CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21-081/S017

Trade Name: Lantus, 10mL vials and 3 mL cartridges

Generic Name: (insulin glargine [rDNA origin] injection)

Sponsor: Aventis Pharmaceuticals Inc.

Approval Date: March 15, 2005

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-081/S017

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-081/S017

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-081/S-017

Aventis Pharmaceuticals Inc.
Attention: Kumara Sekar, Ph.D.
Metabolism
Mail Stop BX2-406B
200 Crossing Boulevard
Bridgewater, NJ 08807-0890

Dear Dr. Sekar

Please refer to your supplemental new drug application dated November 15, 2004, received November 16, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lantus (insulin glargine [rDNA origin] injection), 10 mL vials and 3 mL cartridges.

This supplemental new drug application provides for an additional stabilizing agent, 20 ppm of polysorbate 20, added to the drug product formulation for the 10 mL vial presentation.

We completed our review of this application. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, text for the patient package insert for 10 mL vials, and carton label for 10 mL vials). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved supplement NDA 21-081/S-017**." Approval of this submission by FDA is not required before the labeling is used.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package inserts directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Julie Rhee Regulatory Project Manager, at (301) 827-6424.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic
and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures:
1. Physician insert
2. Patient Information for 10 mL vial
3. Carton container label for 10 mL vial

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

David Orloff
3/15/05 04:00:39 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-081/S017

LABELING

Rev. XXXX **Rx Only**

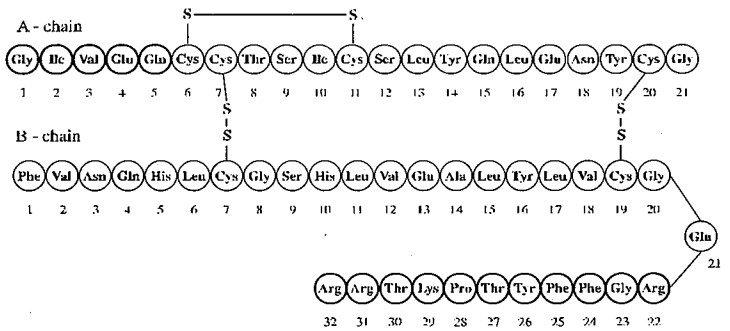
LANTUS®

(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^{B}a-L-Arg-30^{B}b-L-Arg-human insulin and has the empirical formula $C_{267}H_{404}N_{72}O_{78}S_6$ 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.

Inactive ingredients for the 10 mL vial are 30 mcg zinc, 2.7 mg m-cresol, 20 mg glycerol 85%, 20 mcg polysorbate 20, and water for injection.
Inactive ingredients for the 3 mL cartridge are 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,

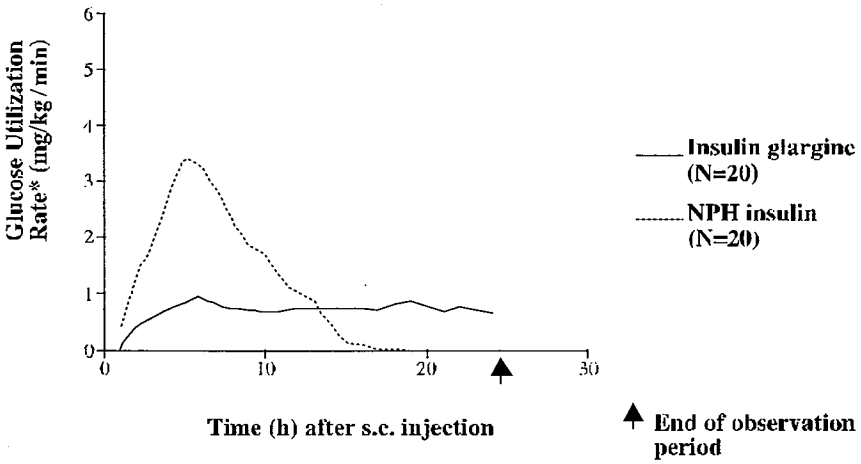
especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin inhibits lipolysis in the adipocyte, inhibits proteolysis, and enhances protein synthesis.

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/m^2, 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

	Study A		Study B		Study C	
Treatment duration	28 weeks		28 weeks		16 weeks	
Treatment in combination with	Regular insulin		Regular insulin		Insulin lispro	
	LANTUS	NPH	LANTUS	NPH	LANTUS	NPH
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

	Study D	
Treatment duration	28 weeks	
Treatment in combination with	Regular insulin	
	LANTUS	NPH
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

	Study E		Study F	
Treatment duration	52 weeks		28 weeks	
Treatment in combination with	Oral agents		Regular insulin	
	LANTUS	NPH	LANTUS	NPH
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 Insulin lispro**			**Study H 24 weeks 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)				NA**	NA	NA
Endstudy mean	53.3	54.7	51.5			
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/m^2. 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/m^2, 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/m^2. 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/m^2, 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. XXXX
Manufactured by:
Aventis Pharma Deutschland GmbH
D-65926 Frankfurt am Main
Frankfurt, Germany
Manufactured for:
Aventis Pharmaceuticals Inc.
Kansas City, MO 64137 USA

Made in Germany
www.lantus.com

OptiClik™ is a trademark of Aventis Pharmaceuticals Inc.

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

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.

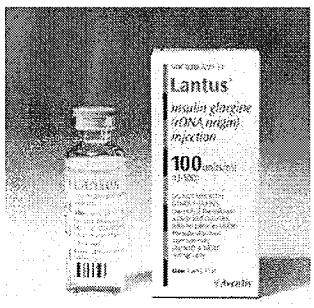
What is LANTUS?

- 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, polysorbate 20 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.**

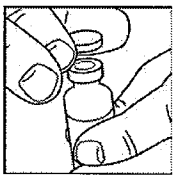
- Disposable syringes and needles should be used only once. Used syringe and needle should be placed in sharps containers (such as red biohazard containers), hard plastic containers (such as detergent bottles), or metal containers (such as an empty coffee can). Such containers should be sealed and disposed 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.**

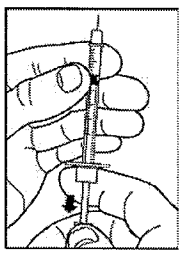
Follow these steps:

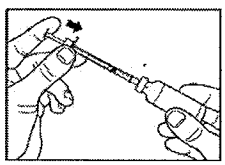
1. Wash your hands with soap and water or with alcohol.
2. Check the insulin to make sure it is clear and colorless. Do not use the insulin after the expiration date stamped on the label, if it is colored or cloudy, or if you see particles in the solution.
3. If you are using a new vial, remove the protective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



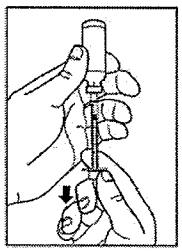
4. Wipe the top of the vial with an alcohol swab. You do not have to shake the vial of LANTUS before use.

