CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 21-081/S-024

Trade Name: LANTUS

Generic Name: Insulin glargine [rDNA origin]

Sponsor: Sanofi-aventis

Approval Date: 4/25/2007

Indications: 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.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-081/S-024

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-081/S-024

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-081/S-024

Sanofi-aventis U.S. Inc.
Attention: Michael Lutz, MSci, MBA, RAC
Regulatory Development
400 Crossing Boulevard
Bridgewater, NJ 08807-0890

Dear Mr. Lutz:

Please refer to your supplemental new drug application dated April 21, 2006, received April 24, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lantus (insulin glargine [rDNA origin]) Injection, 100 U/mL.

We acknowledge receipt of your submissions dated October 24 and December 14, 2006, and March 14, 2007.

Your submission of October 24, 2006, constituted a complete response to our August 24, 2006, action letter.

This supplemental new drug application provides for the addition of the Lantus SoloStar disposable insulin injection device.

We have completed our review of this application, as amended. 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 submitted March 14, 2007, text for the Lantus SoloStar patient package insert (ppisolo) submitted March 14, 2007, text for the Lantus SoloStar Instruction Leaflet (il) submitted March 14, 2007, and the Lantus SoloStar immediate container label submitted March 14, 2007) and the submitted Lantus SoloStar carton label submitted March 14, 2007, and the submitted labeling for the cartridge patient package insert (ppic) submitted March 14, 2007, and the vial patient package insert (ppiv) submitted April 21, 2006.

Please submit an electronic version of the FPL as soon as it is available but no more than 30 days after it is printed. For administrative purposes, designate this submission "**FPL for approved supplement NDA 21-081/S-024**." Approval of this submission by FDA is not required before the labeling is used.

Upon verification, the content of labeling in structured product labeling (SPL) format for the package insert submitted March 14, 2007, will be transmitted to the National Library of Medicine for public dissemination.

We also refer to your April 10, 2007, agreement to implement the following changes to the Lantus SoloStar container and carton labels at the time of the next printing - in approximately 60 days.

- Delete the proposed "Initial Use Date" feature on the Lantus SoloStar pen (container) label.

- Display all the text on the primary display panel of the Lantus SoloStar carton in upper and lower case lettering. The labels submitted March 14, 2007, use all capital letters for the statements: "SOLUTION FOR INJECTION IN A DISPOSABLE INSULIN DELIVERY DEVICE" and "USE ONLY IF SOLUTION IS CLEAR AND COLORLESS WITH NO PARTICLES VISIBLE." Display these statements in upper and lower case lettering.

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 insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

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
Food and Drug Administration
5515 Security Lane
HFD-001, Suite 5100
Rockville, MD 20852

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 Enid Galliers, Chief, Project Management Staff, at 301-796-1211.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products (DMEP)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures:

(1) Package Insert
(2) Patient Package Insert – Lantus SoloStar
(3) Instruction Leaflet (IL) – Lantus SoloStar
(4) Container Label – Lantus SoloStar Injection Device

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/s/

Mary Parks

4/25/2007 09:33:59 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-081/S-024

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-081/S-024
NDA 21-629/S-008

sanofi-aventis U.S. LLC
Attention: Michael Lutz
US Regulatory Development
200 Crossing Boulevard, PO Box 6890
Bridgewater, ND 08807-0890

Dear Mr. Lutz:

Please refer to your supplemental new drug applications dated April 21, 2006, received April 24, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for

NDA 21-018/S-024 Lantus (insulin glargine [rDNA origin]) Injection
NDA 21-629/S-008 Apidra (insulin glulisine [rDNA origin]) Injection.

These supplemental new drug applications provide for the addition of disposable injector pens, Lantus SoloStar and Apidra SoloStar.

We completed our review of these applications, and they are approvable. Before the applications may be approved, however, you must address the following deficiencies:

CHEMISTRY, MANUFACTURING, AND CONTROLS

1. For each 3 mL drug product cartridge (NDA 21-018 and NDA 21-629) in the SoloStar device, submit six months of long term stability data. (b) (4)

DEVICE ISSUES

2. Please describe the method by which the SoloStar indicates that the injection has been completed.
3. You have indicated that the dialing mechanism allows dosage in 1 insulin unit increments and provides a maximum of 80 insulin units in one dosing. Describe how the design limits dosing to 80 units. Also describe the testing that has been conducted on the dose setting mechanism. Specifically, has testing been performed to assess functionality if the user rapidly turns the dial or if the user turns the dial clockwise past 80 units and then attempts to turn the dial counterclockwise?
4. Describe the method and mechanism for ensuring that the last dose delivered from the insulin cartridge satisfies requirements for dose accuracy.

5. Indicate whether the device has a safety mechanism to prevent accidental firing.
6. Identify the pen injector needles that are compatible with the SoloStar in your Instructions for Use.
7. You state that the dose is delivered by pressing the injection button until it is in its original end position. Clarify the meaning of this statement.
8. There is no indication in the submission that user testing has been performed for this device. The number of steps involved in performing a successful injection with this device could lead to user errors and potential life threatening situations. You should perform a risk analysis to identify the device use tasks that could lead to patient safety issues and then conduct user testing to identify and test mitigation measures that adequately reduce the risk of patient injury. Potential problems such as overdosing, underdosing, or misdosing can result from a variety of user-related tasks such as improper use of the dialing mechanism, failure to properly attach the needle, etc. User testing should be performed to determine and mitigate all potential use-related issues. Without results from usability testing leading to mitigation of hazards and changes in system requirements, it is not possible to determine whether the future marketed device will be safe and effective. Provide a test plan and test results for usability testing for the new device. We recommend that you consult the following guidance documents for information about acceptable usability testing:
   - Do It By Design - An Introduction to Human Factors in Medical Devices http://www.fda.gov/cdrh/humfac/doitpdf.pdf
   - Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management http://www.fda.gov/cdrh/humfac/1497.pdf

LABELING

9. In addition, you must submit draft labeling revised as follows:

   A. PEN LABEL

   a. [redacted] (b) (4)

   b. Both Lantus SoloStar and Apidra SoloStar use a "candy stripe" design on their labels and labeling. This similarity in graphic design is a safety concern as post-marketing reports have stated that errors have arisen due to the similar packaging of Lantus and Apidra. Therefore, we recommend that the graphic design between Lantus SoloStar and Apidra SoloStar can be differentiated from one another.

   c. [redacted] (b) (4)

B. CARTON LABELING

a. Both Lantus SoloStar and Apidra SoloStar use a "candy stripe" design on their labels and labeling. This similarity in graphic design is a safety concern as post-marketing reports have stated that errors have arisen due to the similar packaging of Lantus and Apidra. Therefore, we recommend that the graphic design between Lantus SoloStar and Apidra SoloStar can be differentiated from one another.

b. (b) (4)

C. PEN DEVICE

a. The Lantus SoloStar device has a purple injection button whereas the Apidra SoloStar device has a "dark blue" injection button. However, in observation of the devices you provided to us, these colors are not easily distinguishable and we suggest that you consider using colors that are more stark in contrast.

b. From the post-marketing error reports received, it is clear that the labels and labeling as well as any packaging (i.e., pen color) must be differentiated clearly. Although you utilized two different colors (grey and blue-grey) to differentiate Lantus SoloStar and Apidra SoloStar, we believe that those colors are still similar in nature. Thus, we recommend using more contrasting colors.

We will provide complete comments on labeling when the deficiencies listed above have been addressed.

If additional information relating to the safety or effectiveness of these drugs becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the applications under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

These products may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if they are marketed with these changes before approval of these supplemental applications.

If you have any questions, call Enid Galliers, Supervisory Project Manager, at (301) 796-1211.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Mary Parks

8/24/2006 09:39:59 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-081/S-024

LABELING

Rev. March 2007 **Rx Only**

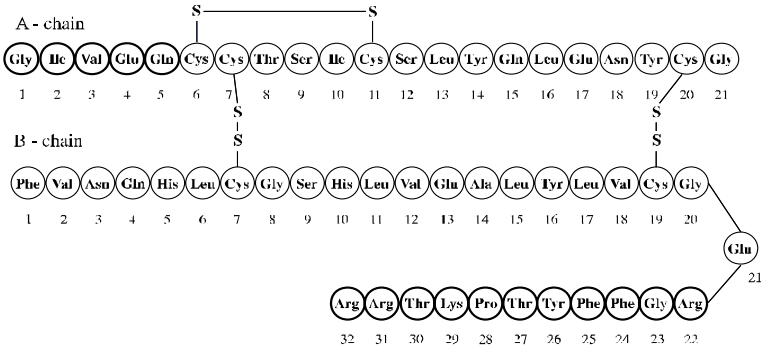
LANTUS®

(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,

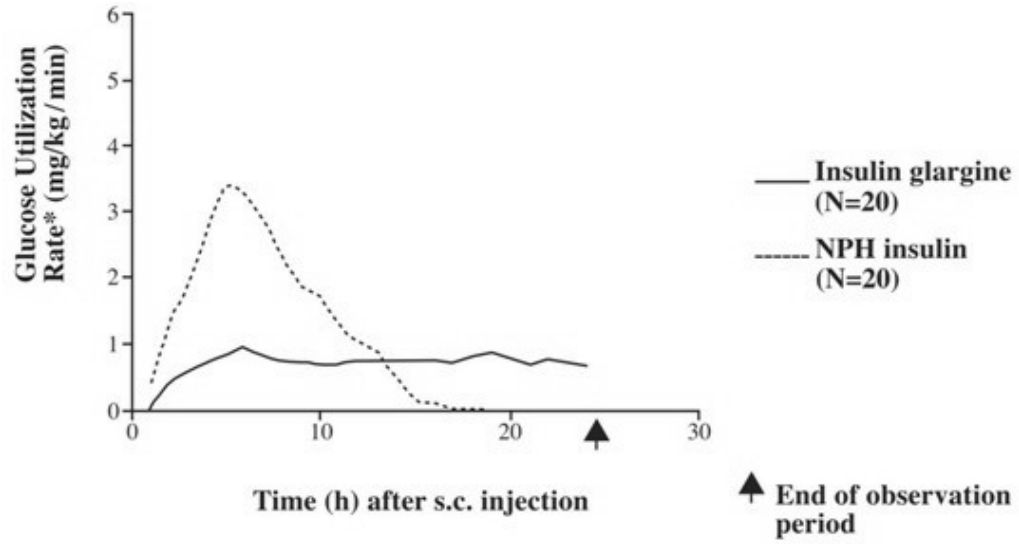
especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin inhibits lipolysis in the adipocyte, inhibits proteolysis, and enhances protein synthesis.

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), protease inhibitors and atypical antipsychotic medications (e.g. olanzapine and clozapine).

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/SoloStar: If OptiClik®, the Insulin Delivery Device used with the LANTUS cartridge system, or SoloStar, disposable insulin device, malfunctions, LANTUS may be drawn from the cartridge system or from SoloStar 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)
3 mL SoloStar® disposable insulin device, package of 5 (NDC 0088-2220-60)

Needles are not included in the packs.

BD Ultra-Fine™ needles‡ to be used in conjunction with SoloStar and OptiClik are sold separately and are manufactured by BD.

Storage:

Unopened Vial/Cartridge system/SoloStar® disposable insulin device:
Unopened LANTUS vials, cartridge systems and SoloStar® 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:
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).
Open (In-Use) Cartridge system:
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.
Open (In-Use) SoloStar® disposable insulin device:

The opened (in-use) SoloStar® 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) SoloStar® kept at room temperature must be discarded after 28 days.

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)
3 mL SoloStar® disposable insulin device	Until expiration date	28 days	28 days Room temperature only (Do not refrigerate)

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sanofi-aventis U.S. LLC
Bridgewater, NJ 08807

Country of Origin: Germany

www.lantus.com

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Patient Information

LANTUS® SOLOSTAR® 3 mL disposable insulin delivery device (300 units per device)
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 glucose.

- LANTUS is a clear, colorless, sterile solution for injection under the skin (subcutaneously).

- The active ingredient in LANTUS is insulin glargine. The concentration of insulin glargine is 100 units per milliliter (mL), or U-100. LANTUS also contains zinc, metacresol, glycerol, and water for injection as inactive ingredients. Hydrochloric acid and/or sodium hydroxide may be added to adjust the pH.

- You need a prescription to get LANTUS. Always be sure you receive the right insulin from the pharmacy.

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.
  - **are taking any other medicines including** prescription and non-prescription medicines, vitamins and herbal supplements.

How should I use LANTUS?

See the "**Instructions for SoloStar® Use" 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.

- **NEEDLES AND SOLOSTAR® MUST NOT BE SHARED.**

- Disposable needles should be used only once. Used 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 SoloStar® Use

It is important to read, understand, and follow the step-by-step instructions in the "SoloStar® Instruction Leaflet" before using SoloStar® disposable insulin Pen. Failure to follow the instructions may result in getting too much or too little insulin. If you have lost your leaflet or have a question, go to www.lantus.com or call 1-800-633-1610.

The following general notes should be taken into consideration before injecting Lantus:
- Always wash your hands before handling the SoloStar® disposable insulin Pen.
- Always attach a new needle before use. BD Ultra-Fine™ needles† are compatible with SoloStar. These are sold separately and are manufactured by BD.
- Always perform the safety test before use.
- Check the insulin solution in the pen to make sure it is clear, colorless, and free of particles. If it is not, throw it away.
- Do NOT mix or dilute LANTUS with any other insulin or solution. LANTUS will not work if it is mixed or diluted and you may lose blood sugar control, which could be serious.
- Decide on an injection area - either upper arm, thigh, or abdomen. Do not use the same injection site as your last injection.
- After injecting LANTUS, leave the needle in the skin for an additional 10 seconds. Then pull the needle straight out. Gently press on the spot where you injected yourself for a few seconds. **Do not rub the area.**
- Do not drop the SoloStar® disposable insulin Pen.

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

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 and pharmacists 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. It 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 SoloStar®:**
  Store new unopened SoloStar® disposable insulin pen 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 disposable insulin pen has been frozen or overheated, throw it away.
- **Open (In-Use) SoloStar®**:
  Once SoloStar® is opened (in-use), SoloStar® 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) SoloStar® kept at room temperature must be discarded after 28 days.

These storage conditions are summarized in the following table:

	Not in-use (unopened) **Refrigerated**	**Not in-use (unopened)** **Room Temperature**	**In-use (opened)** **Room Temperature (Do not refrigerate)**
3 mL SoloStar® disposable insulin device	Until expiration date	28 days	28 days

- Do not use SoloStar® with 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 healthcare provider 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. March 2007

sanofi-aventis U.S. LLC
Bridgewater, NJ 08807

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Lantus® and SoloStar® are a registered trademark of sanofi-aventis U.S. LLC
† The brands listed are the trademarks of their respective owners and are not trademarks of sanofi-aventis U.S. LLC

LANTUS® SOLOSTAR®

(insulin glargine [rDNA origin] injection)

Instruction Leaflet

Your healthcare professional has decided that SoloStar® is right for you. Talk with your healthcare professional about proper injection technique before using SoloStar®.

