sterile solution for injection under the skin (subcutaneously).
- The active ingredient in LANTUS is insulin glargine. The concentration of insulin glargine is 100 units per milliliter (mL), or U-100. LANTUS also contains zinc, metacresol, glycerol, and water for injection as inactive ingredients. Hydrochloric acid and/or sodium hydroxide may be added to adjust the pH.
- You need a prescription to get LANTUS. Always be sure you receive the right insulin from the pharmacy. The carton and vial should look like the ones in this picture.



Who should NOT take LANTUS?

Do not take LANTUS if you are allergic to insulin glargine or any of the inactive ingredients in LANTUS. Check with your healthcare provider if you are not sure.

Before starting LANTUS, tell your healthcare provider about all your medical conditions including if you:

- **have liver or kidney problems.** Your dose may need to be adjusted.

- **are pregnant or plan to become pregnant.** It is not known if LANTUS may harm your unborn baby. It is very important to maintain control of your blood sugar levels during pregnancy. Your healthcare provider will decide which insulin is best for you during your pregnancy.
- **are breast-feeding or plan to breast-feed.** It is not known whether LANTUS passes into your milk. Many medicines, including insulin, pass into human milk, and could affect your baby. Talk to your healthcare provider about the best way to feed your baby.
- **about all the medicines you take including** prescription and non-prescription medicines, vitamins, and herbal supplements.

How should I use LANTUS?

See the "**Instructions for Use**" including the "**How do I draw the insulin into the syringe?**" section for additional information.

- Follow the instructions given by your healthcare provider about the type or types of insulin you are using. Do not make any changes with your insulin unless you have talked to your healthcare provider. Your insulin needs may change because of illness, stress, other medicines, or changes in diet or activity level. Talk to your healthcare provider about how to adjust your insulin dose.
- You may take LANTUS at any time during the day but you must take it at the same time every day.
- Only use LANTUS that is clear and colorless. If your LANTUS is cloudy or slightly colored, return it to your pharmacy for a replacement.
- Follow your healthcare provider's instructions for testing your blood sugar.
- Inject LANTUS under your skin (subcutaneously) in your upper arm, abdomen (stomach area), or thigh (upper leg). Never inject it into a vein or muscle.
- Change (rotate) injection sites within the same body area.

What kind of syringe should I use?

- Always use a syringe that is marked for U-100 insulin. If you use other than U-100 insulin syringe, you may get the wrong dose of insulin causing serious problems for you, such as a blood sugar level that is too low or too high. Always use a new needle and syringe each time you give LANTUS injection.
- **NEEDLES AND SYRINGES MUST NOT BE SHARED.**
- Disposable syringes and needles should be used only once. Used syringe and needle should be placed in sharps containers (such as red biohazard containers), hard plastic containers (such as detergent bottles), or metal containers (such as an empty coffee can). Such containers should be sealed and disposed of properly.

Mixing with LANTUS

- **Do NOT dilute or mix LANTUS with any other insulin or solution.** It will not work as intended and you may lose blood sugar control, which could be serious.

Instructions for Use

How do I draw the insulin into the syringe?

- **The syringe must be new and does not contain any other medicine.**
- **Do not mix LANTUS with any other type of insulin.**

Follow these steps:

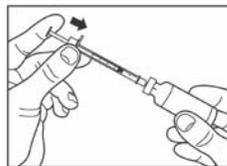
1. Wash your hands with soap and water or with alcohol.
2. Check the insulin to make sure it is clear and colorless. Do not use the insulin after the expiration date stamped on the label, if it is colored or cloudy, or if you see particles in the solution.
3. If you are using a new vial, remove the protective cap. **Do not** remove the stopper.



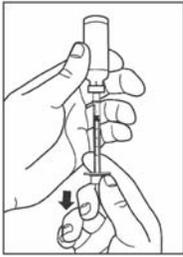
4. Wipe the top of the vial with an alcohol swab. You do not have to shake the vial of LANTUS before use.



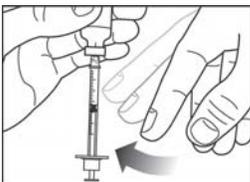
5. Use a new needle and syringe every time you give an injection. Use disposable syringes and needles only once. Throw them away properly. **Never** share needles and syringes.
6. Draw air into the syringe equal to your insulin dose. Put the needle through the rubber top of the vial and push the plunger to inject the air into the vial.



7. Leave the syringe in the vial and turn both upside down. Hold the syringe and vial firmly in one hand.
8. Make sure the tip of the needle is in the insulin. With your free hand, pull the plunger to withdraw the correct dose into the syringe.



9. Before you take the needle out of the vial, check the syringe for air bubbles. If bubbles are in the syringe, hold the syringe straight up and tap the side of the syringe until the bubbles float to the top. Push the bubbles out with the plunger and draw insulin back in until you have the correct dose.



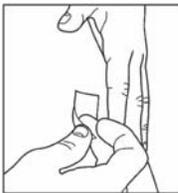
10. Remove the needle from the vial. Do not let the needle touch anything. You are now ready to inject.

How do I inject LANTUS?

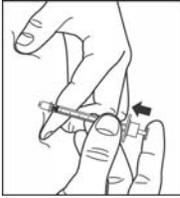
Inject LANTUS under your skin. Take LANTUS as prescribed by your healthcare provider.

Follow these steps:

1. Decide on an injection area - either upper arm, thigh or abdomen. Injection sites within an injection area must be different from one injection to the next.
2. Use alcohol or soap and water to clean the injection site. The injection site should be dry before you inject.