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.

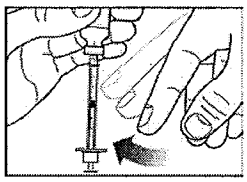




7. Leave the syringe in the vial and turn both upside down. Hold the syringe and vial firmly in one hand.
8. Make sure the tip of the needle is in the insulin. With your free hand, pull the plunger to withdraw the correct dose into the syringe.



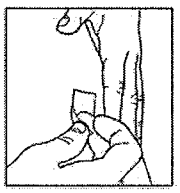
9. Before you take the needle out of the vial, check the syringe for air bubbles. If bubbles are in the syringe, hold the syringe straight up and tap the side of the syringe until the bubbles float to the top. Push the bubbles out with the plunger and draw insulin back in until you have the correct dose.



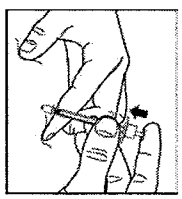
10. Remove the needle from the vial. Do not let the needle touch anything. You are now ready to inject.

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) **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

- 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.

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.

Rev. XXXX
Aventis Pharmaceuticals Inc.
Kansas City, MO 64137 USA

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Aventis

Date: 10-25-04
ID number: 50073216
VERSION: A
Component: Carton, Lantus, 1x10mL Vial
Supplier: Frankfurt
Graphic Operator: Doris Moore
Logo or brand name: Brand name
Colors: Relfex Blue ■ PMS Proc Black ■
PMS 2645C ▒ No Varnish ▒

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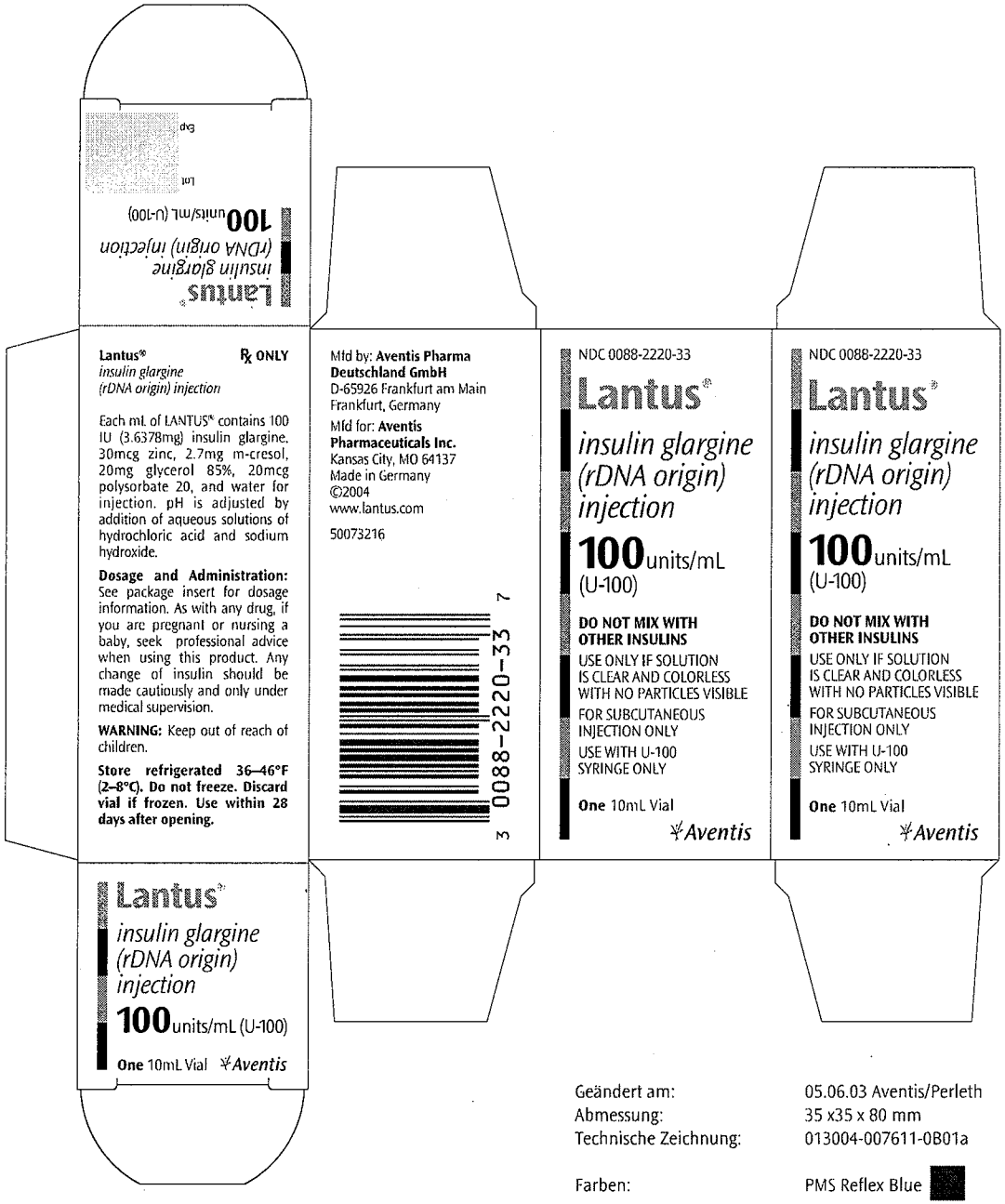

Geändert am:	05.06.03 Aventis/Perleth
Abmessung:	35 x35 x 80 mm
Technische Zeichnung:	013004-007611-0B01a
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	unlackierter Bereich ▒ PMS 2645 ▒

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-081/S017

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW

1. Organization CDER/HFD-510
Division of Metabolism and Endocrine Drug Products

2. NDA # 21-081
Approved 20-APR-2000

3. Name and Address of Applicant:
Aventis Pharmaceuticals
Route 202-208
P.O. Box 6800
Bridgewater, NJ 08870-0800
Phone: (908) 231-4000 Fax: (908) 452-1218

4. Supplement SCF-017
Doc. 15-NOV-2004

5. Name of the Drug
Lantus®

6. Nonproprietary Name
Insulin glargine (rDNA origin)

7. Supplement provides for a change to the currently approved qualitative and quantitative composition of in insulin glargine solution for injection (Lantus®) in 10 mL vials.