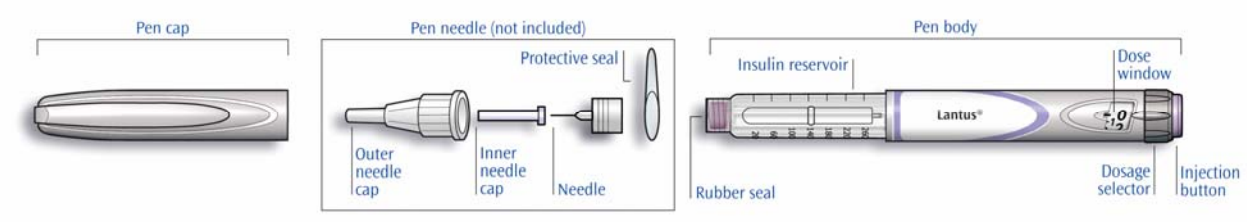
Read these instructions carefully before using your SoloStar®. If you are not able to follow all the instructions completely on your own, use SoloStar® only if you have help from a person who is able to follow the instructions.

Follow these instructions completely each time you use SoloStar® to ensure that you get an accurate dose. If you do not follow these instructions you may get too much or too little insulin, which may affect your blood glucose.

SoloStar® is a disposable pen for the injection of insulin. Each SoloStar® contains in total 300 units of insulin. You can set doses from 1 to 80 units in steps of 1 unit.

Keep this leaflet for future reference.

If you have any questions about Solostar® or about diabetes, ask your healthcare professional, go to www.lantus.com or call sanofi aventis at 1-800-633-1610.



Important information for use of SoloStar®:

- Always attach a new needle before each use.
  BD Ultra-Fine needles are compatible with SoloStar® . These are sold separately and are manufactured by BD. Contact your healthcare professional for further information.
- Always perform the safety test before each injection.
- This pen is only for your use. Do not share it with anyone else.
- If your injection is given by another person, special caution must be taken by this person to avoid accidental needle injury and transmission of infection.
- Never use SoloStar® if it is damaged or if you are not sure that it is working properly.
- Always have a spare SoloStar® in case your SoloStar® is lost or damaged.

Storage Instructions

Please check the leaflet for the insulin for complete instructions on how to store SoloStar®.

If your SoloStar® is in cool storage, take it out 1 to 2 hours before you inject to allow it to warm up. Cold insulin is more painful to inject.

Keep SoloStar® out of the reach and sight of children.

Keep your SoloStar® in cool storage (36°F - 46°F [2°C – 8°C]) until first use. Do not allow it to freeze. Do not put it next to the freezer compartment of your refrigerator, or next to a freezer pack.

Once you take your SoloStar® out of cool storage, for use or as a spare, you can use it for up to 28 days. During this time it can be safely kept at room temperature up to 86°F (30°C). Do not use it after this time. SoloStar® in use must not be stored in a refrigerator.

Do not use SoloStar® after the expiration date printed on the label of the pen or on the carton.

Protect SoloStar® from light.

Discard your used SoloStar® as required by your local authorities.

Maintenance

Protect your SoloStar® from dust and dirt.

You can clean the outside of your SoloStar® by wiping it with a damp cloth.

Do not soak, wash or lubricate the pen as this may damage it.

Your SoloStar® is designed to work accurately and safely. It should be handled with care. Avoid situations where SoloStar® might be damaged. If you are concerned that your SoloStar® may be damaged, use a new one.

Step 1. Check the insulin

A. Check the label on your SoloStar® to make sure you have the correct insulin.. The Lantus® SoloStar® is grey with a purple injection button.

B. Take off the pen cap.

C. Check the appearance of your insulin. Lantus® is a clear insulin. Do not use this SoloStar® if the insulin is cloudy, colored or has particles.

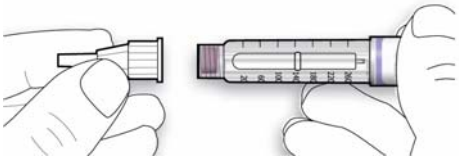
Step 2. Attach the needle

Always use a new sterile needle for each injection. This helps prevent contamination, and potential needle blocks.

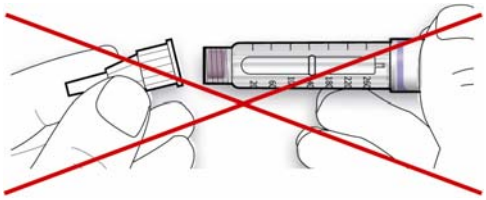
A. Wipe the Rubber Seal with alcohol.

B. Remove the protective seal from a new needle.

C. Line up the needle with the pen, and keep it straight as you attach it (screw or push on, depending on the needle type).



- If the needle is not kept straight while you attach it, it can damage the rubber seal and cause leakage, or break the needle.



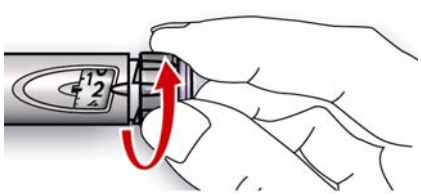
Step 3. Perform a Safety test

<u>Always</u> perform the safety test before each injection.

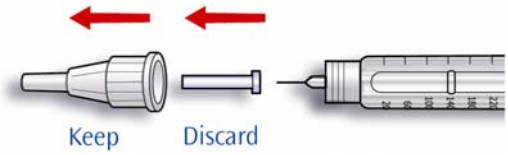
Performing the safety test ensures that you get an accurate dose by:

- ensuring that pen and needle work properly
- removing air bubbles

A. Select a dose of 2 units by turning the dosage selector.



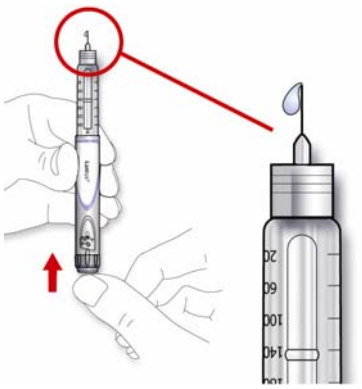
B. Take off the outer needle cap and keep it to remove the used needle after injection. Take off the inner needle cap and discard it.



C. Hold the pen with the needle pointing upwards.

D. Tap the insulin reservoir so that any air bubbles rise up towards the needle.

E. Press the injection button all the way in. Check if insulin comes out of the needle tip.



You may have to perform the safety test several times before insulin is seen.

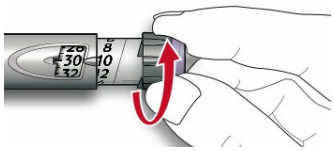
- If no insulin comes out, check for air bubbles and repeat the safety test two more times to remove them.
- If still no insulin comes out, the needle may be blocked. Change the needle and try again.
- If no insulin comes out after changing the needle, your SoloStar® may be damaged. Do not use this SoloStar®.

Step 4. Select the dose

You can set the dose in steps of 1 unit, from a minimum of 1 unit to a maximum of 80 units. If you need a dose greater than 80 units, you should give it as two or more injections.

A. Check that the dose window shows “0” following the safety test.

B. Select your required dose (in the example below, the selected dose is 30 units). If you turn past your dose, you can turn back down.



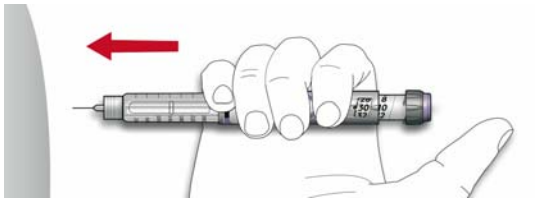
- Do not push the injection button while turning, as insulin will come out.

- You cannot turn the dosage selector past the number of units left in the pen. Do not force the dosage selector to turn. In this case, either you can inject what is remaining in the pen and complete your dose with a new SoloStar® or use a new SoloStar® for your full dose.

Step 5. Inject the dose

A. Use the injection method as instructed by your healthcare professional.

B. Insert the needle into the skin.



C. Deliver the dose by pressing the injection button in all the way. The number in the dose window will return to "0" as you inject.

D. Keep the injection button pressed all the way in.
Slowly count to 10 before you withdraw the needle from the skin. This ensures that the full dose will be delivered.

Step 6. Remove and discard the needle

Always remove the needle after each injection and store SoloStar without a needle attached. This helps prevent:

- Contamination and/or infection
- Entry of air into the insulin reservoir and leakage of insulin, which can cause inaccurate dosing.

A. Put the outer needle cap back on the needle, and use it to unscrew the needle from the pen. To reduce the risk of accidental needle injury, never replace the inner needle cap.

- If your injection is given by another person, special caution must be taken by this person when removing and disposing the needle. Follow recommended safety measures for removal and disposal of needles (e.g. a one handed capping technique) in order to reduce the risk of accidental needle injury and transmission of infectious diseases.

B. Dispose of the needle safely. Used needles 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.
If you are giving an injection to a third person, you should remove the needle in an approved manner to avoid needle-stick injuries.

C. Always put the pen cap back on the pen, then store the pen until your next injection.

sanofi-aventis U.S. LLC
Bridgewater, NJ 08807

Country of Origin: Germany

Date of revision:
March 2007

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Lot

Exp

NDC 0088-2220-60

Lantus® SoloStar®

insulin glargine (rDNA origin) injection

100 units/mL (U-100) **Rx ONLY**

Initial Use Date: _____

Do Not Mix with Other Insulins
For subcutaneous injection Only
Use within 28 days after opening
3 mL Prefilled Pen
sanofi-aventis U.S. LLC Origin Germany 50082820

sanofi aventis

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-081/S-024

CHEMISTRY REVIEW(S)

NDA 21-081, SCP-024

DIVISION OF POST-MARKETING
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-081 **DATE REVIEWED: 2/7/07**

REVIEW #: 2 **REVIEWER:** Donald N. Klein, Ph.D.

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
PA (EDR)	4/21/06	4/24/06	8/15/06
Consult to CDRH	5/15/06	5/15/06	*n/a*
CDRH Review	7/10/06	8/15/06 (DFS)	*n/a*
CMC Review	8/17/06	8/17/06	*n/a*
AE Letter	**8/24/06**	**8/24/06**	*n/a*
Telecon	9/12/06	*n/a*	*n/a*
(AZ) Response	**10/24/06**	**10/25/06**	10/25/06
Consult to DMETS, OSE	11/15/06	11/15/06	*n/a*
Consult to CDRH	11/15/06	11/15/06	*n/a*
CMC Information Request via e-mail	12/4/06	12/4/06	*n/a*
(BC) Amendment	12/14/06	12/15/06	12/15/06

NAME & ADDRESS OF APPLICANT:

Sanofi-Aventis U.S. LLC
300 Somerset Corporate Boulevard
Bridgewater, NJ 08807

DRUG PRODUCT NAME:

Proprietary: Lantus®
Established USAN (1999): insulin glargine [rDNA origin].
Code: HOE901 and HOE 71GT.

INDICATION: Pediatric and adult patients with Type 1 diabetes mellitus; Adult patients with Type 2 diabetes mellitus who require basal (long-acting) insulin for the control of hyperglycemia.

DOSAGE FORM: Injection.

STRENGTHS: 100 IU/mL in 3 mL cartridges and 10 mL vials.

ROUTE OF ADMINISTRATION: Subcutaneous.

Rx/OTC: *Rx*

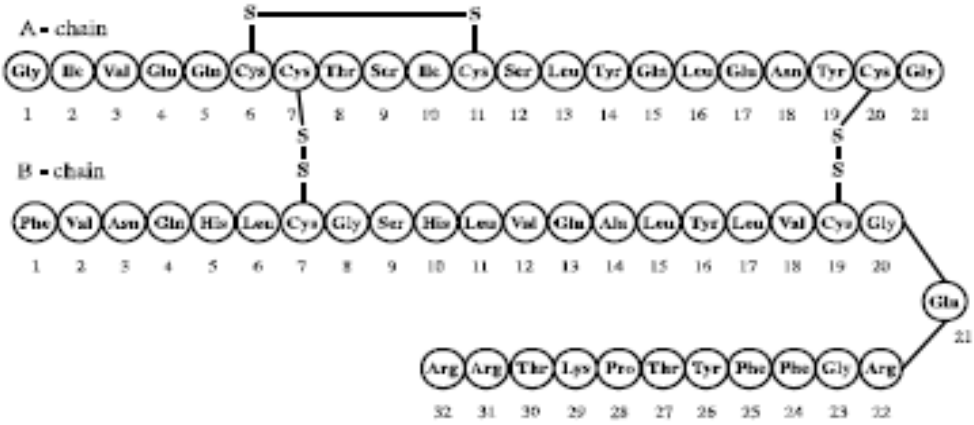
SPECIAL PRODUCTS: __ Yes xx No

SUPPORTING DOCUMENTS: N21-081, S-011 (OptiClik® reusable insulin pen delivery device) was approved on 8/10/04.

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, and MOLECULAR WEIGHT:

(1) Insulin (human), 21^{A}-glycine-30^{B}a-L-arginine-30^{B}b-L-arginine-;
(2) 21^{A}-Glycine-30^{B}a-L-arginine-30^{B}b-L-arginine insulin (human).

Molecular formula: $C_{267}H_{404}N_{72}O_{78}S_6$.
MW: 6062.89 daltons.



SUPPLEMENT PROVIDES FOR: New insulin pen delivery device SoloStar®.

CONSULT: CDRH *(review # 2 is pending).*

CONCLUSION: Recommend Approval from the CMC standpoint.

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/s/

Donald Klein
2/14/2007 10:34:20 AM
CHEMIST
The applicant submitted the stability data as requested and discussed (Telecon).
Submitting to DFS as requested on 2/13/07

Eric Duffy
2/15/2007 08:59:18 AM
CHEMIST

NDA 21-629, SCP-008
NDA 21-081, SCP-024

DIVISION OF POST-MARKETING
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-629 **DATE REVIEWED: 8/16/2006**
NDA #: 21-081

REVIEW #: 1 **REVIEWER:** Donald N. Klein, Ph.D.

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
N21-081 PA (EDR)	4/21/06	4/24/06	8/15/06
N21-620 PA (EDR)	4/21/06	4/24/06	8/15/06
Consult to CDRH	5/15/06	5/15/06	*n/a*
CDRH review	7/10/06	8/15/06 (DFS)	*n/a*

NAME & ADDRESS OF APPLICANT:

Sanofi-Aventis U.S. LLC
300 Somerset Corporate Blvd.
Bridgewater, NJ 08807

DRUG PRODUCT NAME:

N21-629 Proprietary: Apidra®
Nonproprietary (USAN)(2003): Insulin glulisine.
CAS: 207748-29-6.
Code: HMR 1964.

