Limitations of Use:

pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus. (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.

RECENT MAJOR CHANGES

Initial U.S. Approval: 2000

CONTRAINDICATIONS

LANTUS is not recommended for the treatment of diabetic ketoacidosis.

DOSAGE AND ADMINISTRATION

Administer LANTUS subcutaneously once daily at any time of day, but at the same time every day.

• Individualize dosage based on metabolic needs, blood glucose monitoring, glycemic control, type of diabetes prior insulin use (2.1, 2.3, 2.4)
• Administer subcutaneously once daily at any time of day, but at the same time every day. (2.1)
• Do not dilute or mix with any other insulin or solution. (2.1)
• Rotate injection sites to reduce the risk of lipodystrophy. (2.2)
• Closely monitor glucose when changing to LANTUS and during initial weeks thereafter. (2.4)

DOSAGE FORMS AND STRENGTHS

Injection: 100 units/mL insulin glargine is available as:
• 10 mL vials (3)
• 3 mL SoloStar prefilled pen (3)

CONTRAINdications

• During episodes of hypoglycemia (4)
• Hypersensitivity to LANTUS or one of its excipients (4)

ADVERSE REACTIONS

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

WARNINGS AND PRECAUTIONS

• Never share a LANTUS SoloStar prefilled pen between patients, even if the needle is changed (5.1)
• Hyper- or hypoglycemia with changes in insulin regimen: Carry out under close medical supervision (5.2)
• Hypoglycemia: May be life-threatening. Increase frequency of glucose monitoring with changes to: insulin dosage, co-administered glucose lowering medications, meal pattern, physical activity; and in patients with renal or hepatic impairment and hypoglycemia unawareness (5.3, 6.1)
• Medication Errors: Accidental mix-ups between insulin products can occur. Instruct patients to check insulin labels before injection. (5.4, 6.3)
• Hypersensitivity reactions: Severe, life-threatening, generalized allergy, including anaphylaxis, can occur. Discontinue LANTUS. Monitor and treat if indicated. (5.5, 6.1)
• Hypokalemia: May be life-threatening. Monitor potassium levels in patients at risk of hypokalemia and treat if indicated. (5.6)
• Fluid retention and heart failure 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 (5.7)

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.

DRUG INTERACTIONS

• Drugs that affect glucose metabolism: Adjustment of insulin dosage may be needed; closely monitor of blood glucose. (7)
• Anti-Adrenergic Drugs (e.g., beta-blockers, clonidine, guanethidine, and reserpine): Signs and symptoms of hypoglycemia may be reduced or absent. (7)

USE IN SPECIFIC POPULATIONS

• Use during pregnancy only if the potential benefit justifies the potential risk to the fetus (8.1)

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

Revised: 08/2015

FULL PRESCRIBING INFORMATION: CONTENTS

1. INDICATIONS AND USAGE
2. DOSAGE AND ADMINISTRATION
3. DOSAGE FORMS AND STRENGTHS
4. CONTRAINDICATIONS
5. WARNINGS AND PRECAUTIONS
6. ADVERSE REACTIONS
7. DRUG INTERACTIONS
8. USE IN SPECIFIC POPULATIONS
9. DRUG INFORMATION
10. OVERDOSE
11. DESCRIPTION
12. CLINICAL PHARMACOLOGY
13. NONCLINICAL TOXICOLOGY
14. CLINICAL STUDIES
15. HOW SUPPLIED/STORAGE AND HANDLING
16. PATIENT COUNSELING INFORMATION

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.

Limitations of Use:

LANTUS is not recommended for the treatment of diabetic ketoacidosis.

2. DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

• Administer LANTUS subcutaneously once daily at any time of day but at the same time every day.

• Prior to initiation of LANTUS, train patients on proper use and injection technique.
• Patient should follow the Instructions for Use to correctly administer LANTUS.
• Administer LANTUS subcutaneously into the abdominal area, thigh, or deltoid, and rotate injection sites within the same region from one injection to the next to reduce the risk of lipodystrophy (see Adverse Reactions (6.1)).
• Visually inspect LANTUS vials and SoloStar prefilled pens for particulate matter and discoloration prior to administration. Only use if the solution is clear and colorless with no visible particles.
• Refrigerate unused (unopened) LANTUS vials and SoloStar® prefilled pens.
• Do not administer intravenously or via an insulin pump.
Do not dilute or mix LANTUS with any other insulin or solution.

• The SoloStar prefilled pen is for single patient use only [see Warnings and Precautions (5.1)].

2.2 General Dosing Instructions

• Individualize and adjust the dosage of LANTUS based on the individual’s metabolic needs, blood glucose monitoring results and glycemic control goal.

• Dosage adjustments may be needed with changes in physical activity, changes in meal patterns (i.e., macronutrient content or timing of food intake), during acute illness, or changes in renal or hepatic function. Dosage adjustments should only be made under medical supervision with appropriate glucose monitoring [see Warnings and Precautions (5.2)].

2.3 Initiation of LANTUS Therapy

Type 1 Diabetes:

• In patients with type 1 diabetes, LANTUS must be used concomitantly with short-acting insulin. 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, premixed insulin should be used to satisfy the remainder of the daily insulin requirements.

Type 2 Diabetes:

• The recommended starting dose of LANTUS in patients with type 2 diabetes who are not currently treated with insulin is 0.2 units/kg or up to 10 units once daily. One may need to adjust the amount and timing of short- or rapid-acting insulins and dosages of any oral anti-diabetic drugs.

2.4 Changing to LANTUS from Other Insulin Therapies

• If changing patients from once daily TOUJEO (insulin glargine) 300 Units/mL to once daily LANTUS, the recommended initial LANTUS dose is 80% of the TOUJEO dose that is being discontinued. This dose reduction will lower the likelihood of hypoglycemia [see Warnings and Precautions (5.3)].

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

• If changing 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 changing patients from twice-daily NPH insulin to once-daily LANTUS, the recommended initial LANTUS dosage is 80% of the total NPH dose that is being discontinued. This dose reduction will lower the likelihood of hypoglycemia [see Warnings and Precautions (5.3)].