8. Amendment(s)
--

9. Pharmacological Category
Treatment of Diabetes Mellitus

10. How Dispensed
Subcutaneous Injection
Rx

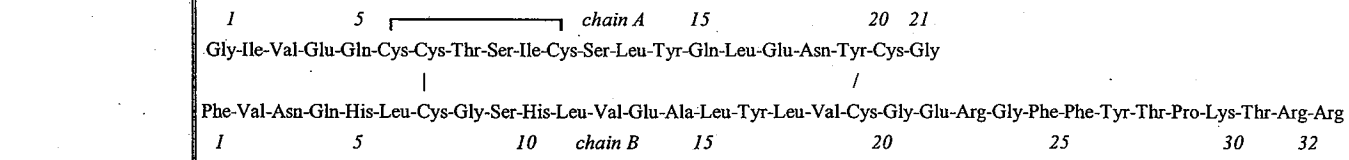
11. Supporting Documents
--

12. Dosage Form 10 mL Vial, 3 mL Cartridge

13. Potencies 100 units/mL

14. Chemical Name and Structure Insulin glargine

21A-Gly-30Ba-Arg-30Bb-Arg *human* Insulin (Aventis' code: HOE 901) $C_{267}H_{404}N_{72}O_{78}S_6$ MW = 6063



15. Comments: This Prior Approval Supplement provides for a change to the currently approved qualitative and quantitative composition of in insulin glargine solution for injection (Lantus®) in 10 mL vials. An additional stabilizing agent, 20 ppm Polysorbate 20, will be added to the product formulation for the 10 mL presentation. The change in the composition does not affect the currently approved for the 3 mL cartridge formulation. This change has been judged inconsequential from the clinical viewpoint (see attached e-mail correspondence). **Evaluation of the study to establish bioequivalence between the current and proposed formulation is being reviewed by the Office of Clinical Pharmacology and Biopharmaceutics (OCPB).**

16. Conclusions and Recommendation: Adequate CMC information has been provided to support the use of the reformulated insulin glargine solution for injection packaged into 10 mL vials. **From the Chemistry point of view, this supplement can be approved.**

17. Date Completed: 14-FEB-2005	Xavier Ysern, PhD
R/D Init. Stephen Moore, PhD Chemist team Leader /nda/21081s17.doc	**filename:**

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11 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

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_____ Draft Labeling (b5)

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/s/

Xavier Ysern
3/9/05 10:32:57 AM
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Stephen Moore
3/9/05 11:09:34 AM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-081/S017

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-081(SCF-17)	Submission Date(s): 11/15/04
Brand Name	Lantus™
Generic Name	Insulin glargine [rDNA origin] injection
Reviewer	Jaya bharathi Vaidyanathan, Ph.D.
Team Leader	Hae-Young Ahn, Ph.D.
OCPB Division	DPE-2
ORM division	Metabolic and Endocrine Drug Products
Sponsor	Aventis Pharmaceuticals
Submission Type; Code	Prior Approval Supplement; CMC
Formulation; Strength(s)	10 ml vials (1ml contains 21^{A}-Gly-30^{B}a-L-Arg-30^{B}b-L-Arg-human insulin equimolar to 100IU human insulin)
Indication	Type 1 and Type 2 diabetes mellitus

Table of Contents

I. Executive Summary

Lantus™ (Insulin glargine) is B31-B32-Di-Arg human insulin with further substitution of asparagine in position A21 by glycine. Lantus™ has been marketed in the USA since May 2001. It is approved for once-daily subcutaneous administration in the treatment of adult and pediatric patients with type 1 diabetes mellitus or adult patients with type 2 diabetes mellitus who require basal insulin for the control of hyperglycemia.

Aventis has submitted this prior approval supplement for Lantus™ (insulin glargine injection) which provides for a change in the composition of the approved insulin glargine injection 100 IU/ml presented in 10 ml vials. A stabilizing agent polysorbate 20 (20 ppm) has been added to the drug product formulation. The sponsor proposes to add Tween 20 in order to stabilize the preparation against aggregation and thus improve the in-use stability. The aggregations were observed in some of the current commercialized 10 ml vials.

A bioequivalence study was conducted between the current commercialized Lantus™ and Lantus™ formulated with Tween 20 in healthy male volunteers using the euglycemic clamp technique. Equivalence in pharmacodynamics was established between Lantus™ and Lantus™ with Tween 20. The proposed formulation had similar exposure as the currently marketed formulation. Although the C_{max} of the proposed formulation fell slightly below the commercial formulation, the product being basal insulin (long-acting), slight changes in C_{max} should not have a significant impact on the overall efficacy.

A Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation 2 (OCPB/DPE-2) has reviewed NDA 21-081 SCF-17 submitted on 15 November 2004, and finds it acceptable. Recommendation should be conveyed to the sponsor as appropriate.

B Phase IV Commitments

Not applicable.

C Summary of CPB Findings

Bioequivalence study

The bioavailability of Lantus™ with Tween 20 was compared to that of currently commercialized Lantus™ formulation using the euglycemic clamp technique. A replicate study design was used. The average bioequivalence was determined. The area under the

serum insulin glargine concentration time curve from 0-24 h as well as all fractional AUCs were equivalent for Lantus™ and Lantus™ with Tween 20. The 90% confidence intervals for ratios of point estimate for AUC were within 80-125%. However, the C_{max} fell slightly below on the lower side of the confidence interval, [77.77 -99.13%]. The sponsor removed certain data points because of inconsistency in the concentration time profiles and performed BE analysis. The results from this analysis indicated that the 90% confidence interval for ratios of point estimate for AUC and C_{max} were within 80-125%.

