

# CENTER FOR DRUG EVALUATION AND RESEARCH

## Approval Package for:

### *APPLICATION NUMBER:*

**021081Orig1s062**

*Trade Name:* LANTUS

*Generic or Proper Name:* insulin glargine [rDNA origin] injection

*Sponsor:* sanofi-aventis U.S. LLC

*Approval Date:* February 25, 2015

*Indication:* Lantus is a long-acting human insulin analog indicated to improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus.

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## 021081Orig1s062

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**CENTER FOR DRUG EVALUATION AND  
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*APPLICATION NUMBER:*

**021081Orig1s062**

**APPROVAL LETTER**



NDA 021081/S-062

**SUPPLEMENT APPROVAL**

sanofi-aventis U.S. LLC  
Attention: Antonella Lozito, PharmD  
Associate Director, Global Regulatory Affairs  
55 Corporate Drive, Mail Stop: 55D-215A  
Bridgewater, NJ 08807

Dear Dr. Lozito:

Please refer to your Supplemental New Drug Application (sNDA) dated and received August 15, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Lantus (insulin glargine [rDNA origin]), injection, 100 Units/mL.

We acknowledge receipt of your amendments dated October 24 and December 5, 2014, and January 12, 2015.

We also refer to our letter dated July 17, 2014, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for products indicated for diabetes mellitus that have multi-dose pen presentations. This information pertains to the risk of transmission of bloodborne pathogens resulting from pen devices and pen cartridges that are intended for single patient use only, being shared among numerous patients.

This supplemental new drug application provides for revisions to the labeling for Lantus consistent with our July 17, 2014, letter.

In our July 17, 2014, letter, we also required you to submit a plan for how you would modify the pen device to include a statement warning against the sharing of pens, on the body of the pen. In your submission dated August 15, 2014, you provided a rationale for why you believe that adding the warning statement to the body of the pen is not necessary and/or feasible. We have reviewed this rationale and found it acceptable that the warning not be placed on the body of the pen at this time.

**APPROVAL & LABELING**

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

## **CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert, patient package insert and Instructions for Use), with the addition of any labeling changes in pending “Changes Being Effectuated” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

## **PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>. Information and Instructions for completing the form can be found at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

### **REPORTING REQUIREMENTS**

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 Richard Whitehead, Regulatory Project Manager, at (301) 796-4945.

Sincerely,

*{See appended electronic signature page}*

Jennifer Rodriguez Pippins, M.D., M.P.H.  
Deputy Director for Safety  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

### ENCLOSURES:

- Lantus Package Insert
- Lantus Vial Patient Package Insert
- Lantus SoloStar Patient Package Insert
- Lantus SoloStar Instructions for Use
- Lantus Carton and Container labels

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JENNIFER R PIPPINS  
02/25/2015

**CENTER FOR DRUG EVALUATION AND  
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*APPLICATION NUMBER:*

**021081Orig1s062**

**LABELING**

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use LANTUS safely and effectively. See full prescribing information for LANTUS.

LANTUS (insulin glargine [rDNA origin] injection) solution for subcutaneous injection  
Initial U.S. Approval: 2000

-----RECENT MAJOR CHANGES-----

Warnings and Precautions (5.1) 02/2015

-----INDICATIONS AND USAGE-----

LANTUS is a long- acting human insulin analog indicated to improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus. (1)

Important Limitations of Use:

- Not recommended for treating diabetic ketoacidosis. Use intravenous, short-acting insulin instead.

-----DOSAGE AND ADMINISTRATION-----

- Individualize dose based on the type of diabetes and whether the patient is insulin-naïve (2.1, 2.2, 2.3)
- Administer subcutaneously once daily at any time of day, but at the same time every day. (2.1)
- Rotate injection sites within an injection area (abdomen, thigh, or deltoid) to reduce the risk of lipodystrophy. (2.1)
- Converting from other insulin therapies may require adjustment of timing and dose of LANTUS. Closely monitor glucoses especially upon converting to LANTUS and during the initial weeks thereafter. (2.3)

-----DOSAGE FORMS AND STRENGTHS-----

Solution for injection 100 units/mL (U-100) in

- 10 mL vials
- 3 mL SoloStar disposable insulin device (3)

-----CONTRAINDICATIONS-----

- In patients with hypersensitivity to LANTUS or one of its excipients (4)

-----WARNINGS AND PRECAUTIONS-----

- Never share a LANTUS SoloStar pen between patients, even if the needle is changed (5.1)
- Do not reuse or share needles or syringes between patients (5.1)

- *Dose adjustment and monitoring* Monitor blood glucose in all patients treated with insulin. Modify insulin regimen cautiously and only under medical supervision (5.2)
- *Administration* Do not dilute or mix with any other insulin or solution. Do not administer subcutaneously via an insulin pump or intravenously because severe hypoglycemia can occur (5.3)
- *Hypoglycemia* May be life-threatening. Monitor glucose, administer rescue therapy and treat underlying cause.(5.4, 6.1)
- *Allergic reactions:* Severe, life-threatening, generalized allergy, including anaphylaxis, can occur. Discontinue LANTUS. Monitor and treat if indicated (5.5, 6.1)
- *Renal or hepatic impairment* Reduce dose of LANTUS if indicated (5.6, 5.7)
- *Fluid retention and heart failure can occur with concomitant use of thiazolidinediones (TZDs):* Observe for signs and symptoms of heart failure; consider dosage reduction or discontinuation of TZD if heart failure occurs (5.9)

-----ADVERSE REACTIONS-----

Adverse reactions commonly associated with LANTUS include hypoglycemia, allergic reactions, injection site reactions, lipodystrophy, pruritus, rash, edema and weight gain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact sanofi-aventis at 1-800-633-1610 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

-----DRUG INTERACTIONS-----

- Certain drugs may affect glucose metabolism, requiring insulin dose adjustment and close monitoring of blood glucose. (7)
- The signs of hypoglycemia may be reduced or absent in patients taking anti-adrenergic drugs (e.g., beta-blockers, clonidine, guanethidine, and reserpine). (7)

-----USE IN SPECIFIC POPULATIONS-----

- Pregnancy category C: Use during pregnancy only if the potential benefit justifies the potential risk to the fetus (8.1)
- Pediatric: Has not been studied in children with type 2 diabetes. Has not been studied in children with type 1 diabetes <6 years of age (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 02/2015

**FULL PRESCRIBING INFORMATION: CONTENTS\***

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- 17.2 Instructions for patients
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\*Sections or subsections omitted from the full prescribing information are not listed.

## FULL PRESCRIBING INFORMATION

### 1. INDICATIONS AND USAGE

LANTUS is indicated to improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus.

Important Limitations of Use:

- LANTUS is not recommended for the treatment of diabetic ketoacidosis. Intravenous short-acting insulin is the preferred treatment for this condition.

### 2. DOSAGE AND ADMINISTRATION

#### 2.1 Dosing

LANTUS is a recombinant human insulin analog for once daily subcutaneous administration with potency that is approximately the same as the potency of human insulin. LANTUS 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. The dose of LANTUS must be individualized based on clinical response. Blood glucose monitoring is essential in all patients receiving insulin therapy.

Patients adjusting the amount or timing of dosing with LANTUS, should only do so under medical supervision with appropriate glucose monitoring [*see Warnings and Precautions (5.2).*]

In patients with type 1 diabetes, LANTUS must be used in regimens with short-acting insulin.

The intended duration of activity of LANTUS is dependent on injection into subcutaneous tissue [*see Clinical pharmacology (12.2)*]. LANTUS should not be administered intravenously or via an insulin pump. Intravenous administration of the usual subcutaneous dose could result in severe hypoglycemia [*see Warnings and Precautions (5.3)*].

As with all insulins, injection sites should be rotated within the same region (abdomen, thigh, or deltoid) from one injection to the next to reduce the risk of lipodystrophy [*See Adverse Reactions (6.1)*].

In clinical studies, there was no clinically 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, such as stress, intercurrent illness, or changes in co-administered drugs or meal patterns.

#### 2.2 Initiation of LANTUS therapy

The recommended starting dose of LANTUS in patients with type 1 diabetes should be approximately one-third of the total daily insulin requirements. Short-acting, premeal insulin should be used to satisfy the remainder of the daily insulin requirements.

The recommended starting dose of LANTUS in patients with type 2 diabetes who are not currently treated with insulin is 10 units (or 0.2 Units/kg) once daily, which should subsequently be adjusted to the patient's needs.

The dose of LANTUS should be adjusted according to blood glucose measurements. The dosage of LANTUS should be individualized under the supervision of a healthcare provider in accordance with the needs of the patient.

### **2.3 Converting to LANTUS from other insulin therapies**

If changing from a treatment regimen with an intermediate-or long-acting insulin to a regimen with LANTUS, the amount and timing of shorter-acting insulins and doses of any oral anti-diabetic drugs may need to be adjusted.

- If transferring patients from once-daily NPH insulin to once-daily LANTUS, the recommended initial LANTUS dose is the same as the dose of NPH that is being discontinued.
- If transferring patients from twice-daily NPH insulin to once-daily LANTUS, the recommended initial LANTUS dose is 80% of the total NPH dose that is being discontinued. This dose reduction will lower the likelihood of hypoglycemia [*see Warnings and Precautions (5.4)*].

## **3. DOSAGE FORMS AND STRENGTHS**

LANTUS solution for injection 100 Units per mL is available as:

- 10 mL Vial (1000 Units/10 mL)
- 3 mL SoloStar<sup>®</sup> disposable insulin device (300 Units/3 mL)

## **4. CONTRAINDICATIONS**

LANTUS is contraindicated

- In patients with hypersensitivity to LANTUS or one of its excipients [*See Warnings and Precautions (5.4)*].

## **5. WARNINGS AND PRECAUTIONS**

### **5.1 Never share a LANTUS SoloStar pen or syringe or needle between patients**

LANTUS SoloStar pens must never be shared between patients, even if the needle is changed. Patients using LANTUS vials must never reuse or share needles or syringes with another person. Sharing poses a risk for transmission of blood-borne pathogens.

## 5.2 Dosage adjustment and monitoring

Glucose monitoring is essential for all patients receiving insulin therapy. Changes to an insulin regimen should be made cautiously and only under medical supervision.

Changes in insulin strength, manufacturer, type, or method of administration may result in the need for a change in insulin dose or an adjustment in concomitant oral anti-diabetic treatment.

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

## 5.3 Administration

Do not administer LANTUS intravenously or via an insulin pump. The intended duration of activity of LANTUS is dependent on injection into subcutaneous tissue

Intravenous administration of the usual subcutaneous dose could result in severe hypoglycemia [*see Warnings and Precautions (5.4)*].

Do not dilute or mix LANTUS with any other insulin or solution. If LANTUS is diluted or mixed, the solution may become cloudy, and the pharmacokinetic or pharmacodynamic profile (e.g., onset of action, time to peak effect) of LANTUS and 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 a delayed 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 unknown.

## 5.4 Hypoglycemia

Hypoglycemia is the most common adverse reaction of insulin, including LANTUS. The risk of hypoglycemia increases with intensive glycemic control. Patients must be educated to recognize and manage hypoglycemia. Severe hypoglycemia can lead to unconsciousness or convulsions and may result in temporary or permanent impairment of brain function or death. Severe hypoglycemia requiring the assistance of another person or parenteral glucose infusion or glucagon administration has been observed in clinical trials with insulin, including trials with LANTUS.

The timing of hypoglycemia usually reflects the time-action profile of the administered insulin formulations. Other factors such as changes in food intake (e.g., amount of food or timing of meals), exercise, and concomitant medications may also alter the risk of hypoglycemia [*See Drug Interactions (7)*].