3. DOSAGE FORMS AND STRENGTHS

Injection: 100 units per mL of insulin glargine. LANTUS is available as:

• 10 mL vial

• 3 mL SoloStar prefilled pen

4. CONTRAINDICATIONS

LANTUS is contraindicated

• During episodes of hypoglycemia [see Warnings and Precautions (5.3)].

• In patients with hypersensitivity to LANTUS or one of its excipients [see Warnings and Precautions (5.5)].

5. WARNINGS AND PRECAUTIONS

5.1 Never Share a LANTUS SoloStar Prefilled Pen, Syringe, or Needle between Patients

LANTUS SoloStar prefilled 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 Hypoglycemia or Hypoglycemia with Changes in Insulin Regimen

Changes in insulin strength, manufacturer, type, or method of administration may affect glycemic control and predispose to hypoglycemia [see Warnings and Precautions (5.3)] or hypoglycemia. These changes should be made cautiously and only under close medical supervision, and the frequency of blood glucose monitoring should be increased. For patients with type 2 diabetes, dosage adjustments of concomitant oral and anti-diabetic products may be needed.

5.3 Hypoglycemia

Hypoglycemia is the most common adverse reaction associated with insulin, including LANTUS. Severe hypoglycemia can cause serious harm or death. Hypoglycemia may be induced by a decreased concentration ability and reaction time; this may place an individual and others at risk in situations where these abilities are important (e.g., driving or operating other machinery). Hypoglycemia can happen suddenly and symptoms may differ in each individual and change over time in the same individual. Symptomatic awareness of hypoglycemia may be less pronounced in patients with longstanding diabetes, in patients with diabetic nerve disease, in patients using medications that block the sympathetic nervous system (e.g., beta-blockers) [see Drug Interactions (7)], or in patients who experience recurrent hypoglycemia.

Risk Factors for Hypoglycemia

The risk of hypoglycemia after an injection is related to the duration of action of the insulin and, in general, is highest when the glucose lowering effect of the insulin is maximal. As with all insulin preparations, the glucose lowering effect time course of LANTUS may vary in different individuals or at different times in the same individual and depends on many conditions, including the area of injection as well as local insulin absorption [see Clinical Pharmacology (12.2)]. Other factors which may increase the risk of hypoglycemia include changes in meal pattern (e.g., macronutrient content or timing of meals), changes in level of physical activity, or changes to co-administered medication [see Drug Interactions (7)]. Patients with renal or hepatic impairment may be at higher risk of hypoglycemia [See Use in Specific Populations (8.6, 8.7)].

Risk Mitigation Strategies for Hypoglycemia

Patients and caregivers must be educated to recognize and manage hypoglycemia. Self-monitoring of blood glucose plays an essential role in the prevention and management of hypoglycemia. In patients at higher risk for hypoglycemia and patients who have reduced symptomatic awareness of hypoglycemia, increased frequency of blood glucose monitoring should be considered. The long-acting effect of LANTUS may delay recovery from hypoglycemia.

5.4 Medication Errors

Accidental mix-ups among insulin products, particularly between long-acting insulins and rapid-acting insulins, have been reported. To avoid medication errors between LANTUS and other insulins, instruct patients to always check the insulin label before each injection [see Adverse Reactions (6.3)].

5.5 Hypersensitivity and Allergic Reactions

Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products, including LANTUS. If hypoglycemic reactions occur, discontinue LANTUS; treat per standard of care and monitor until symptoms and signs resolve [see Adverse Reactions (6.1)]. LANTUS is contraindicated in patients who have had hypersensitivity reactions to insulin glargine or one of the excipients [see Contraindications (4)].

5.6 Hypokalemia

All insulin products, including LANTUS, cause a shift in potassium from the extracellular to intracellular space, predisposing to hypokalemia. Untreated hypokalemia may cause respiratory paralysis, ventricular arrhythmia, and death. Monitor potassium levels in patients at risk for hypokalemia if indicated (e.g., patients using potassium-lowering medications, patients taking medications sensitive to serum potassium concentrations).

5.7 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 (5.3)]

• Hypersensitivity and allergic reactions [see Warnings and Precautions (5.5)]

• Hypokalemia [see Warnings and Precautions (5.6)].

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trial of another drug and may not reflect the rates observed in practice.

The data in Table 1 reflect the exposure of 2327 patients with type 1 diabetes to LANTUS or NPH. The type 1 diabetes population had the following characteristics: Mean age was 38.5 years. Fifty four percent were male, 96.9% were Caucasian, 1.8 % were Black or African American and 2.7 % were Hispanic. The mean BMI was 25.1 kg/m². In Table 2, the clinical trial experience of 1563 patients with type 2 diabetes to LANTUS or NPH. The type 2 diabetes population had the following characteristics: Mean age was 59.3 years. Fifty eight percent were male, 86.7% were Caucasian, 7.8 % were Black or African American and 9 % were Hispanic. The mean BMI was 29.2 kg/m².

The frequencies of 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: Adverse events in pooled clinical trials up to 28 weeks duration in adults with type 1 diabetes (adverse events with frequency ≥5%)

<table>
<thead>
<tr>
<th>Event</th>
<th>LANTUS, % (n=1070)</th>
<th>NPH, % (n=1070)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory tract infection</td>
<td>22.4</td>
<td>23.1</td>
</tr>
<tr>
<td>Infection</td>
<td>9.4</td>
<td>10.3</td>
</tr>
<tr>
<td>Accidental injury</td>
<td>5.7</td>
<td>6.4</td>
</tr>
<tr>
<td>Headache</td>
<td>5.5</td>
<td>4.7</td>
</tr>
</tbody>
</table>

### Table 2: Adverse events in pooled clinical trials up to 1 year duration in adults with type 2 diabetes (adverse events with frequency ≥5%)