3. Pinch the skin. Stick the needle in the way your healthcare provider showed you. Release the skin.
4. Slowly push in the plunger of the syringe all the way, making sure you have injected all the insulin. Leave the needle in the skin for about 10 seconds.



5. Pull the needle straight out and gently press on the spot where you injected yourself for several seconds. **Do not rub the area.**
6. Follow your healthcare provider's instructions for throwing away the used needle and syringe. Do not recap the used needle. Used needle and syringe should be placed in sharps containers (such as red biohazard containers), hard plastic containers (such as detergent bottles), or metal containers (such as an empty coffee can). Such containers should be sealed and disposed of properly.

What can affect how much insulin I need?

Illness. Illness may change how much insulin you need. It is a good idea to think ahead and make a "sick day" plan with your healthcare provider in advance so you will be ready when this happens. Be sure to test your blood sugar more often and call your healthcare provider if you are sick.

Medicines. Many medicines can affect your insulin needs. Other medicines, including prescription and non-prescription medicines, vitamins, and herbal supplements, can change the way insulin works. You may need a different dose of insulin when you are taking certain other medicines. **Know all the medicines you take**, including prescription and non-prescription medicines, vitamins, and herbal supplements. You may want to keep a list of the medicines you take. You can show this list to your healthcare provider anytime you get a new medicine or refill. Your healthcare provider will tell you if your insulin dose needs to be changed.

Meals. The amount of food you eat can affect your insulin needs. If you eat less food, skip meals, or eat more food than usual, you may need a different dose of insulin. Talk to your healthcare provider if you change your diet so that you know how to adjust your LANTUS and other insulin doses.

Alcohol. Alcohol, including beer and wine, may affect the way LANTUS works and affect your blood sugar levels. Talk to your healthcare provider about drinking alcohol.

Exercise or Activity level. Exercise or activity level may change the way your body uses insulin. Check with your healthcare provider before you start an exercise program because your dose may need to be changed.

Travel. If you travel across time zones, talk with your healthcare provider about how to time your injections. When you travel, wear your medical alert identification. Take extra insulin and supplies with you.

Pregnancy or nursing. The effects of LANTUS on an unborn child or on a nursing baby are unknown. Therefore, tell your healthcare provider if you planning to have a baby, are pregnant, or nursing a baby. Good control of diabetes is especially important during pregnancy and nursing.

What are the possible side effects of LANTUS and other insulins?

Insulins, including LANTUS, can cause hypoglycemia (low blood sugar), hyperglycemia (high blood sugar), allergy, and skin reactions.

Hypoglycemia (low blood sugar):

Hypoglycemia is often called an "insulin reaction" or "low blood sugar". It may happen when you do not have enough sugar in your blood. Common causes of hypoglycemia are illness, emotional or physical stress, too much insulin, too little food or missed meals, and too much exercise or activity.

Early warning signs of hypoglycemia may be different, less noticeable or not noticeable at all in some people. That is why it is important to check your blood sugar as you have been advised by your healthcare provider.

Hypoglycemia can happen with:

- **Taking too much insulin.** This can happen when too much insulin is injected.
- **Not enough carbohydrate (sugar or starch) intake.** This can happen if a meal or snack is missed or delayed.
- **Vomiting or diarrhea** that decreases the amount of sugar absorbed by your body.
- **Intake of alcohol.**
- **Medicines that affect insulin.** Be sure to discuss all your medicines with your healthcare provider. **Do not start any new medicines until you know how they may affect your insulin dose.**
- **Medical conditions that can affect your blood sugar levels or insulin.** These conditions include diseases of the adrenal glands, the pituitary, the thyroid gland, the liver, and the kidney.
- **Too much glucose use by the body.** This can happen if you exercise too much or have a fever.
- **Injecting insulin the wrong way or in the wrong injection area.**

Hypoglycemia can be mild to severe. Its onset may be rapid. Some patients have few or no warning symptoms, including:

- patients with diabetes for a long time
- patients with diabetic neuropathy (nerve problems)

- or patients using certain medicines for high blood pressure or heart problems.

Hypoglycemia may reduce your ability to drive a car or use mechanical equipment and you may risk injury to yourself or others.

Severe hypoglycemia can be dangerous and can cause temporary or permanent harm to your heart or brain. **It may cause unconsciousness, seizures, or death.**

Symptoms of hypoglycemia may include:

- anxiety, irritability, restlessness, trouble concentrating, personality changes, mood changes, or other abnormal behavior
- tingling in your hands, feet, lips, or tongue
- dizziness, light-headedness, or drowsiness
- nightmares or trouble sleeping
- headache
- blurred vision
- slurred speech
- palpitations (fast heart beat)
- sweating
- tremor (shaking)
- unsteady gait (walking).

If you have hypoglycemia often or it is hard for you to know if you have the symptoms of hypoglycemia, talk to your healthcare provider.

Mild to moderate hypoglycemia is treated by eating or drinking carbohydrates, such as fruit juice, raisins, sugar candies, milk or glucose tablets. Talk to your healthcare provider about the amount of carbohydrates you should eat to treat mild to moderate hypoglycemia.

Severe hypoglycemia may require the help of another person or emergency medical people. A person with hypoglycemia who is unable to take foods or liquids with sugar by mouth, or is unconscious needs medical help fast and will need treatment with a glucagon injection or glucose given intravenously (IV). Without medical help right away, serious reactions or even death could happen.