The pharmacodynamic parameters were also compared between the two formulations. The area under the glucose infusion rate (GIR)-time curve from 0-24 h as well all the fractional areas under the GIR-time curve were equivalent for Lantus™ and Lantus™ with Tween 20. The time to maximum glucose infusion rate (GIR_{max}) and time to GIR_{max} were also similar between the two formulations.

The proposed formulation had similar exposure and pharmacodynamics as the currently marketed formulation. Although the C_{max} fell slightly below the commercial formulation, the product being basal insulin (long-acting), slight changes in C_{max} should not have a significant impact on the overall efficacy.

II QBR

A General Attributes

What is the proposed formulation?

Insulin glargine (21^{A}-Gly-30^{B}a-L-Arg-30^{B}b-L-Arg-human insulin) is a peptide hormone produced by recombinant DNA techniques. It has a molecular weight of 6063 and an isoelectric point of 6.7 (native insulin's pI is 5.6). It is insoluble in water and organic solvents, but is soluble in acidic conditions. It is a clear solution in vial and precipitates at physiological pH (at injection site).

The proposed formulation is shown is Table 1. The only difference between the proposed formulation and the currently marketed product is the presence of polysorbate 20.

Table 1: Components and Composition of proposed formulation

COMPONENTS[a]	REFERENCE TO STANDARDS[b]
1. Insulin glargine [equimolar to IU (International Units) of insulin]	in-house
2. Metacresol [m-Cresol] [c]	USP
3. Polysorbate 20	Ph.Eur., NF
4. Zinc chloride [d]	Ph.Eur., USP
5. Glycerol (85 per cent)	Ph.Eur.
6. Sodium hydroxide [e]	Ph.Eur., NF
7. Hydrochloric acid, concentrated [Hydrochloric acid] [f]	Ph.Eur., NF
8. Water for injection	Ph.Eur., USP

b(4)

b(4)

What is the mechanism of action, therapeutic indication, proposed dosage and route of administration?

The primary mechanism of insulin glargine is regulation of glucose metabolism. It lowers blood glucose levels by stimulating peripheral glucose uptake.

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.

Lantus™ 100 units/ml is available in 10 ml vials and as 3 ml cartridge system, package of 5 (for use only in OptiClik, an insulin delivery device).

B General Clinical Pharmacology

What is known about the general pharmacology of Lantus™?

This is discussed in the review for original submission of NDA 21-081.

How does the pharmacodynamic properties of proposed formulation compare with currently marketed Lantus™ formulation?

During the 4 treatment periods, subjects were connected to a Biostator for measurement of blood glucose and adjustment of glucose infusion rate (GIR). Blood glucose levels were monitored for 90 minutes (baseline) before S.C. injection and for 30 h after dose. 20% glucose solution was infused to maintain the blood glucose level at 5% below the individual fasting blood glucose level (determined as mean of 3 fasting blood glucose values measured at 60, 30 and 5 min before study medication administration). Profiles of GIR were obtained.

The blood glucose concentrations were maintained with low variability over the entire clamp period. The mean fasting plasma glucose levels before the first and second Lantus™ treatment were 85 mg/dL (72-97 mg/dL) and 85 mg/dL (74-102 mg/dL) respectively. The mean fasting plasma glucose levels before the first and second Lantus™ with Tween 20 treatment were 85 mg/dL (75-93 mg/dL) and 83 mg/dL (67-98 mg/dL) respectively. The median blood glucose concentration time profile after each treatment is shown in figure 1.

Figure 1: Median blood glucose concentrations (mg/dl) N=24

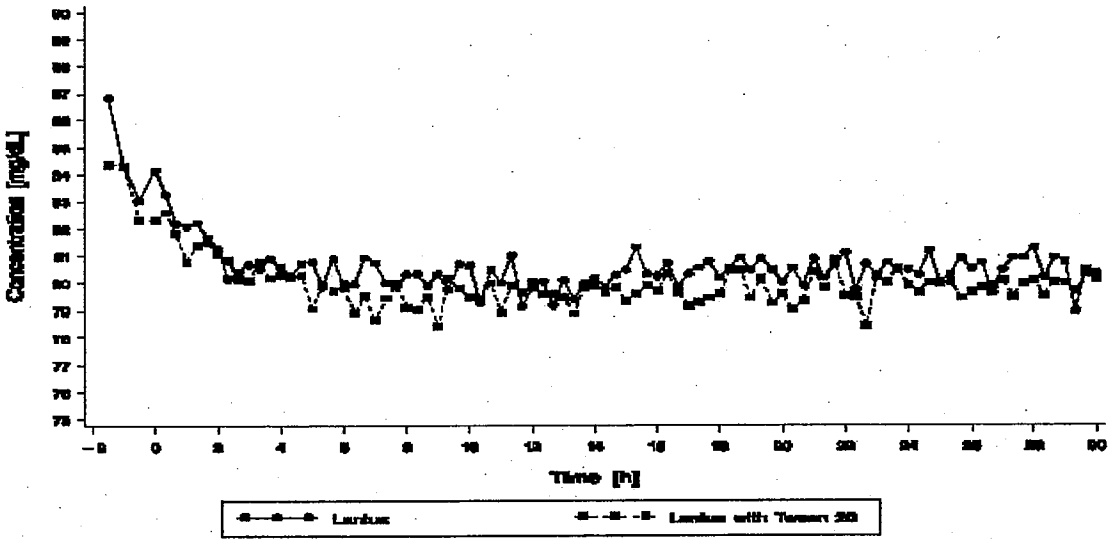

Table 2 shows the AUCs of glucose infusion rate (GIR) time curve for Lantus™ with Tween 20 and Lantus™ over the periods 0 to 30 h, 0-24 h (primary variable), 0-12 h, 12-24 h, and 4-20 h. The 90% confidence interval for the ratio of point estimates were within the acceptable range of 80-125%. Both formulations had same GIR_{max} and T_{max}.