<table>
<thead>
<tr>
<th>Event</th>
<th>LANTUS, % (n=1074)</th>
<th>NPH, % (n=1074)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory tract infection</td>
<td>11.4</td>
<td>13.3</td>
</tr>
<tr>
<td>Infection</td>
<td>10.4</td>
<td>11.6</td>
</tr>
<tr>
<td>Retinal vascular disorder</td>
<td>5.8</td>
<td>7.4</td>
</tr>
</tbody>
</table>

### Table 3: Adverse events in a 5-year trial of adults with type 2 diabetes (adverse events with frequency ≥10%)

<table>
<thead>
<tr>
<th>Event</th>
<th>LANTUS, % (n=503)</th>
<th>NPH, % (n=503)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory tract infection</td>
<td>29.0</td>
<td>33.6</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>20.0</td>
<td>22.7</td>
</tr>
<tr>
<td>Hypertension</td>
<td>19.6</td>
<td>18.9</td>
</tr>
<tr>
<td>Influenza</td>
<td>18.7</td>
<td>19.5</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>18.5</td>
<td>17.9</td>
</tr>
<tr>
<td>Cataract</td>
<td>18.1</td>
<td>15.9</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>15.2</td>
<td>14.1</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>14.2</td>
<td>16.1</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>13.0</td>
<td>13.1</td>
</tr>
<tr>
<td>Back pain</td>
<td>12.8</td>
<td>12.3</td>
</tr>
<tr>
<td>Cough</td>
<td>12.1</td>
<td>7.4</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>10.7</td>
<td>10.1</td>
</tr>
</tbody>
</table>
Table 7 displays the proportion of patients experiencing severe symptomatic hypoglycemia in the LANTUS and Standard Care groups in the ORIGIN trial [see Clinical Studies (14)].

Table 7: Severe Symptomatic Hypoglycemia in the ORIGIN Trial

<table>
<thead>
<tr>
<th>Group</th>
<th>Median duration of follow-up: 6.2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>LANTUS N=6231</td>
<td>5.6</td>
</tr>
<tr>
<td>Standard Care N=6273</td>
<td>1.8</td>
</tr>
</tbody>
</table>

Peripheral Edema
Some patients taking LANTUS have experienced sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

Lipohypertrophy
Administration of insulin subcutaneously, including LANTUS, has resulted in lipohypertrophy (depression in the skin) or lipomatosis (enlargement or thickening of tissue) in some patients [see Dosage and Administration (2.2)].

Table 4: Adverse events in a 28-week clinical trial of children and adolescents with type 1 diabetes (adverse events with frequency ≥ 5%)

Table 4 displays the proportion of patients experiencing severe symptomatic hypoglycemia in the LANTUS clinical trials. Severe symptomatic hypoglycemia was defined as an event with symptoms consistent with hypoglycemia requiring the assistance of another person for at least 10 minutes to recover. Percentages of LANTUS-treated adult patients experiencing severe symptomatic hypoglycemia in the LANTUS clinical trials [see Clinical Studies (14)] were comparable to percentages of NPH-treated patients 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 LANTUS group compared to the NPH group.

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

Table 5 displays the proportion of patients experiencing severe symptomatic hypoglycemia in the LANTUS and NPH treatment groups for all treatment regimens in the LANTUS clinical trials [see Clinical Studies (14)].

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

Table 6 displays the proportion of patients experiencing severe symptomatic hypoglycemia in the LANTUS and NPH treatment groups for all treatment regimens in the LANTUS clinical trials [see Clinical Studies (14)].

Table 3: Adverse events in a 5-year trial of adults with type 2 diabetes (adverse events with frequency ≥ 10%)

Table 8 includes clinically significant drug interactions with LANTUS.
Subcutaneous reproduction and teratology studies have been performed with insulin glargine and regular human insulin in rabbits and rats. Insulin glargine was given by 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/m². 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/m² were administered during organogenesis. The effects of insulin glargine did not generally differ from those observed with regular human insulin in rats or rabbits. However, in rabbits, five fetuses from two litters of the high-dose group exhibited dilation of the cerebral ventricles. Fertility and early embryonic development appeared normal.

8.3 Nursing Mothers
Endogenous insulin is present in human milk; 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 LANTUS have been established in pediatric patients (age 6 to 15 years) with type 1 diabetes (see Clinical Studies (14.2)). The safety and effectiveness of LANTUS in pediatric patients younger than 6 years of age with type 1 diabetes and pediatric patients with type 2 diabetes have not been established.

The dosage recommendation when changing to LANTUS in pediatric patients (age 6 to 15 years) with type 1 diabetes is the same as that described for adults (see Dosage and Administration (2.2, 2.4) and Clinical Studies (14)). As in adults, the dosage of LANTUS must be individualized in pediatric patients (age 6 to 15 years) with type 1 diabetes based on metabolic needs and frequent monitoring of blood glucose. In the pediatric clinical trial, pediatric patients (age 6 to 15 years) with type 1 diabetes had a higher incidence of severe symptomatic hypoglycemia compared to the adults in trials with type 1 diabetes (see Adverse Reactions (6.1)).

8.5 Geriatric Use
Of the total number of subjects in controlled clinical studies of patients with type 1 and type 2 diabetes, who were treated with LANTUS, 15% were ≥65 years of age and 2% were ≥75 years of age. The only difference in safety or effectiveness in the subpopulation of patients ≥65 years of age compared to the entire study population was a higher incidence of cardiovascular events typically seen in an older population in the LANTUS and NPH treatment groups. 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.

8.6 Hepatic Impairment
The effect of hepatic impairment on the pharmacokinetics of LANTUS has not been studied. Frequent glucose monitoring and dose adjustment may be necessary for LANTUS in patients with hepatic impairment (see Warnings and Precautions (5.3)).

8.7 Renal Impairment
The effect of renal impairment on the pharmacokinetics of LANTUS has not been studied. Some studies with human insulin have shown increased circulating levels of insulin in patients with renal failure. Frequent glucose monitoring and dose adjustment may be necessary for LANTUS in patients with renal impairment (see Warnings and Precautions (5.3)).

8.8 Obesity
In controlled clinical trials, subgroup analyses based on BMI did not show differences in safety and efficacy between LANTUS and NPH.