N21-081 Proprietary: Lantus®
Nonproprietary (USAN)(1999): Insulin glargine.
CAS: 160337-95-1.
Code: HOE 901 and HOE 71GT.

INDICATION: **N21-629:** For the treatment of adults with diabetes mellitus for the control of hyperglycemia.

N21-081: For the treatment of adults 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 hypergylycemia.

DOSAGE FORM: N21-629 and N21-081: Injectable.

STRENGTHS: N21-629 and N21-081: 100 IU/mL in 3 mL cartridges (OptiClik® Pen) and 10 mL vials.

ROUTE OF ADMINISTRATION: N21-629 and N21-081: Injection.

Rx/OTC: *Rx.*

SPECIAL PRODUCTS: __Yes **xx** No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, and MOLECULAR WEIGHT:

N21-629: (1) Insulin (human), 3^{B}-L-lysine,29^{B}-L-glutamic acid-;
(2) [3^{B}-L-Lysine,29^{B}-L-glutamic acid]insulin (human).

$C_{258}H_{384}N_{64}O_{78}S_6$.

MW: 5822.58 daltons.

N21-081: (1) Insulin (human), 21^{A}-glycine-30^{B}a-L-arginine-30^{B}b-L-arginine-;
(2) 21^{A}-Glycine-30^{B}a-L-arginine-30^{B}b-L-arginine insulin (human).

$C_{267}H_{404}N_{72}O_{78}S_6$.

MW: 6062.89 daltons.

SUPPLEMENT PROVIDES FOR: New insulin pen delivery device SoloStar®.

SUPPORTING DOCUMENTS: N21-081, S-011 (OptiClik® reusable insulin pen delivery device) was approved on 8/10/04; N21-629, S-002 (OptiClik® reusable insulin pen delivery device) was approved on 12/20/05.

CONSULT: CDRH (submitted 5/15/06; completed 7/10/06; in DFS on 8/15/06).

CONCLUSIONS: From the CMC standpoint approvable is recommended.

(b) (4)

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/s/

Donald Klein
8/16/2006 06:05:31 PM
CHEMIST

These PAs were assigned to me yesterday.

Jim Vidra
8/17/2006 08:35:42 AM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-081/S-024

OTHER REVIEW(S)

Division of Metabolism and Endocrinology Products

REGULATORY PROJECT MANAGER REVIEW

Application Number: NDA 21-081/S-024

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

Applicant: sanofi-aventis LLC

Material Reviewed:

Submission Date: March 14 2007 (official submission)
Receipt Date: March 15, 2007 (official submission)

Background and Summary

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.

It is available in 10 mL vials and 3 mL cartridges for use with the OptiClik injection device.

Lantus (insulin glargine) NDA 21-081 - Labeling piece	Appl. No.	AP date	Comments
Package Insert	S-017	3.15.2005	2 drug interactions were submitted to S-018 as CBE w/o FPL and were AE'd 9.16.2005
PPI vial (ppi-v) – 10 mL vials	S-017	3.15.2005	
10 mL vial - Carton	S-017	3.15.2007	
10 mL vial - Container	N-000		27-JUL-2000 FA was AR 18-JAN-2005
PPI cartridge (ppi-c) – 3 mL cart.	S-011	8.10.2004	
OptiClik IL (instrux for use)	S-014	2.11.2005	
OptiClik pen – carton	S-011	8.10.2004	
OptiClik pen - container	S-011	8.10.2004	
3 mL cartridge – carton	S-011	8.10.2004	
3 mL cartridge - container	S-011	8.10.2004	

This supplement proposes to add a new disposable insulin injector pen, Lantus SoloStar, with a new PPI (ppi-solo); IL-SoloStar; SoloStar pen label; SoloStar carton label; and revised PI.

Review of Package Insert

The March 14, 2007, submission (S-024) of the package insert was compared to the PI approved March 15, 2005, (S-017) and the following changes were noted.

The new revision date is "March 2007" and "OptiClik™" was replaced with "OptiClik®" throughout.

PRECAUTIONS, *Drug interactions* - To the third paragraph the following underlined information (that was previously submitted as a CBE but without final printed labeling in S-018 and received an approvable action on September 16, 2005) was added to the end of the last sentence.

> 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), protease inhibitors and atypical antipsychotic medications (e.g (b) (4) and clozapine).

DOSAGE AND ADMINISTRATION, *Preparation and Handling* – inserts appropriate references to SoloStar, which are underlined below.

> Cartridge system/SoloStar: If OptiClik®, the Insulin Delivery Device used with the LANTUS cartridge system, or SoloStar, disposable insulin device, malfunctions, LANTUS may be drawn from the cartridge system or from SoloStar into a U-100 syringe and injected.

The ™ symbol that followed OptiClik has been replaced with a ® symbol.

HOW SUPPLIED adds the following:

> 3 mL SoloStar® disposable insulin device, package of 5 (NDC 0088-2220-60)
>
> Needles are not included in the packs.
>
> BD Ultra-Fine™ needles‡ to be used in conjunction with SoloStar and OptiClik are sold separately and are manufactured by BD.

The **Storage** subsection adds information for SoloStar and separates Open (In-Use) storage for the Cartridge system from the Open (In-Use) information for the Vial as shown below:

> Unopened Vial/Cartridge system/SoloStar® disposable insulin device:

Unopened LANTUS vials, cartridge systems and SoloStar® 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:

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).

Open (In-Use) Cartridge system:

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.

Open (In-Use) SoloStar® disposable insulin device:

The opened (in-use) SoloStar® 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) SoloStar® kept at room temperature must be discarded after 28 days.

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

The last row in the following table has been added.

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)
3 mL SoloStar® disposable insulin device	Until expiration date	28 days	28 days Room temperature only (Do not refrigerate)

The "Manufactured by" and "Manufactured for" sections were eliminated, and the company name & copyright, address, and website changed from Aventis Pharmaceuticals Inc., Kansas City, MO 64137; Made in Germany to the following:

Rev. March 2007

sanofi-aventis U.S. LLC
Bridgewater, NJ 08807

Country of Origin: Germany

(b) (4)

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† OptiClik® and SoloStar® are a registered trademark of sanofi-aventis U.S. LLC
‡ The brands listed are the registered trademarks of their respective owners and are not trademarks of sanofi-aventis U.S. LLC

Review of Patient Package Insert-Lantus SoloStar

DMETS' April 9, 2007, review concluded that the March 14, 2007, PPI-SoloStar (ppi-solo) labeling was satisfactory.

Review of Instructions for Use for Lantus SoloStar

DMETS' April 9, 2007, review found the March 14, 2007, IL-SoloStar (il-solo) labeling satisfactory.

Review of Pen Label and Carton Label for Lantus SoloStar

Review of the March 14, 2007, carton label and March 14, 2007, container (SoloStar pen) label for Lantus SoloStar completed by DMETS April 9, 2007, found them satisfactory with two minor exceptions.

The April 5, 2007, (signed April 9, 2007) DMETS review asked for two additional changes that had been overlooked in previous reviews.

- "Although DMETS appreciates the Sponsor's efforts in exploring ways to include the "Initial Use Date" feature on the pen label itself, DMETS **recommends that the Sponsor delete the proposed "Initial Use Date" feature on the pen label,** particularly since the Sponsor has addressed the concern by incorporating a feature on the rear of the carton for patients to record the date of initial use for each of the five pens."
- "Although the Sponsor's response to DMETS's recommendation is adequate, there was an error made in DMETS recommendation. DMETS intended the Sponsor to display all

of the text on the primary display panel [SoloStar carton] in upper and lower case lettering, not just the statements noted in the recommendation. The most recently submitted labels use all capital letters for the statements: "SOLUTION FOR INJECTION IN A DISPOSABLE INSULIN DELIVERY DEVICE" and "USE ONLY IF SOLUTION IS CLEAR AND COLORLESS WITH NO PARTICLES VISIBLE." DMETS apologizes for the oversight, and recommends that the Sponsor also display these statements in upper and lower case lettering to improve the readability of the statements."

In a secure email dated April 10, 2007, the sponsor agreed to incorporate the changes at the next printing, i.e., within approximately 60 days after approval, and the DMEP director agreed.

Review of Patient Package Insert-Cartridges

S-024 included a cartridge PPI (ppi-c) dated March 14, 20007, which was compared to the ppi-c approved in S-011 on August 10, 2004.

The trademark symbol for OptiClik was replaced with the registered trademark symbol, and (b) (4)

The illustration of the cartridge and carton and statement "The carton and cartridge system should look like the ones in this picture" were deleted.

The revision date, company name and address, copyright information, and the trademark statement were changed, and a statement regarding products not owned by sanofi-aventis was added.

These minor editorial changes are acceptable.

(b) (4)

These minor editorial changes are acceptable.

Conclusions

The labeling changes to the PI regarding SoloStar, were acceptable to the safety reviewers and other consultant reviewers. The Drug Interactions changes were acceptable per the approvable letter for S-018. Labeling listed below with submission date is acceptable and may be approved.

However, the sponsor's agreement to implement minor changes to the SoloStar pen and carton labels will be included in the approval letter.

Lantus (insulin glargine) NDA 21-081 - Labeling piece	sNDA No.	Submission date
Package Insert	S-024	3.14.2007
PPI SoloStar (ppisolo)	S-024	3.14.2007
PPI vial (ppiv) – 10 mL vials	S-024	4.21.2006
PPI cartridge (ppic) – 3 mL cart.	S-024	3.14.2007
SoloStar IL (instructions for use)	S-024	3.14.2007
SoloStar pen – carton	S-024	3.14.2007
SoloStar pen - container	S-024	3.14.2007

{See attached electronic signature page.}

Enid Galliers
Chief, Project Management Staff, DMEP

CSO LABELING REVIEW

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

/s/

Enid Galliers
4/25/2007 09:35:32 PM
CSO

Mary Parks
4/25/2007 09:38:29 PM
MEDICAL OFFICER

Office of Surveillance and Epidemiology

MEMO

To: Mary Parks, M.D.
Director, Division of Metabolism and Endocrinology Products
HFD-510

Through: Denise P. Toyer, Pharm.D., Deputy Director
Carol A. Holquist, R.Ph., Director
Division of Medication Errors and Technical Support, Office of Surveillance and Epidemiology
HFD-420; White Oak Bldg. 22, Mail Stop 4447

From: Kellie Taylor, Pharm.D, MPH.
Safety Evaluator, Division of Medication Errors and Technical Support, Office of Surveillance and Epidemiology HFD-420; White Oak Bldg. 22, Mail Stop 4447

Date: April 5, 2007

Re: OSE# 2007-752
Lantus SoloStar [Insulin glargine (rDNA origin) injection]
3 mL prefilled syringes
NDA#: 21-081/S-024

This memorandum is in response to a March 21, 2007 request from your Division for evaluation of the Sponsor's Complete Response (dated March 14, 2007) for a Supplemental New Drug Application (NDA 21-081/S-024) for Lantus®. This supplement provides for a new pen injector for Lantus. The Complete Response was submitted to the Agency to address deficiencies noted by DMEP and DMETS review of Lantus SoloStar (OSE# 2006-853, dated February 9, 2007).

DMETS believes that the Sponsor has adequately responded to the issues raised in the DMETS' review, and commends the Sponsor for their successful incorporation of our recommendations. However, DMETS has two additional areas of concern regarding the date of initial use on the pen label and the use of capital letters for statements displayed on the primary display panel of the carton.

1. Space on the pen label to record the date of initial use

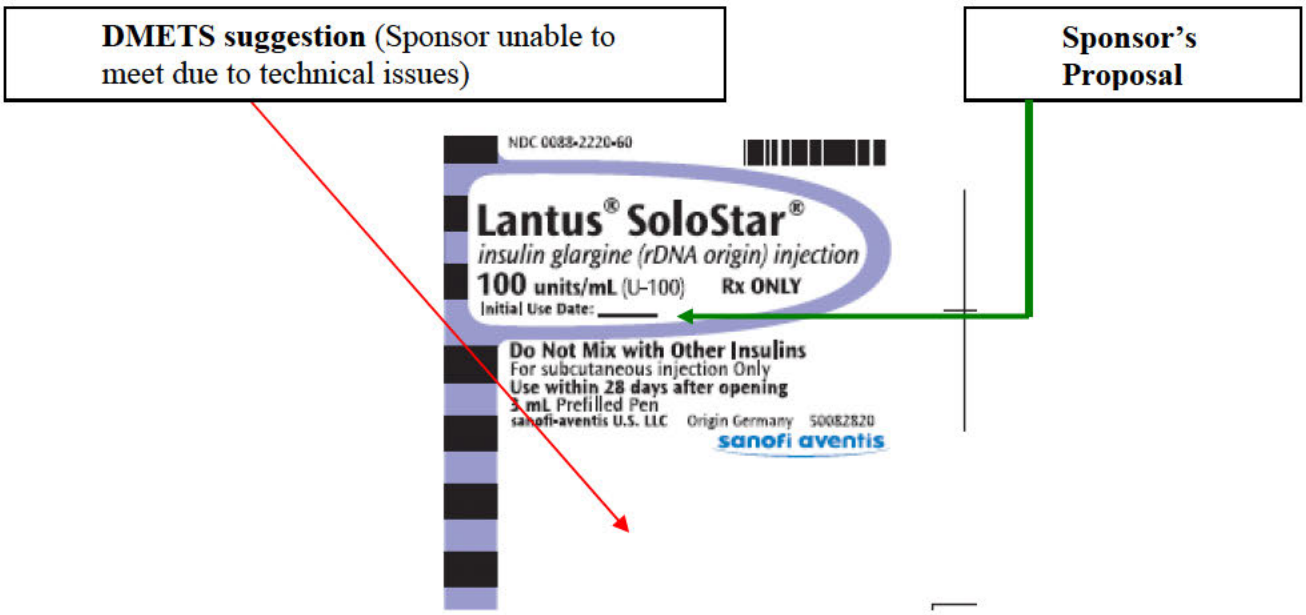
From page 1 of the Complete Response:

> **2. DMETS recommends that the sponsor provide space on the open label for patients to record date of initial use. DMETS believes there is sufficient room on the label beneath the sponsor's name to accommodate this addition.**

Sanofi-aventis response:

> **We have supplied the technical drawing indicating where graphics are printed See *Attachment 2: Technical Drawing* . There is no room here for the patient initial use date because label wraps around to the lot number, expiration date and manufacturers mark. We have placed it in the white oval below the concentration. See *Container Label* (pen label).**

DMETS acknowledges that technical limitations preclude the implementation of DMETS's recommendation to provide a space for patients to record the date of initial use beneath the Sponsor's name (see image below). DMETS commends the Sponsor's attempt to accommodate our recommendation by placing the "Initial Use Date" feature beneath the concentration (see image below). However, DMETS notes that space afforded to this feature is small and is positioned in close proximity to other product information. Given the space constraints and curved surface of the pen body, DMETS suspects that patients may not be able to use this feature to record the initial date as the Sponsor intends.