Table 2: Pharmacodynamic results (GIR)

Variable	Sample mean (n = 24)		Estimated ratio (90% CI)#
	Lantus™ (Reference)	Lantus™ with Tween 20 (Test)	Test/ Reference
$AUC_{(0-24h)}$ [mg/kg]	2367	2373	100.1 (88.1; 113.8)
$AUC_{(4-20h)}$ [mg/kg]	1915	1890	98.6 (85.8; 113.3)
$AUC_{(0-12h)}$ [mg/kg]	1119	1105	98.8 (84.1; 116.0)
$AUC_{(12-24h)}$ [mg/kg]	1251	1270	101.3 (89.3; 114.9)
$AUC_{(0-end)}$ [mg/kg]	2743	2796	101.9 (90.6; 114.7)
GIR_{max}** [mg/min/kg]	3	3	95.6 (83.3; 109.7)
Time to GIR_{max} [h]	12.5*	12.8*	-0.2h (-2.5; 1.4h)$

Point estimates and 90% CIs for the ratio of treatment means, according to Fieller's Theorem, based on untransformed data
$ Point estimates and 90% CIs for the respective median differences, from non-parametric data analysis
* Median
** Maximum GIR and time to maximum GIR were determined from "smoothed" GIR profiles

Comments:

- Both the formulations were equivalent in terms of pharmacodynamics based on AUC of GIR indicating similar glucose disposal.
- The 90% confidence interval of the ratio of point estimates were within the goal post of 80-125%.

C Intrinsic Factors

What is known about Lantus™ pharmacokinetics in adult patients?

Please refer original submission review for NDA 21-081.

What is the influence of age, gender, body weight and race on PK in pediatric patients?

Please refer the original submission review for NDA 21-081.

D Extrinsic Factors

Not applicable.

E General Biopharmaceutics

Is the proposed formulation bioequivalent to the currently approved Lantus™ formulation?

In order to test bioequivalence between the Lantus™ commercial formulation and Lantus™ with Tween 20 using the euglycemic clamp technique, a two replicate single dose, double-blind four way-crossover study was conducted in healthy male volunteers (N=24; 22-48 yrs age). Subjects received two replicate single doses each of reference drug 0.4 IU/kg Lantus™ (R) and test product Lantus™ with Tween 20 (T) injected into the periumbelical area on 4 different days. There were 2 sequences. R-T-R-T or T-R-T-R. A washout period of 14-21 days separated the 4 treatments. Blood samples were taken at specified times during the euglycemic clamp period for determination of serum insulin glargine concentrations.

The sponsor performed a bioequivalence analysis based on pharmacokinetic parameters as well as based on pharmacodynamic parameters. The method used for pharmacokinetic analysis was baseline uncorrected. Figure 2 shows the median insulin plasma concentration time profiles for the two treatments and Table 3 shows the summary statistics of the pharmacokinetic parameters. As shown in the table the AUC_{0-24} and C_{max} for Lantus™ and Lantus™ with Tween 20 were bioequivalent indicating similar rate and extent of exposure. In addition the AUCs of Lantus™ with Tween 20 over the periods 0 to 30 h, 0-24 h, 0-12 h, 12-24 h, and 4-20 h were equivalent to those for Lantus™. The 90% confidence interval for the ratios of point estimates were within the 80-125% accepted range.

Figure 2 : Median serum insulin concentrations (µIU/ml)

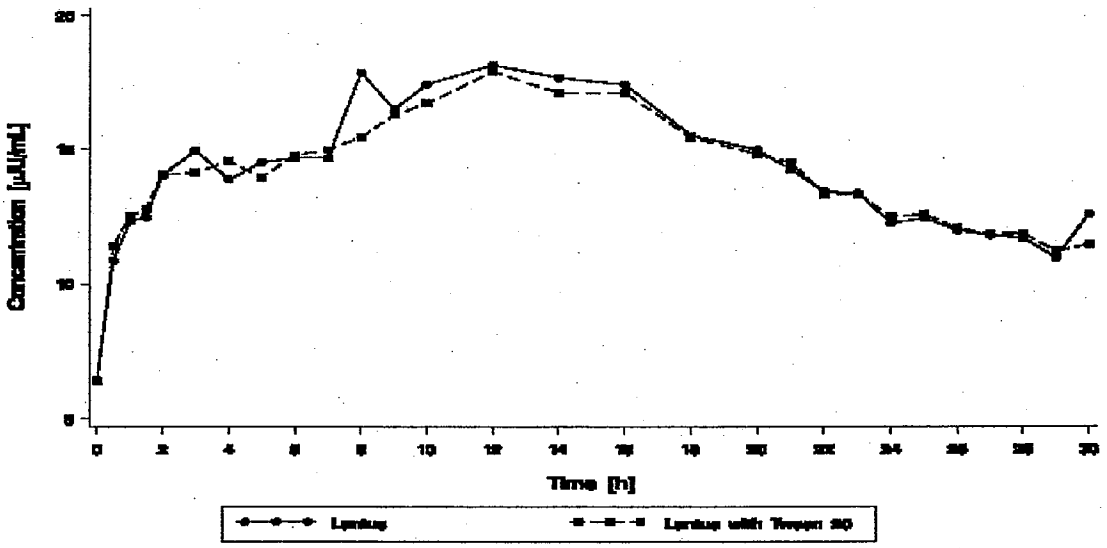

Table 3: Summary statistics of pharmacokinetic parameters: Average Bioequivalence (Sponsor's results)

Variable	Geometric mean (arithmetic mean) (n = 24)		Point estimate (90% CI)#
	Lantus™	Lantus™+Tween 20	Lantus™+Tween 20/ Lantus™
$AUC_{(0-24h)}$ [µIU.h/mL]	355 (367)	343 (359)	96.6 (91.0 ; 102.6)
$AUC_{(4-28h)}$ [µIU.h/mL]	251 (261)	242 (254)	96.3 (90.0 ; 102.9)
$AUC_{(0-12h)}$ [µIU.h/mL]	171 (178)	163 (174)	95.3 (88.6 ; 102.5)
$AUC_{(12-24h)}$ [µIU.h/mL]	182 (188)	179 (185)	97.9 (92.6 ; 103.6)
$AUC_{(0-end)}$ [µIU.h/mL]	425 (438)	414 (431)	97.3 (92.1 ; 102.9)
C_{max} [µIU/mL]	22 (23)	20 (21)	89.6 (83.5 ; 96.1)
T_{max} [h]	12.5**	14.4**	0.5 (-2.5 ; 3.5)##

Point estimates and 90% CIs for the ratio of treatment means, based on ln-transformed data.
Point estimates and 90% CIs for the difference "Lantus™+Tween 20 / Lantus™"(median), based on untransformed data
** Median

Reviewer's Reanalysis:

The reviewer reanalyzed the results using raw data submitted by the sponsor and obtained individual PK data using WinNonlin® and ANOVA using SAS® PROC MIXED procedure. Analysis revealed that sponsor had made certain changes in the dataset and certain values in both treatments were set to missing. The reason provided by the sponsor was due to inconsistent concentration time profiles due to haemolised samples. The results obtained without elimination of these values are provided in the Table 4. As shown the 90% confidence interval for the ratios of point estimates of $AUC_{(0-24)}$ the primary variable was within the 80-125% accepted range. However, the C_{max} fell slightly below on the lower side of the confidence interval, [77.77 -99.13%].