The prolonged effect of subcutaneous LANTUS may delay recovery from hypoglycemia. 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 (2.3)*].

As with all insulins, use caution in patients with hypoglycemia unawareness and in patients who may be predisposed to hypoglycemia (e.g., the pediatric population and patients who fast or have erratic food intake). The patient's ability to concentrate and react may be impaired as a result of hypoglycemia. This may present a risk in situations where these abilities are especially important, such as driving or operating other machinery.

Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as longstanding diabetes, diabetic neuropathy, use of medications such as beta-blockers, or intensified glycemic control. These situations may result in severe hypoglycemia (and, possibly, loss of consciousness) prior to the patient's awareness of hypoglycemia.

### **5.5 Hypersensitivity and allergic reactions**

Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products, including LANTUS.

### **5.6 Renal impairment**

Due to its long duration of action, Lantus is not recommended during periods of rapidly declining renal function because of the risk for prolonged hypoglycemia.

Although studies have not been performed in patients with diabetes and renal impairment, a reduction in the LANTUS dose may be required in patients with renal impairment because of reduced insulin metabolism, similar to observations found with other insulins. [*See Clinical Pharmacology (12.3)*].

### **5.7 Hepatic impairment**

Due to its long duration of action, Lantus is not recommended during periods of rapidly declining hepatic function because of the risk for prolonged hypoglycemia.

Although studies have not been performed in patients with diabetes and hepatic impairment, a reduction in the LANTUS dose may be required in patients with hepatic impairment because of reduced capacity for gluconeogenesis and reduced insulin metabolism, similar to observations found with other insulins. [*See Clinical Pharmacology (12.3)*].

### **5.8 Drug interactions**

Some medications may alter insulin requirements and subsequently increase the risk for hypoglycemia or hyperglycemia [*See Drug Interactions (7)*].

### **5.9 Fluid retention and heart failure with concomitant use of PPAR-gamma agonists**

Thiazolidinediones (TZDs), which are peroxisome proliferator-activated receptor (PPAR)-gamma agonists, can cause dose-related fluid retention, particularly when used in combination with insulin. Fluid retention may lead to or exacerbate heart failure. Patients treated with insulin, including LANTUS, and a PPAR-gamma agonist should be observed for signs and symptoms of heart failure. If heart failure develops, it should be managed according to current standards of care, and discontinuation or dose reduction of the PPAR-gamma agonist must be considered.

## **6. ADVERSE REACTIONS**

The following adverse reactions are discussed elsewhere:

- Hypoglycemia [*See Warnings and Precautions (5.4)*]

- Hypersensitivity and allergic reactions [See Warnings and Precautions (5.5)]

### 6.1 Clinical trial experience

Because clinical trials are conducted under widely varying designs, the adverse reaction rates reported in one clinical trial may not be easily compared to those rates reported in another clinical trial, and may not reflect the rates actually observed in clinical practice.

The frequencies of treatment-emergent adverse events during LANTUS clinical trials in patients with type 1 diabetes mellitus and type 2 diabetes mellitus are listed in the tables below.

**Table 1: Treatment –emergent adverse events in pooled clinical trials up to 28 weeks duration in adults with type 1 diabetes (adverse events with frequency  $\geq$  5%)**

	LANTUS, % (n=1257)	NPH, % (n=1070)
Upper respiratory tract infection	22.4	23.1
Infection *	9.4	10.3
Accidental injury	5.7	6.4
Headache	5.5	4.7

\*Body System not Specified

**Table 2: Treatment –emergent adverse events in pooled clinical trials up to 1 year duration in adults with type 2 diabetes (adverse events with frequency  $\geq$  5%)**

	LANTUS, % (n=849)	NPH, % (n=714)
Upper respiratory tract infection	11.4	13.3
Infection*	10.4	11.6
Retinal vascular disorder	5.8	7.4

\*Body System not Specified

**Table 3: Treatment –emergent adverse events in a 5-year trial of adults with type 2 diabetes (adverse events with frequency  $\geq$  10%)**

	LANTUS, % (n=514)	NPH, % (n=503)
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Upper respiratory tract infection	29.0	33.6
Edema peripheral	20.0	22.7
Hypertension	19.6	18.9
Influenza	18.7	19.5
Sinusitis	18.5	17.9
Cataract	18.1	15.9
Bronchitis	15.2	14.1
Arthralgia	14.2	16.1
Pain in extremity	13.0	13.1
Back pain	12.8	12.3
Cough	12.1	7.4
Urinary tract infection	10.7	10.1
Diarrhea	10.7	10.3
Depression	10.5	9.7
Headache	10.3	9.3

**Table 4: Treatment –emergent adverse events in a 28-week clinical trial of children and adolescents with type 1 diabetes (adverse events with frequency  $\geq$  5%)**

	LANTUS, % (n=174)	NPH, % (n=175)
Infection*	13.8	17.7
Upper respiratory tract infection	13.8	16.0
Pharyngitis	7.5	8.6
Rhinitis	5.2	5.1

\*Body System not Specified

- Severe Hypoglycemia

Hypoglycemia is the most commonly observed adverse reaction in patients using insulin, including LANTUS [See Warnings and Precautions (5.3)]. Tables 5, and 6 and 7 summarize the incidence of severe hypoglycemia in the LANTUS individual clinical trials. Severe symptomatic hypoglycemia was defined as an event with symptoms consistent with hypoglycemia requiring the assistance of another person and associated with either a blood glucose below 50 mg/dL ( $\leq$ 56 mg/dL in the 5-year trial and  $\leq$ 36 mg/dL in the ORIGIN trial) or prompt recovery after oral carbohydrate, intravenous glucose or glucagon administration.

The proportion of patients experiencing severe symptomatic hypoglycemia in the LANTUS clinical trials [See Clinical Studies (14)] in adults with type 1 diabetes and type 2 diabetes were comparable for all treatment regimens (see Tables 5 and 6). In the pediatric phase 3 clinical trial, children and adolescents with type 1 diabetes had a higher incidence of severe symptomatic hypoglycemia in the two treatment groups compared to the adult trials with type 1 diabetes.

**Table 5: Severe Symptomatic Hypoglycemia in Patients with Type 1 Diabetes**

	Study A Type 1 Diabetes Adults 28 weeks In combination with regular insulin		Study B Type 1 Diabetes Adults 28 weeks In combination with regular insulin		Study C Type 1 Diabetes Adults 16 weeks In combination with insulin lispro		Study D Type 1 Diabetes Pediatrics 26 weeks In combination with regular insulin	
	LANTUS	NPH	LANTUS	NPH	LANTUS	NPH	LANTUS	NPH
Percent of patients (n/total N)	10.6 (31/292)	15.0 (44/293)	8.7 (23/264)	10.4 (28/270)	6.5 (20/310)	5.2 (16/309)	23.0 (40/174)	28.6 (50/175)

**Table 6: Severe Symptomatic Hypoglycemia in Patients with Type 2 Diabetes**

	Study E Type 2 Diabetes Adults 52 weeks In combination with oral agents		Study F Type 2 Diabetes Adults 28 weeks In combination with regular insulin		Study G Type 2 Diabetes Adults 5 years In combination with regular insulin	
	LANTUS	NPH	LANTUS	NPH	LANTUS	NPH
Percent of patients (n/total N)	1.7 (5/289)	1.1 (3/281)	0.4 (1/259)	2.3 (6/259)	7.8 (40/513)	11.9 (60/504)

Table 7 displays the proportion of patients experiencing severe symptomatic hypoglycemia in the Lantus and Standard Care groups in the ORIGIN Trial [*see Adverse Reactions (cardiovascular safety)*].

**Table 7: Severe Symptomatic Hypoglycemia in the ORIGIN trial**

	ORIGIN Trial Median duration of follow-up: 6.2 years	
	LANTUS	Standard Care
Percent of patients (n/total N)	5.6 (352/6231)	1.8 (113/6273)

- Retinopathy

Retinopathy was evaluated in the LANTUS clinical studies by analysis of reported retinal adverse events and fundus photography. The numbers of retinal adverse events reported for LANTUS and NPH insulin treatment groups were similar for patients with type 1 and type 2 diabetes.

LANTUS was compared to NPH insulin in a 5-year randomized clinical trial that evaluated the progression of retinopathy as assessed with fundus photography using a grading protocol derived from the Early Treatment Diabetic Retinopathy Scale (ETDRS). Patients had type 2 diabetes (mean age 55 yrs) with no (86%) or mild (14%) retinopathy at baseline. Mean baseline HbA1c was 8.4%. The primary outcome was progression by 3 or more steps on the ETDRS scale at study endpoint. Patients with pre-specified post-baseline eye procedures (pan-retinal photocoagulation for proliferative or severe nonproliferative diabetic retinopathy, local photocoagulation for new vessels, and vitrectomy for diabetic retinopathy) were also considered as 3-step progressors regardless of actual change in ETDRS score from baseline. Retinopathy graders were blinded to treatment group assignment. The results for the primary endpoint are shown in Table 8 for both the per-protocol and Intent-to-Treat populations, and indicate

similarity of Lantus to NPH in the progression of diabetic retinopathy as assessed by this outcome.

**Table 8: Number (%) of patients with 3 or more step progression on ETDRS scale at endpoint**

	Lantus (%)	NPH (%)	Difference <sup>a,b</sup> (SE)	95% CI for difference
<b>Per-protocol</b>	53/374 (14.2%)	57/363 (15.7%)	-2.0% (2.6%)	-7.0% to +3.1%
<b>Intent-to-Treat</b>	63/502 (12.5%)	71/487 (14.6%)	- 2.1% (2.1%)	-6.3% to +2.1%

a: Difference = Lantus – NPH

b: using a generalized linear model (SAS GENMOD) with treatment and baseline HbA1c strata (cutoff 9.0%) as the classified independent variables, and with binomial distribution and identity link function

- Insulin initiation and intensification of glucose control

Intensification or rapid improvement in glucose control has been associated with a transitory, reversible ophthalmologic refraction disorder, worsening of diabetic retinopathy, and acute painful peripheral neuropathy. However, long-term glycemic control decreases the risk of diabetic retinopathy and neuropathy.

- Lipodystrophy

Long-term use of insulin, including LANTUS, can cause lipodystrophy at the site of repeated insulin injections. Lipodystrophy includes lipohypertrophy (thickening of adipose tissue) and lipoatrophy (thinning of adipose tissue), and may affect insulin absorption. Rotate insulin injection or infusion sites within the same region to reduce the risk of lipodystrophy. [See *Dosage and Administration (2.1)*].

- Weight gain

Weight gain can occur with insulin therapy, including LANTUS, and has been attributed to the anabolic effects of insulin and the decrease in glucosuria.

- Peripheral Edema

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

- Allergic Reactions

Local Allergy

As with any insulin therapy, patients taking LANTUS may experience injection site reactions, including redness, pain, itching, urticaria, edema, and inflammation. 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 did not result in discontinuation of therapy.

Rotation of the injection site within a given area from one injection to the next may help to reduce or prevent these reactions. In some instances, these reactions may be related to factors other than insulin, such as irritants in a skin cleansing agent or poor injection technique. Most minor reactions to insulin usually resolve in a few days to a few weeks.

### *Systemic Allergy*

Severe, life-threatening, generalized allergy, including anaphylaxis, generalized skin reactions, angioedema, bronchospasm, hypotension, and shock may occur with any insulin, including LANTUS and may be life threatening.

- *Antibody production*

All insulin products can elicit the formation of insulin antibodies. The presence of such insulin antibodies may increase or decrease the efficacy of insulin and may require adjustment of the insulin dose. In phase 3 clinical trials of LANTUS, increases in titers of antibodies to insulin were observed in NPH insulin and insulin glargine treatment groups with similar incidences.