From a safety perspective, the ideal placement would be on the container label of in-use pens since that information is most readily visible to patients and thereby would have greater leverage to minimize errors related to the use of pens beyond 28 days. However, it seems to DMETS that technical challenges limit the ability of the Sponsor to incorporate this feature in a user-friendly format on the label itself. Although DMETS appreciates the Sponsor's efforts in exploring ways to include the "Initial Use Date" feature on the pen label itself, DMETS recommends that the Sponsor delete the proposed "Initial Use Date" feature on the pen label, particularly since the Sponsor has

addressed the concern by incorporating a feature on the rear of the carton for patients to record the date of initial use for each of the five pens.

2. Use of upper and lower case letters

From page 3 of the Complete response

> 5. [redacted] (b) (4) **"Do Not Mix with Other Insulins," "For subcutaneous injection Only," and "Use within 28 days after opening" is difficult to read. DMETS recommends that these statements be displayed using upper and lower case lettering to improve readability of the statements.**
>
> **Sanofi-aventis response:**
>
> **The above statements are displayed using upper and lower case lettering. See** *Carton Label*

Although the Sponsor's response to DMETS's recommendation is adequate, there was an error made in DMETS recommendation. DMETS intended the Sponsor to display all of the text on the primary display panel in upper and lower case lettering, not just the statements noted in the recommendation. The most recently submitted labels use all capital letters for the statements: "SOLUTION FOR INJECTION IN A DISPOSABLE INSULIN DELIVERY DEVICE" and "USE ONLY IF SOLUTION IS CLEAR AND COLORLESS WITH NO PARTICLES VISIBLE."

DMETS apologizes for the oversight, and recommends that the Sponsor also display these statements in upper and lower case lettering to improve the readability of the statements.

If you have any other questions or need clarification, please contact the project manager, Nancy Clark, at 301-796-1187. Additionally, please copy DMETS in any correspondence sent to the Sponsor concerning this review.

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/s/

Kellie Taylor
4/9/2007 02:30:14 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
4/9/2007 03:10:45 PM
DRUG SAFETY OFFICE REVIEWER
Also signing for Carol Holquist, DMETS Director, in her absence

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
(DMETS; White Oak 22, Mail Stop 4447)

DATE RECEIVED: 11/12/2006 **DATE OF DOCUMENT**: 10/24/2006	**DESIRED COMPLETION DATE:** 02/02/2007 **PDUFA DATE:** 02/20/2007	**OSE REVIEW #:** 2006-853

TO: Mary Parks, M.D.
Director, Division of Metabolism and Endocrinology Products
HFD-510

THROUGH: Alina R. Mahmud, R.Ph., M.S., Team Leader
Denise P. Toyer, Pharm.D., Deputy Director
Carol A. Holquist, R.Ph., Director
Division of Medication Errors and Technical Support, HFD-420

FROM: Kellie Taylor, Pharm.D., M.P.H., Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

PRODUCT NAME: **Lantus SoloStar** (Insulin Glargine [rDNA origin]) Injection 100 units/mL (3 mL prefilled pen) **NDA #:** 21-081/SCM24	**SPONSOR:** Sanofi Aventis

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name Lantus SoloStar. DMETS considers this a final review. However, if approval of the application is delayed beyond 90 days from the signature date of this review then the name and its labels and labeling must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document

2. DMETS recommends that DMEP consult DMETS for review of the labeling and packaging of Apidra SoloStar, if the Sponsor submits a response to the Apidra® deficiencies (NDA 21-629/S-008).

3. DMETS recommends implementation of the label and labeling recommendations outlined in Section III of this review in order to minimize potential errors with the use of this product.

4. DDMAC finds the proprietary name, Lantus SoloStar, acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Nancy Clark, Project Manager, at 301-796-1187.

Division of Medication Errors and Technical Support (DMETS)
Office of Surveillance and Epidemiology
White Oak 22, Mail Stop 4447
Center for Drug Evaluation and Research

PROPRIETARY NAME, LABEL AND PACKAGING REVIEW

DATE OF REVIEW: 01/19/2007

NDA #: 21-081/SCM-024

NAMES OF DRUG: Lantus SoloStar (Insulin Glargine [rDNA origin]) Injection

NDA HOLDER: Sanofi Aventis

I. INTRODUCTION:

This review is in response to a November 12, 2006 request from your Division for a final review of the proprietary name, Lantus SoloStar. The proposed name, Lantus SoloStar, was initially found acceptable in OSE Review 06-0106 (dated May 9, 2006). The container and carton labeling were also submitted for review and comment. The Sponsor also submitted a "Complete Response to Approvable Letter" on October 24, 2006 which included a usability analysis of the SoloStar device that was performed for diabetes type 1 and type 2 audiences.

PRODUCT INFORMATION

Although we are reviewing the proprietary name, Lantus SoloStar, the sponsor has not yet submitted the insert labeling for the product. Lantus SoloStar is a disposable pen injector with the Lantus cartridges irreversibly integrated into the system and will be an addition to the Lantus product lines. Since the "SoloStar" product will contain the active ingredient, Lantus, we will describe the product information for these already approved and marketed product.

Lantus

Lantus (insulin glargine [rDNA origin]) is a recombinant human insulin analog that is a long-acting parenteral blood-glucose-lowering agent. Lantus is indicated for once-daily subcutaneous administration for the treatment of adult and pediatric patients with type 1 diabetes mellitus who require basal insulin for the control of hyperglycemia. Lantus is usually started at an average dose of 10 international units once daily, and subsequently adjusted according to the patient's need to a total daily dose ranging from 2 to 100 international units. Lantus SoloStar will be available as a 3 mL prefilled pen.

The sponsor is currently marketing Lantus as 10 mL vials and a 3 mL cartridge system for use only with OptiClik (Insulin Delivery Device), containing insulin glargine Lantus, which was approved on April 20, 2000, is available in a 100 unit/mL strength.

II. RISK ASSESSMENT:

A. ADVERSE EVENT REPORTING SYSTEM (AERS) AND DRUG QUALITY REPORTING SYSTEM (DQRS) SEARCH

Lantus has been marketed since April 20, 2000. DMETS has previously identified and analyzed medication errors related to Lantus, and presented the results in OSE Consult # 02-0037 (dated March 15, 2003) and OSE Consult #06-0106 (dated May 9, 2006). Therefore, DMETS searched the FDA Adverse Events Reporting System (AERS) database to determine any post-marketing safety reports of medication errors associated with Lantus occurring since May 2006, the date of the last post-marketing errors review, that could relate to the nomenclature or labeling of the proposed Lantus SoloStar product.

In a consult reviewed March 15, 2003 (ODS Consult # 02-0037), 17 cases of confusion between Lantus and Lente were reported. A follow up search of AERS for OSE Consult# 06-0106, dated May 9, 2006, identified one additional report of confusion between Lantus and Lente, and six medication errors involving confusion between Lantus and Apidra.

For this review, the MedDRA High Level Group Term (HLGT) "Medication Error", tradename “Lantus” and active drug “insulin glargine” were used to perform the searches. Dates were limited to reports received between April 15, 2006 and January 19, 2007. This search strategy identified nine medication errors involving that could relate to the nomenclature or labeling of the proposed Lantus SoloStar product. Of the nine cases: four involve Apidra, one involved the flu shot, one involved Symlin, one involved Humalog, and one involved Humalog and Novolog. Additionally, in one of the medication error reports, Lantus was the only medication involved. No additional reports of contusion between Lantus and Lente were identified.

D. SAFETY EVALUATOR RISK ASSESSMENT

Since the initial review of Lantus SoloStar, DMETS identified the names Trelstar, Solodyn, Solatene, Lantrisul, Cilostazol, and Silostar as names that have the potential to look similar to Lantus SoloStar. However, Trelstar, Solodyn, and Cilostazol will not be reviewed further due to a lack of convincing orthographic similarity in addition to differentiating product characteristics such as route of administration, product strength, dosage form, usual dose, frequency, and/or indication of use. Additionally, the names Solatene, Lantrisul, and Silostar will not be reviewed further since these products are not available in the U.S. marketplace. Solatene (Beta-carotene capsules 30 mg) and Lantrisul (Trisulfapyrimidines oral suspension 167 mg/5 mL) are discontinued according to drugs@fda. Silostar is a proprietary name used in Spain, and it is thought to present minimal risk for product confusion with Lantus SoloStar in the U.S. marketplace.

1. Post-Marketing Error Review

Lantus has been marketed in the United States since April of 2001. Routine post-marketing surveillance has previously identified medication errors related to name confusion, as well as the label, labeling and packaging of Lantus. The most recent AERS search was limited to April 15, 2006 through January 19, 2006, and identified an additional nine cases of medication errors related to Lantus. These errors will be

discussed according to type of error and the potential for the error to occur with Lantus Solostar.

a) Existing and potential confusion with Lantus and Apidra

DMETS is concerned about the existing and potential confusion between Lantus and Apidra. A forthcoming consult will analyze the medication errors between these two products in detail, and provide recommendations to help minimize confusion (OSE Consult # 06-0183). However, the root cause analysis of the errors consistently indicates that the errors are the result of similar packaging rather than name confusion.

One case (ISR 5152930-3) described a near miss in which an Apidra vial was mistakenly selected instead of a Lantus vial in an institutional facility. The reported cited the similar appearance of the products as a contributing factor. Three of the nine cases identified in the AERS search involved product selection errors between Lantus and Apidra which occurred in the consumer's home. This finding underscores the importance of differentiating the labeling and packaging of Lantus and Apidra since the products appear to be vulnerable to confusion and concomitant use by patients.

> In one report a 12-year-old patient was prescribed Lantus 60 units daily and 5 to 10 units of Apidra before meals on a sliding scale (ISR 5123096-0). The patient used OptiClik pens, which both were the same color. The report stated that it was not known whether the patient administered Apidra in place of Lantus or Lantus instead of Apidra, but that the patient was admitted to a hospital intensive care unit for diabetic ketoacidosis (blood glucose of 426 mg/dL). In another report a 64-year-old patient administered 70 units of Apidra instead of Lantus (ISR 5036955-4). The patient used syringes to administer the drug, indicating that she probably confused the Lantus and Apidra vials. The report stated that the patient was "in fear of going into hypoglycemic shock" and was driven to a nearby emergency room by her husband. The patient was subsequently treated with intravenous dextrose, food, and admitted to hospital for overnight observation. Blood glucose reading the following day morning were 194 mg/dL, and then 125 mg/dL at noon. The third report only states that the patient administered insulin glargine (Lantus) instead of insulin glusine (Apidra).

DMETS believes that the proposed Lantus SoloStar pen injector may lessen the potential for confusion in the consumer home. Particularly since the packaging of the Lantus SoloStar pen injector is differentiated from the Apidra vials and OptiClik reusable pen injector that is used with the Apidra cartridges.

However, DMETS is aware that the Sponsor has submitted a supplemental application for the Apidra SoloStar pen injector (NDA #32-639/SCP-08). DMETS had the opportunity to review the proposed device and labeling for Apidra SoloStar, and recommended that modifications be made to avoid confusion between Apidra and Lantus if the SoloStar pen injector is approved for use with both products (please refer to OSE Review # 06-0106 & 06-0179 dated May 9, 2006 for detail).

The Sponsor has subsequently submitted a "COMPLETE RESPONSE to Approvable Letter" for Lantus SoloStar (dated October 24, 2006), and noted in response to "Agency Question/Request for Information" item #9(b) that "Any similarities in the graphic design between Lantus® and Apidra® SoloStar® will be addressed in the Apidra® submission to be submitted at a later date in

response to the Apidra® deficiencies (NDA 21-629/S-008)." Given the existing and potential confusion between Lantus and Apidra, DMETS recommends that our Division be consulted on this submission if and when the Sponsor submits the aforementioned response. DMETS believes that post-marketing medication error analysis indicates that differentiation of the packaging and labeling for these products will be critical to minimizing the existing and potential confusion between Lantus SoloStar and Apidra SoloStar.

b) Patient misuse of the Lantus OptiClik pen

DMETS identified one report in which a patient was trying to affix the wrong needles to an OptiClik pen (Novo needles instead of BD needles) and trying to inject 85 units of Lantus (maximum injection with the OptiClik pen is 80 units) (ISR 5143990-4).

As it relates to the proposed SoloStar pen review, DMETS believes this error could potentially occur since the proposed Lantus SoloStar device can only inject 80 units and requires the attachment of the BD Ultrafine needles.

DMETS believes that the information provided in the proposed "SoloStar Instruction Leaflet" may help to minimize this potential source of error. According to the answer provide by the Sponsor to Item # 3 in the "Complete Response" submission, if a patient were to attempt to dial the device past 80 units in error, the design of the device will prevent the patient from doing so. DMETS believes that greater prominence should be given to the type of needles that can be used with the device, and has provided recommendations in Section III of this review.

c) Confusion between Lantus and injectable products used to treat diabetes

DMETS identified several reports in AERS that describe mix-ups with Lantus and other injectable products used to manage diabetes. An anectdotal report in AERS from a physician stated that "Several patients" had mistaken their insulin glargine (Lantus) dose with their insulin lispro (Humalog) or insulin aspart (Novolog) insulin, and required treatment consisting of "admission to hospital for glucose monitoring or continuous testing at home (ISR 5066638-6). Another report stated that the patient's physician suspected that a patient had confused Lantus with Humalog or Lantus with a Symlin vial. The report stated that the patient may have "inadvertently reversed the dose of Lantus (15 units) with the dose of Humalog (2 units) that morning," resulting in the administration of 15 units Humalog and 2 units Lantus (ISR 5006448-9). The patient injected the medications along with 60 mcg from a Symlin vial at breakfast, and shortly afterwards she reported that she felt her blood glucose was "low". The patient checked her blood glucose which was 45 mg/dL. A short time after, the patient lost consciousness and was unresponsive to verbal stimuli. Emergency medical services were called, and the patient was treated with glucose jelly and icing sublingually. The patient's blood glucose returned to normal values.

Because these reports lack sufficient detail about the factors contributing to the errors, DMETS cannot evaluate the impact of the proposed SoloStar injector will have on the existing and potential confusion between Lantus and the Humalog and Novolog insulin products. However, DMETS believes that it is likely that

confusion could persist since the patients are likely to continue concomitant use of short-acting insulin product or Symlin with Lantus therapy. At this time, DMETS has no recommendations to offer regarding the labeling or packaging of SoloStar that could minimize dosing confusion between Lantus and other injectable products used to manage blood glucose in the diabetic population. However, DMETS will continue to monitor for reports of medication errors.

d) Confusion between Lantus and the Flu Shot

DMETS identified one report in which a patient was mistakenly given 50 units of Lantus intramuscularly instead of "a flu shot" (no product details provided) (ISR 5190743-7). The patient was admitted to hospital and observed for 24 hours. Because no details about the factors contributing to this error were provided, DMETS cannot evaluate the impact of the proposed SoloStar injector will have on the existing and potential confusion between Lantus and the influenza vaccine. However, DMETS will continue to monitor for reports of medication errors.