Table 4: Average bioequivalence summary (without exclusion of data points).

Variable	Geometric Mean (Arithmetic mean)		Point Estimate	90% CI
	Lantus (R)	Lantus with Tween 20 (T)		
$AUC_{(0-24)}$ [µIU*h/ml]	356.24 (369.48)	343.81 (364.35)	96.5	89.76-103.6
C_{max} [µIU/ml]	22.62 (24.36)	19.86 (21.58)	87.8	77.77-99.13

Comments

- The new Lantus™ formulation was pharmacodynamically equivalent to the currently marketed formulation.
- Addition of Tween 20 did not affect the exposure of Lantus™, however there was a slight decrease in C_{max} in the proposed formulation.
- Although the C_{max} fell slightly below that of the commercial formulation, the product being basal insulin (long-acting), slight changes in C_{max} should not have a significant impact on the overall efficacy since the two products have equivalent exposure and pharmacodynamics.
- The C-peptide from samples for serum insulin glargine concentration was not analyzed.
- The sponsor also evaluated individual and population bioequivalence. Population bioequivalence was established for all PK variables, and individual bioequivalence was established for all variables except $AUC_{0\text{-}24h}$, $AUC_{4\text{-}20h}$, and $AUC_{0\text{-}12h}$.

F Analytical

Was the analytical method used in this study validated?

Serum insulin glargine concentration

Serum insulin concentrations were determined using a radioimmunoassay for human insulin calibrated for insulin glargine. This assay is a competitive heterologous assay between insulin glargine and ^{125}I-insulin for a limited and constant quantity of guinea pig anti-insulin serum. The lower limit for quantification for this assay was 4.92 µl/IU/ml. The precision and accuracy were within limits.
Accuracy (% Difference) of QC samples -7.6 to 7%
Precision (CV) of QC samples 4.8 to 8.7%
% Difference of calibration standards -5.5 to 8.3%
Precision (CV) of calibration standards 2.9 to 11.1%

Blood glucose concentration

Online blood glucose determination was done by the Biostator with a glucose analyzer, which is based on an electrochemical measuring principle by a biosensor using the glucose oxidase method. The range was from 11-900 mg/dl, with a precision expressed as coefficient of variation of less than 1.5%.

Glucose infusion rate
The 20% glucose solution was infused by the Biostator using a high precision infusion pump. Flow accuracy was within ± 3% to ± 5%.

III Labeling Comments

Not applicable.

IV Appendix

A Proposed Labeling

Not applicable.

B Individual Study Synopsis

STUDY SYNOPSIS

HOE901/1022

Title
Bioequivalence (bioavailability and bioefficacy) of Lantus™ and Lantus™ with Tween 20 in healthy male volunteers receiving two replicate single subcutaneous doses of 0.4 IU/kg using the euglycemic clamp technique

Investigators, study site
Klaus Rave, MD, and Leszek Nosek, MD, PROFIL Institut für Stoffwechselforschung GmbH, 41460 Neuss, Germany

Safety and tolerance phase
I

Indication
Not applicable

Objectives
Primary Objective:

To assess average bioequivalence (ABE) in bioavailability and bioefficacy of Lantus™ (commercial formulation) and Lantus™ with Tween 20 using the euglycemic clamp technique

Secondary Objectives:

To assess individual (IBE) and population bioequivalence (PBE) in bioavailability and bioefficacy of Lantus™ and Lantus™ with Tween 20, and safety and tolerance of Lantus™ with Tween 20

Design
This study was designed as a single center, randomized, controlled, double-blind, four-way crossover trial in healthy male volunteers to test for bioequivalence in bioavailability and bioefficacy of Lantus™ with Tween 20 (test, T) and Lantus™ (reference, R) using the euglycemic clamp technique. Each subject was to receive two replicate single subcutaneous (s.c.) doses each of 0.4 IU/kg Lantus™ (R) and Lantus™ with Tween 20 (T), injected into the periumbilical area on four different days. Treatments were administered in the sequence R-T-R-T (reference-test-reference-test) or T-R-T-R. The study consisted of a screening visit (TP0), four treatment visits (TP1 – 4) separated by a washout period of 14 to 21 days between each trial period, and a follow-up visit (TP5). TP0 was to be performed within 3 to 21 days before TP1, and TP5 was to be performed 7 to 14 days after TP4.

Population
The study population was to comprise 24 healthy male subjects, non-smokers for at least 3 months and aged 18 to 50 years (inclusive), with Body Mass Indices (BMIs) of 18 to 27 kg/m² (inclusive), and metabolic parameters (oral glucose tolerance test) and laboratory values within

normal ranges, and normal or not clinically relevant findings in their medical/surgical history and physical examination, and without regular use of prescription drugs.

Treatments

Lantus™ (commercial formulation, Reference):

10 mL vials (100 IU/mL) solution

Dose: 0.4 IU/kg body weight; two replicate single doses injected s.c. in the periumbilical abdomen

Batch number: A159, batch size: [redacted] of total batch [redacted] vials (trial). [redacted] vials (total) b(4)

Lantus™ with Tween 20 (Test):

10 mL vials (100 IU/mL) solution

Dose: 0.4 IU/kg body weight; two replicate single doses injected s.c. in the periumbilical abdomen

Batch number: 1473, batch size: [redacted] % of total batch; [redacted] vials (trial) [redacted] vials (total) b(4)

The blinded labels contained information required about the insulin and handling, the trial period, randomization number and subject number.