Hyperglycemia (high blood sugar):

Hyperglycemia happens when you have too much sugar in your blood. Usually, it means there is not enough insulin to break down the food you eat into energy your body can use. Hyperglycemia can be caused by a fever, an infection, stress, eating more than you should, taking less insulin than prescribed, or it can mean your diabetes is getting worse.

Hyperglycemia can happen with:

- **Insufficient (too little) insulin.** This can happen from:
 - injecting too little or no insulin
 - incorrect storage (freezing, excessive heat)

- use after the expiration date.

- **Too much carbohydrate intake.** This can happen if you eat larger meals, eat more often, or increase the amount of carbohydrate in your meals.
- **Medicines that affect insulin.** Be sure to discuss all your medicines with your healthcare provider. **Do not start any new medicines until you know how they may affect your insulin dose.**
- **Medical conditions that affect insulin.** These medical conditions include fevers, infections, heart attacks, and stress.
- **Injecting insulin the wrong way or in the wrong injection area.**

Testing your blood or urine often will let you know if you have hyperglycemia. If your tests are often high, tell your healthcare provider so your dose of insulin can be changed.

Hyperglycemia can be mild or severe. Hyperglycemia can **progress to diabetic ketoacidosis (DKA) or very high glucose levels (hyperosmolar coma) and result in unconsciousness and death.**

Although diabetic ketoacidosis occurs most often in patients with type 1 diabetes, it can also happen in patients with type 2 diabetes who become very sick. Because some patients get few symptoms of hyperglycemia, it is important to check your blood sugar/urine sugar and ketones regularly.

Symptoms of hyperglycemia include:

- confusion or drowsiness
- increased thirst
- decreased appetite, nausea, or vomiting
- rapid heart rate
- increased urination and dehydration (too little fluid in your body).

Symptoms of DKA also include:

- fruity smelling breath
- fast, deep breathing
- stomach area (abdominal) pain.

Severe or continuing hyperglycemia or DKA needs evaluation and treatment right away by your healthcare provider.

Do not use LANTUS to treat diabetic ketoacidosis.

Other possible side effects of LANTUS include:

Serious allergic reactions:

Some times severe, life-threatening allergic reactions can happen with insulin. If you think you are having a severe allergic reaction, get medical help right away. Signs of insulin allergy include:

- rash all over your body
- shortness of breath
- wheezing (trouble breathing)
- fast pulse
- sweating
- low blood pressure.

Reactions at the injection site:

Injecting insulin can cause the following reactions on the skin at the injection site:

- little depression in the skin (lipoatrophy)
- skin thickening (lipohypertrophy)
- red, swelling, itchy skin (injection site reaction).

You can reduce the chance of getting an injection site reaction if you change (rotate) the injection site each time. An injection site reaction should clear up in a few days or a few weeks. If injection site reactions do not go away or keep happening, call your healthcare provider.

Tell your healthcare provider if you have any side effects that bother you.

These are not all the side effects of LANTUS. Ask your healthcare provider or pharmacist for more information.

How should I store LANTUS?

- **Unopened vial:**

Store new (unopened) LANTUS vials in a refrigerator (not the freezer) between 36°F to 46°F (2°C to 8°C). Do not freeze LANTUS. Keep LANTUS out of direct heat and light. If a vial has been frozen or overheated, throw it away.

- **Open (In-Use) vial:**

Once a vial is opened, you can keep it in a refrigerator or at room temperature (below 86°F [30°C]) but away from direct heat and light. Opened vial, either kept in a refrigerator or at room temperature, should be discarded 28 days after the first use even if it still contains LANTUS. Do not leave your insulin in a car on a summer day.

These storage conditions are summarized in the following table:

	Not in-use (unopened)	Not in-use (unopened)	In-use (opened)
	Refrigerated	Room Temperature	Refrigerated or Room Temperature
10 mL Vial	Until expiration date	28 days	28 days

- Do not use a vial of LANTUS after the expiration date stamped on the label.
- Do not use LANTUS if it is cloudy, colored, or if you see particles.

General Information about LANTUS

- Use LANTUS only to treat your diabetes. **Do not** give or share LANTUS with another person, even if they have diabetes also. It may harm them.
- This leaflet summarizes the most important information about LANTUS. If you would like more information, talk with your healthcare provider. You can ask your doctor or pharmacist for information about LANTUS that is written for healthcare professionals. For more information about LANTUS call 1-800-633-1610 or go to website www.lantus.com.

NDA 21-081/S-011

Final draft

Page 12

ADDITIONAL INFORMATION

DIABETES FORECAST is a national magazine designed especially for patients with diabetes and their families and is available by subscription from the American Diabetes Association (ADA), P.O.Box 363, Mt. Morris, IL 61054-0363, 1-800-DIABETES (1-800-342-2383). You may also visit the ADA website at www.diabetes.org.

Another publication, **COUNTDOWN**, is available from the Juvenile Diabetes Research Foundation International (JDRF), 120 Wall Street, 19th Floor, New York, New York 10005, 1-800-JDF-CURE (1-800-533-2873). You may also visit the JDRF website at www.jdf.org.

To get more information about diabetes, check with your healthcare professional or diabetes educator or visit www.DiabetesWatch.com.

Additional information about LANTUS can be obtained by calling 1-800-633-1610 or by visiting www.lantus.com.

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Aventis Pharmaceuticals Inc.

Kansas City, MO 64137 USA

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OptiClik™

INSTRUCTION LEAFLET

OptiClik™ is a reusable insulin delivery device (insulin Pen) for use with 3 mL LANTUS cartridge (U-100) system.

OptiClik™ allows you to dial the dose in one-unit step increments between one unit and a maximum of 80 units per injection.