- *Cardiovascular Safety*

The Outcome Reduction with Initial Glargine Intervention trial (i.e., ORIGIN) was an open-label, randomized, 2-by-2, factorial design study. One intervention in ORIGIN compared the effect of LANTUS to standard care on major adverse cardiovascular outcomes in 12,537 participants  $\geq 50$  years of age with abnormal glucose levels [i.e., impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT)] or early type 2 diabetes mellitus and established cardiovascular (i.e., CV) disease or CV risk factors at baseline.

The objective of the trial was to demonstrate that LANTUS use could significantly lower the risk of major cardiovascular outcomes compared to standard care. Two co-primary composite cardiovascular endpoints were used in ORIGIN. The first co-primary endpoint was the time to first occurrence of a major adverse cardiovascular event defined as the composite of CV death, nonfatal myocardial infarction and nonfatal stroke. The second co-primary endpoint was the time to the first occurrence of CV death or nonfatal myocardial infarction or nonfatal stroke or revascularization procedure or hospitalization for heart failure.

Participants were randomized to either LANTUS (N=6264) titrated to a goal fasting plasma glucose of  $\leq 95$  mg/dL or to standard care (N=6273). Anthropometric and disease characteristics were balanced at baseline. The mean age was 64 years and 8% of participants were 75 years of age or older. The majority of participants were male (65%). Fifty nine percent were Caucasian, 25% were Latin, 10% were Asian and 3% were Black. The median baseline BMI was 29 kg/m<sup>2</sup>. Approximately 12% of participants had abnormal glucose levels (IGT and/or IFG) at baseline and 88% had type 2 diabetes. For patients with type 2 diabetes, 59% were treated with a single oral antidiabetic drug, 23% had known diabetes but were on no antidiabetic drug and 6% were newly diagnosed during the screening procedure. The mean HbA1c (SD) at baseline was 6.5% (1.0). Fifty nine percent of participants had had a prior cardiovascular event and 39% had documented coronary artery disease or other cardiovascular risk factors.

Vital status was available for 99.9% and 99.8% of participants randomized to LANTUS and standard care respectively at end of trial. The median duration of follow-up was 6.2 years [range: 8 days to 7.9 years]. The mean HbA1c (SD) at the end of the trial was 6.5% (1.1) and 6.8% (1.2) in the LANTUS and standard care group respectively. The median dose of LANTUS at end of trial was 0.45 U/kg. Eighty-one percent of patients randomized to LANTUS were

using LANTUS at end of the study. The mean change in body weight from baseline to the last treatment visit was 2.2 kg greater in the LANTUS group than in the standard care group.

Overall, the incidence of major adverse cardiovascular outcomes was similar between groups (see Table 9). All-cause mortality was also similar between groups.

**Table 9: Cardiovascular Outcomes in ORIGIN - Time to First Event Analyses**

	LANTUS N=6264	Standard Care N=6273	LANTUS vs Standard Care
	n (Events per 100 PY)	n (Events per 100 PY)	Hazard Ratio (95% CI)
<b>Co-primary endpoints</b>			
CV death, nonfatal myocardial infarction, or nonfatal stroke	1041 (2.9)	1013 (2.9)	1.02 (0.94, 1.11)
CV death, nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure or revascularization procedure	1792 (5.5)	1727 (5.3)	1.04 (0.97, 1.11)
<b>Components of co-primary endpoints</b>			
CV death	580	576	1.00 (0.89, 1.13)
Myocardial Infarction (fatal or non-fatal)	336	326	1.03 (0.88, 1.19)
Stroke (fatal or non-fatal)	331	319	1.03 (0.89, 1.21)
Revascularizations	908	860	1.06 (0.96, 1.16)
Hospitalization for heart failure	310	343	0.90 (0.77, 1.05)

- Cancer

In the ORIGIN trial, the overall incidence of cancer (all types combined) or death from cancer (Table 10) was similar between treatment groups.

**Table 10: Cancer Outcomes in ORIGIN - Time to First Event Analyses**

	LANTUS N=6264	Standard Care N=6273	LANTUS vs Standard Care
	n (Events per 100 PY)	n (Events per 100 PY)	Hazard Ratio (95% CI)
<b>Cancer endpoints</b>			
Any cancer event (new or recurrent)	559 (1.56)	561 (1.56)	0.99 (0.88, 1.11)
New cancer events	524 (1.46)	535 (1.49)	0.96 (0.85, 1.09)
Death due to Cancer	189 (0.51)	201 (0.54)	0.94 (0.77, 1.15)

## 6.2 Postmarketing experience

The following adverse reactions have been identified during post-approval use of LANTUS.

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate reliably their frequency or establish a causal relationship to drug exposure.

Medication errors have been reported in which other insulins, particularly short-acting insulins, have been accidentally administered instead of LANTUS [*See Patient Counseling Information (17)*]. To avoid medication errors between LANTUS and other insulins, patients should be instructed to always verify the insulin label before each injection.

## **7. DRUG INTERACTIONS**

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

The following are examples of drugs that may increase the blood-glucose-lowering effect of insulins including LANTUS and, therefore, increase the susceptibility to hypoglycemia: oral anti-diabetic products, pramlintide, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, propoxyphene, pentoxifylline, salicylates, somatostatin analogs, and sulfonamide antibiotics.

The following are examples of drugs that may reduce the blood-glucose-lowering effect of insulins including LANTUS: corticosteroids, niacin, danazol, diuretics, sympathomimetic agents (e.g., epinephrine, albuterol, terbutaline), glucagon, 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.

The signs of hypoglycemia may be reduced or absent in patients taking sympatholytic drugs such as beta-blockers, clonidine, guanethidine, and reserpine.

## **8. USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

Pregnancy Category C: Subcutaneous reproduction and teratology studies have been performed with insulin glargine and regular human insulin in rats and Himalayan rabbits. Insulin glargine 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 Units/day (0.008 mg/kg/day), based on mg/m<sup>2</sup>. In rabbits, doses of 0.072 mg/kg/day, which is approximately 2 times the recommended human subcutaneous starting dose of 10 Units/day (0.008 mg/kg/day), based on mg/m<sup>2</sup>, 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 LANTUS in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. 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 these patients.

### **8.3 Nursing Mothers**

It is unknown whether insulin glargine is excreted in human milk. Because many drugs, including human insulin, are excreted in human milk, caution should be exercised when LANTUS is administered to a nursing woman. Use of LANTUS is compatible with breastfeeding, but women with diabetes who are lactating may require adjustments of their insulin doses.

### **8.4 Pediatric Use**

The safety and effectiveness of subcutaneous injections of LANTUS have been established in pediatric patients (age 6 to 15 years) with type 1 diabetes [*see Clinical Studies (14)*]. LANTUS has not been studied in pediatric patients younger than 6 years of age with type 1 diabetes. LANTUS has not been studied in pediatric patients with type 2 diabetes.

Based on the results of a study in pediatric patients, the dose recommendation when switching to LANTUS is the same as that described for adults [*see Dosage and Administration (2.3)* and *Clinical Studies (14)*]. As in adults, the dosage of LANTUS must be individualized in pediatric patients based on metabolic needs and frequent monitoring of blood glucose.

### **8.5 Geriatric Use**

In controlled clinical studies comparing LANTUS to NPH insulin, 593 of 3890 patients (15%) with type 1 and type 2 diabetes were  $\geq 65$  years of age and 80 (2%) patients were  $\geq 75$  years of age. The only difference in safety or effectiveness in the subpopulation of patients  $\geq 65$  years of age compared to the entire study population was a higher incidence of cardiovascular events typically seen in an older population in both LANTUS and NPH insulin-treated patients. Nevertheless, caution should be exercised when LANTUS is administered to geriatric 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 Warnings and Precautions (5.4)*].

## **10. OVERDOSAGE**

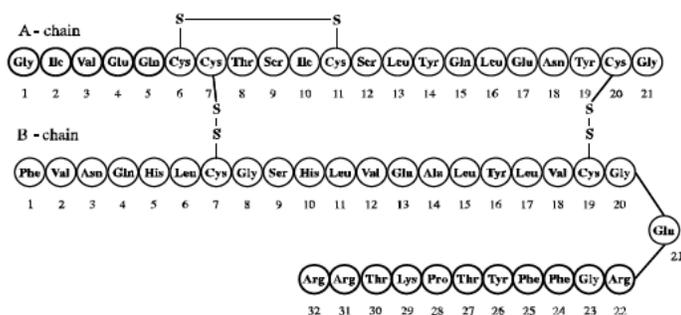
An excess of insulin relative to food intake, energy expenditure, or both may lead to severe and sometimes prolonged and life-threatening hypoglycemia. Mild episodes of hypoglycemia can usually be treated with oral carbohydrates. Adjustments in drug dosage, meal patterns, or exercise may be needed.

More severe episodes of hypoglycemia 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 recurrence of hypoglycemia.

## 11. DESCRIPTION

LANTUS (insulin glargine [rDNA origin] injection) is a sterile solution of insulin glargine for use as a subcutaneous 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 (12)*]. 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, insulin glargine is 21<sup>A</sup>-Gly-30<sup>B</sup>a-L-Arg-30<sup>B</sup>b-L-Arg-human insulin and has the empirical formula C<sub>267</sub>H<sub>404</sub>N<sub>72</sub>O<sub>78</sub>S<sub>6</sub> and a molecular weight of 6063. Insulin glargine 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 Units (3.6378 mg) insulin glargine.

The 10 mL vial presentation contains the following inactive ingredients per mL: 30 mcg zinc, 2.7 mg m-cresol, 20 mg glycerol 85%, 20 mcg polysorbate 20, and water for injection.

The 3 mL cartridge presentation contains the following inactive ingredients per mL: 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.

## 12. CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

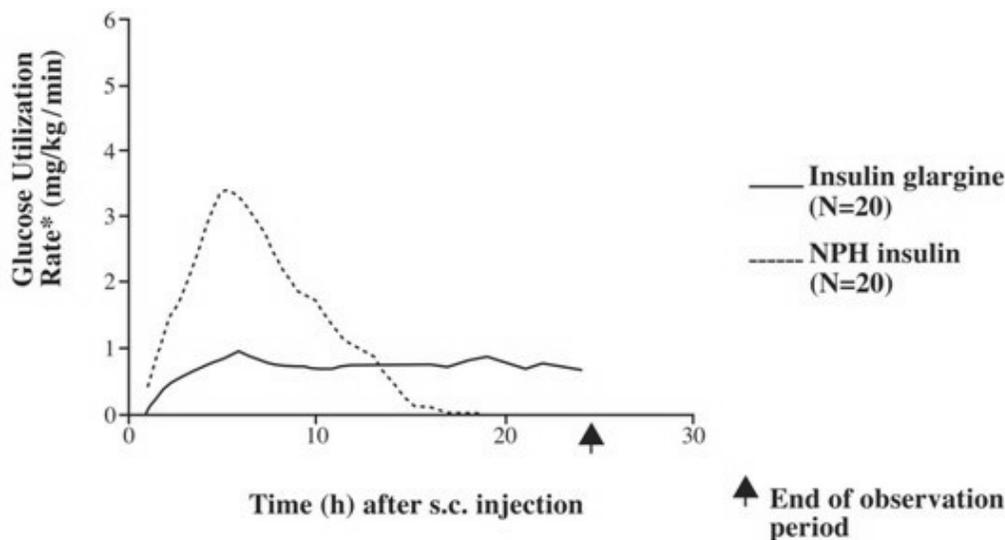
The primary activity of insulin, including insulin glargine, is regulation of glucose metabolism. Insulin and its analogs lower blood glucose by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin inhibits lipolysis and proteolysis,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

## 12.2 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, insulin glargine 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 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 that for 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 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 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 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.