E. (b) (4)

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III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container and carton labeling of Lantus SoloStar, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which may minimize potential user errors.

A. PEN LABEL

1. DMETS recommends that the (b) (4) be removed from the pen label. The (b) (4) has minimal visual contrast with the black lettering used to display the proprietary name, established name, concentration and "Rx only" warning. DMETS believes that elderly or visually impaired diabetic patients could have difficultly reading the proposed labeling because of the poor visual contrast.

2. DMETS recommends that the Sponsor provide space on the pen label for patients to record date of initial use. DMETS believes there is sufficient room on the label beneath the Sponsor's name to accommodate this addition.

3. (b) (4) "Do Not Mix with Other Insulins," "For subcutaneous injection Only," and "Use within 28 days after opening" is difficult to read. DMETS recommends that these statements be displayed using upper and lower case lettering to improve readability of the statements.

B. CARTON LABELING

1. DMETS is unclear if the insulin delivery device is packaged with needles or if the needles are sold separately. If the needles are sold separately, DMETS recommends that this information be conveyed prominently on the primary display panel to alert practitioners and patients to this fact. Also, please specify the brand or type of needles that can be used safely with the device.

2. DMETS recommends adding "SoloStar® pens **in use** must not be stored in the refrigerator." This statement could be displayed on the rear panel of the carton, immediate following the "Use Pen within 28 days after initial use." DMETS believes this could help avoid the inadvertent storage of Pens in the refrigerator while in use.

3. DMETS recommends providing space on the rear panel of the carton for patients to record date of initial use for each pen. DMETS believes there is sufficient room on the label beneath the Sponsor's name to accommodate this addition. DMETS believes this could help avoid the inadvertent use of expired pens.

4. DMETS recommends that the graphic on the primary and auxiliary panels of the SoloStar® pen device be modified to more accurately reflect the color of the Lantus SoloStar product. As it currently appears, the graphic could lead the patient or practitioner to believe the pen is white instead of grey. To avoid any confusion that could ensue, DMETS recommends that the graphic be modified.

5. (b) (4) "Do Not Mix with Other Insulins," "For subcutaneous injection Only," and "Use within 28 days after opening"

is difficult to read. DMETS recommends that these statements be displayed using upper and lower case lettering to improve readability of the statements.

C. PATIENT INSTRUCTION MANUAL

1. DMETS recommends that DMEP consult DSRCS to review the SoloStar® Instruction Leaflet, if they have not done so already. From a medication errors perspective, DMETS believes that the safe use of the pen device a function of the patient's ability to read, understand, and follow the instruction manual.

2. DMETS recommends that the statement "Always perform the safety test before each injection" in Step 3 be further highlighted (and the word Always underlined) to increase the prominence of this information. DMETS acknowledges that the Sponsor has highlighted the "Safety Test" section (Step 3) in red, but believes further emphasis should be drawn to the need to always perform the safety test prior to injection.

3. DMETS also recommends that the sponsor include explicit information in plain language regarding potential consequences that may occur if the patient fails to perform the safety test (e.g., "If you fail to perform the safety test before each injection, you may get too much or too little insulin which could affect your blood glucose.") DMETS believes that linking the safety test to avoidance of adverse outcomes may help to reinforce the importance of the process and hopefully, have a positive influence on patient adherence to the instruction.

4. DMETS recommends that the statement "Slowly count to 10 before you withdraw the needle from the skin" in Step 5 be highlighted to increase the prominence of this information.

D. PEN DEVICE

No comments.

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

/s/

Kellie Taylor
2/9/2007 09:47:29 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
2/9/2007 12:21:33 PM
DRUG SAFETY OFFICE REVIEWER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

MEMORANDUM

Food and Drug Administration
Office of Device Evaluation
9200 Corporate Avenue
Rockville, MD 20850

Date: July 10, 2006

From: Biomedical Engineer
DAGID/GHDB, HFZ-480

Subject: NDA 21-081/S024
Company Name: Sanofi-Aventis
Device: Lantus SoloStar (insulin glargine [rDNA origin])
Indications for Use: To treat adult and pediatric patients with type 1 diabetes or adult patients with type 2 diabetes

NDA 21-629/S008
Company Name: Sanofi-Aventis
Device: Apidra SoloStar (insulin glulisine [rDNA origin])
Indications for Use: For treatment of adult patients with diabetes mellitus for the control of hyperglycemia

To: Dr. Janice Brown, CDER/OPS/ONDQA/DPE, HFD-510

Thru: Branch Chief, Anthony Watson /RC For AW

1.0 Background

This consult review was requested for the disposable insulin pen, SoloStar. The requesting reviewer has asked that I focus on the accuracy and precision of the device and the information provided in section 3.2.P.7 for the container closure system which includes device components, specifications, methods, and assembly process description. The same SoloStar device is being used for two separate NDA applications which are both being addressed in this review.

The SoloStar injection system is a device that provides a method of accurately injecting a selected dose of insulin through a single lumen hypodermic needle. The device is intended to be used for self-injection by patients. Patients who are not able to handle the device properly (according to Health Care Professional's assessment) require assistance from a third person. The device is disposable and cannot be reused. The device does not contain electronic components. The device has a pen cap for safety and to protect the cartridge.

The dose is pre-selected by rotating a dosage selector at the rear end of the device. The number of selected insulin units is displayed in the dose window on the side of the pen. The dialing mechanism allows dosage in 1 insulin unit increments. It provides a maximum of 80 insulin units in one dosing. The total content of the cartridge is 300 insulin units. Before the injection, a pen injector needle is mounted onto the front end of the device and inserted under the skin. The dose is delivered by pressing the injection button.

The SoloStar cartridge holder into which the 3mL cartridge is irreversibly attached, is considered secondary packaging. No part of the SoloStar has contact with the drug product. The SoloStar device does not influence the container closure integrity or stability of the insulin. Therefore, the shelf-life and storage directions of the SoloStar are the same as the approved cartridges (i.e., 24 months at 2-8°C). All plastic parts that could come into skin contact during use have been tested for skin sensitivity according to (b) (4)

2.0 Review

The SoloStar was tested according to ISO 11608-1:2000 "Pen injectors for medical use – Part 1: Pen injectors – Requirements and test methods". The cartridge in conjunction with the SoloStar was assessed according to ISO 11608-3:2000 "Pen injectors for medical use – Part 3: Finished cartridges – Requirements and test methods" and (b) (4). The sponsor performed the following tests:

- Functional inspection (visual, audible, tactile)
- Dose accuracy (ambient, cool atmosphere, hot atmosphere, cold storage atmosphere, dry heat atmosphere)
- Free fall (dose accuracy, visual inspection, functional inspection)

The sponsor has indicated that the dose accuracy of the device is (b) (4). ISO 11608-1 specifies that single-compartment cartridge doses less than 200µL should have an absolute error not exceeding 10µL and single-compartment cartridge doses greater than 200µL should have a dose accuracy not exceeding 5%. Therefore, the sponsor's dose accuracy specification meets the requirements of ISO 11608-1.

The sponsor adequately described the assembly process of the mechanism subassembly and cap and cartridge holder subassembly.

3.0 Correspondence

The submission that Sanofi submitted described a device with no electrical components. However, the sample provided by the company had an LCD for dose setting. On June 20, 2006, I called Mr. Kevin Malobisky to determine which device the company intended to submit. Mr. Malobisky indicated that I had the sample of the OptiClick and not the SoloStar.

4.0 Comments

1. Please provide a copy of the SoloStar Instructions for Use.
2. Please describe the method by which the SoloStar indicates that the injection has been completed.
3. You have indicated that the dialing mechanism allows dosage in 1 insulin unit increments and provides a maximum of 80 insulin units in one dosing. Please describe how the design limits dosing to 80 units. Please describe the testing that has been conducted on the dose setting mechanism. Specifically, has testing been performed to assess functionality if the user rapidly turns the dial or if the user turns the dial clockwise past 80 units and then attempts to turn the dial counterclockwise.
4. Please describe the method and mechanism for ensuring that the last dose delivered from the insulin cartridge satisfies requirements for dose accuracy.
5. Please indicate whether the device has a safety mechanism to prevent accidental firing.
6. Please identify the pen injector needles that are compatible with the SoloStar in your Instructions for Use.
7. You state that the dose is delivered by pressing the injection button until it is in its original end position. Please clarify what is meant by this statement.
8. There is no indication in the submission that user testing has been performed for this device. The number of steps involved in performing a successful injection with this device could lead to user errors and potential life threatening situations. You should perform a risk analysis to identify the device use tasks that could lead to patient safety issues and then conduct user testing to identify and test mitigation measures that adequately reduce the risk of patient injury. Potential problems such as overdosing, underdosing, or misdosing can result from a variety of user-related tasks such as improper use of the dialing mechanism, failure to properly attach the needle, etc. User testing should be performed to determine and mitigate all potential use-related issues. Without results from usability testing leading to mitigation of hazards and changes in system requirements, it is not possible to determine whether the future marketed device will be safe and effective. Please provide a test plan and test results for usability testing for the new device. We recommend that you consult the following guidance documents for information about acceptable usability testing:

- Do It By Design - An Introduction to Human Factors in Medical Devices
  http://www.fda.gov/cdrh/humfac/doitpdf.pdf
- Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management
  http://www.fda.gov/cdrh/humfac/1497.pdf

5.0 Recommendation

REQUEST ADDITIONAL INFORMATION

Jason Lipman

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

/s/

Janice Brown
8/15/2006 08:51:33 AM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-081/S-024

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Galliers, Enid M
From: Watson, Anthony [anthony.watson@fda.hhs.gov]
Sent: Friday, February 23, 2007 3:12 PM
To: Galliers, Enid M
Subject: FW: NDA 21-081 S024

Attachments: NDA 21-081 S024 Lantus SoloStar Rv1 Final.doc

Anthony D. Watson, BS, MS, MBA
Chief, General Hospital Devices Branch
Division of Anesthesiology, General Hospital, Infection Control, and Dental Devices
Center for Devices and Radiological Health
U.S. Food and Drug Administration
Tel: (240) 276-3707
Fax: (240) 276-3789

From: Soprey, Pandu
Sent: Monday, February 05, 2007 11:11 AM
To: Galliers, Enid M
Cc: Watson, Anthony; OC Combination Products
Subject: NDA 21-081 S024

NDA 21-081
:4 Lantus SoloSt

Attached is Consult Review Memo

Pandu R Soprey Ph D
Microbiologist
FDA/ODE/DAGID/GHDB
Tel: 240-276-3707 Fax 240-276-3789
Pandu.Soprey@fda.hhs.gov

COSULT REVIEW MEMO

DATE: February 2, 2007

TO: Enid M. Galliers CDER/DMEP/HFD-510

FROM: Pandu R. Soprey, Ph.D.
Review Scientist, CDRH/ODE/DAGID HFZ-480

THROUGH: Anthony Watson Branch Chief GHDB/DAGID/CDRH/ HFZ-480

SUBMISSION: NDA 21-081/S-024 Lantus (insulin glargine [rDNA origin]) Injection
NDA 21-629/S-008 Apidra (insulin glulisine [rDNA origin]) Injection

DEVICE:
Proprietary Name: SoloStar disposable Pen Injector for Lantus insulin and SoloStar disposable Pen Injector for Apidra insulin
Non-proprietary: Pen injector, Syringe containing insulin in a 3mL disposable cartridge

APPLICANT / SPONSOR:
Sanofi-Aventis

INTENT/PURPOSE OF THIS SUBMISSION:
The applicant has provided responses to the deficiencies listed in the approvable letter (dated August 24, 2006) for Lantus SoloStar and Apidra SoloStar. The responses to the deficiencies are provided in Supplement #24 dated October 24, 2006 and December 14, 2006

REVIEW OF DEVICE RELATED RESPONSES:

Response #2
In its initial position, tactile features on the dosage selector and the pen body are aligned "0" is displayed in the dose window and the dial will be at zero. The dose to be injected is then pre-selected by rotating a dosage selector at the rear end of the device and then the number of selected insulin units is displayed in the dose window on the side of the pen. After an injection of the selected dose the injection button reverts back to the original position and "0" is displayed in the dose window. Display of "0" assures that the dose delivery is complete.

The response explains how the dose delivery is complete, the response is acceptable.

Response #3
Dialing beyond the maximum dose of 80 units is not possible. If the patient tries to select a higher dose, the number sleeve and dose window engage rotationally preventing the number sleeve from moving further. The dosage selector and number sleeve are firmly affixed to each other during the assembly process.

All physical dose-setting limits (maximum dose, minimum dose, end of cartridge) have been tested and demonstrate a mechanical strength that will withstand forces typically applied by patients. Furthermore, torque required to set the dose was evaluated as well as the correlation between visual and audible feedback (i.e. the number of clicks correspond to units displayed in dose window).

Since SoloStar is a mechanically operated device, rapid dialing has no effect on accuracy of dose setting or injection. The number sleeve of the pen has two functions; it indicates the number of insulin units to be injected

and simultaneously sets the dose in the pen. Thus, dose indication and dose setting are physically linked and rapid dialing has no impact on the accuracy of the insulin pen.

The device was evaluated according to ISO Standard (ISO 11608:2000, Pen-injectors for medical use, Part 1: Requirements and test methods) test requirements. The device set at three different doses (1-unit, 40 units and 80 units) were tested at standard atmosphere (ISO 11608-1 Section 6.1), cool atmosphere (ISO 11608-1 Section 6.2), hot atmosphere (ISO 11608-1 Section 6.3), after preconditioning (ISO 11608-1 Section 7.1 and 7.2) and free fall testing (ISO 11608-1 Section 7.4b). The various tests results met the specification limits for all of the three dose volumes (1 U, 40 U and 80 U). The columns "calculated lower end of distribution (LED)" and "calculated upper end of distribution (UED)" are calculated from the confidence interval.

The response provided in the supplement shows that the device meets the dose selection and dose delivery requirements. The response is acceptable.

Response #4

The accuracy of the last dose was determined and found to be in compliance with the standard (ISO11608-1). Testing is performed in accordance with the ISO 11608-2 instructions. The test is conducted by placing a cartridge in an apparatus described in the ISO norm (ISO 11608-2). The liquid expelled from the cartridge is collected, and the volume delivered after the plunger displacement is then measured. All dose accuracy calculations are carried out in units of milliliters.

The initial position of the rubber stopper related to the shoulder of the glass cartridge defines how many units can be accurately delivered in total, i.e. the length of the cylindrical part of the cartridge. The mechanism was designed to ensure the rubber stopper cannot be pushed further than the cylindrical part of the glass cartridge during dosing. This is accomplished through the presence of a physical part which prevents additional advance of the mechanism beyond the last dose. Therefore the patient can dial only up to the dose left in the cartridge.