This instruction leaflet explains how to use OptiClik™. It is important for you to read and follow all the instructions in this leaflet carefully. If you do not follow these instructions completely, you may get too much or too little insulin. Keep this leaflet for future reference for each time you use OptiClik™.

You will find further useful information on the back side of this leaflet in the chapters:

- (A.) General Notes
- (B.) Troubleshooting
- (C.) Storage Instructions
- (D.) Other Information

Please read this Instruction Leaflet carefully and completely before using OptiClik™ for the first time. Keep this leaflet for future reference for each time you use OptiClik™.

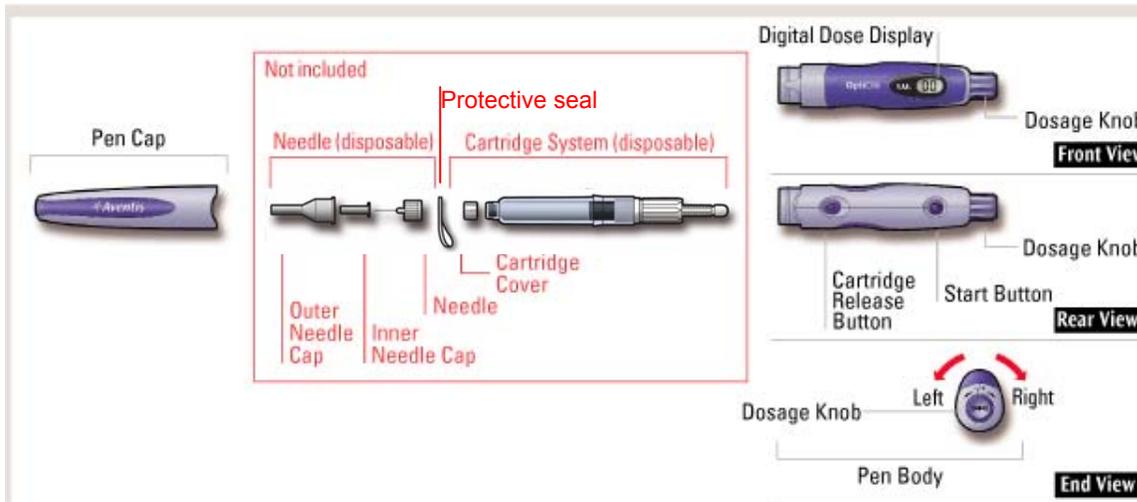
Talk with your healthcare provider before using OptiClik™ about proper injection technique.

If you have visual problems, use OptiClik™ only if you have help from a trained person with good vision.

Additional items needed for use with OptiClik™

- Alcohol swabs
- Appropriate needles
- Cartridge System, at room temperature

If you have any questions about OptiClik™ or about diabetes, ask your healthcare professional, go to www.opticlik.com or call Aventis at 1-800-633-1610.



38

39

40

41 **General Warnings and Precautions**

42 **Needles**

43 You must use a new sterile needle (intact protective seal) for each injection. This prevents a
 44 blocked needle and air bubbles.

45 In order to avoid injuries, replace Outer Needle Cap before removing and disposing of used
 46 needles.

47 **Safety test**

48 Before each injection, carry out the Safety Test (Step 1). If you do not follow the instructions
 49 completely, you may get too much or too little insulin. Injecting too much or too little insulin
 50 dose may lead to unwanted blood sugar changes (see the package leaflet for your insulin). Do not
 51 perform the safety test without the needle attached.

52 **Damage to OptiClik™**

53 OptiClik™ may become damaged by rough handling, dropping, or turning of the Dosage Knob
 54 by force. Make sure that no dirt gets in contact with the mechanical parts. You should always
 55 make sure that:

- 56 a) The Cartridge System is undamaged.
- 57 b) The Start Button, Dosage Knob, and Digital Dose Display operate properly.

58 **Do not use tools on OptiClik™. If you are not sure whether or not your OptiClik™ is**
 59 **damaged, contact your healthcare professional or call 1-800-633-1610. If damaged, it is no**
 60 **longer safe to use. In an emergency, you can draw up the insulin from the Cartridge**
 61 **System using a U-100 insulin syringe.**

62 OptiClik™ should not be used near electrical and electronic equipment.

63

64

65 **Step 1: Inserting the Cartridge System**

66

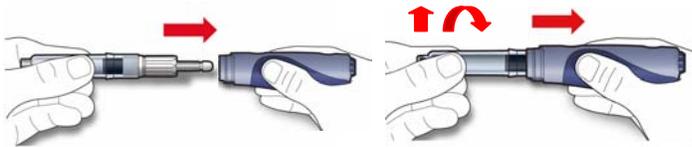
67 Do not shake the cartridge system before use. You should look at the solution in the cartridge
 68 system before inserting it into OptiClik™. If the solution is cloudy, slightly colored, or has

69 particles in it, do not use the cartridge. Before the next steps, remove the Cartridge Cover by
70 pulling it out.



71
72 A Make sure the Dosage Knob is pushed in.

73
74



75
76
77 B Hold the Pen Body with the release button facing up. Insert the Cartridge System straight into
78 the Pen Body. If you meet resistance, slightly raise and rotate the Cartridge System while
79 inserting it. Make sure that it clicks in. Do not use force.

80
81



82
83 C To make sure that the Cartridge System clicked in place properly, gently try pulling out the
84 Cartridge System. The Cartridge System should not come out. Make sure you do not press the
85 Cartridge Release button during or after this check.

86
87 OptiClik™ is now ready for Step 2 (Attaching the needle), or it can be stored with the attached
88 Pen Cap.