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 within the same individual.

## 12.3 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 insulin. Serum insulin concentrations were thus consistent with the time profile of the pharmacodynamic activity of insulin glargine.

After subcutaneous injection of 0.3 Units/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<sup>A</sup>-Gly-insulin) and M2 (21<sup>A</sup>-Gly-des-30<sup>B</sup>-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 insulin [see *Clinical Studies (14)*].

*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 *Use in Specific Populations (8.1)*].

*Obesity.* In controlled clinical trials, which included patients with Body Mass Index (BMI) up to and including 49.6 kg/m<sup>2</sup>, subgroup analyses based on BMI did not show differences in safety and efficacy between insulin glargine and NPH insulin [see *Clinical Studies (14)*].

*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 impairment [See *Warnings and Precautions (5.6)*].

*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 impairment [See *Warnings and Precautions (5.7)*].

## 13. NONCLINICAL TOXICOLOGY

### 13.1 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 was for the rat approximately 10 times and for the mouse approximately 5 times the recommended human subcutaneous starting dose of 10 Units/day

(0.008 mg/kg/day), based on mg/m<sup>2</sup>. 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 was approximately 7 times the recommended human subcutaneous starting dose of 10 Units/day (0.008 mg/kg/day), based on mg/m<sup>2</sup>, 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 insulin.

## 14. CLINICAL STUDIES

The safety and effectiveness of LANTUS given once-daily at bedtime was compared to that of once-daily and twice-daily NPH insulin in open-label, randomized, active-controlled, parallel studies of 2,327 adult patients and 349 pediatric patients with type 1 diabetes mellitus and 1,563 adult patients with type 2 diabetes mellitus (see Tables 9-11). In general, the reduction in glycated hemoglobin (HbA1c) with LANTUS was similar to that with NPH insulin. The overall rates of hypoglycemia did not differ between patients with diabetes treated with LANTUS compared to NPH insulin [*See Adverse Reactions (6.1)*].

### **Type 1 Diabetes—Adult** (see Table 11).

In two clinical studies (Studies A and B), patients with type 1 diabetes (Study A; n=585, Study B; n=534) were randomized to 28 weeks of basal-bolus treatment with LANTUS or NPH insulin. Regular human insulin was administered before each meal. LANTUS was administered at bedtime. NPH insulin was administered once daily at bedtime or in the morning and at bedtime when used twice daily.

In another clinical study (Study C), patients with type 1 diabetes (n=619) were randomized to 16 weeks of basal-bolus treatment with LANTUS or NPH insulin. Insulin lispro was used before each meal. LANTUS was administered once daily at bedtime and NPH insulin was administered once or twice daily.

In these 3 studies, LANTUS and NPH insulin had similar effects on HbA1c (Table 11) with a similar overall rate of hypoglycemia [*See Adverse Reactions (6.1)*].

**Table 11: Type 1 Diabetes Mellitus–Adult**

	<u>Study A</u>		<u>Study B</u>		<u>Study C</u>	
	28 weeks Regular insulin		28 weeks Regular insulin		16 weeks Insulin lispro	
	<u>LANTUS</u>	<u>NPH</u>	<u>LANTUS</u>	<u>NPH</u>	<u>LANTUS</u>	<u>NPH</u>
Treatment duration						
Treatment in combination with						
Number of subjects treated	292	293	264	270	310	309
HbA1c						
Baseline HbA1c	8.0	8.0	7.7	7.7	7.6	7.7
Adj. mean change from baseline	+0.2	+0.1	-0.2	-0.2	-0.1	-0.1
LANTUS – NPH	+0.1		+0.1		0.0	
95% CI for Treatment difference	(0.0; +0.2)		(-0.1; +0.2)		(-0.1; +0.1)	
Basal insulin dose						
Baseline mean	21	23	29	29	28	28
Mean change from baseline	-2	0	-4	+2	-5	+1
Total insulin dose						
Baseline mean	48	52	50	51	50	50
Mean change from baseline	-1	0	0	+4	-3	0
Fasting blood glucose (mg/dL)						
Baseline mean	167	166	166	175	175	173
Adj. mean change from baseline	-21	-16	-20	-17	-29	-12
Body weight (kg)						
Baseline mean	73.2	74.8	75.5	75.0	74.8	75.6
Mean change from baseline	0.1	-0.0	0.7	1.0	0.1	0.5

**Type 1 Diabetes–Pediatric (see Table 12).**

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 insulin was administered once or twice daily. Similar effects on HbA1c (Table 12) and the incidence of hypoglycemia were observed in both treatment groups [See *Adverse Reactions (6.1)*].

**Table 12: Type 1 Diabetes Mellitus–Pediatric**

Treatment duration Treatment in combination with	Study D 28 weeks Regular insulin	
	<u>LANTUS</u>	<u>NPH</u>
Number of subjects treated	174	175
HbA1c		
Baseline mean	8.5	8.8
Adj. mean change from baseline	+0.3	+0.3
LANTUS – NPH	0.0	
95% CI for Treatment difference	(-0.2; +0.3)	
Basal insulin dose		
Baseline mean	19	19
Mean change from baseline	-1	+2
Total insulin dose		
Baseline mean	43	43
Mean change from baseline	+2	+3
Fasting blood glucose (mg/dL)		
Baseline mean	194	191
Adj. mean change from baseline	-23	-12
Body weight (kg)		
Baseline mean	45.5	44.6
Mean change from baseline	2.2	2.5

**Type 2 Diabetes–Adult (see Table 13).**

In a randomized, controlled clinical study (Study E) (n=570), LANTUS was evaluated for 52 weeks in combination with oral anti-diabetic medications (a sulfonylurea, metformin, acarbose, or combinations of these drugs). LANTUS administered once daily at bedtime was as effective as NPH insulin administered once daily at bedtime in reducing HbA1c and fasting glucose (Table 13). The rate of hypoglycemia was similar in LANTUS and NPH insulin treated patients [See Adverse Reactions (6.1)].

In a randomized, controlled clinical study (Study F), in patients with type 2 diabetes not using oral anti-diabetic medications (n=518), a basal-bolus regimen of LANTUS once daily at bedtime or NPH 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 insulin in reducing HbA1c and fasting glucose (Table 13) with a similar incidence of hypoglycemia [See Adverse Reactions (6.1)].

In a randomized, controlled clinical study (Study G), patients with type 2 diabetes were randomized to 5 years of treatment with once-daily LANTUS or twice-daily NPH insulin. For patients not previously treated with insulin, the starting dose of LANTUS or NPH insulin was 10 units daily. Patients who were already treated with NPH insulin either continued on the same total daily NPH insulin dose or started LANTUS at a dose that was 80% of the total previous NPH insulin dose. The primary endpoint for this study was a comparison of the progression of diabetic retinopathy by 3 or more steps on the Early Treatment Diabetic Retinopathy Study (ETDRS) scale. HbA1c change from baseline was a secondary endpoint. Similar glycemic control in the 2 treatment groups was desired in order to not confound the interpretation of the retinal data. Patients or study personnel used an algorithm to adjust the LANTUS and NPH insulin doses to a target fasting plasma glucose  $\leq 100$  mg/dL. After the LANTUS or NPH insulin dose was adjusted, other anti-diabetic agents, including pre-meal insulin were to be adjusted or added. The LANTUS group had a smaller mean reduction from baseline in HbA1c compared to

the NPH insulin group, which may be explained by the lower daily basal insulin doses in the LANTUS group (Table 13). Both treatment groups had a similar incidence of reported symptomatic hypoglycemia. The incidences of severe symptomatic hypoglycemia are given in Table 6 [See Adverse Reactions (6.1)].

**Table 13: Type 2 Diabetes Mellitus–Adult**

	<u>Study E</u>		<u>Study F</u>		<u>Study G</u>	
	52 weeks		28 weeks		5 years	
	Oral agents		Regular insulin		Regular insulin	
Treatment in combination with	<u>LANTUS</u>	<u>NPH</u>	<u>LANTUS</u>	<u>NPH</u>	<u>LANTUS</u>	<u>NPH</u>
Number of subjects treated	289	281	259	259	513	504
HbA1c						
Baseline mean	9.0	8.9	8.6	8.5	8.4	8.3
Adj. mean change from baseline	-0.5	-0.4	-0.4	-0.6	-0.6	-0.8
LANTUS – NPH	-0.1		+0.2		+0.2	
95% CI for Treatment difference	(-0.3; +0.1)		(0.0; +0.4)		(+0.1, +0.4)	
Basal insulin dose*						
Baseline mean	14	15	44.1	45.5	39	44
Mean change from baseline	+12	+9	-1	+7	+23	+30
Total insulin dose*						
Baseline mean	14	15	64	67	48	53
Mean change from baseline	+12	+9	+10	+13	+41	+40
Fasting blood glucose (mg/dL)						
Baseline mean	179	180	164	166	190	180
Adj. mean change from baseline	-49	-46	-24	-22	-45	-44
Body weight (kg)						
Baseline mean	83.5	82.1	89.6	90.7	100	99
Adj. mean change from baseline	2.0	1.9	0.4	1.4	3.7	4.8

\*In Study G, the baseline dose of basal or total insulin was the first available on-treatment dose prescribed during the study (on visit month 1.5).

#### **LANTUS Timing of Daily Dosing (see Table 14).**

The safety and efficacy of LANTUS administered pre-breakfast, pre-dinner, or at bedtime were evaluated in a randomized, controlled clinical study in patients with type 1 diabetes (study H, n=378). Patients were also treated with insulin lispro at mealtime. LANTUS administered at different times of the day resulted in similar reductions in HbA1c compared to that with bedtime administration (see Table 14). In these patients, data are available from 8-point home glucose monitoring. The maximum mean blood glucose was observed just prior to injection of LANTUS regardless of time of administration.

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. The safety and efficacy of LANTUS administered pre-breakfast or at bedtime were also evaluated in a randomized, active-controlled clinical study (Study I, n=697) in patients with type 2 diabetes not adequately controlled on oral anti-diabetic therapy. All patients in this study also received glimepiride 3 mg daily. LANTUS given before breakfast was at least as effective in lowering HbA1c as LANTUS given at bedtime or NPH insulin given at bedtime (see Table 14).

**Table 14: LANTUS Timing of Daily Dosing in Type 1 (Study H) and Type 2 (Study I) Diabetes Mellitus**

Treatment duration Treatment in combination with:	Study H 24 weeks			Study I 24 weeks		
	Insulin lispro			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	7.6	7.5	7.6	9.1	9.1	9.1
Mean change from baseline	-0.2	-0.1	0.0	-1.3	-1.0	-0.8
Basal insulin dose (U)						
Baseline mean	22	23	21	19	20	19
Mean change from baseline	5	2	2	11	18	18
Total insulin dose (U)						
Baseline mean	52	52	49	NA***	NA	NA
Mean change from baseline	2	3	2			
Body weight (kg)						
Baseline mean	77.1	77.8	74.5	80.7	82	81
Mean change from baseline	0.7	0.1	0.4	3.9	3.7	2.9

\*Intent to treat \*\*total number of patients evaluable for safety \*\*\*Not applicable

## 16. HOW SUPPLIED/STORAGE AND HANDLING

### 16.1 How supplied

LANTUS solution for injection 100 units per mL (U-100) is available as:

Dosage Unit/Strength	Package size	NDC # <b>0088</b>
<b>10 mL vials</b> 100 Units/mL	Pack of 1	2220-33
<b>3 mL SoloStar<sup>®</sup> disposable insulin device</b> 100 Units/mL	package of 5	2219-05

Needles are not included in the packs.