10. OVERDOSAGE
Excess insulin administration may cause hypoglycemia and hypokalemia (see Warnings and Precautions (5.3, 5.6)). 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, observation and additional carbohydrate intake may be necessary to avoid recurrence of hypoglycemia. Hypokalemia must be corrected appropriately.

The 3 mL prefilled pen 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 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 protein synthesis, and enhances protein synthesis.

12.2 Pharmacodynamics
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. Figure 1 shows the mean changes in glycemic excursions in patients with type 2 diabetes, randomized for a maximum of 24 hours after the first injection. The median time between injection and the end of pharmacodynamic 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.

The duration of action after abdominal, deltoid, or thigh subcutaneous administration was similar. The time course of action of insulin, including LANTUS, may vary between individuals and within the same individual.

12.3 Pharmacokinetics
Absorption and Bioavailability
After subcutaneous injection of LANTUS 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.

Metabolism and Elimination
A metabolism study in humans indicates that insulin glargine is partially metabolized at the carboxyl terminus of the B chain in the subcutaneous depot to form two active metabolites with in vivo activity similar to that of human insulin, M1 (21'-Gly-insulin) and M2 (21'-Gly-des-20-30-Thr-insulin). Unchanged drug and these degradation products are also present in the circulation.

Special Populations
Age, Race, and Gender.
Effect of age, race, and gender on the pharmacokinetics of LANTUS has not been evaluated. 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 LANTUS and NPH insulin (see Clinical Studies (14)).

Obesity. Effect of Body Mass Index (BMI) on the pharmacokinetics of LANTUS has not been evaluated.

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 455 mg/kg/day, 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/m². The findings in female mice were not conclusive due to excessive mortality in all dose groups during the study. Histioctyomas 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/m², maternal toxicity due to dose-dependent hypoglycemia, including some deaths, was observed. Consequently, a reduction in the rearing rate occurred in the high-dose group only. Similar effects were observed with NPH insulin.

14. CLINICAL STUDIES
14.1 Overview of 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, 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.

14.2 Clinical Studies in Adult and Pediatric Patients with Type 1 Diabetes
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 either as once daily at bedtime or in the morning and at bedtime when used twice daily.

![Figure 1. Activity Profile in Patients with Type 1 Diabetes](image-url)
In Study A, the average age was 39.2 years. The majority of patients were White (99%) and 55.7% were male. The mean BMI was approximately 24.2 kg/m². The mean duration of diabetes was 15.5 years.

In Study B, the average age was 38.5 years. The majority of patients were White (95.3%) and 50.6% were male. The mean BMI was approximately 25.8 kg/m². The mean duration of diabetes was 17.4 years.

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. The average age was 39.2 years. The majority of patients were White (96.9%) and 50.6% were male. The mean BMI was approximately 25.6 kg/m². The mean duration of diabetes was 16.5 years.

In these 3 studies, LANTUS and NPH insulin had similar effects on HbA1c (Table 9) with a similar overall rate of severe symptomatic hypoglycemia [see Adverse Reactions (6.1)].

<table>
<thead>
<tr>
<th>Table 9: Type 1 Diabetes Mellitus–Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment duration</td>
</tr>
<tr>
<td>Treatment in combination with</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>LANTUS</td>
</tr>
<tr>
<td>NPH</td>
</tr>
<tr>
<td>HbA1c Baseline</td>
</tr>
<tr>
<td>Baseline HbA1c Baseline change at end</td>
</tr>
<tr>
<td>Treatment Difference (95% CI)</td>
</tr>
<tr>
<td>Basal insulin dose</td>
</tr>
<tr>
<td>Mean change from baseline</td>
</tr>
<tr>
<td>Total insulin dose</td>
</tr>
<tr>
<td>Mean change from baseline</td>
</tr>
<tr>
<td>Fasting blood glucose (mg/dL)</td>
</tr>
<tr>
<td>Mean change from baseline</td>
</tr>
<tr>
<td>Body weight (kg)</td>
</tr>
<tr>
<td>Mean change from baseline</td>
</tr>
</tbody>
</table>

Type 1 Diabetes – Pediatric (see Table 10).

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. The average age was 11.7 years. The majority of patients were White (96.8%) and 51.9% were male. The mean BMI was approximately 18.9 kg/m². The mean duration of diabetes was 4.8 years. Similar effects on HbA1c (Table 10) were observed in both treatment groups [see Adverse Reactions (6.1)].

<table>
<thead>
<tr>
<th>Table 10: Type 1 Diabetes Mellitus–Pediatric</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment duration</td>
</tr>
<tr>
<td>Treatment in combination with</td>
</tr>
<tr>
<td>LANTUS + Regular insulin</td>
</tr>
<tr>
<td>Number of subjects treated</td>
</tr>
<tr>
<td>HbA1c</td>
</tr>
<tr>
<td>Baseline mean</td>
</tr>
<tr>
<td>Change from baseline (adjusted mean)</td>
</tr>
<tr>
<td>Difference from NPH (adjusted mean) (95% CI)</td>
</tr>
</tbody>
</table>

14.3 Clinical Studies in Adults with Type 2 Diabetes

In a randomized, controlled clinical study (Study E) (n=670), LANTUS was evaluated for 52 weeks in combination with oral anti-diabetic medications (a sulfonylurea, metformin, acarbose, or combinations of these drugs). The average age was 59.5 years. The majority of patients were White (92.8%) and 53.7% were male. The mean BMI was approximately 29.1 kg/m². The mean duration of diabetes was 13.7 years. LANTUS had similar effectiveness as either once- or twice-daily NPH insulin in reducing HbA1c and fasting glucose (Table 11). LANTUS was evaluated for 52 weeks in combination with 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. The average age was 59.3 years. The majority of patients were White (80.7%) and 60% were male. The mean BMI was approximately 30.5 kg/m². The mean duration of diabetes was 13.7 years. LANTUS had similar effectiveness as either once- or twice-daily NPH insulin in reducing HbA1c and fasting glucose (Table 11) with a similar incidence of hypoglycemia [see Adverse Reactions (6.1)].