89
90 **DO NOT STORE YOUR OPTICLIK™ IN A REFRIGERATOR AFTER CARTRIDGE**
91 **SYSTEM IS INSERTED IN OPTICLIK™**

92
93 **Step 2: Attaching the needle**

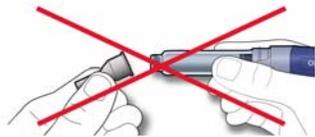


94
95 A Peel off the Protective Seal on the needle.

96
97
98

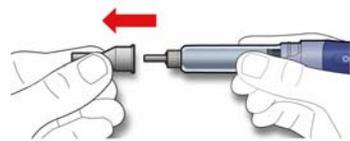


99



100

101 **B** Use an alcohol swab to wipe the rubber seal on the end of the cartridge. Connect a new needle
102 without removing the Outer and Inner Needle Caps straight to the Cartridge System.
103



104

105 **C** Remove Outer Needle Cap from the needle.
106 Save Outer Needle Cap for use later on in discarding the needle.
107

108 **Step 3: Safety Test**

109

110 Before each injection, carry out the Safety Test or you may get too much or too little insulin.
111 **Make sure a needle is attached to OptiClik™ before you do the Safety Test.** Do not press
112 the Cartridge Release Button during these steps.
113



114

115

116 **A** Press the Start Button.
117



118

119

120 **B** The Dosage Knob must come out. "00" appears in the Digital Dose Display.
121



122
123
124
125

C Turn the Dosage Knob to the right (clockwise) until it clicks. “01” appears in the Digital Dose Display.



126
127
128
129

D Remove and discard the Inner Needle Cap. Handle the exposed needle carefully.



130
131
132
133

E Hold OptiClik™ with the needle pointing up.

134
135
136
137

Press the Dosage Knob fully until it stays in.

Insulin must appear at the tip of the needle. If not, repeat the Safety Test. When replacing an empty cartridge system with a new one, it might require repeating this procedure several times. A Safety Test must be carried out before each injection.

138
139
140
141

Additional information about “Cartridge System” and “Removing air bubbles” is on the back side of this leaflet.

142 **Step 4: Setting the dose**

143



144

145

146 A Press the Start Button.



147

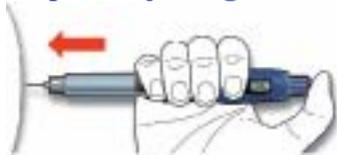
148

149 B Turn the Dosage Knob slowly to the right (clockwise) until you reach your required dosage.
150 You must feel and hear a click.

151 If you have selected a dose that is too high, simply turn the Dosage Knob back (to the left). If
152 you have dialed past 80 units, see (B.) TROUBLESHOOTING, Dose-setting on the back of this
153 manual.

154

155 **Step 5: Injecting the dose**

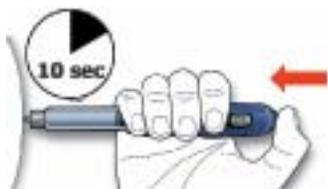


156

157

158 A Clean the injection area with alcohol. Insert the needle as recommended by your healthcare
159 professional (e.g., lightly pinch a fold of skin on your stomach, thigh, or buttock. Insert the
160 needle straight into the pinched skin).

161



162

163

164 B Press the Dosage Knob slowly and completely. The Dosage Knob must stay in. Then slowly
165 count to 10 while holding the Dosage Knob down before withdrawing the needle.

166

167 Do not press the Cartridge Release Button or the Start Button while injecting.

168

169 **Step 6: Removing the needle**



170
171
172

A Replace Outer Needle Cap carefully.



173
174

B Remove the needle after the injection. For safe disposal of needles see (A.) GENERAL NOTES, Needles for OptiClik™ on the back of this manual. Always replace Pen Cap on the Pen Body after use.

178

OptiClik™ can be stored with the attached Cartridge System until your next injection. See (C.) STORAGE INSTRUCTIONS.

181

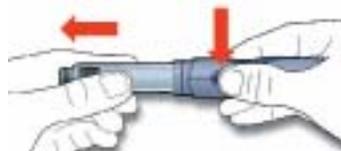
182

183 Step 7: Replacing an empty Cartridge System



184
185

A Make sure the Dosage Knob is pushed in.



187
188

B Press the Cartridge Release Button, and remove the entire Cartridge System. Dispose of the Cartridge System.

191

Start again at Step 1 (Inserting the Cartridge System).

193

194



195
196

197

198 **A. GENERAL NOTES**

199

200 **Cartridge System**

201 The Cartridge System is sold separately. Before every injection, check the appearance of the
202 solution in the Cartridge System and follow the instructions in the patient information leaflet for
203 Lantus. It is important to follow the directions of this Instruction Leaflet closely to help avoid
204 side effects (e.g., infections, improper dosing). Consult with your healthcare professional before
205 using OptiClik™.

206

207 Before the use of an unopened, refrigerated Cartridge System, take it out of the refrigerator and
208 leave it at room temperature for about 1 to 2 hours. Do not remove the Cartridge System from
209 packaging until ready to use. This will prevent dust or dirt from getting into the mechanical parts
210 of the Cartridge System. Use an alcohol swab to wipe the rubber seal on the end of the cartridge
211 before inserting the needle. Do not open or manipulate the Cartridge System in any way.

212

213 **Needles for OptiClik™**

214 Needles are available from BD Consumer Healthcare. Contact your healthcare professional for
215 further information. Please note there are two types of needles available: one type which needs to
216 be screwed on and another type which only needs to be pushed on (“clicks on”). Both needle
217 types can be used. Please consult the manual of the needle package.