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

### 16.2 Storage:

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

Unopened Vial/ SoloStar disposable insulin device:

Unopened LANTUS vials and SoloStar device should be stored in a refrigerator, 36°F - 46°F (2°C - 8°C). Discard after the expiration date.

Open (In-Use) Vial:

Vials must be discarded 28 days after being opened. 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) 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 device must be discarded 28 days after being opened.

These storage conditions are summarized in the following table:

	<b>Not in-use (unopened)</b> <b>Refrigerated</b>	<b>Not in-use (unopened)</b> <b>Room Temperature</b>	<b>In-use (opened)</b> <b>(See Temperature Below)</b>
10 mL Vial	Until expiration date	28 days	28 days Refrigerated or room temperature
3 mL SoloStar <sup>®</sup> disposable insulin device	Until expiration date	28 days	28 days Room temperature only (Do not refrigerate)

### 16.3 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 *Warnings and Precautions (5.3)*].

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

SoloStar: If SoloStar disposable insulin device, malfunctions, LANTUS may be drawn from the cartridge system or from SoloStar into a U-100 syringe and injected.

## 17. PATIENT COUNSELING INFORMATION

### 17.1 Never share a LANTUS SoloStar pen or syringe or needle between patients

Advise patients that they must never share a LANTUS SoloStar pen with another person, even if the needle is changed. Advise patients using LANTUS vials not to reuse or share needles or syringes with another person. Sharing carries a risk for transmission of blood-borne pathogens.

### 17.2 Instructions for patients

Patients should be informed that changes to insulin regimens must be made cautiously and only under medical supervision.

Patients should be informed about the potential side effects of insulin therapy, including lipodystrophy (and the need to rotate injection sites within the same body region), weight gain, allergic reactions, and hypoglycemia. Patients should be informed that the ability to concentrate and react may be impaired as a result of hypoglycemia. This may present a risk in situations where these abilities are especially important, such as driving or operating other machinery. Patients who have frequent hypoglycemia or reduced or absent warning signs of hypoglycemia should be advised to use caution when driving or operating machinery.

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

LANTUS must only be used if the solution is clear and colorless with no particles visible. Patients must be advised that LANTUS must NOT be diluted or mixed with any other insulin or solution.

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

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

Refer patients to the LANTUS “Patient Information” for additional information.

### **17.3 FDA approved patient labeling**

See attached document at end of Full Prescribing Information.

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

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

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

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

- **Do not share your LANTUS SoloStar pen with other people, even if the needle has been changed. You may give other people a serious infection, or get a serious infection from them.**
- **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.
  - **if you take any other medicines,** especially ones commonly called TZDs (thiazolidinediones).
  - **if you have heart failure or other heart problems.** If you have heart failure, it may get worse while you take TZDs with LANTUS.

## **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.
- **Do not share your LANTUS SoloStar pen with other people, even if the needle has been changed.** You may give other people a serious infection, or get a serious infection from them.
- Do not reuse needles. 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 SoloStarUse**

**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](http://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<sup>†</sup> 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 are 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.

### **Swelling of your hands and feet (edema)**

### **Weight gain**

**Heart Failure.** Taking certain diabetes pills called thiazolidinediones or “TZDs” with LANTUS may cause heart failure in some people. This can happen even if you have never had heart failure or heart problems before. If you already have heart failure it may get worse while you take TZDs with LANTUS. Your healthcare provider should monitor you closely while you are taking TZDs with LANTUS. Tell your healthcare provider if you have any new or worse symptoms of heart failure including:

- shortness of breath
- swelling of your ankles or feet
- sudden weight gain

During treatment with TZDs and LANTUS, the TZD dose may need to be adjusted or stopped by your healthcare provider if you have new or worse heart failure.

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:

	<b>Not in-use (unopened)</b>	<b>Not in-use (unopened)</b>	<b>In-use (opened)</b>
	<b>Refrigerated</b>	<b>Room Temperature</b>	<b>Room Temperature (Do not refrigerate)</b>
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 other people, 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](http://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](http://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.jdrf.org](http://www.jdrf.org).

To get more information about diabetes, check with your healthcare professional or diabetes educator or visit [www.DiabetesWatch.com](http://www.DiabetesWatch.com).

Additional information about LANTUS can be obtained by calling 1-800-633-1610 or by visiting [www.lantus.com](http://www.lantus.com).

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

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

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

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

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

### **What is Diabetes?**

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

### **What is LANTUS?**

- LANTUS (insulin glargine [recombinant DNA origin]) is a long-acting insulin. Because LANTUS is made by recombinant DNA technology (rDNA) and is chemically different from the insulin made by the human body, it is called an insulin analog. LANTUS is used to treat patients with diabetes for the control of high blood sugar. It is used once a day to lower blood sugar.
- LANTUS is a clear, colorless, sterile solution for injection under the skin (subcutaneously).
- The active ingredient in LANTUS is insulin glargine. The concentration of insulin glargine is 100 units per milliliter (mL), or U-100. LANTUS also contains zinc, metacresol, glycerol, polysorbate 20 and water for injection as inactive ingredients. Hydrochloric acid and/or sodium hydroxide may be added to adjust the pH.
- You need a prescription to get LANTUS. Always be sure you receive the right insulin from the pharmacy.

### **Who should NOT take LANTUS?**

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

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

- **have liver or kidney problems.** Your dose may need to be adjusted.
- **are pregnant or plan to become pregnant.** It is not known if LANTUS may harm your unborn baby. It is very important to maintain control of your blood sugar levels during pregnancy. Your healthcare provider will decide which insulin is best for you during your pregnancy.
- **are breast-feeding or plan to breast-feed.** It is not known whether LANTUS passes into your milk. Many medicines, including insulin, pass into human milk, and could affect your baby. Talk to your healthcare provider about the best way to feed your baby.
- **about all the medicines you take including** prescription and non-prescription medicines, vitamins, and herbal supplements.
- **if you take any other medicines**, especially ones commonly called TZDs (thiazolidinediones).

- **if you have heart failure or other heart problems.** If you have heart failure, it may get worse while you take TZDs with LANTUS.

### **How should I use LANTUS?**

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

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

### **What kind of syringe should I use?**

- Always use a syringe that is marked for U-100 insulin. If you use other than U-100 insulin syringe, you may get the wrong dose of insulin causing serious problems for you, such as a blood sugar level that is too low or too high.
- **Do not reuse or share your syringes with other people.** Always use a new syringe each time you give LANTUS injection. **You may give other people a serious infection, or get a serious infection from them.**
- **Do not reuse needles.** Always use a new needle each time you give LANTUS injection.
- Disposable syringes and needles should be used only once. Used syringes and 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.

### **Mixing with LANTUS**

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

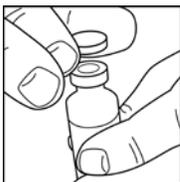
### **Instructions for Use**

#### **How do I draw the insulin into the syringe?**

- **The syringe must be new and does not contain any other medicine.** Do not reuse or share your syringes with other people. You may give other people a serious infection, or get a serious infection from them.
- **Do not mix LANTUS with any other type of insulin.**

Follow these steps:

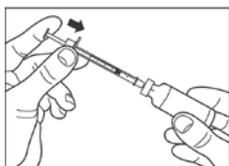
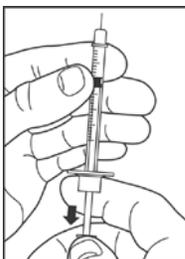
1. Wash your hands with soap and water or with alcohol.
2. Check the insulin to make sure it is clear and colorless. Do not use the insulin after the expiration date stamped on the label, if it is colored or cloudy, or if you see particles in the solution.
3. If you are using a new vial, remove the protective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



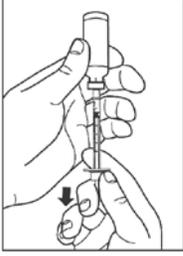
4. Wipe the top of the vial with an alcohol swab. You do not have to shake the vial of LANTUS before use.



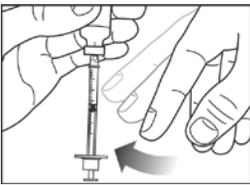
5. Use a new needle and syringe every time you give an injection. Use disposable syringes and needles only once. Throw them away properly. Do not reuse or share your syringes with other people. You may give other people a serious infection, or get a serious infection from them. Do not reuse needles.
6. Draw air into the syringe equal to your insulin dose. Put the needle through the rubber top of the vial and push the plunger to inject the air into the vial.



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



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



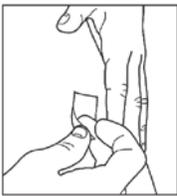
10. Remove the needle from the vial. Do not let the needle touch anything. You are now ready to inject.

### **How do I inject LANTUS?**

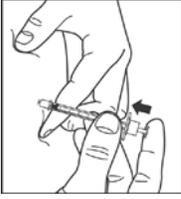
Inject LANTUS under your skin. Take LANTUS as prescribed by your healthcare provider.

Follow these steps:

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



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



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

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

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

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

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

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

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

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

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

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

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

#### **Hypoglycemia (low blood sugar):**

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

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

#### **Hypoglycemia can happen with:**

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

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

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

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

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

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

Symptoms of hypoglycemia may include:

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

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

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

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

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

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

### **Hyperglycemia can happen with:**

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

- use after the expiration date.

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

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

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

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

**Symptoms of hyperglycemia include:**

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

**Symptoms of DKA also include:**

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

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

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

Other possible side effects of LANTUS include:

**Serious allergic reactions:**

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

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

### **Reactions at the injection site:**

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

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

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

### **Swelling of your hands and feet (edema)**

### **Weight gain**

**Heart Failure.** Taking certain diabetes pills called thiazolidinediones or “TZDs” with LANTUS may cause heart failure in some people. This can happen even if you have never had heart failure or heart problems before. If you already have heart failure it may get worse while you take TZDs with LANTUS. Your healthcare provider should monitor you closely while you are taking TZDs with LANTUS. Tell your healthcare provider if you have any new or worse symptoms of heart failure including:

- shortness of breath
- swelling of your ankles or feet
- sudden weight gain

During treatment with TZDs and LANTUS, the TZD dose may need to be adjusted or stopped by your healthcare provider if you have new or worse heart failure.

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

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

### **How should I store LANTUS?**

- **Unopened vial:**

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

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

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

These storage conditions are summarized in the following table:

	<b>Not in-use (unopened)</b>	<b>Not in-use (unopened)</b>	<b>In-use (opened)</b>
	<b>Refrigerated</b>	<b>Room Temperature</b>	<b>(See Temperature Below)</b>
10 mL Vial	Until expiration date	28 days	28 days Refrigerated or room temperature

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

**General Information about LANTUS**

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

To get more information about diabetes, check with your healthcare professional or diabetes educator or visit [www.DiabetesWatch.com](http://www.DiabetesWatch.com).

Additional information about LANTUS can be obtained by calling 1-800-633-1610 or by visiting [www.lantus.com](http://www.lantus.com).