Pharmacokinetic data

Primary variable:

- Area under the serum insulin glargine concentration time curve from 0 to 24 hours, [$AUC_{(0\text{-}24h)}$ (µIU.h/mL)]

Secondary variables:

- Fractional areas under the serum insulin glargine concentration time curve [$AUC_{(4\text{-}20h)}$, $AUC_{(0\text{-}12h)}$ and $AUC_{(12\text{-}24h)}$, as well as $AUC_{(0\text{-}end)}$ (µIU.h/mL)]
- Maximum serum insulin glargine concentration [C_{max} (µIU/mL)]
- Time to maximum concentration [T_{max} (h)]

Serum concentrations of insulin glargine were analyzed using a radioimmunoassay (RIA) kit [redacted] by the laboratory [redacted] b(4)
[redacted] with a lower limit of quantification (LLOQ) of 4.92 µIU/mL. b(4)

Pharmacodynamic data

Primary variable:

- Area under the glucose infusion rate (GIR)-time curve from 0 to 24 hours, [$AUC_{(0\text{-}24h)}$ (mg/kg)]

Secondary variables:

- Fractional areas under the GIR-time curve [$AUC_{(4\text{-}20h)}$, $AUC_{(0\text{-}12h)}$ and $AUC_{(12\text{-}24h)}$, as well as $AUC_{(0\text{-}end)}$ (mg/kg)]
- Maximum glucose infusion rate [GIR_{max} (mg/min/kg)]
- Time to GIR_{max} [t_{max} (h)]

Blood glucose concentration was determined on site with a Super GL glucose analyzer, using the glucose oxidase method b(4) with a measuring range of 11 to 900 mg/dL.

The 20% glucose solution was infused by the Biostator using a high precision infusion pump b(4) with a flow-rate accuracy within ± 3% to ± 5%.

Safety data
Hematology, clinical chemistry, urinalysis, urine test (drugs of abuse), vital signs, standard 12-lead ECG, physical examinations and adverse events (AEs) reported by the subject or noted by the investigator.

Study duration and dates
The duration of the study was 15 weeks. The study took place between August 30, 2002 (screening) and finished on December 13, 2002 (last follow-up).

Statistical procedures
Assessment of the primary objective ABE and the secondary objectives IBE and PBE in bioavailability and bioefficacy was based on AUCs following a standard two-sequence, four-period (i.e., R-T-R-T, T-R-T-R) crossover design. To assess ABE, natural log-transformed AUCs and C_{max} and ranked raw T_{max} of the two Lantus™ formulations were analyzed using a mixed effects model that included fixed effect terms for sequence, period and treatment (Lantus™ or Lantus™ with Tween 20) and random effects for subjects within sequences and replications. IBE and PBE analyses were computed using method of moments as described in current Food and Drug Administration (FDA) guidelines.

Interim analysis
No interim analysis was planned and performed for this study.

Results – Study subjects and conduct
A total of 30 healthy male subjects were screened, of whom 28 were randomized and 25 received at least one dose of study medication. Two screened subjects did not meet the inclusion criteria. Of the 28 randomized subjects, 3 subjects withdrew before receiving any study medication, and 1 subject withdrew from the study due to an AE occurring 6 days after the first dose of study medication. Twenty-four (24) subjects completed the study according to the protocol and were included in the pharmacodynamic (PD) and pharmacokinetic (PK) analyses. All but one Asian subject were White (Caucasian), aged between 22 and 48 years (inclusive), with BMI between 20 and 27 kg/m² (inclusive). All 25 treated subjects were included in the safety evaluation.
There were no major protocol deviations.

Results – Pharmacodynamics
The two treatment groups, Lantus™ and Lantus™ with Tween 20, were similar regarding the individuals' fasting baseline blood glucose concentrations, which served to define the individuals' glucose clamp level.

Primary objective:

ABE in bioefficacy for Lantus™ and Lantus™ with Tween 20 was established.

Primary variable:

The area under the GIR *versus* time curve from 0 to 24 hours ($AUC_{(0-24h)}$) was equivalent for Lantus™ and Lantus™ with Tween 20.

Secondary variables:

The area under the GIR *versus* time curve, from all fractional AUCs and GIR_{max}, was equivalent for Lantus™ and Lantus™ with Tween 20.

The following table summarizes the PD results:

	Arithmetic mean (n = 24)		ABE	IBE	PBE
Variable	Lantus™	Lantus™+Tween 20	Point estimate (90% CI)#	Upper CI#	Upper CI#
$AUC_{(0-24h)}$ [mg/kg]	2367	2373	100.1 (88.1; 113.8)	-0.2414	-0.2036
$AUC_{(4-30h)}$ [mg/kg]	1915	1890	98.6 (85.8; 113.3)	-0.2548	-0.2188
$AUC_{(0-12h)}$ [mg/kg]	1119	1105	98.8 (84.1; 116.0)	-0.0625	0.0053
$AUC_{(12-24h)}$ [mg/kg]	1251	1270	101.3 (89.3; 114.9)	-0.3272	-0.3291
$AUC_{(0-end)}$ [mg/kg]	2743	2796	101.9 (90.6; 114.7)	-0.2241	-0.1743
GIR_{max}** [mg/min/kg]	3	3	95.6 (83.3; 109.7)	-0.0749	-0.2124
Time to GIR_{max} [h]	12.5*	12.8*	-0.2h (-2.5; 1.4h)$		

\# Point estimates and 90% confidence intervals (CIs) for the ratio of treatment means, according to Fieller's Theorem, based on untransformed data

$ Point estimates and 90% CIs for the respective median differences, from non-parametric data analysis

* Median

** Maximum GIR and time to maximum GIR were determined from LOESS (locally weighted regression in smoothing scatterplots) "smoothed" GIR profiles

◆ Confidence interval reference-scaled criterion

Secondary objective:

IBE in bioefficacy was established for all PD variables, and PBE for all but one variable.

Results – Pharmacokinetics

Primary objective:

ABE in bioavailability for Lantus™ and Lantus™ with Tween 20 was established.

Primary variable:

The area under the serum insulin glargine concentration time curve from 0 to 24 hours ($AUC_{(0-24h)}$) was equivalent for Lantus™ and Lantus™ with Tween 20.

Secondary variables:

The area under the serum insulin glargine concentration time curve from all fractional AUCs and C_{max}, were equivalent for Lantus™ and Lantus™ with Tween 20.