218 Needles may vary from country to country and may not be interchangeable. If you intend to
219 travel abroad, make sure that you have sufficient needles and insulin with you.

220

221 **Do not store OptiClik™ with a needle attached.** Storing OptiClik™ with the needle attached
222 may allow insulin to leak from OptiClik™ and air bubbles to form in the cartridge.

223 Used needles should be placed in sharps containers (such as red biohazard containers), hard
224 plastic containers (such as detergent bottles), or metal containers (such as an empty coffee can).
225 Such containers should be sealed and disposed of properly.

226

227 **Removing air bubbles**

228 Air bubbles must be removed before each injection during the Safety Test (Step 3 for Safety
229 Test). If air bubbles still remain, repeat the Safety Test, turning the Dosage Knob to the right
230 until “02” appears on the display. Gently tap the Cartridge System until the air rises to the top of
231 the Cartridge System tip. Then press the Dosage Knob until it stays in. If necessary, keep
232 repeating the Safety Test until insulin appears at the tip of the needle.

233

234 **Setting the dose and Display feature**

235 To set the dose, hold OptiClik™ as shown in Step 4 for setting the dose. The printed “I.U.” must
236 be legible left of the Digital Dose Display. The Digital Dose Display shows the delivered dose
237 for 2 minutes after every injection. After 30 minutes the display will go off to conserve battery
238 power. With the Dosage Knob released the display switches off after 2 minutes.

239

240 **How long will OptiClik™ last**

241 The expected lifetime of OptiClik™ is 3 years.

242



flashes when the Start Button is pressed:

243
244 OptiClik™ is reaching the end of its expected lifetime (3 years). The Digital Dose Display will
245 continue to operate for about 4 more weeks. Please obtain a new OptiClik™.

246



stays when the Start Button is pressed:

247
248 OptiClik™ has reached the end of its lifetime. When you continue to turn the Dosage Knob, the
249 display still shows . Please obtain a new OptiClik™.

250

251 **B. TROUBLESHOOTING**

252 **Safety test**

253 **No insulin appears at the needle tip during the Safety Test (Step 3, Safety Test):**

254 Repeat (Step 3 – Safety Test). If no insulin appears this time either, confirm that:

- 255 1. The needle is firmly in position. Replace a blocked or defective needle with a new one.
256 2. The Dosage Knob has been set correctly (always turn the Dosage Knob to the right/clockwise
257 to preselect the dose).

258 Turn the Dosage Knob one click to the right, equal to one unit.

259 3. The Cartridge System has been inserted correctly. Check by trying to pull the Cartridge
260 System gently out. If the Cartridge System comes out, reinsert it completely (Step 1– Inserting
261 the Cartridge System,). Repeat (Step 3 – Safety Test).

262 4. The Cartridge System is not empty. If it is empty, insert a new one. Repeat Step 3 – Safety
263 Test.

264

265 **You hear no clicking sound during dose-setting:**

266 The Cartridge System may have been inserted incorrectly. Check by trying to pull the Cartridge
267 System gently out. If the Cartridge System comes out, reinsert it completely (Step 1– Inserting
268 the Cartridge System). Repeat (Step 3– Safety Test).

269 If you still hear no clicking sound, try a new Cartridge System and listen for clicking sound. In
270 case there is still no clicking sound, obtain a new OptiClik™.

271

272 **Dose-setting**

273 **Insulin drips from the needle tip during dose-setting:**

274 The maximum dose of OptiClik™ is 80 units. If you continue to dial after reaching 80 units,
275 insulin will drip from the needle and the display will continue to show “80”. In such a case, DO
276 NOT turn back to the required dose, instead dial back (to the left) to “00”. Press the Dosage
277 Knob to expel excess insulin and to reset OptiClik™. OptiClik™ is now again ready for dose
278 setting. If you need a dose greater than 80 units, you should give it as more than one injection.

279 **You feel resistance during dose-setting and the Dosage Knob will not turn further forward
280 (to the right):**

281 a) You are turning to the left and trying to dial down below zero. Turn the Dosage Knob to the
282 right to dial your dose.

283 b) The Cartridge System is almost empty and no longer contains a sufficient amount of insulin
284 for the dose you need. For example, if there are only 20 units left in the cartridge and you need
285 25 units, the dosage knob will stop at 20 units. You can choose to do one of the following:

286 1) Do not force the Dosage Knob any further (to the right). Inject the partial dose (20 units in
287 the example), and replace the empty Cartridge System with a new one. Perform the Safety
288 Test as described in Step 3, then inject the remainder of the dose to equal your total
289 prescribed dose. In the above example the remaining dose is 5 units.

290 OR

291 2) Dial back (to the left) to “00”. Follow Step 7 (Replacing an empty Cartridge System),
292 Step 1 (Inserting the Cartridge System), Step 2 (Attaching the needle), and Step 3 (Safety
293 Test).

294 c) You have dialed (to the right) past the maximum dose of 80 units and have no needle (or a
295 clogged needle) mounted. Dial completely back (to the left) to “00”, and perform Step 2
296 (Attaching the needle) and Step 3 (Safety Test). Do not force the Dosage Knob to turn further.

297

298 **The Dosage Knob does not stop at “00”:**

299 When turned back completely, the Dosage Knob should stop at “00”, however, sometimes it may
300 stop at “02” or “01”. Make sure that a needle is attached; then press the Dosage Knob down
301 (insulin will appear at the tip of the needle). OptiClik™ is now ready for dose setting.