In a randomized, controlled clinical study (Study F), 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. The average age was 59.3 years. The majority of patients were White (92.8%) and 53.7% were male. The mean BMI was approximately 29.1 kg/m². The mean duration of diabetes was 13.7 years. LANTUS had similar effectiveness as either once- or twice-daily NPH insulin in reducing HbA1c and fasting glucose (Table 11) 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 renal data. Patients or study personnel used an algorithm to adjust the LANTUS and NPH insulin doses to a target fasting plasma glucose <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 average age was 55.1 years. The majority of patients were White (85.3%) and 53.9% were male. The mean BMI was approximately 34.3 kg/m². The mean duration of diabetes was 10.8 years. 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 11). The incidences of severe symptomatic hypoglycemia were similar between groups [see Adverse Reactions (6.1)].

<table>
<thead>
<tr>
<th>Table 11: Type 2 Diabetes Mellitus–Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment duration</td>
</tr>
<tr>
<td>Treatment in combination with</td>
</tr>
<tr>
<td>LANTUS + Regular Insulin</td>
</tr>
<tr>
<td>Number of subjects treated</td>
</tr>
<tr>
<td>HbA1c Baseline</td>
</tr>
<tr>
<td>Baseline mean</td>
</tr>
<tr>
<td>Adjusted mean change from baseline</td>
</tr>
<tr>
<td>LANTUS – NPH</td>
</tr>
<tr>
<td>95% CI for Treatment difference</td>
</tr>
</tbody>
</table>

[see Adverse Reactions (6.1)]
Study F

In Study G, the baseline dose of basal or total insulin was the first available on-treatment dose evaluated in a randomized, controlled clinical study in patients with type 1 diabetes (study H, n=378). The safety and efficacy of LANTUS administered pre-breakfast, pre-dinner, or at bedtime were similar for patients with type 1 and type 2 diabetes. 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 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 end or more steps on the ETDRS scale at study end. 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 13 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 12: LANTUS Timing of Daily Dosing in Type 1 (Study H) and Type 2 (Study I) Diabetes Mellitus

<table>
<thead>
<tr>
<th>Treatment duration</th>
<th>Treatment in combination with:</th>
<th>Study H 24 weeks</th>
<th>Study I 24 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Insulin lispro</td>
<td>LANTUS (%)</td>
<td>LANTUS (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NPH (%)</td>
<td>Glimepiride (%)</td>
</tr>
<tr>
<td>Basal insulin dose</td>
<td>Breakfast</td>
<td>53/374 (14.2%)</td>
<td>57/363 (15.7%)</td>
</tr>
<tr>
<td></td>
<td>Dinner</td>
<td>-2.0 (2.9%)</td>
<td>-2.1 (2.1%)</td>
</tr>
<tr>
<td></td>
<td>Bedtime</td>
<td>-6.0 to +3.1%</td>
<td>-6.3% to +2.1%</td>
</tr>
<tr>
<td>HbA1c</td>
<td>Per-protocol</td>
<td>53/502 (12.5%)</td>
<td>71/487 (14.6%)</td>
</tr>
<tr>
<td></td>
<td>Intent-to-Treat</td>
<td>-2.1 (2.1%)</td>
<td>-2.1 (2.1%)</td>
</tr>
</tbody>
</table>

*Difference = Lantus − NPH
fusing 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.

The Study

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 ≥ 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 CV death or nonfatal myocardial infarction or 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 ≤ 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/m². The mean BMI was approximately 24.7 kg/m². The mean duration of diabetes was 10.1 years. 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 12).

Table 12: LANTUS Timing of Daily Dosing in Type 1 (Study H) and Type 2 (Study I) Diabetes Mellitus

<table>
<thead>
<tr>
<th>Treatment duration</th>
<th>Treatment in combination with:</th>
<th>Study H 24 weeks</th>
<th>Study I 24 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Insulin lispro</td>
<td>LANTUS (%)</td>
<td>LANTUS (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NPH (%)</td>
<td>Glimepiride (%)</td>
</tr>
<tr>
<td>Basal insulin dose</td>
<td>Breakfast</td>
<td>53/374 (14.2%)</td>
<td>57/363 (15.7%)</td>
</tr>
<tr>
<td></td>
<td>Dinner</td>
<td>-2.0 (2.9%)</td>
<td>-2.1 (2.1%)</td>
</tr>
<tr>
<td></td>
<td>Bedtime</td>
<td>-6.0 to +3.1%</td>
<td>-6.3% to +2.1%</td>
</tr>
<tr>
<td>HbA1c</td>
<td>Per-protocol</td>
<td>53/502 (12.5%)</td>
<td>71/487 (14.6%)</td>
</tr>
<tr>
<td></td>
<td>Intent-to-Treat</td>
<td>-2.1 (2.1%)</td>
<td>-2.1 (2.1%)</td>
</tr>
</tbody>
</table>

*Difference = Lantus − NPH
fusing 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.
Overall, the incidence of major adverse cardiovascular outcomes was similar between groups (see Table 14). All-cause mortality was also similar between groups.

Table 14: Cardiovascular Outcomes in ORIGIN - Time to First Event Analyses

<table>
<thead>
<tr>
<th></th>
<th>LANTUS (N=6264)</th>
<th>Standard Care (N=6273)</th>
<th>LANTUS vs Standard Care</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (Events per 100 PY)</td>
<td>n (Events per 100 PY)</td>
<td>Hazard Ratio (95% CI)</td>
</tr>
<tr>
<td>Co-primary endpoints</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV death, nonfatal myocardial infarction, or nonfatal stroke</td>
<td>1041 (2.9)</td>
<td>1013 (2.9)</td>
<td>1.02 (0.94, 1.11)</td>
</tr>
<tr>
<td>CV death, nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure or revascularization procedure</td>
<td>1792 (5.5)</td>
<td>1727 (5.3)</td>
<td>1.04 (0.97, 1.11)</td>
</tr>
</tbody>
</table>

Components of co-primary endpoints

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)

In the ORIGIN trial, the overall incidence of cancer (all types combined) or death from cancer (Table 15) was similar between treatment groups.