The following table summarizes the PK results:

Variable	Geometric mean (arithmetic mean) (n = 24)		ABE	IBE	PBE
	Lantus™	Lantus™+Tween 20	Point estimate (90% CI)#	Upper CI*	Upper CI*
$AUC_{(0-336)}$ [µIU.h/mL]	355 (367)	343 (359)	96.6 (91.0 ; 102.6)	0.0021	-0.0276
$AUC_{(0-336)}$ [µIU.h/mL]	251 (261)	242 (254)	96.3 (90.0 ; 102.9)	0.0039	-0.0463
$AUC_{(0-336)}$ [µIU.h/mL]	171 (178)	163 (174)	95.3 (88.6 ; 102.5)	0.0170	-0.0151
$AUC_{(12-336)}$ [µIU.h/mL]	182 (188)	179 (185)	97.9 (92.6 ; 103.6)	-0.0214	-0.0608
$AUC_{(0-end)}$ [µIU.h/mL]	425 (438)	414 (431)	97.3 (92.1 ; 102.9)	-0.0032	-0.0304
C_{max} [µIU/mL]	22 (23)	20 (21)	89.6 (83.5 ; 96.1)	-0.0109	-0.0501
T_{max} [h]	12.5**	14.4**	0.5 (-2.5 ; 3.5)##		

\# Point estimates and 90% CIs for the ratio "Lantus™+Tween 20 / Lantus™"(means), based on ln-transformed data.
Point estimates and 90% CIs for the difference "Lantus™+Tween 20 / Lantus™"(median), based on untransformed data
** Median
* Confidence interval reference-scaled criterion

Secondary objective:

PBE in bioavailability was established for all PK variables, and IBE for all but three variables.

Results - Safety

No serious adverse events (AEs) were reported.

A total of 11 subjects reported 23 AEs, all of which were of mild intensity, and resolved without sequelae. The most frequently reported event was headache (13 episodes) followed by phlebitis (2), abdominal pain (1), diarrhea (1), dizziness (1), influenza (1), bradycardia (1), bronchitis (1), nausea (1), and back pain (1).

Sixteen (16) AEs reported by eight (32%) subjects during the treatment period were classified as treatment-emergent. Six of these events were reported by four (17%) subjects during treatment with Lantus™ and ten were reported by six (24%) subjects during treatment with Lantus™ with Tween 20.

Fourteen (14) of the 16 reported treatment-emergent adverse events (TEAEs) were judged by the investigator as related to the study medication (13 headaches and 1 nausea): eight events [1 nausea and 7 headaches] were reported by four (16%) subjects while receiving Lantus™ with Tween 20 and 6 headaches were reported by four (17%) subjects during treatment with Lantus™. The system organ class "Nervous system disorders" was the most affected, with headache being the most frequent event (13 episodes).

One subject (Subject 102) withdrew from the study due to AEs (pain of the abdomen, diarrhea and dizziness) occurring 6 days after receiving Lantus™ with Tween 20 (TP1). The events, judged by the investigator as mild in intensity and not related to the study medication, resolved without sequelae. These events were not assessed to be TEAEs.

No clinically relevant abnormalities or changes in parameters of hematology or clinical chemistry, in urinalysis, physical examination, vital signs, 12-lead electrocardiogram (ECG) or other parameters were observed.

No injection site reactions were reported.

In conclusion, both treatments were assessed to be safe and well tolerated.

Conclusions

Bioequivalence for both bioavailability and bioefficacy was established for Lantus™ and Lantus™ with Tween 20.

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/s/

Jayabharathi Vaidyanathan
3/4/05 11:36:44 AM
PHARMACOLOGIST

Hae-Young Ahn
3/8/05 04:38:07 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-081/S017

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Division of Metabolic and Endocrine Drug Products

REGULATORY PROJECT MANAGER REVIEW

Application Number: NDA 21-081/S-017

Name of Drug: Lantus (insulin glargine [rDNA origin] injection)

Applicant: Aventis

Material Reviewed:

1. Physician insert (submitted November 15, 2004)
2. Patient insert for 10 mL vial (submitted November 15, 2004)

Background and Summary:

Lantus was approved on April 20, 2000, 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.

Supplement 017 was submitted on November 15, 2004, and provides to add an additional stabilizing agent, 20 ppm of Polysorbate 20, to the drug product formulation to improve the occasional appearance of turbidity reported for the 10 mL vial presentation.

Since the appearance of turbidity only occurred with 10 mL vial presentation, and not 3 mL cartridge presentation, this formulation change is for 10 mL vial presentation only.

Review:

Physician Insert:

The proposed PI submitted on November 15, 2004 is compared to the last approved PI (under S-011, approved August 10, 2004) and found to be identical with an exception in the DESCRIPTION section.

1. DESCRIPTION:

   A description of inactive ingredients are separated for 10 mL vial presentation and 3 mL cartridge presentation since "20 mcg polysorbate 20" is add to a vial presentation only.

   This change is acceptable.

Patient insert for 10 mL vial presentation:

The proposed patient insert, submitted November 15, 2004, for 10 mL vial presentation is compared to the last approved PPI for vial under S-011 (approved August 10, 2004) and to be identical with the following exceptions:

"What is LANTUS?" section:

Polysorbate 20 is added as an inactive ingredient.

This addition is acceptable since the supplement provides for this addition.

Conclusions:

The proposed physician insert and patient insert for 10 mL vial presentation (submitted November 15, 2004) is acceptable.

Issue an approval letter.

CSO LABELING REVIEW

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/s/

Julie Rhee
3/16/05 03:56:55 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-081/S-017

PRIOR APPROVAL SUPPLEMENT

Aventis Pharmaceuticals Inc.
Attention: Craig Ostroff, Pharm.D.
Associate Director, Regulatory Liaison
P.O. Box 6890
200 Crossing Boulevard
Bridgewater, NJ 08807-0890

Dear Dr. Ostroff:

We have received your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Lantus (insulin glargine [rDNA origin] injection)
NDA Number:	21-081
Supplement number:	S-017
Date of supplement:	November 15, 2004
Date of receipt:	November 16, 2004

This supplemental application proposes the following change: To add an additional stabilizing agent, 20 ppm of Polysorbate 20, to the drug product formulation for the 10 mL vial presentation.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on January 15, 2005, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be March 16, 2005.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service/Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Document Room, 8B45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any question, call me at (301) 827-6424.

Sincerely,

{See appended electronic signature page}

Julie Rhee
Regulatory Project Manager
Division of Metabolic
and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Julie Rhee
11/26/04 11:08:47 AM