The response provided satisfies the dose delivery requirements. The response is acceptable.

Response #5:

Lantus® SoloStar® is not an auto injector and does not contain any external source of energy to deliver an insulin dose and the dose must be delivered manually by constant pressure from the patient on the activator. The dose is delivered manually by pressing the button inward until it is in its starting position and the dose window displays "0". Thus accidental firing is not possible. In addition, the patient leaflet mentioned that the needle needs to be removed after each injection by the patient. Without a needle the cartridge is sealed and no accidental firing is possible

The response is acceptable.

Response #6:

The applicant has identified the needles to be used with SoloStar pen injector. For Lantus SoloStar, the needles to be used with SoloStar injector are BD Ultra-Fine needles. This sentence will also be included in the Lantus "Instructions for SoloStar use": (b) (4)

The response is acceptable.

Response #7:

The sponsor has clarified function of the injection button and provided rationale for end position of the injection delivery button. When the injector button is in its initial position, tactile features on the dosage selector and the pen body are aligned, "0" is displayed in the dose window. The dose to be injected is pre-selected by rotating the

dosage selector at the rear end of the device. The number of selected insulin units is displayed in the dose window on the side of the pen. The dose is delivered by pressing the button until it is in its original position, in which "0" is displayed in the dose window. Mechanical constraints prevent the user from pushing the button any further beyond zero. Finally, the patient instruction manual instructs the patient to delay removal of the SoloStar for 10 seconds after the injection button is in the original position (when the injection button is in the original position and 0 is displayed in the dose window) to assure dose delivery is complete.

The response is acceptable.

Response #8:
This risk management process study is performed according to (b) (4) and applicable internal SOPs. In this process human factors and device specific factors as well as misuse or abuse scenarios are investigated, evaluated, corresponding mitigations if necessary were planned and implemented. The successful implementations of these factors were verified.

Usability studies are conducted to predict the potential for human error and misuse/abuse to occur. Final user testing is performed in a design validation study before market release of the device and after launch a post-market surveillance system is in place. Complaints and adverse events are continuously monitored, trended, investigated when necessary and used to update the risk management. Findings out of the Risk Management Process are used to improve the product if necessary and provide valuable contributions for the development of new devices.

The detailed information related to the performance and safety of the device is provided under the following description:

Intended Use:
The detailed description of intended use of SoloStar pen injector under different use different conditions are listed and described.

Functional Analysis:
Analysis of SoloStar was prepared which described logical representation of the relations of the input and output functions and this information was used as basis for a systematic review of all hazards related to each identifiable output function of the device.

(b) (4)

[redacted] (b) (4)

RISK MANAGEMENT:
The definition of the acceptable risk level was based on the standard [redacted] (b) (4), risk analysis for medical devices. In order to estimate the risks and to establish acceptable risk levels for SoloStar, a Risk Chart (Pg. 12) was used as qualitative categorization method. Using this chart the estimation of the risk of harm is divided into the probability of its occurrence and its severity. Seven severity classes were identified (fatal, life threatening, serious, non-serious, negligible, customer complaint, and customer reassurance. Performing a risk assessment the probability of occurrence of harm was estimated for all defined hazards associated with the output functions identified in the functional analysis.

The risk assessment was performed by an expert team consisting of representatives of various functions in the company. Additionally ergonomic specialists from an external company created abuse/misuse scenario and human factors assessments for SoloStar. These studies were taken into consideration while preparing the risk assessment. The results of the risk assessment for SoloStar before and after mitigation (risk control) were considered and summarized in the figures (Pg. 14).

Individual risks (128 risks) were evaluated and the occurrence of the adverse effect of basal (Lantus insulin) and short acting insulin (Apidra) were evaluated separately. After mitigation, for both the majority was found in the Generally Acceptable category, none of the risks are in the Not Acceptable category. 30 cases for both basal and short acting insulin remained in the region ("ALARP"). This represents a risk to patients with an extremely low probability of occurrence.

RISK - BENEFIT ANALYSIS:
The results of the risk assessment show that the use of SoloStar with insulin, like Lantus®, is associated with some risks that require risk control measures. A number of mitigations are already in place and effectiveness was verified.

The better part of the remaining overall residual risk can be associated with the proper use of the pen, with needle handling, with the potential risk to apply the wrong insulin or to use training pens filled with water (mix-up) and with needle pricking.

As per plan complaints and adverse events will be continuously monitored, trended and investigated (when required) after launch during post-market surveillance and used to update the risk management. The overall residual risk of SoloStar® was discussed and agreed in a cross-functional team meeting together with the Risk Management Board. All individual risks falling into the ALARP (As Low As Reasonably Practicable) region were presented to the Risk Management Board. Mitigations were discussed and agreed.

It was concluded that the intended benefit for the patients associated with the use of the SoloStar with insulin, like Lantus, outweighs the remaining overall residual risk

DESIGN VALIDATION STUDY
SoloStar pen injector was tested in a design validation study and the primary objective was to validate the use of the pen device by the target patient population (patients diagnosed with type 1 or type 2 diabetes mellitus) under two different scenarios, with or without face-to-face training by a healthcare professional:

Scenario #1 (Phase 1): This scenario was designed to simulate a clinical practice environment where active face-to-face training by the healthcare professional would take place, prior to the subjects receiving the pen injector.
Scenario #2 (Phase 2): This scenario was designed to simulate a clinical practice environment where the subject

would receive the pen and instructional leaflet, without any training by a healthcare professional. The subject would then self-train on how to use the pen with the instructions provided, and if necessary, request additional training via the sanofi-aventis (S-A) Help Line Call Center, or by contacting the healthcare professional by telephone. After training or self training, subjects were asked to show how to correctly deliver a dose, three times, each time with 3 different pens.

The study objective was assessed for each phase separately by the following endpoints: a) Primary endpoint: The proportion of subjects who delivered a successful dose on all three-dose delivery repetitions. b) Secondary endpoints: The proportion of subjects who performed the safety test (pre-dose actuation) correctly before each of the three dose delivery repetitions, the proportion of dose delivery repetitions with correctly performed safety tests, the proportion of repetitions for which a successful dose was delivered, the proportion of subjects who used the S-A Help Line Call Center or requested additional instructions (in person [Phase 1 only] or by telephone) from a healthcare professional after the initial training session, the proportion of subjects who made use of the instructional leaflet after the initial training session, and the accuracy and precision of the device based on the three dose injections (weights) per subject. Safety variables included the following: The incidence of adverse events (AEs) by primary term and Product Technical Complaints (PTCs).

The study population consisted of a total of 181 subjects (86 in Phase 1; 95 in Phase 2) and the safety population consisted of a total of 204 subjects (100 in Phase 1; and 104 in Phase 2). There were 50 validation subjects Phase 1 and 54 in Phase 2.

The results of the Efficacy and Safety study showed that the primary and secondary study criteria were meet and the conclusions of the design validation study were:

i) The use of the SoloStar pen device was successfully validated by subjects with type 1 and 2 diabetes mellitus (the target population) in both the Phase 1 and Phase 2 scenarios, with and without face-to-face training, respectively.
ii) Subjects using the SoloStar pen device accurately delivered the dose that was dialed.
iii) In Phase 1, the subjects delivered dose was confirmed to be accurate and the variability of the delivered dose was low. Although in Phase 2, accuracy could not be confirmed based on the SAP pre-defined interval when the outliers were excluded the delivered dose was observed to be accurate with a reduction in the among subject variability.
iv) The effect of safety test performance on the delivered dose was deemed not to be clinically relevant.
v) There were no adverse events or pen malfunctions. One PTC was reported however was determined to be due to a bent needle and not the pen device.

The response is acceptable.

COMMENTS AND CONCLUSION:
The applicant has provided adequate responses to the device related deficiencies (deficiencies #2 through #8). From a device viewpoint the pen-injector described in NDA 21-32 S024 may be approved.

Pandu R. Soprey
Scientific Reviewer, CDRH, HFZ-480

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/s/

Enid Galliers
2/23/2007 03:44:34 PM
CSO

Checking CDRH review into DFS on behalf of Pandu Soprey & Anthony Watson.

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

/s/

Rachel E Hartford
9/21/2007 06:30:42 PM
CSO
Entering this review on behafl CDRH

Galliers, Enid M

From: Galliers, Enid M
Sent: Monday, April 09, 2007 3:40 PM
To: 'Michael.Lutz@sanofi-aventis.com'
Subject: RE: Lantus Solostar

Dear Mike:

I just received the DMETS review of your Marcy 14, 2007, response for NDa 21-081/S-024 Lantus SoloStar Pen labeling and am providing the following excerpt to you.

DMETS believes that the Sponsor has adequately responded to the issues raised in the DMETS' review, and commends the Sponsor for their successful incorporation of our recommendations. However, DMETS has two additional areas of concern regarding the date of initial use on the pen label and the use of capital letters for statements displayed on the primary display panel of the carton.

1. Space on the pen label to record the date of initial use
From page 1 of the Complete Response:

2. DMETS recommends that the sponsor provide space on the open label for patients to record date of initial use. DMETS believes there is sufficient room on the label beneath the sponsor's name to accommodate this addition.

Sanofi-aventis response:

We have supplied the technical drawing indicating where graphics are printed See Attachment 2: Technical Drawing. There is no room for the patient initial use date because label wraps around to the lot number, expiration date and manufacturer's mark. We have placed it in the white oval below the concentration. See Container Label (pen label).

DMETS acknowledges that technical limitations preclude the implementation of DMETS's recommendation to provide a space for patients to record the date of initial use beneath the Sponsor's name (see image below). DMETS commends the Sponsor's attempt to accommodate our recommendation by placing the "Initial Use Date" feature beneath the concentration (see image below). However, DMETS notes that space afforded to this feature is small and is positioned in close proximity to other product information. Given the space constraints and curved surface of the pen body, DMETS suspects that patients may not be able to use this feature to record the initial date as the Sponsor intends.

From a safety perspective, the ideal placement would be on the container label of in-use pens since that information is most readily visible to patients and thereby would have greater leverage to minimize errors related to the use of pens beyond 28 days. However, it seems to DMETS that technical challenges limit the ability of the Sponsor to incorporate this feature in a user-friendly format on the label itself. Although DMETS appreciates the Sponsor's efforts in exploring ways to include the "Initial Use Date" feature on the pen label itself, DMETS recommends that the Sponsor delete the proposed "Initial Use Date" feature on the pen label, particularly since the Sponsor has addressed the concern by incorporating a feature on the rear of the carton for patients to record the date of initial use for each of the five pens.

2. Use of upper and lower case letters
From page 3 of the Complete response

5. [redacted] (b) (4) "Do Not Mix with Other Insulins," "For subcutaneous injection Only," and "Use within 28 days after opening" is difficult to read. DMETS recommends that these statements be displayed using upper and lower case lettering to improve readability of the statements.

Sanofi-aventis response:

The above statements are displayed using upper and lower case lettering. See Carton Label

Although the Sponsor's response to DMETS's recommendation is adequate, there was an error made in DMETS recommendation. DMETS intended the Sponsor to display all of the text on the primary display panel in upper and lower case lettering, not just the statements noted in the recommendation. The most recently submitted labels use all capital letters for the statements: "SOLUTION FOR INJECTION IN A DISPOSABLE INSULIN DELIVERY DEVICE" and "USE ONLY IF SOLUTION IS CLEAR AND COLORLESS WITH NO PARTICLES VISIBLE."

DMETS apologizes for the oversight, and recommends that the Sponsor also display these statements in upper and lower case lettering to improve the readability of the statements.

Regards,

Enid

Enid Galliers
Chief, Project Management Staff
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: 301-796-1211
Fax: 301-796-9712
email: enid.galliers@fda.hhs.gov

4/9/2007

From: Michael.Lutz@sanofi-aventis.com [mailto:Michael.Lutz@sanofi-aventis.com]
Sent: Monday, April 09, 2007 3:00 PM
To: Galliers, Enid M
Subject: RE: Lantus Solostar
Importance: High

Dear Enid,

Item 2 for the PEN LABEL

The pen label wraps around the pen body. It is shown flat in the graphic design. If you look at the technical drawing (attachment 2 - at manufacture the lot number, expiration date and manufacturers mark are printed in the blank space where DMETS suggested we place the line to record initial use date. The final printed labels at manufacture will use up this space where the lot no. and exp. date wrap around behind the pen body to the NDC no. and bar code at the top of the label. That is why we suggested putting the line to record initial use date in the oval where it will be in the front of the pen body instead of behind the pen body.

Item 2 for the IL

See third paragraph on page 1 of the IL.

"**Follow these instructions completely each time you use SoloStar® to ensure that you get an accurate dose. If you do not follow these instructions you may get too much or too little insulin, which may affect your blood glucose. "**

The sponsor is of the opinion that following the complete instructions is important. Therefore, this overall statement was added instead of only highlighting step 3.

Let's discuss

Thanks and regards,
Mike

Michael Lutz
Regulatory Development

sanofi-aventis U.S. Inc.
400 Crossing Boulevard
P.O. Box 6890
Mail Stop BX4-209A
Bridgewater, NJ 08807-0890

Tel:: +908.231.5620
Fax: +908.304.6560
email: michael.lutz@sanofi-aventis.com

> -----Original Message-----
> **From:** Galliers, Enid M [mailto:enid.galliers@fda.hhs.gov]
> **Sent:** Friday, April 06, 2007 12:26 PM
> **To:** Lutz, Michael (Regulatory Affairs) PH/US
> **Subject:** Lantus Solostar
>
> Dear Mike:
>
> I told Dr. Gerrell I would compare the 3/14/07 response to the deficiencies in the 2/28/07 fax for a

quick look at your responses for Lantus Solostar (NDA 21-018/S-024). However, my review does not supersede the pending review by DMETS. It looks to me like you have corrected everything except for item 2 for the PEN LABEL and item 2 for the PATIENT INSTRUCTION MANUAL (IL).

For the PEN LABEL, I can't tell where the borders of the draft label are, so I don't know how much room is available for writing.

For the IL, in Step 3 I saw the benefits of conducting the safety test - but not the explicit statement of consequences recommended in the fax. If you have added such a statement, it was not in that part of the IL, and I think that location is the appropriate one for that message.