Table 15: Cancer Outcomes in ORIGIN - Time to First Event Analyses

<table>
<thead>
<tr>
<th></th>
<th>LANTUS (N=6264)</th>
<th>Standard Care (N=6273)</th>
<th>LANTUS vs Standard Care</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (Events per 100 PY)</td>
<td>n (Events per 100 PY)</td>
<td>Hazard Ratio (95% CI)</td>
</tr>
<tr>
<td>Cancer endpoints</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| 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)

16. HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied
LANTUS (insulin glargine injection) is supplied as a solution containing 100 units per mL (U-100) of insulin glargine and is available in:

- 10 mL vials
- 3 mL SoloStar prefilled pen

Dosage Unit/Strength | Package size | NDC #
--- | --- | ---
10 mL vials | Pack of 1 | 2220-33
3 mL SoloStar prefilled pen | package of 5 | 2219-05

Needles are not included in the packs.

BD Ultra-Fine™ needles1 to be used in conjunction with SoloStar are sold separately and are manufactured by BD.

1The brands listed are the registered trademarks of their respective owners and are not trademarks of sanofi-aventis U.S. LLC

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. Protect LANTUS from direct heat and light.

Store LANTUS 10 mL vials at 36°F – 46°F (2°C – 8°C) in a refrigerator until first use, then at room temperature (77°F – 86°F or 25°C – 30°C) for the duration of the 28-day expiration period. Do not refrigerate 3 mL SoloStar prefilled pens after initial use. SoloStar pens should be used within 28 days of first use.

17. PATIENT COUNSELING INFORMATION

Advise the patient to read FDA-approved patient labeling (Patient Information and Instructions for Use).

Never Share a LANTUS SoloStar Prefilled Pen or Syringe between Patients

Advise patients that they must never share a LANTUS SoloStar prefilled 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 [see Warnings and Precautions (5.1)].

Hyperglycemia or Hypoglycemia [see Warnings and Precautions (5.2),(5.3)]

Instruct patients that hyperglycemia is the most common adverse reaction with insulin. Inform patients of the symptoms of hypoglycemia. Inform patients 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. Advise patients who have frequent hypoglycemia or reduced or absent warning signs of hypoglycemia to use caution when driving or operating machinery.

Advise patients that changes in insulin regimen can predispose to hyper- or hypoglycemia. Advise patients that changes in insulin regimen should be made under close medical supervision.

Medications Errors [see Warnings and Precautions (5.4)]

Instruct patients to always check the insulin label before each injection.

Administration [see Dosage and Administration (2)]

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

Management of Hypoglycemia and handling of Special Situations

Instruct patients on self-management procedures including glucose monitoring, proper injection technique, and management of hypoglycemia and hyperglycemia. Instruct patients 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.

Pregnancy

Advise patients to inform their health care professional if they are pregnant or are contemplating pregnancy.

Refer patients to the LANTUS "Patient Information" for additional information about the potential side effects of insulin therapy, including hypoglycemia (and the need to rotate injection sites within the same body region), weight gain, allergic reactions, and hypoglycemia.

FDA Approved Patient Labeling

See attached document at end of Full Prescribing Information.

©2015 sanofi-aventis U.S. LLC

LANTUS, TOUJEO and SoloStar are registered trademarks of sanofi-aventis U.S. LLC.

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

<table>
<thead>
<tr>
<th></th>
<th>LANTUS (N=6264)</th>
<th>Standard Care (N=6273)</th>
<th>LANTUS vs Standard Care</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (Events per 100 PY)</td>
<td>n (Events per 100 PY)</td>
<td>Hazard Ratio (95% CI)</td>
</tr>
<tr>
<td>Co-primary endpoints</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV death, nonfatal myocardial infarction, or nonfatal stroke</td>
<td>1041 (2.9)</td>
<td>1013 (2.9)</td>
<td>1.02 (0.94, 1.11)</td>
</tr>
<tr>
<td>CV death, nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure or revascularization procedure</td>
<td>1792 (5.5)</td>
<td>1727 (5.3)</td>
<td>1.04 (0.97, 1.11)</td>
</tr>
</tbody>
</table>

Components of co-primary endpoints

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)

In the ORIGIN trial, the overall incidence of cancer (all types combined) or death from cancer (Table 15) was similar between treatment groups.

Table 15: Cancer Outcomes in ORIGIN - Time to First Event Analyses

<table>
<thead>
<tr>
<th></th>
<th>LANTUS (N=6264)</th>
<th>Standard Care (N=6273)</th>
<th>LANTUS vs Standard Care</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (Events per 100 PY)</td>
<td>n (Events per 100 PY)</td>
<td>Hazard Ratio (95% CI)</td>
</tr>
<tr>
<td>Cancer endpoints</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| 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)
Who should not use LANTUS?
Do not use LANTUS if you:
• are having an episode of low blood sugar (hypoglycemia)
• have an allergy to insulin glargine or any of the ingredients in LANTUS. See the end of this Patient Information leaflet for a complete list of ingredients in LANTUS.

What should I tell my healthcare provider before using LANTUS?
Before using LANTUS, tell your healthcare provider about all your medical conditions including if you:
• have liver or kidney problems
• take other medicines, especially ones called TZDs (thiazolidinediones)
• have heart failure or other heart problems. If you have heart failure, it may get worse while you take TZDs with LANTUS.
• are pregnant, planning to become pregnant, or are breastfeeding baby.
Tell your healthcare provider about all the medicines you take including prescription and over-the-counter medicines, vitamins, and herbal supplements.
Before you start using LANTUS, talk to your healthcare provider about low blood sugar and how to manage it.