Rev. February 2015

sanofi-aventis U.S. LLC  
Bridgewater, NJ 08807  
A SANOFI COMPANY

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For FDA Submission Only

OPEN HERE

**SANOFI**



**Lantus<sup>®</sup> soloStar<sup>®</sup>**  
*insulin glargine (rDNA origin) injection*  
**100 units/mL (U-100)**  
 For Single Patient Use Only  
 Five 3 mL Prefilled Pens

NDC 0088-2219-05

**Rx ONLY**

Solution for injection in a disposable insulin delivery device  
 Do not mix with other insulins  
 For subcutaneous injection only  
 Use only if solution is clear and colorless with no particles visible  
 Use within 28 days after initial use \*Needles not included (see back panel)

**Lantus<sup>®</sup> soloStar<sup>®</sup>**  
*insulin glargine (rDNA origin) injection*  
**100 units/mL (U-100)**  
 Five 3 mL Prefilled Pens  
 Do not mix with other insulins

Lot \_\_\_\_\_  
 Exp \_\_\_\_\_

**Lantus<sup>®</sup> soloStar<sup>®</sup>**  
*insulin glargine (rDNA origin) injection*  
**100 units/mL (U-100)**  
 Five 3 mL Prefilled Pens  
 Do not mix with other insulins

**Rx ONLY**

Each mL of LANTUS<sup>®</sup> contains 100 U (3.6378mg) insulin glargine, 30mcg zinc, 2.7mg metacresol, 20mg glycerol 85%, and water for injection. pH is adjusted by addition of aqueous solutions of hydrochloric acid and sodium hydroxide.

**Dosage and Administration:** See package insert for dosage information. As with any drug, if you are pregnant or nursing a baby, seek professional advice when using this product. Any change of insulin should be made cautiously and only under medical supervision.

**WARNING:** Keep out of reach of children.

**Unopened SoloStar<sup>®</sup>:** Unopened LANTUS<sup>®</sup> SoloStar<sup>®</sup> devices should be stored in a refrigerator, 36°F - 46°F (2°C - 8°C). Do not freeze. Discard if frozen. Discard after the expiration date.

**Open (In-Use) SoloStar<sup>®</sup>:** The opened (in-use) SoloStar<sup>®</sup> 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<sup>®</sup> device must be discarded 28 days after being opened.

\*BD Ultra-Fine<sup>™</sup> needles are compatible with SoloStar<sup>®</sup>. These are sold separately and manufactured by BD.

**sanofi-aventis U.S. LLC**  
 Bridgewater, NJ 08807  
 A SANOFI COMPANY ©20XX  
 1-800-633-1610 www.lantus.com  
 Origin Germany  
 50XXXXXX

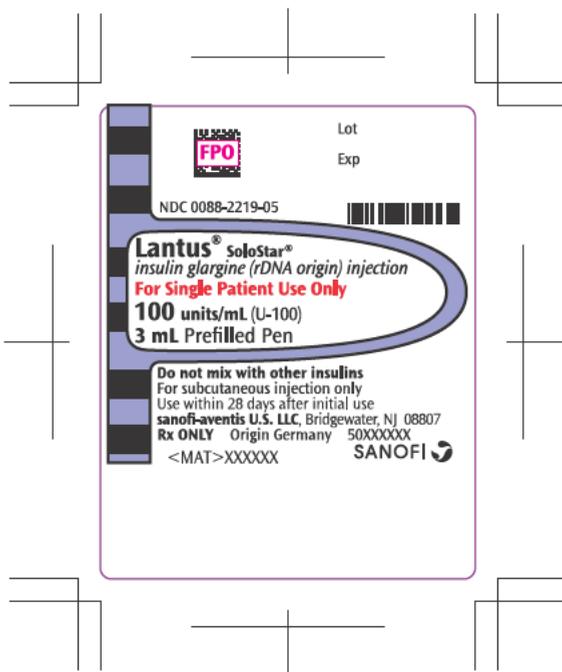
**Initial Use Date**  
 Pen 1: \_\_\_\_\_  
 Pen 2: \_\_\_\_\_  
 Pen 3: \_\_\_\_\_  
 Pen 4: \_\_\_\_\_  
 Pen 5: \_\_\_\_\_

N 3 00882 21905 8

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# For FDA Submission Only



**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**021081Orig1s062**

**OTHER REVIEW(S)**

**REGULATORY PROJECT MANAGER LABELING REVIEW**  
**Division of Metabolism and Endocrinology Products**

**Application Number:** NDA 021081/S-062

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

**Applicant:** sanofi-aventis U.S. LLC

**Background and Summary**

On July 17, 2014, Safety Labeling Change (SLC) notification letters were issued for all diabetes products that have approved pen presentations (see list below). The SLC letters required the applicants of these products to add a warning against the sharing of pens between patients, due to the serious risk of transmission of blood borne pathogens (see DMEPA review in DARRTS dated August 22, 2013). The warning was required to be added to all the labeling pertaining to the pens for these products, including the content of labeling and the carton and container labels. The applicants were also required to propose a plan for adding the warning to the body of the pen.

The applicants submitted supplements in response to this SLC notification on August 15, 2014, and included all the required labeling with the pen-sharing warning. They also provided a rationale for why they believe that adding the warning statement to the body of the pen is not necessary or warranted. DMEPA reviewed this rationale and found it acceptable that the warning not be placed on the body of the pen at this time (see DMEPA review in DARRTS dated October 7, 2014).

DMEPA also reviewed the carton and container labels submitted with these supplements, and asked the applicants to revise the labels (DMEPA review in DARRTS dated October 7, 2014). They reviewed the revised labels and found them acceptable and ready for approval (DMEPA review in DARRTS dated January 12, 2015). CMC was also informed about the changes being requested to the carton and container labels. Dr. Su Tran confirmed in an email dated August 21, 2014 (checked into DARRTS on February 17, 2015) that since these labeling changes do not affect the approved technical CMC information, no CMC review is necessary, and that CMC will defer to DMEPA's evaluation of the new safety language.

DMEP reviewed the package inserts submitted for these supplements, and asked the applicants to make revisions. The revised labels were found acceptable.

DMPP and DMEP reviewed the patient labeling submitted for these supplements, and asked the applicants to make revisions (DMPP review in DARRTS dated November 13, 2014). A second round of revisions was requested for some products. The revised labels were found acceptable.

The following is the list of supplements that were submitted in response to the SLC notification:

sanofi-aventis U.S. LLC

- NDA 021081/S-062 Lantus (insulin glargine [rDNA origin]), injection, 100 Units/mL
- NDA 021629/S-030 Apidra (insulin glulisine [rDNA origin] injection), 100 Units/mL

AstraZeneca AB

- NDA 021332/S-023 Symlin (pramlintide acetate) injection, 600 mcg/ml and 1000 mcg/ml
- NDA 021773/S-040 Byetta (exenatide) injection

Novo Nordisk, Inc.

- NDA 019959/S-075 Novolin N (NPH, human insulin isophane suspension [rDNA origin]), injection, 100 Units/mL
- NDA 020986/S-081 NovoLog (insulin aspart [rDNA origin] injection), 100 Units/ml
- NDA 021172/S-063 NovoLog Mix 70/30 (70% insulin aspart protamine suspension and 30% insulin aspart [rDNA origin] injection), 100 Units/ml
- NDA 021810/S-010 NovoLog Mix 50/50 (50% insulin aspart protamine suspension and 50% insulin aspart [rDNA origin] injection), 100 Units/mL
- NDA 021536/S-051 Levemir (insulin detemir [rDNA origin] injection), 100 Units/mL
- NDA 022341/S-022 Victoza (liraglutide [rDNA origin]) injection

Eli Lilly and Company

- NDA 018780/S-150 Humulin R (insulin human injection, USP [rDNA origin])
- NDA 018781/S-154 Humulin N NPH (human insulin isophane suspension [rDNA origin])
- NDA 019717/S-133 Humulin 70/30 (70% human insulin isophane suspension/30% insulin human injection, rDNA origin)
- NDA 020563/S-157 Humalog (insulin lispro [rDNA origin] injection), 100 Units/mL
- NDA 021017/S-108 Humalog Mix 75/25 (75% insulin lispro protamine suspension /25% insulin lispro [rDNA origin] injection), 100 Units/mL
- NDA 021018/S-100 Humalog Mix 50/50 (50% insulin lispro protamine suspension /50% insulin lispro [rDNA origin] injection), 100 Units/mL

This labeling review is for NDA 021081/S-062 for Lantus (insulin glargine [rDNA origin]), injection, 100 Units/mL. Lantus (approved April 20, 2000) is an insulin analog indicated to improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus.

**Materials Reviewed:**

<b>Labeling Reviewed</b>	<b>Submission Date</b>	<b>Currently approved (date and supplement)</b>
Package Insert	12/05/14	10/18/13 (S-057)
Patient Package Insert (SoloStar)	1/12/15	10/18/13 (S-057)
Patient Package Insert (10 mL vial)	1/12/15	10/18/13 (S-057)
SoloStar Instruction Leaflet (IFU)	1/12/15	05/16/13 (S-055)

**Review**

Each piece of proposed labeling was compared to the currently approved version, using either the Microsoft Word or the Adobe Acrobat electronic comparison functions. The comparison documents are attached below.

**Recommendations**

The labeling was reviewed and found acceptable by Clinical (Dr. Jennifer Pippins), DMPP (Robin Duer, Shawna Hutchins and Aman Sarai) and DMEPA (Sarah Vee and Yelena Maslov). This supplement is ready for approval.

Michael White	2/19/2015
<hr/>	
Regulatory Project Manager	Date
Mehreen Hai	2/19/15
<hr/>	
Safety Regulatory Project Manager	Date

Drafted: Mehreen Hai/2.10.15  
Reviewed: Julie Van der Waag/2.11.15  
Completed: Michael White/02.19.15  
Finalized: Mehreen Hai/2.19.15

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/s/  
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MEHREEN HAI  
02/25/2015

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## MEMORANDUM

### REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

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**Date of This Review:** January 9, 2015

**Requesting Office or Division:** Division of Metabolic and Endocrinology Products (DMEP)

**Applicant, Application Type,  
Number and Product Names:**

Applicant	Product (and labeling attached to SLC letter)	Application #
Sanofi	Apidra	NDA 21629
	Lantus	NDA 21081
BMS	Symlin Pen	NDA 21332
	Byetta	NDA 21773
Novo	Victoza	NDA 22341
	Novolin N	NDA 19959
	Novolog	NDA 20986
	Novolog 50/50	NDA 21810
	Novolog 70/30	NDA 21172
	Levemir	NDA 21536
Lilly	Humulin N	NDA 18781
	Humulin R	NDA 18780
	Humulin 70/30	NDA 19717
	Humalog	NDA 20563
	Humalog 50/50	NDA 21018
	Humalog 75/25	NDA 21017

**OSE RCM #:** 2014-1753-1

**DMEPA Primary Reviewer:** Sarah K. Vee, PharmD

**DMEPA Team Leader:** Yelena Maslov, PharmD

**DMEPA Associate Director:** Lubna Merchant, PharmD, MS

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## **1 PURPOSE OF MEMO**

DMEP requested that we review the revised container label and carton labeling (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.<sup>1</sup>

## **2 CONCLUSIONS**

The revised container label and carton labeling are acceptable from a medication error perspective.

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<sup>1</sup> VEE S. Label and Labeling Review for Multiple Insulin Pen Products. Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 OCT 07. 32 p. OSE RCM No.: 2014-1753.