Regards,

Enid

Enid Galliers
Chief, Project Management Staff
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: 301-796-1211
Fax: 301-796-9712
email: enid.galliers@fda hhs.gov

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/s/

Enid Galliers
4/9/2007 04:22:34 PM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: DMETS, OSE

FROM: Enid Galliers, DMETS, x 61211, WO 22, 3356

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
21-MAR-2007		21-081/S-024	BL (complete response to deficiencies from 2/9/07 DMETS review)	14-MAR--2007

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Lantus (insulin glargine[rDNA origin] injection)	Action goal = 25-APR-2007 This supplement is overdue; this is the 6-month date.		13-APR-2007

NAME OF FIRM: SANOFI-AVENTIS

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

This will be the 3rd DMETS review for this new packaging supplement. The supplement provides for a new pen injector for the insulin analog Lantus. This submission was made based on the labeling deficiencies identified in the DMETS review signed 2/9/07. The primary reviewer was Kellie Taylor.

Please indicate whether the firm has adequately responded to the issued raised in your previous reviews.
The network path location is: \\CDSESUB1\N21081\S_024\2007-03-14

The action date (4/25/07) is 6 months after the date of the resubmission of this supplement. (This type CMC packaging supplement was on a 4-month clock and is overdue. DMEP decided to try to get acceptable labeling so the supplement can be approved without needing another review cycle.)

SIGNATURE OF REQUESTER
Enid Galliers

METHOD OF DELIVERY (Check one)
☐ EMAIL ☑ DFS ☐ HAND

SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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

/s/

Enid Galliers
3/21/2007 07:04:27 PM
This electronic submission became available in the EDR on 3-20-07.

facsimile
TRANSMITTAL

to: **Mike Lutz, Reg. Aff., sanofi-aventis**
fax #: **908-304-6560** **phone: 908-231-5620**
re: **Labeling changes for Lantus SoloStar, NDA 21-081/S-024**
date: **28 FEB 2007**
pages: **4 (including cover page)**

Please respond to the recommendations from DMETS and DMEP listed in the attachment.

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Division of Metabolism and Endocrinology Products

Please note that ALL regulatory submissions must be sent to the following address:

CDR/CDER/FDA
Attention: DMEP
5901-B Ammendale Road
Beltsville, MD 20705-1266

From the desk of... Enid Galliers
Chief, Project Management Staff
Division of Metabolism & Endocrinology Products (DMEP; HFD-510)
ODE II, OND, CDER, FDA
10903 New Hampshire Avenue
White Oak Bldg. 22, Rm 3356
Silver Spring, MD 20993-0002
Email: enid.galliers@fda.hhs.gov
Phone: 301-796-1211
Fax: 301-796-9712

For NDA 21-081/S-024, we have the following labeling change and information requests.

Division of Medication Errors and Technical Support (DMETS)

In the review of the container and carton labeling of Lantus SoloStar, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which may minimize potential user errors.

A. PEN LABEL

1. DMETS recommends that the (b) (4) be removed from the pen label. The (b) (4) has minimal visual contrast with the black lettering used to display the proprietary name, established name, concentration and "Rx only" warning. DMETS believes that elderly or visually impaired diabetic patients could have difficulty reading the proposed labeling because of the poor visual contrast.

2. DMETS recommends that the sponsor provide space on the pen label for patients to record date of initial use. DMETS believes there is sufficient room on the label beneath the sponsor's name to accommodate this addition.

3. (b) (4) "Do Not Mix with Other Insulins," "For subcutaneous injection Only," and "Use within 28 days after opening" is difficult to read. DMETS recommends that these statements be displayed using upper and lower case lettering to improve readability of the statements.

B. CARTON LABELING

1. DMETS is unclear if the insulin delivery device is packaged with needles or if the needles are sold separately. If the needles are sold separately, DMETS recommends that this information be conveyed prominently on the primary display panel to alert practitioners and patients to this fact. Also, please specify the brand or type of needles that can be used safely with the device.

2. DMETS recommends adding "SoloStar® pens in use must not be stored in the refrigerator." This statement could be displayed on the rear panel of the carton, immediate following the "Use Pen within 28 days after initial use." DMETS believes this could help avoid the inadvertent storage of Pens in the refrigerator while in use.

3. DMETS recommends providing space on the rear panel of the carton for patients to record date of initial use for each pen. DMETS believes there is sufficient room on the label beneath the sponsor's name to accommodate this addition. DMETS believes this could help avoid the inadvertent use of expired pens.

4. DMETS recommends that the graphic on the primary and auxiliary panels of the SoloStar® pen device be modified to more accurately reflect the color of the Lantus SoloStar product. As it currently appears, the graphic could lead the patient or

practitioner to believe the pen is white instead of grey. To avoid any confusion that could ensue, DMETS recommends that the graphic be modified.

5. [redacted] (b) (4) "Do Not Mix with Other Insulins," "For subcutaneous injection Only," and "Use within 28 days after opening" is difficult to read. DMETS recommends that these statements be displayed using upper and lower case lettering to improve readability of the statements.

C. PATIENT INSTRUCTION MANUAL (IL)

1. DMETS recommends that the statement "Always perform the safety test before each injection" in Step 3 be further highlighted (and the word "Always" underlined) to increase the prominence of this information. DMETS acknowledges that the sponsor has highlighted the "Safety Test" section (Step 3) in red, but believes further emphasis should be drawn to the need to always perform the safety test prior to injection.

2. DMETS also recommends that the sponsor include explicit information in plain language regarding potential consequences that may occur if the patient fails to perform the safety test (e.g., "If you fail to perform the safety test before each injection, you may get too much or too little insulin which could affect your blood glucose.") DMETS believes that linking the safety test to avoidance of adverse outcomes may help to reinforce the importance of the process and hopefully, have a positive influence on patient adherence to the instruction.

3. DMETS recommends that the statement "Slowly count to 10 before you withdraw the needle from the skin" in Step 5 be highlighted to increase the prominence of this information.

D. PEN DEVICE

1. No comments.

Division of Metabolism and Endocrinology Products (DMEP)

A. PATIENT INSTRUCTION MANUAL (IL)

If only one kind of needle is suitable for use with SoloStar, specify the needle type in addition to naming the manufacturer.

B. PACKAGE INSERT

To the HOW SUPPLIED section, add a statement that needles are not included. Addition of a description of the types/brands of needles that may be used with SoloStar is recommended.

Please indicate whether the needles appropriate for SoloStar are already marketed.

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

/s/

Enid Galliers
2/28/2007 03:22:21 PM
CSO

Galliers, Enid M
From: Watson, Anthony [anthony.watson@fda.hhs.gov]
Sent: Friday, February 23, 2007 3:12 PM
To: Galliers, Enid M
Subject: FW: NDA 21-081 S024

Attachments: NDA 21-081 S024 Lantus SoloStar Rv1 Final.doc

Anthony D. Watson, BS, MS, MBA
Chief, General Hospital Devices Branch
Division of Anesthesiology, General Hospital, Infection Control, and Dental Devices
Center for Devices and Radiological Health
U.S. Food and Drug Administration
Tel: (240) 276-3707
Fax: (240) 276-3789

From: Soprey, Pandu
Sent: Monday, February 05, 2007 11:11 AM
To: Galliers, Enid M
Cc: Watson, Anthony; OC Combination Products
Subject: NDA 21-081 S024

NDA 21-081
:4 Lantus SoloSt

Attached is Consult Review Memo

Pandu R Soprey Ph D
Microbiologist
FDA/ODE/DAGID/GHDB
Tel: 240-276-3707 Fax 240-276-3789
Pandu.Soprey@fda.hhs.gov

COSULT REVIEW MEMO

DATE: February 2, 2007

TO: Enid M. Galliers CDER/DMEP/HFD-510

FROM: Pandu R. Soprey, Ph.D.
Review Scientist, CDRH/ODE/DAGID HFZ-480

THROUGH: Anthony Watson Branch Chief GHDB/DAGID/CDRH/ HFZ-480

SUBMISSION: NDA 21-081/S-024 Lantus (insulin glargine [rDNA origin]) Injection
NDA 21-629/S-008 Apidra (insulin glulisine [rDNA origin]) Injection

DEVICE:
Proprietary Name: SoloStar disposable Pen Injector for Lantus insulin and SoloStar disposable Pen Injector for Apidra insulin
Non-proprietary: Pen injector, Syringe containing insulin in a 3mL disposable cartridge

APPLICANT / SPONSOR:
Sanofi-Aventis

INTENT/PURPOSE OF THIS SUBMISSION:
The applicant has provided responses to the deficiencies listed in the approvable letter (dated August 24, 2006) for Lantus SoloStar and Apidra SoloStar. The responses to the deficiencies are provided in Supplement #24 dated October 24, 2006 and December 14, 2006

REVIEW OF DEVICE RELATED RESPONSES:

Response #2
In its initial position, tactile features on the dosage selector and the pen body are aligned "0" is displayed in the dose window and the dial will be at zero. The dose to be injected is then pre-selected by rotating a dosage selector at the rear end of the device and then the number of selected insulin units is displayed in the dose window on the side of the pen. After an injection of the selected dose the injection button reverts back to the original position and "0" is displayed in the dose window. Display of "0" assures that the dose delivery is complete.

The response explains how the dose delivery is complete, the response is acceptable.

Response #3
Dialing beyond the maximum dose of 80 units is not possible. If the patient tries to select a higher dose, the number sleeve and dose window engage rotationally preventing the number sleeve from moving further. The dosage selector and number sleeve are firmly affixed to each other during the assembly process.

All physical dose-setting limits (maximum dose, minimum dose, end of cartridge) have been tested and demonstrate a mechanical strength that will withstand forces typically applied by patients. Furthermore, torque required to set the dose was evaluated as well as the correlation between visual and audible feedback (i.e. the number of clicks correspond to units displayed in dose window).

Since SoloStar is a mechanically operated device, rapid dialing has no effect on accuracy of dose setting or injection. The number sleeve of the pen has two functions; it indicates the number of insulin units to be injected

and simultaneously sets the dose in the pen. Thus, dose indication and dose setting are physically linked and rapid dialing has no impact on the accuracy of the insulin pen.

The device was evaluated according to ISO Standard (ISO 11608:2000, Pen-injectors for medical use, Part 1: Requirements and test methods) test requirements. The device set at three different doses (1-unit, 40 units and 80 units) were tested at standard atmosphere (ISO 11608-1 Section 6.1), cool atmosphere (ISO 11608-1 Section 6.2), hot atmosphere (ISO 11608-1 Section 6.3), after preconditioning (ISO 11608-1 Section 7.1 and 7.2) and free fall testing (ISO 11608-1 Section 7.4b). The various tests results met the specification limits for all of the three dose volumes (1 U, 40 U and 80 U). The columns "calculated lower end of distribution (LED)" and "calculated upper end of distribution (UED)" are calculated from the confidence interval.

The response provided in the supplement shows that the device meets the dose selection and dose delivery requirements. The response is acceptable.

Response #4

The accuracy of the last dose was determined and found to be in compliance with the standard (ISO11608-1). Testing is performed in accordance with the ISO 11608-2 instructions. The test is conducted by placing a cartridge in an apparatus described in the ISO norm (ISO 11608-2). The liquid expelled from the cartridge is collected, and the volume delivered after the plunger displacement is then measured. All dose accuracy calculations are carried out in units of milliliters.

The initial position of the rubber stopper related to the shoulder of the glass cartridge defines how many units can be accurately delivered in total, i.e. the length of the cylindrical part of the cartridge. The mechanism was designed to ensure the rubber stopper cannot be pushed further than the cylindrical part of the glass cartridge during dosing. This is accomplished through the presence of a physical part which prevents additional advance of the mechanism beyond the last dose. Therefore the patient can dial only up to the dose left in the cartridge.

The response provided satisfies the dose delivery requirements. The response is acceptable.

Response #5:

Lantus® SoloStar® is not an auto injector and does not contain any external source of energy to deliver an insulin dose and the dose must be delivered manually by constant pressure from the patient on the activator. The dose is delivered manually by pressing the button inward until it is in its starting position and the dose window displays "0". Thus accidental firing is not possible. In addition, the patient leaflet mentioned that the needle needs to be removed after each injection by the patient. Without a needle the cartridge is sealed and no accidental firing is possible

The response is acceptable.

Response #6:

The applicant has identified the needles to be used with SoloStar pen injector. For Lantus SoloStar, the needles to be used with SoloStar injector are BD Ultra-Fine needles. This sentence will also be included in the Lantus "Instructions for SoloStar use": (b) (4)

The response is acceptable.

Response #7:

The sponsor has clarified function of the injection button and provided rationale for end position of the injection delivery button. When the injector button is in its initial position, tactile features on the dosage selector and the pen body are aligned, "0" is displayed in the dose window. The dose to be injected is pre-selected by rotating the

dosage selector at the rear end of the device. The number of selected insulin units is displayed in the dose window on the side of the pen. The dose is delivered by pressing the button until it is in its original position, in which "0" is displayed in the dose window. Mechanical constraints prevent the user from pushing the button any further beyond zero. Finally, the patient instruction manual instructs the patient to delay removal of the SoloStar for 10 seconds after the injection button is in the original position (when the injection button is in the original position and 0 is displayed in the dose window) to assure dose delivery is complete.

The response is acceptable.

Response #8:
This risk management process study is performed according to (b) (4) and applicable internal SOPs. In this process human factors and device specific factors as well as misuse or abuse scenarios are investigated, evaluated, corresponding mitigations if necessary were planned and implemented. The successful implementations of these factors were verified.

Usability studies are conducted to predict the potential for human error and misuse/abuse to occur. Final user testing is performed in a design validation study before market release of the device and after launch a post-market surveillance system is in place. Complaints and adverse events are continuously monitored, trended, investigated when necessary and used to update the risk management. Findings out of the Risk Management Process are used to improve the product if necessary and provide valuable contributions for the development of new devices.

The detailed information related to the performance and safety of the device is provided under the following description:

Intended Use:
The detailed description of intended use of SoloStar pen injector under different use different conditions are listed and described.

Functional Analysis:
Analysis of SoloStar was prepared which described logical representation of the relations of the input and output functions and this information was used as basis for a systematic review of all hazards related to each identifiable output function of the device.

(b) (4)

[redacted] (b) (4)

RISK MANAGEMENT:
The definition of the acceptable risk level was based on the standard [redacted] (b) (4), risk analysis for medical devices. In order to estimate the risks and to establish acceptable risk levels for SoloStar, a Risk Chart (Pg. 12) was used as qualitative categorization method. Using this chart the estimation of the risk of harm is divided into the probability of its occurrence and its severity. Seven severity classes were identified (fatal, life threatening, serious, non-serious, negligible, customer complaint, and customer reassurance. Performing a risk assessment the probability of occurrence of harm was estimated for all defined hazards associated with the output functions identified in the functional analysis.

The risk assessment was performed by an expert team consisting of representatives of various functions in the company. Additionally ergonomic specialists from an external company created abuse/misuse scenario and human factors assessments for SoloStar. These studies were taken into consideration while preparing the risk assessment. The results of the risk assessment for SoloStar before and after mitigation (risk control) were considered and summarized in the figures (Pg. 14).