How should I use LANTUS?
• Read the detailed Instructions for Use that come with your LANTUS insulin.
• Use LANTUS exactly as your healthcare provider tells you to. Your healthcare provider should tell you how much LANTUS to use and when to use it.
• Know the amount of LANTUS you use. Do not change the amount of LANTUS you use unless your healthcare provider tells you to.
• Check your insulin label each time you give your injection to make sure you are using the correct insulin.
• Do not re-use needles. Always use a new needle for each injection. Re-use of needles increases your risk of having blocked needles, which may cause you to get the wrong dose of LANTUS. Using a new needle for each injection lowers your risk of getting an infection.
• 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.
• LANTUS is injected under your skin (subcutaneously). Do not use LANTUS in an insulin pump or inject LANTUS into your vein (intravenously).
• Change (rotate) injection sites within the area you chose with each dose. Do not use the exact spot for each injection.
• Do not mix LANTUS with any other type of insulin or liquid medicine.
• Check your blood sugar levels. Ask your healthcare provider what your blood sugar should be and when you should check your blood sugar levels.
Keep LANTUS and all medicines out of the reach of children.

Your dose of LANTUS may need to change because of:
• a change in level of physical activity or exercise, weight gain or loss, increased stress, illness, change in diet, or because of the medicines you take.

What should I avoid while using LANTUS? While using LANTUS do not:
• drive or operate heavy machinery, until you know how LANTUS affects you
• drink alcohol or use over-the-counter medicines that contain alcohol

What are the possible side effects of LANTUS and other insulins?
LANTUS may cause serious side effects that can lead to death, including:
• low blood sugar (hypoglycemia). Signs and symptoms that may indicate low blood sugar include:
  o dizziness or light-headedness, sweating, confusion, headache, blurred vision, slurred speech, shakiness, fast heartbeat, anxiety, irritability or mood change, hunger
• severe allergic reaction (whole body reaction). Get medical help right away if you have any of these signs or symptoms of a severe allergic reaction:
  o a rash over your whole body, trouble breathing, a fast heartbeat, or sweating
• low potassium in your blood (hypokalemia).
• Heart failure. Taking certain diabetes pills called TZDs (thiazolidinediones) 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:
  o shortness of breath, swelling of your ankles or feet, sudden weight gain
Treatment with TZDs and LANTUS may need to be changed or stopped by your healthcare provider if you have new or worse heart failure.

Get emergency medical help if you have:
• trouble breathing; shortness of breath; fast heartbeat; swelling of your face, tongue, or throat; sweating; extreme drowsiness; dizziness; confusion.

The most common side effects of LANTUS include:
• low blood sugar (hypoglycemia); weight gain; allergic reactions, including reactions at your injection site; skin thickening or pits at the injection site (lipodystrophy).
These are not all the possible side effects of LANTUS. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of LANTUS.
Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use LANTUS for a condition for which it was not prescribed. It may harm them. This Patient Information leaflet summarizes the most important information about LANTUS. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about LANTUS that is written for healthcare professionals. For more information, go to www.lantus.com or call 1-800-633-1610.

What are the ingredients in LANTUS?
• Active ingredient: insulin glargine
• 10 ml vial inactive ingredients: zinc, m-cresol, glycerol, polysorbate, and water for injection

Manufactured By: sanofi-aventis U.S. LLC, Bridgewater, NJ 08807

This Patient Information has been approved by the U.S. Food and Drug Administration
Approved: July/2015

Instructions for Use
LANTUS® (LAN-tus) (insulin glargine injection) for subcutaneous use
10 mL Vial (100 Units/mL, U-100)
Read the Instructions for Use before you start taking LANTUS and each time you get a new LANTUS vial. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.
Do not share your LANTUS 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.

Supplies needed to give your injection:
- a LANTUS 10 mL vial
- a U-100 insulin syringe and needle
- 2 alcohol swabs
- 1 sharps container for throwing away used needles and syringes.

See “Disposing of used needles and syringes” at the end of these instructions.

Preparing your LANTUS dose:
- Wash your hands with soap and water or with alcohol.
- Check the LANTUS label to make sure you are taking the right type of insulin. This is especially important if you use more than 1 type of insulin.
- Check the insulin to make sure it is clear and colorless. Do not use LANTUS if it is colored or cloudy, or if you see particles in the solution.
- Do not use LANTUS after the expiration date stamped on the label or 28 days after you first use it.
- Always use a syringe that is marked for U-100 insulin. If you use a syringe other than a U-100 insulin syringe, you may get the wrong dose of insulin.
- Always use a new syringe or needle for each injection. Do not reuse or share your syringes or needles with other people. You may give other people a serious infection or get a serious infection from them.

Step 1:
If you are using a new vial, remove the protective cap. Do not remove the stopper.

Step 2:
Wipe the top of the vial with an alcohol swab. You do not have to shake the vial of LANTUS before use.

Step 3:
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.

Step 4:
Leave the syringe in the vial and turn both upside down. Hold the syringe and vial firmly in one hand. 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.

Step 5:
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.

Step 6:
Remove the needle from the vial. Do not let the needle touch anything. You are now ready to inject.

Giving your LANTUS injection:
- Inject your insulin exactly as your healthcare provider has shown you.
- Change (rotate) your injection site for each injection.

Choosing your injection site: LANTUS is injected under the skin (subcutaneously) of your upper arm, thigh, or stomach area (abdomen). Wipe the skin with an alcohol swab to clean the injection site. Let the injection site dry before you inject your dose.

Step 7:
- Pinch the skin.
- Insert the needle in the way your healthcare provider showed you.
- Release the skin.
- 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.

Step 8:
- Pull the needle straight out of your skin.
- Gently press the injection site for several seconds. Do not rub the area.
- Do not recap the used needle. Recapping the needle can lead to a needle stick injury.

Disposing of used needles and syringes:
- Put your used needles and syringes in a FDA-cleared sharps disposal container right away after use. Do not throw away (dispose of) loose needles and syringes in your household trash.
- If you do not have a FDA-cleared sharps container, you may use a household container that is:
  - made of a heavy-duty plastic,
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
  - upright and stable during use,
  - leak resistant, and
How should I store LANTUS?

- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA’s website at: http://www.fda.gov/safesharpsdisposal.
- **Do not** dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. **Do not** recycle your used sharps disposal container.

How should I store LANTUS?