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/s/  
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SARAH K VEE  
01/12/2015

YELENA L MASLOV  
01/12/2015

LUBNA A MERCHANT  
01/12/2015

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Medical Policy Initiatives  
Division of Medical Policy Programs**

**PATIENT LABELING REVIEW**

Date: November 12, 2014

To: Jean-Marc Guettier, MD  
Director  
**Division of Metabolism and Endocrinology Products (DMEP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Associate Director for Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

Shawna Hutchins, MPH, BSN, RN  
Acting Team Leader, Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

From: Aman Sarai, BSN, RN  
Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

Subject: Focused Review of Patient Labeling: Patient Package Insert (PPIs) and Instructions for Use (IFUs)

Drug Name (established name), Dosage Form and Route: APIDRA (insulin glulisine [rDNA origin]) injection  
LANTUS (insulin glargine [rDNA origin]) injection  
solution for subcutaneous injection

Application Type/Numbers/Supplement Numbers: NDA 21629/S-030 (APIDRA)  
NDA 21081/S-062 (LANTUS)

Applicant: Sanofi Aventis U.S. LLC

## 1 INTRODUCTION

On August 15, 2014, Sanofi Aventis U.S. LLC submitted for the Agency's review Safety Labeling Changes (SLCs), Prior Approval Labeling Supplements (PASS) for APIDRA (insulin glulisine [rDNA origin] injection) and LANTUS (insulin glargine [rDNA origin] injection). The purpose of the submissions was to provide revised labeling in response to the Agency's July 17, 2014 letters requesting a class SLC for APIDRA and LANTUS regarding a new single patient use only warning.

APIDRA (insulin glulisine [rDNA origin] injection) is a rapid acting human insulin analog indicated to improve glycemic control in adults and children with diabetes mellitus.

LANTUS (insulin glargine [rDNA origin] injection) is a long- acting human insulin analog indicated to improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus.

This focused review is written by the Division of Medical Policy Programs (DMPP) in response to a request by the Division of Metabolism and Endocrinology Products (DMEP) on August 20, 2014 for DMPP to provide a focused review of the Applicant's proposed:

- Patient Package Insert (PPI) and Instructions for Use (IFUs) for APIDRA (insulin glulisine [rDNA origin] injection)
- Patient Package Insert (PPI) and Instructions for Use (IFUs) for LANTUS (insulin glargine [rDNA origin] injection)

On October 30, 2014, DMEP and DMPP made the following agreements regarding these patient labeling reviews:

- DMPP will leave the Applicant's track changes in the patient labeling documents so DMEP can easily identify other labeling revisions proposed that are unrelated to the SLC request. DMPP is only providing focused reviews of the proposed SLC. No clean version of the patient labeling will be attached to this review.
- Identical warning language will be added to the beginning of all insulin delivery device patient labeling documents covered under this SLC to reflect the new warning regarding single patient use only added to Section 5.1 of the corresponding Prescribing Information (PI).
- As DMEP and DMPP discussed on October 28, 2014, DMPP will not refer to the PI or proposed SLC language in the Agency's July 17, 2014 letters for our review of the Applicant's submitted patient labeling at this time. DMPP will only refer to the Substantially Complete Prescribing Information (SCPI) for each product sent by DMEP and received by DMPP on October 23, 2014.

## 2 MATERIAL REVIEWED

- Draft APIDRA (insulin glulisine [rDNA origin] injection) PPI and IFUs received on August 15, 2014, and received by DMPP on August 20, 2014.

- Draft LANTUS (insulin glargine [rDNA origin] injection) PPI and IFUs received on August 15, 2014, and received by DMPP on August 20, 2014.
- Draft APIDRA (insulin glulisine [rDNA origin] injection) Prescribing Information (PI) received on August 15, 2014, revised by the Review Division throughout the review cycle, and received by DMPP on October 23, 2014.
- Draft LANTUS (insulin glargine [rDNA origin] injection) Prescribing Information (PI) received on August 15, 2014, revised by the Review Division throughout the review cycle, and received by DMPP on October 23, 2014.

### **3 REVIEW METHODS**

In our focused review of the PPIs and IFUs appropriate to the SLC we have:

- simplified wording and clarified concepts where possible
- ensured that the PPIs and IFUs are consistent with the Prescribing Information (PI)

### **4 CONCLUSIONS**

The PPIs and IFUs are acceptable with our recommended changes.

### **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Consult DMPP during the next review cycle for a comprehensive review of the Patient Labeling to bring it up to current Patient Labeling standards.
- Our focused review of the PPIs and IFUs are appended to this memorandum. Consult DMPP regarding any additional revisions made to the PIs to determine if corresponding revisions need to be made to the PPIs and IFUs.

Please let us know if you have any questions.

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/s/  
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AMANPREET K SARAI  
11/12/2014

SHAWNA L HUTCHINS  
11/12/2014

LASHAWN M GRIFFITHS  
11/13/2014

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**LABEL AND LABELING REVIEW**

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

**\*\*\* This document contains proprietary information that cannot be released to the public\*\*\***

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**Date of This Review:** October 7, 2014

**Requesting Office or Division:** Division of Metabolic and Endocrinology Products (DMEP)

**Applicant, Application Type,  
Number and Product Names:**

Applicant	Product (and labeling attached to SLC letter)	Application #
Sanofi	Apidra	NDA 21629
	Lantus	NDA 21081
BMS	Symlyn Pen	NDA 21332
	Byetta	NDA 21773
Novo	Victoza	NDA 22341
	Novolin N	NDA 19959
	Novolog	NDA 20986
	Novolog 50/50	NDA 21810
	Novolog 70/30	NDA 21172
	Levemir	NDA 21536
Lilly	Humulin N	NDA 18781
	Humulin R	NDA 18780
	Humulin 70/30	NDA 19717
	Humalog	NDA 20563
	Humalog 50/50	NDA 21018
	Humalog 75/25	NDA 21017

**OSE RCM #:** 2014-1753

**DMEPA Primary Reviewer:** Sarah K. Vee, PharmD

**DMEPA Team Leader:** Yelena Maslov, PharmD

**DMEPA Associate Director:** Lubna Merchant, PharmD, MS

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## 1 REASON FOR REVIEW

On July 17, 2014, FDA sent a letter invoking our authority under section 505(o)(4) of the FDCA to require safety related changes to the labeling to address the risk of transmission of bloodborne pathogens resulting from pen devices and pen cartridges that are intended for single patient use only, being shared among numerous patients, for products indicated for patients with diabetes mellitus, based on new safety information about this risk identified since the product was approved.

The letters stated the following:

In accordance with section 505(o)(4) of the FDCA, we are notifying you that based on the new safety information described above, we believe that the new safety information should be included in the labeling as per the attached package insert, patient package insert, instructions for use, and carton and container labels. In addition, for your pen device, you should add the following statement to the body of the pen:

**WARNING: For Single Patient Use Only**

This statement should be prominent and indelible to ensure this warning is visible for the life of the device. Please position the statement in a location that is unlikely to be overlooked when administering the drug or to be covered by a pharmacy label.

As multiple Applicants submitted their responses to the notification letters, DMEP requested that we review the Applicants' proposals regarding the addition of the warning statement on the body of the pen. We also reviewed the carton labeling for the products.

## 2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

<b>Table 1. Materials Considered for this Label and Labeling Review</b>	
<b>Material Reviewed</b>	<b>Appendix Section (for Methods and Results)</b>
Product Information/Prescribing Information	N/A
FDA Adverse Event Reporting System (FAERS)	N/A
Previous DMEPA Reviews	A
Human Factors Study	N/A
ISMP Newsletters	N/A
Other	N/A
Labels and Labeling	B

N/A=not applicable for this review

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)

### 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

In response to add the safety statement to the body of the pen, the Applicants stated that adding the warning statement to the body of the pen is not necessary or warranted due to various reasons outlined below:

1. With the adoption of the requested language in the USPI, PPI, IFU, and front panel of the pen carton, the warning of not sharing the pen, and/or the risks of doing so, occurs 5 to 10 times throughout the labeling for the various products.
2. Including the statement directly on the pen container label ensures that this important information is prominently displayed at the point of use.
3. Summative readability study results also demonstrated that the warning to [REDACTED] (b) (4) [REDACTED] in the HOE901-U300 (Toujeo) SoloStar IFU was successfully located and understood by representative users.
4. Durability of the label, and its indelible properties ensure that the warning statement will remain visible to the user throughout the life of the device.
5. Embossing the dosing lines and the warning is not an adequate solution, as the readability is very poor, putting patients at risk of medication errors due to faint dosing lines and/or omitting the warning text altogether.
6. The cartridge holder manufacturer identified significant technical issues with printing the warning directly onto the cartridge holder, requiring a substantial modification to the current equipment or new equipment altogether.

In considering the rationale provided, we find it acceptable that the warning will not be placed on the body of the pen at this time. However, we recommend that the Applicants be consistent regarding how these warning statements should appear on pen labels in terms of placement, prominence, and color, so that they are readily seen and legible. We provide these recommendations in Section 4. Additionally, we plan to monitor medication error reports to ensure that the labeling changes are adequate to address the pen sharing safety issue identified in the notification letter. In the event that the labeling changes are inadequate and we continue to receive pen sharing reports, we may recommend additional regulatory action at that time to address the issue, which may include requiring the placement of the warning statement on the body of the pen as stated in the original letters.

### 4 CONCLUSION & RECOMMENDATIONS

Although we are not requiring the warning to be placed on the body of the pen, we have recommendations for the pen labels in terms of placement, prominence, and the color of the warning to increase the visibility of the warning statement and to be consistent across different

manufacturers. We also recommend that the same changes to be made to the carton labeling for consistency.

**RECOMMENDATIONS FOR THE APPLICANTS:**

A. Pen Label and Carton Labeling

1. Placement: The safety warning, “For Single Patient Use Only”, should be placed immediately below the established name so that there is no intervening matter between the established name and the warning. This will ensure that the warning is in the same viewing angle and field as the drug name and less likely to be overlooked.
2. Prominence and color: We recommend using a red-shaded and bolded letters in a contrasting colored box to enhance visibility and prominence.

Please note that we plan to monitor medication error reports to ensure that the labeling changes are adequate to address the pen sharing safety issue identified in the notification letter. In the event that the labeling changes are inadequate and we continue to receive pen sharing reports, we may recommend additional regulatory action at that time to address the issue, which may include requiring the placement of the warning statement on the body of the pen as stated in the original letters.

## **APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED**

### **APPENDIX C. PREVIOUS DMEPA REVIEWS**

#### **C.1 Methods**

We searched the L: Drive on September 18, 2014 using the terms, “2011-4403” to identify reviews previously performed by DMEPA.

#### **C.2 Results**

Our search identified one previous review<sup>1</sup>.

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<sup>1</sup> Vee, S. 2011-4403 Sharing of Insulin Pens Post Marketing Review TSI651. Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2013 Aug 21. OSE RCM No.: 2011-4403.

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/s/  
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SARAH K VEE  
10/07/2014

YELENA L MASLOV  
10/07/2014

LUBNA A MERCHANT  
10/07/2014

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**021081Orig1s062**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

**From:** [Tran, Suong T](#)  
**To:** [Hai, Mehreen](#); [Kumar, Priyanka](#)  
**Cc:** [Pippins, Jennifer R.](#); [Dharia, Pooja](#); [CappellLynch, Callie](#); [Whitehead, Richard](#)  
**Subject:** RE: Response to pen-sharing SLC letters  
**Date:** Thursday, August 21, 2014 3:25:45 PM

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Hi Mehreen- Since these supplements appear to be labeling changes that do not affect the approved technical cmc information, no cmc review is necessary. We defer to DMEPA's evaluation of the added safety language.

Thanks for letting us know,

su

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**From:** Hai, Mehreen  
**Sent:** Thursday, August 21, 2014 1:25 PM  
**To:** Tran, Suong T; Kumar, Priyanka  
**Cc:** Pippins, Jennifer R.; Dharia, Pooja; CappellLynch, Callie; Whitehead, Richard  
**Subject:** Response to pen-sharing SLC letters

Hello Su and Priyanka,

On 7/17/2014, DMEP issued FDAAA safety labeling change (SLC) notifications to the sponsors of all diabetes pen products, requiring them to add a warning against the sharing of pens between patients to all the labeling, including carton and container labels. We also asked them to propose a plan for how they are going to inscribe the warning on the pen body. For your reference I'm attaching one of the letters, so you can see what we asked for, and am also attaching an email communication that Su and I had last year regarding this SLC.