302

303 **The Dosage Knob no longer turns after a new Cartridge System
304 has been inserted:**

305 Check that the Cartridge System is firmly clicked in. Reseat the Cartridge System and try again.
306 If it still does not work, try again with a new Cartridge System (Step 1, Inserting the Cartridge
307 System). Otherwise, get a new OptiClik™.

308

309 **The Dosage Knob does not come out after you pressed the Start
310 Button:**

311 Do not pull out the Dosage Knob. Check that the Cartridge System is firmly clicked in, see Step
312 1B-Inserting the Cartridge System.

313

314 **Insulin injection**

315 **The Dosage Knob cannot be pressed down for the insulin injection
316 or it does not stay down:**

317 1. In setting the dose, you have turned the Dosage Knob so that it is between two dose steps.
318 Turn the Dosage Knob to the right or the left to the desired dose.

319 2. The needle may be blocked or defective. Use a new needle.

320 3. Avoid pushing the Start Button and Dosage Knob at the same time.

321

322 **After withdrawing the needle from your skin, more than one drop of insulin drips from the
323 needle:**

324 It is possible that you may not have injected your full insulin dose. DO NOT try to make up for
325 the shortfall in your insulin dose by giving a second injection (otherwise you will be at risk for
326 low blood sugar).

327 Please check your blood sugar and consult with your healthcare professional.

328 You can avoid the problem next time by taking the following steps:

329 1. Remove any air bubbles that may be present in the Cartridge System

330 (see “GENERAL NOTES: Removing air bubbles”).

331 2. After delivering the insulin dose, slowly count to 10 before withdrawing the needle from your
332 skin.

333

334 **Cartridge System replacement**

335 **The Cartridge System and Pen Body do not click back together**
336 **properly:**

337 1. Check that the Dosage Knob is pushed in.

338 2. Check that you have put the Cartridge System correctly into the Pen Body. Take the Cartridge
339 System out and insert it again (see under Step 7 for replacing an empty cartridge and Step 1 for
340 inserting the cartridge). Repeat Step 2 for attaching the needle and Step 3 for Safety Test.

341

342 **Digital Dose Display functions**

343  **is displayed:**

344 1. When turned back completely (to the left), the Dosage Knob should stop at “00”, in some
345 cases it stops at “- -”. Perform a Safety Test (Step 3).

346 2. The Dosage Knob has been forced into the negative range with excessive force. The Cartridge
347 System might be damaged and needs to be replaced. Follow the instructions under Step 7 to
348 replace the cartridge and dispose of the damaged Cartridge System. Repeat Step 1 for inserting
349 the cartridge, Step 2 for attaching the needle, and Step 3 for Safety Test.

350

351  **and**  **flash alternately:**

352 a) The Dosage Knob has been forced into the negative range and was pushed in. The Cartridge
353 System might be damaged and needs to be replaced. Repeat Step 7 for replacing an empty
354 cartridge and dispose of the damaged Cartridge System. Repeat Step 1 for inserting the cartridge
355 system, Step 2 for attaching the needle, and Step 3 for Safety Test.

356 b) The Dosage Knob has been turned too quickly. You can choose to do
357 one of the following:

358 1) Dispose of the unknown pre-set dose by pressing the Dosage Knob. Set your dose (Step 4)
359 and inject your dose (Step 5). OR

360 2) Turn the Dosage Knob slowly backward (to the left) until it stops, and then push the
361 Dosage Knob in. Restart OptiClik™ and dial your dose.

362

363 **No numbers appear on the Digital Dose Display when the Start**
364 **Button is pressed or when the Dosage Knob is released:**

365 Press the Dosage Knob. Start with a Safety Test (Step 3).

366 If there are still no numbers on Digital Dose Display, you should obtain a new OptiClik™.

367

368 **The Digital Dose Display goes blank during dose setting (e.g., if you are interrupted in the**
369 **middle of your injection preparations):**

370 The energy save function has automatically come into operation. Turn the Dosage Knob one
371 click further (to the right). OptiClik™ should now be ready to use again; check the Digital Dose
372 Display and adjust for the right dose if needed.

373

374 **Battery Information**



flashes when the Start Button is pressed:

375
376 Your battery is running out. Please obtain a new OptiClik™ as soon as possible.



is displayed when the Start Button is pressed:

377
378 Your battery has run out. Please obtain a new OptiClik™.

379

380 **C. STORAGE INSTRUCTIONS**

381

382 Do not store OptiClik, with or without cartridge system, in a refrigerator at any time. Always
383 store OptiClik™ (without the needle attached) with or without Cartridge System inserted at room
384 temperature below 86°F (30°C). Protect OptiClik™ from moisture and direct heat. When
385 OptiClik™ is not in use, push the Dosage Knob in to conserve the battery and to ensure
386 OptiClik™ functions throughout its expected lifetime. To avoid dust or dirt from getting into
387 OptiClik™, always replace the Pen Cap. Once the Cartridge System is used with OptiClik™,
388 the Cartridge System can be used for up to 28 days under normal carrying conditions (at room
389 temperature below 86°F/30°C). See “Patient Information” for 3 mL cartridge for cartridge
390 storage information.

391

392 **D. OTHER INFORMATION**

393 **Care, cleaning, and maintenance instructions**

394 Handle OptiClik™ carefully. To keep it clean, use a clean damp cloth. Clean it once a week. Dirt
395 can impede the operation. DO NOT use cleaning agents. Use an alcohol swab only for cleaning
396 the Cartridge System’s rubber seal.