Individual risks (128 risks) were evaluated and the occurrence of the adverse effect of basal (Lantus insulin) and short acting insulin (Apidra) were evaluated separately. After mitigation, for both the majority was found in the Generally Acceptable category, none of the risks are in the Not Acceptable category. 30 cases for both basal and short acting insulin remained in the region ("ALARP"). This represents a risk to patients with an extremely low probability of occurrence.

RISK - BENEFIT ANALYSIS:
The results of the risk assessment show that the use of SoloStar with insulin, like Lantus®, is associated with some risks that require risk control measures. A number of mitigations are already in place and effectiveness was verified.

The better part of the remaining overall residual risk can be associated with the proper use of the pen, with needle handling, with the potential risk to apply the wrong insulin or to use training pens filled with water (mix-up) and with needle pricking.

As per plan complaints and adverse events will be continuously monitored, trended and investigated (when required) after launch during post-market surveillance and used to update the risk management. The overall residual risk of SoloStar® was discussed and agreed in a cross-functional team meeting together with the Risk Management Board. All individual risks falling into the ALARP (As Low As Reasonably Practicable) region were presented to the Risk Management Board. Mitigations were discussed and agreed.

It was concluded that the intended benefit for the patients associated with the use of the SoloStar with insulin, like Lantus, outweighs the remaining overall residual risk

DESIGN VALIDATION STUDY
SoloStar pen injector was tested in a design validation study and the primary objective was to validate the use of the pen device by the target patient population (patients diagnosed with type 1 or type 2 diabetes mellitus) under two different scenarios, with or without face-to-face training by a healthcare professional:

Scenario #1 (Phase 1): This scenario was designed to simulate a clinical practice environment where active face-to-face training by the healthcare professional would take place, prior to the subjects receiving the pen injector.
Scenario #2 (Phase 2): This scenario was designed to simulate a clinical practice environment where the subject

would receive the pen and instructional leaflet, without any training by a healthcare professional. The subject would then self-train on how to use the pen with the instructions provided, and if necessary, request additional training via the sanofi-aventis (S-A) Help Line Call Center, or by contacting the healthcare professional by telephone. After training or self training, subjects were asked to show how to correctly deliver a dose, three times, each time with 3 different pens.

The study objective was assessed for each phase separately by the following endpoints: a) Primary endpoint: The proportion of subjects who delivered a successful dose on all three-dose delivery repetitions. b) Secondary endpoints: The proportion of subjects who performed the safety test (pre-dose actuation) correctly before each of the three dose delivery repetitions, the proportion of dose delivery repetitions with correctly performed safety tests, the proportion of repetitions for which a successful dose was delivered, the proportion of subjects who used the S-A Help Line Call Center or requested additional instructions (in person [Phase 1 only] or by telephone) from a healthcare professional after the initial training session, the proportion of subjects who made use of the instructional leaflet after the initial training session, and the accuracy and precision of the device based on the three dose injections (weights) per subject. Safety variables included the following: The incidence of adverse events (AEs) by primary term and Product Technical Complaints (PTCs).

The study population consisted of a total of 181 subjects (86 in Phase 1; 95 in Phase 2) and the safety population consisted of a total of 204 subjects (100 in Phase 1; and 104 in Phase 2). There were 50 validation subjects Phase 1 and 54 in Phase 2.

The results of the Efficacy and Safety study showed that the primary and secondary study criteria were meet and the conclusions of the design validation study were:

i) The use of the SoloStar pen device was successfully validated by subjects with type 1 and 2 diabetes mellitus (the target population) in both the Phase 1 and Phase 2 scenarios, with and without face-to-face training, respectively.
ii) Subjects using the SoloStar pen device accurately delivered the dose that was dialed.
iii) In Phase 1, the subjects delivered dose was confirmed to be accurate and the variability of the delivered dose was low. Although in Phase 2, accuracy could not be confirmed based on the SAP pre-defined interval when the outliers were excluded the delivered dose was observed to be accurate with a reduction in the among subject variability.
iv) The effect of safety test performance on the delivered dose was deemed not to be clinically relevant.
v) There were no adverse events or pen malfunctions. One PTC was reported however was determined to be due to a bent needle and not the pen device.

The response is acceptable.

COMMENTS AND CONCLUSION:
The applicant has provided adequate responses to the device related deficiencies (deficiencies #2 through #8). From a device viewpoint the pen-injector described in NDA 21-32 S024 may be approved.

Pandu R. Soprey
Scientific Reviewer, CDRH, HFZ-480

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/s/

Enid Galliers
2/23/2007 03:44:34 PM
CSO

Checking CDRH review into DFS on behalf of Pandu Soprey & Anthony Watson.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: DMETS, OSE

FROM: Enid Galliers, DMETS, x 61211, WO 22, 3356

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
12 NOV 2006		21-081/S-024	AZ (complete response to AE)	24-oct-2006

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Lantus (insulin glargine[rDNA origin] injection)	Action goal = 20-FEB-2007		02-FEB-2007

NAME OF FIRM: SANOFI-AVENTIS

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please review revisions to carton and pen labeling and the user manual.
The network path location is: \\CDSESUB1\N21081\S_024\2006-10-24

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Enid Galliers	☑ EMAIL (DFS) ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Enid Galliers

11/15/2006 06:18:48 PM

For Consulting Center Use Only:

Date Received: _____
Assigned to: _____
Date Assigned: _____
Assigned by: _____

Completed date: _____
Reviewer Initials: _____
Supervisory Concurrence: _____

Intercenter Request for Consultative or Collaborative Review Form

To (Consulting Center):
Center: CDRH
Division: DAGID/GHDB
Mail Code: HF Z-480
Consulting Reviewer Name: ANTHONY WATSON
Building/Room #: CORP/RM 340D, 9200 CORP BLVD
Phone #: 240-276-3700
Fax #:
Email Address: ANTHONY.WATSON@FDA.HHS.GOV
RPM/CSO Name and Mail Code:

From (Originating Center):
Center: CDER
Division: DMEP
Mail Code: HFD-510
Requesting Reviewer Name: E. GALLIERS
Building/Room #: WO 22/3356
Phone#: 301-796-1211
Fax #: 301-796-9712
Email Address: ENID.GALLIERS@FDA.HHS.GOV
RPM/CSO Name and Mail Code: ENID GALLIERS
Requesting Reviewer's Concurring Supervisor's Name:

Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.

Date of Request: 11/12/2006

Requested Completion Date: 2-2-07

Submission/Application Number: N21-081/s-024
(Not Barcode Number)

Submission Type: sNDA
(510(k), PMA, NDA, BLA, IND, IDE, etc.)

Type of Product: ☑ Drug-device combination ☐ Drug-biologic combination ☐ Device-biologic combination ☐ Drug-device-biologic combination ☐ Not a combination product

Submission Receipt Date: 25-OCT-2006

Official Submission Due Date: _____

Name of Product: LANTUS (INSULIN GLARGINE [RDNA ORIGIN] INJECTION SOLOSTAR PEN

Name of Firm: SANOFI-AVENTIS

Intended Use: The new SOLOSTAR pen contains 3 mL cartridges of insulin. IT IS FOR SUBCUTANEOUS INJECTION OF AN ADJUSTABLE DOSE OF THE INSULIN ANALOG, LANTUS.

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):

RESPONSE TO DEFICIENCIES LISTED IN ORIGINAL CDRH REVIEW. AVAILABLE IN CDER EDR. The EDR has received: NDA# N21081; Incoming Document Type: SCP; Incoming Document Type Sequence Number: 024; Supplement Modification Type: AZ; Letter Date: 10/24/2006. Copies of all pdf documents and TOCs are sent by email.
The network path location is: \\CDSESUB1\N21081\S_024\2006-10-24. You can review this submission and get the benefit of hyperlinking by entering EDR in your browser

Documents to be returned to Requesting Reviewer? ☐ Yes ☐ No

Complete description of the request. Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

Type of Request: ☑ Consultative Review ☐ Collaborative Review

(940 characters max -- use additional sheet if necessary)
Has the applicant responded adequately to the issues identified by a prior CDRH review? Do you recommend approval of the pen?

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

/s/

Enid Galliers

11/15/2006 06:11:27 PM

For Consulting Center Use Only:

Date Received: _____
Assigned to: _____
Date Assigned: _____
Assigned by: _____

Completed date: _____
Reviewer Initials: _____
Supervisory Concurrence: _____

Intercenter Request for Consultative or Collaborative Review Form

To (Consulting Center):
Center: CDRH
Division: ODE/DAGID/GHDB
Mail Code: HF Z-480
Consulting Reviewer Name: Anthony Watson
Building/Room #: Corporate Bldg, RM340D
Phone #: 301-594-1287 x169
Fax #:
Email Address: anthony.watson@hhs.cdrh.gov
RPM/CSO Name and Mail Code:

From (Originating Center):
Center: CDER
Division: DMEP
Mail Code: HFD-510
Requesting Reviewer Name: Janice Brown
Building/Room #: WO Bldg 21, RM 2662
Phone#: 301-796-1652
Fax #:
Email Address: janice.brown@hhs.cder.gov
RPM/CSO Name and Mail Code: Julie Rhee, DMEP
Requesting Reviewer's Concurring Supervisor's Name: James Vidra, Ph.D.

Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.

Date of Request: May 15, 2006

Requested Completion Date: August 15, 2006

Submission/Application Number: NDA 21-081/S-024
(Not Barcode Number)

Submission Type: NDA
(510(k), PMA, NDA, BLA, IND, IDE, etc.)

Type of Product: ☑ Drug-device combination ☐ Drug-biologic combination ☐ Device-biologic combination ☐ Drug-device-biologic combination ☐ Not a combination product

Submission Receipt Date: April 24, 2006

Official Submission Due Date: August 24, 2006

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

Name of Firm: Sanofi-Aventis

Intended Use: To treat adult and pediatric patients with type 1 diabetes or adult patients with type 2 diabetes.

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):

This supplement provides for a disposable insulin pen, Lantus SoloStar

Documents to be returned to Requesting Reviewer? ☐ Yes ☑ No

Complete description of the request. Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

Type of Request: ☑ Consultative Review ☐ Collaborative Review

(940 characters max -- use additional sheet if necessary)

Please review dose accuracy and precision of Lantus SoloStar pen. In addition, please review all information in section 3.2.P.7 Container Closure System which includes device components, specifications, methods, and assembly process description.

The sponsor also submitted a supplement for SoloStar pen to NDA 21-629 for Apidra (S-008). I'll request a separate consult for Apidra.

This supplement is submitted electronically; however, a hard copy of the section 3.2.P.7 is included with this request. If you need any additional information, please call Julie Rhee at 301-796-1280. Thank you.

Rhee, H Julie

From: Brown, Janice
Sent: Monday, May 15, 2006 11:17 AM
To: Rhee, H Julie
Subject: RE: SoloStar supplements (for Lantus and Apidra)

Julie,
In addition, please include a statement to review all information in section 3.2.P.7 Container Closure System which includes device components, specifications, methods, assembly process description.
Janice

From: Rhee, H Julie
Sent: Monday, May 15, 2006 11:09 AM
To: Brown, Janice
Subject: RE: SoloStar supplements (for Lantus and Apidra)

Thank you, Janice

I guess you want them to review accuracy and precision of the pen. Correct?

I am preparing a consult request now. When I am finished with them, I will enter them into DFS for your concurrence.

Thanks again,
Julie

From: Brown, Janice
Sent: Monday, May 15, 2006 11:08 AM
To: Rhee, H Julie
Subject: RE: SoloStar supplements (for Lantus and Apidra)

I think separate, but include a statement so they know that these supplements are related.
Janice

From: Rhee, H Julie
Sent: Monday, May 15, 2006 10:46 AM
To: Brown, Janice
Subject: RE: SoloStar supplements (for Lantus and Apidra)

Janice,

Do we need separate consult requests to CDRH)for Lantus and Apidra? Or could it be combined into one for both products?

Thanks,
Julie

From: Brown, Janice
Sent: Wednesday, May 10, 2006 12:00 PM
To: Rhee, H Julie
Subject: RE: SoloStar supplements (for Lantus and Apidra)

Julie,
Please request a consult to review the device information supplied in section 3.2.P.7 Container Closure System. Device information includes information on the components of SoloStar® as well as the manufacturing and associated testing performed with assembled SoloStar.
Janice

From: Rhee, H Julie
Sent: Wednesday, May 10, 2006 10:45 AM
To: Brown, Janice

Subject: FW: SoloStar supplements (for Lantus and Apidra)

Janice,

NDA number for Lantus is 21-081, not 21-801.

Thanks,
Julie

From: Rhee, H Julie
Sent: Wednesday, May 10, 2006 10:44 AM
To: Brown, Janice
Subject: SoloStar supplements (for Lantus and Apidra)

Hi Janice,

We have 2 supplements from Aventis for their new disposable insulin pen--Lantus SoloStar and Apidra SoloStar. They were submitted electronically to EDR.

I was planning to send a CDRH consult and wondering if you could help which part of the submission needs to be sent to CDRH and what would you like them to review.

The NDA numbers are NDA 21-801/S-024 and 21-629/S-008 and submission date is April 21, 2006.

Thanks,
Julie

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/s/

Janice Brown

5/15/2006 01:16:18 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-081/S-024 **PRIOR APPROVAL SUPPLEMENT**

Sanofi-aventis U.S. LLC
Attention: Mr. Michael Lutz
Regulatory Development
300 Somerset Corporate Blvd
Bridgewater, NJ 08807

Dear Mr. Lutz:

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: 024

Date of supplement: April 21, 2006

Date of receipt: April 24, 2006

This supplemental application proposes the following change: Addition of a new disposable insulin pen device, Lantus® SoloStar®.

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 June 23, 2006, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be August 24, 2006.

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any question, call me at (301) 796-1280.

Sincerely,

{See appended electronic signature page}

Julie Rhee
Regulatory Project Manager
Division of Metabolism
and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Julie Rhee

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Director, Division of Medication Errors and Technical Support (DMETS), HFD-420 WO22, RM 4447

FROM: Julie Rhee, DMEP, WO 3368, 796-1280

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
April 28, 2006		21-081/S-024	Original Supplement	April 21, 2006

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Lantus (insulin glargine [rDNA origin] injection)			August 10, 2006

NAME OF FIRM: Sanofi-Aventis

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: **Trade name review**

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:
This supplement provides for a new disposable insulin delivery device (SoloStar®) for use with Lantus. Please review whether or not the proposed tradename for the device, SoloStar, is acceptable. Also, please let me know if you have any labeling comments on the supplement. Since the submission is available in EDR, no paper copy of the submission is included with this consult request.

The sponsor submitted a separate supplement for the same device under NDA 21-629/S-008. I'll fill out a consult request for that supplement as well. Thank you.
PDUFA DATE: August 24, 2006

NAME AND PHONE NUMBER OF REQUESTER	METHOD OF DELIVERY (Check one)
Julie Rhee	☒ DFS ONLY ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

5/28/05

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/s/

Julie Rhee

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