<< File: NDA 020986 (Novolog)- Sec 901 Labeling Change Notification.pdf >> << Message: RE: Clearance for Pen-Sharing SLC letters >>

The sponsors have submitted the supplements in response to our SLC notification letters. All the submitted labeling has been put into [Sharepoint](#). The sponsors have also included their plan for putting the warning on the pen-body, either in their cover letter or in a separate document, which are also in Sharepoint, with the exception of BMS, who will submit the plan for their products by August 31.

**Please let me know if CMC needs to review the carton and container labels, and if so, please let me know the reviewer assignment.**

DMEPA will also review the labels, and DMPP will review the patient labeling.

Since these are in response to an SLC, they are on a 30-day clock, which can be extended

easily to 90 days, and less easily (ORP approval required) to beyond 90 days. So if we can aim to take action on these by **November 13, 2014**, that would be ideal.

Please let me know if there is anyone else who needs to review this, or if you have any questions.

Thanks!

***Mehreen Hai, Ph.D.***  
***Safety Regulatory Project Manager***  
***Division of Metabolism & Endocrinology Products***  
***Center for Drug Evaluation and Research***  
***Food and Drug Administration***  
***mehreen.hai@fda.hhs.gov***  
***Ph: 301-796-5073***  
***Fax: 301-796-9712***

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/s/  
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MEHREEN HAI  
02/17/2015



NDA 021081

## LABELING DISCUSSION EXTENSION

sanofi-aventis U.S. LLC  
Attention: Antonella Lozito, PharmD  
Associate Director, Global Regulatory Affairs  
55 Corporate Drive, Mail Stop: 55D-215A  
Bridgewater, NJ 08807

Dear Dr. Lozito:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Lantus (insulin glargine [rDNA origin]), injection, 100 Units/mL.

On July 17, 2014, we sent a letter invoking our authority under section 505(o)(4) of the FDCA to require safety related label changes to the labeling of Lantus to address the risk of transmission of bloodborne pathogens resulting from pen devices and pen cartridges that are intended for single patient use only, being shared among numerous patients, for products indicated for patients with diabetes mellitus, based on new safety information about this risk identified since the product was approved. You were directed to submit a supplement proposing changes to the approved labeling in accordance with the above direction, or notify FDA that you do not believe a labeling change is warranted, and submit a statement detailing the reasons why such a change is not warranted.

On August 15, 2014, we received your prior approval supplement of the same date, containing your proposed safety related labeling changes. Section 505(o) requires FDA to promptly review the supplement and if we disagree with the proposed changes, to initiate discussions with you on the content of the changes. These discussions were to be completed within 30 days, unless FDA determined that an extension was warranted.

We refer to our letters dated September 10 and October 14, 2014, informing you that we determined that a 30-day and subsequently, a 60-day extension of the discussion period was warranted to allow us to complete our review and reach agreement on the content of the labeling.

This letter is to inform you that we have determined that another 60-day extension of the discussion period is warranted to allow us to complete our review and reach agreement on the content of the labeling. Therefore, the discussion period for this supplement ends on **February 11, 2015**.

If you have any questions, call Mehreen Hai, Ph.D., Safety Regulatory Project Manager, at (301) 796-5073.

Sincerely,

*{See appended electronic signature page}*

Jennifer R. Pippins, M.D., M.P.H.  
Deputy Director for Safety  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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JENNIFER R PIPPINS  
12/12/2014



NDA 021081

## LABELING DISCUSSION EXTENSION

sanofi-aventis U.S. LLC  
Attention: Antonella Lozito, PharmD  
Associate Director, Global Regulatory Affairs  
55 Corporate Drive, Mail Stop: 55D-215A  
Bridgewater, NJ 08807

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On August 15, 2014, we received your August 15, 2014 prior approval supplement containing your proposed safety related labeling changes. Section 505(o) requires FDA to promptly review the supplement and if we disagree with the proposed changes, to initiate discussions with you on the content of the changes. These discussions were to be completed within 30 days, unless FDA determined that an extension was warranted.

We refer to our letter dated September 10, 2014, informing you that we determined that a 30-day extension of the discussion period was warranted to allow us to complete our review and reach agreement on the content of the labeling.

This letter is to inform you that we have determined that another 60-day extension of the discussion period is warranted to allow us to complete our review and reach agreement on the content of the labeling. Therefore, the discussion period for this supplement ends on **December 13, 2014**.

If you have any questions, call Mehreen Hai, Ph.D., Safety Regulatory Project Manager, at (301) 796-5073.

Sincerely,

*{See appended electronic signature page}*

Jennifer R. Pippins, M.D., M.P.H.  
Deputy Director for Safety  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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JENNIFER R PIPPINS  
10/14/2014



NDA 021081

## LABELING DISCUSSION EXTENSION

sanofi-aventis U.S. LLC  
Attention: Antonella Lozito, PharmD  
Associate Director, Global Regulatory Affairs  
55 Corporate Drive, Mail Stop: 55D-215A  
Bridgewater, NJ 08807

Dear Dr. Lozito:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Lantus (insulin glargine [rDNA origin]), injection, 100 Units/mL.

On July 17, 2014, we sent a letter invoking our authority under section 505(o)(4) of the FDCA to require safety related label changes to the labeling of Lantus to address the risk of transmission of bloodborne pathogens resulting from pen devices and pen cartridges that are intended for single patient use only, being shared among numerous patients, for products indicated for patients with diabetes mellitus, based on new safety information about this risk identified since the product was approved. You were directed to submit a supplement proposing changes to the approved labeling in accordance with the above direction, or notify FDA that you do not believe a labeling change is warranted, and submit a statement detailing the reasons why such a change is not warranted.

On August 15, 2014, we received your August 15, 2014 prior approval supplement containing your proposed safety related labeling changes. Section 505(o) requires FDA to promptly review the supplement and if we disagree with the proposed changes, to initiate discussions with you on the content of the changes. These discussions were to be completed within 30 days, unless FDA determined that an extension was warranted.

This letter is to inform you that we have determined that a 30-day extension of the discussion period is warranted to allow us to complete our review and reach agreement on the content of the labeling. Therefore, the discussion period for this supplement ends on **October 14, 2014**.

If you have any questions, call Mehreen Hai, Ph.D., Safety Regulatory Project Manager, at (301) 796-5073.

Sincerely,

*{See appended electronic signature page}*

Jennifer R. Pippins, M.D., M.P.H.  
Deputy Director for Safety (Acting)  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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JENNIFER R PIPPINS  
09/10/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR CONSULTATION</b>		
TO (Division/Office): <b>Mail: OSE</b> <b>Attention: Yelena Maslov, DMEPA</b>		FROM: <b>Mehreen Hai</b> <b>Safety Regulatory Project Manager, DMEP</b>		
DATE <b>8/20/14</b>	IND NO.	NDA NO. <b>Multiple</b>	TYPE OF DOCUMENT <b>Carton and Container labeling</b>	DATE OF DOCUMENT <b>8/15/14</b>
NAME OF DRUG <b>Multiple diabetes pen products</b>		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG <b>Diabetes pen products</b>	DESIRED COMPLETION DATE
NAME OF FIRM: Eli Lilly				
<b>REASON FOR REQUEST</b>				
<b>I. GENERAL</b>				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):				
<b>II. BIOMETRICS</b>				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
<b>III. BIOPHARMACEUTICS</b>				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
<b>IV. DRUG EXPERIENCE</b>				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
<b>V. SCIENTIFIC INVESTIGATIONS</b>				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
<b>COMMENTS/SPECIAL INSTRUCTIONS:</b>				
<p>The sponsors for all diabetes pen products have submitted labeling supplements to add to all labeling a warning against the sharing of pens between patients, in response to the SLC notification letters that FDA issued on 7/17/14. All the submitted labeling has been put into <u>Sharepoint</u> for DMEPA to review. The sponsors have also included their plan for putting the warning on the pen-body, either in their cover letter or in a separate document, which are also in Sharepoint, which the exception of BMS, who will submit the plan for their products by August 31. Since this is a response to an SLC notification, we need to take action on these supplements by <b>November 13, 2014</b>. Please let me know if you have any questions.</p> <p>Sharepoint link: <a href="http://sharepoint.fda.gov/orgs/CDER-ODEII-DMEP/apps/Class/Pen%20Sharing%20Diabetes%20Products">http://sharepoint.fda.gov/orgs/CDER-ODEII-DMEP/apps/Class/Pen%20Sharing%20Diabetes%20Products</a></p>				
SIGNATURE OF REQUESTER <b>Mehreen Hai</b>		METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

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/s/  
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MEHREEN HAI  
08/21/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR PATIENT LABELING REVIEW CONSULTATION</b>			
TO: <b>CDER-DMPP-PatientLabelingTeam</b>			FROM: (Name/Title, Office/Division/Phone number of requestor) <b>Mehreen Hai Safety Regulatory Project Manager, DMEP</b>		
REQUEST DATE: <b>8/20/14</b>		NDA/BLA NO.: <b>Multiple</b>	TYPE OF DOCUMENTS: (PLEASE CHECK OFF BELOW)		
NAME OF DRUG: <b>Multiple diabetes pen products</b>	PRIORITY CONSIDERATION:		CLASSIFICATION OF DRUG: <b>Diabetes pen products</b>	DESIRED COMPLETION DATE (Generally 2 Weeks after receiving substantially complete labeling)	
SPONSOR: <b>Multiple</b>			PDUFA Date:		
<b>TYPE OF LABEL TO REVIEW</b>					
<b>TYPE OF LABELING:</b> (Check all that apply) <input type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE(IFU)		<b>TYPE OF APPLICATION/SUBMISSION</b> <input type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> MANUFACTURING (CMC) SUPPLEMENT <input type="checkbox"/> PLR CONVERSION		<b>REASON FOR LABELING CONSULT</b> <input type="checkbox"/> INITIAL PROPOSED LABELING <input type="checkbox"/> LABELING REVISION	
<b>EDR link to submission:</b>					
<b>Please Note: DMPP uses substantially complete labeling, which has already been marked up by the CDER Review Team, when reviewing MedGuides, IFUs, and PPIs. Once the substantially complete labeling is received, DMPP will complete its review within 14 calendar days. Please provide a copy of the sponsor's proposed patient labeling in Word format.</b>					
<b>COMMENTS/SPECIAL INSTRUCTIONS:</b>  On 7/17/2014, DMEP issued FDAAA safety labeling change (SLC) notifications to the sponsors of all diabetes pen products, requiring them to add a warning against the sharing of pens between patients to all the labeling, including patient labeling. The sponsors have submitted the supplements in response to our SLC notification letters. All the submitted labeling has been put into Sharepoint.  Sharepoint link: <a href="http://sharepoint.fda.gov/orgs/CDER-ODEII-DMEP/apps/Class/Pen%20Sharing%20Diabetes%20Products">http://sharepoint.fda.gov/orgs/CDER-ODEII-DMEP/apps/Class/Pen%20Sharing%20Diabetes%20Products</a>  Since these are in response to an SLC, they are on a 30-day clock, which can be extended easily to 90 days, and less easily (ORP approval required) to beyond 90 days. So we are aiming to take action on these by <b>November 13, 2014</b> . We will let you know when the labeling is substantially complete.					
SIGNATURE OF REQUESTER					
SIGNATURE OF RECEIVER			METHOD OF DELIVERY (Check one) <input type="checkbox"/> eMAIL (BLAs Only) <input type="checkbox"/> DARRTS		

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MEHREEN HAI  
08/21/2014