397 **Lifetime**

398 OptiClik™ has a lifetime of 3 years. See “(A.) GENERAL NOTES, How long will OptiClik™
399 last” for details.

400 **Manufactured for and**
401 **distributed by:**

402 Aventis Pharmaceuticals Inc., Kansas City, MO 64137 USA

403 Made in Switzerland

404 OptiClik™ is a trademark and Lantus® is a registered trademark of Aventis Pharmaceuticals Inc.

405 **For more information call toll free 1-800-633-1610 or please visit www.lantus.com or**
406 **www.opticlik.com**

407

408 **Date of revision:**

409 xxxx

410



411

412

01015158.300

Lantus®

insulin glargine (rDNA origin) injection

Five 3mL Cartridge Systems

100units/mL
(U-100)

Aventis

DO NOT MIX WITH OTHER INSULINS

100units/mL
(U-100)
Aventis

Lantus®
insulin glargine (rDNA origin) injection

Five 3mL Cartridge Systems

DO NOT MIX WITH OTHER INSULINS



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Made in Germany
Kansas City, MO 64137 ©2003
Aventis Pharmaceuticals Inc.

Mfd for:

Aventis Pharma Deutschland GmbH
D-65926 Frankfurt am Main
Frankfurt, Germany

U.S. Patents 5,656,722; 5,370,629; 5,509,905

Store cartridge system in refrigerator 36–46°F (2–8°C). Do not freeze. Discard if frozen. Use within 28 days after opening.

WARNING: Keep out of reach of children.

under medical supervision.
using this product. Any change of insulin should be made cautiously and only

Dosage and Administration: See package insert for dosage information. As with any drug, if you are pregnant or nursing a baby, seek professional advice when

addition of aqueous solutions of hydrochloric acid and sodium hydroxide.
Each mL of LANTUS® contains 100 IU (3.6378mg) insulin glargine, 30mcg zinc, 2.7mg m-cresol, 20mg glycerol 85%, and water for injection. pH is adjusted by

Lantus®
insulin glargine (rDNA origin) injection

Lantus®
insulin glargine (rDNA origin) injection

Five 3mL Cartridge Systems

DO NOT MIX WITH OTHER INSULINS

100units/mL
(U-100)
Aventis

No copy area
For Lot & Exp

Lantus®
insulin glargine (rDNA origin) injection
100units/mL
(U-100)

NDC 0088-2220-52

Lantus®
insulin glargine
(rDNA origin) injection

100units/mL
(U-100)

FOR USE ONLY IN OPTICLIK™ INSULIN DELIVERY DEVICE

DO NOT MIX WITH OTHER INSULINS

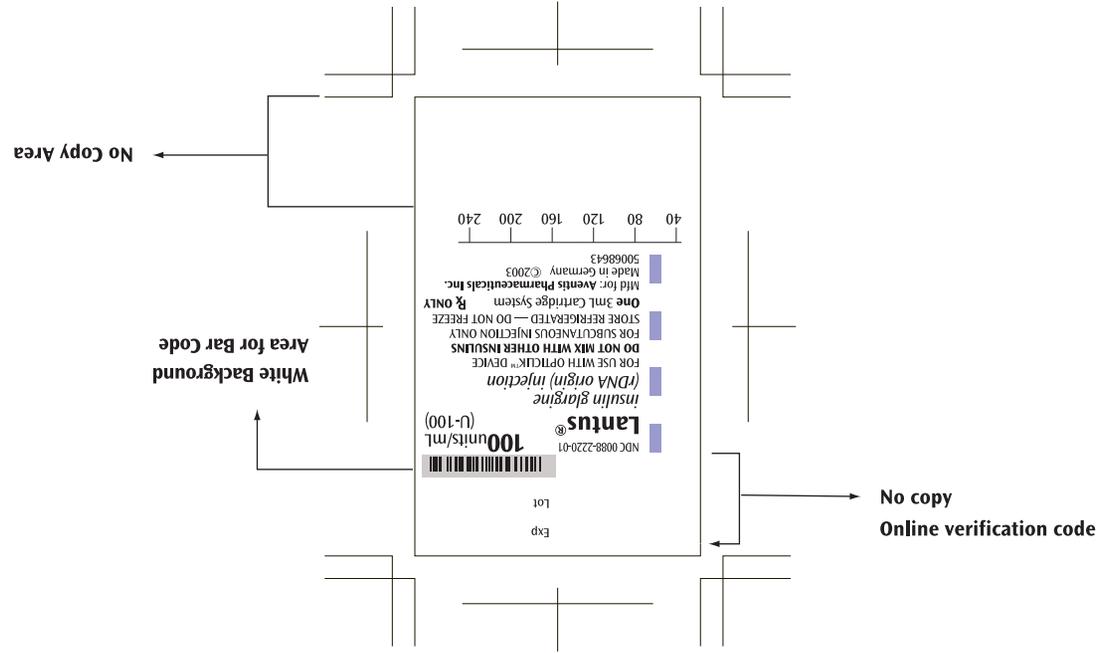
FOR SUBCUTANEOUS INJECTION ONLY

USE ONLY IF SOLUTION IS CLEAR AND COLORLESS
WITH NO PARTICLES VISIBLE

Rx ONLY

Five 3mL Cartridge Systems

Aventis



01015452.300

OptiClik™: Labeling of the Pen Carton (dialing module):

Illustrations of final artworks
02nd May 2003



PEN WITH “OPTICLIK” PRINTED



Pen Cap



Pen Body

Digital Dose Display

Front View



Dosage Knob

Rear View



Cartridge Release Button Start Button

Dosage Knob