- Store unused LANTUS vials in the refrigerator between 36°F to 46°F (2°C to 8°C).
- Store in-use (opened) LANTUS vials in a refrigerator or at room temperature below 86°F (30°C).
- **Do not** freeze LANTUS.
- Keep LANTUS out of direct heat and light.
- If a vial has been frozen or overheated, throw it away.
- The LANTUS vials you are using should be thrown away after 28 days, even if it still has insulin left in it.

This Instructions for Use have been approved by the U.S. Food and Drug Administration. Revised: July/2015

<table>
<thead>
<tr>
<th>Patient Information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LANTUS® (LAN-tus)</strong></td>
</tr>
<tr>
<td>(insulin glargine injection) for subcutaneous use, 100 Units/mL (U-100)</td>
</tr>
</tbody>
</table>

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.

What is LANTUS?

LANTUS is a long-acting man-made insulin used to control high blood sugar in adults with diabetes mellitus.
- **LANTUS** is not for use to treat diabetic ketoacidosis.
- It is not known if LANTUS is safe and effective in children less than 6 years of age with type 1 diabetes.
- It is not known if LANTUS is safe and effective in children with type 2 diabetes.

Who should not use LANTUS?

- Do not use LANTUS if you:
  - are having an episode of low blood sugar (hypoglycemia)
  - have an allergy to insulin glargine or any of the ingredients in LANTUS. See the end of this Patient Information leaflet for a complete list of ingredients in LANTUS.

What should I tell my healthcare provider before using LANTUS?

Before using LANTUS, tell your healthcare provider about all your medical conditions including if you:
- have liver or kidney problems
- take other medicines, especially ones called TZDs (thiazolidinediones)
- have heart failure or other heart problems. If you have heart failure, it may get worse while you take TZDs with LANTUS.
- are pregnant, planning to become pregnant, or are breastfeeding. It is not known if LANTUS may harm your unborn baby or breastfeeding baby.

Tell your healthcare provider about all the medicines you take including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Before you start using LANTUS, talk to your healthcare provider about low blood sugar and how to manage it.

<table>
<thead>
<tr>
<th>How should I use LANTUS?</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Read the detailed Instructions for Use that come with your LANTUS SoloStar disposable prefilled pen.</td>
</tr>
<tr>
<td>- Use LANTUS exactly as your healthcare provider tells you to. Your healthcare provider should tell you how much LANTUS to use and when to use it.</td>
</tr>
<tr>
<td>- Know the amount of LANTUS you use. <strong>Do not</strong> change the amount of LANTUS you use unless your healthcare provider tells you to.</td>
</tr>
<tr>
<td>- Check your insulin label each time you give your injection to make sure you are using the correct insulin.</td>
</tr>
<tr>
<td>- LANTUS comes in a SoloStar disposable prefilled pen that you must use to give your LANTUS. The dose counter on your pen shows your dose of LANTUS. Do not make any dose changes unless your healthcare provider tells you to.</td>
</tr>
<tr>
<td>- <strong>Do not</strong> use a syringe to remove LANTUS from your SoloStar disposable prefilled pen.</td>
</tr>
<tr>
<td>- <strong>Do not</strong> re-use needles. Always use a new needle for each injection. Re-use of needles increases your risk of having blocked needles, which may cause you to get the wrong dose of LANTUS. Using a new needle for each injection lowers your risk of getting an infection. If your needle is blocked, follow the instructions in Step 3 of the Instructions for Use.</td>
</tr>
<tr>
<td>- You may take LANTUS at any time during the day but you must take it at the same time every day.</td>
</tr>
<tr>
<td>- LANTUS is injected under your skin (subcutaneously). Do not use LANTUS in an insulin pump or inject LANTUS into your vein (intravenously).</td>
</tr>
<tr>
<td>- Change (rotate) injection your sites within area you chose with each dose. Do not use the exact spot for each injection.</td>
</tr>
<tr>
<td>- <strong>Do not</strong> mix LANTUS with any other type of insulin or liquid medicine.</td>
</tr>
<tr>
<td>- <strong>Check your blood sugar levels.</strong> Ask your healthcare provider what your blood sugar should be and when you should check your blood sugar levels.</td>
</tr>
</tbody>
</table>

Keep LANTUS and all medicines out of the reach of children.

Your dose of LANTUS may need to change because of:
- a change in level of physical activity or exercise, weight gain or loss, increased stress, illness, change in diet, or because of the medicines you take.

What should I avoid while using LANTUS?

While using LANTUS do not:
- drive or operate heavy machinery, until you know how LANTUS affects you
- drink alcohol or use over-the-counter medicines that contain alcohol

- properly labeled to warn of hazardous waste inside the container.
- **Do not** dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. **Do not** recycle your used sharps disposal container.
- **Do not** freeze LANTUS.
- Keep LANTUS out of direct heat and light.
- If a vial has been frozen or overheated, throw it away.
- The LANTUS vials you are using should be thrown away after 28 days, even if it still has insulin left in it.
What are the possible side effects of LANTUS and other insulins?

LANTUS may cause serious side effects that can lead to death, including:

- **low blood sugar (hypoglycemia).** Signs and symptoms that may indicate low blood sugar include:
  - dizziness or light-headedness, sweating, confusion, headache, blurred vision, slurred speech, shakiness, fast heartbeat, anxiety, irritability or mood change, hunger
- **severe allergic reaction (whole body reaction).** Get medical help right away if you have any of these signs or symptoms of a severe allergic reaction:
  - a rash over your whole body, trouble breathing, a fast heartbeat, or sweating
- **low potassium in your blood (hypokalemia).**
- **Heart failure.** Taking certain diabetes pills called TZDs (thiazolidinediones) 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
Treatment with TZDs and LANTUS may need to be changed or stopped by your healthcare provider if you have new or worse heart failure.

Get emergency medical help if you have:

- trouble breathing; shortness of breath; fast heartbeat; swelling of your face, tongue, or throat; sweating; extreme drowsiness; dizziness; confusion.

The most common side effects of LANTUS include:

- low blood sugar (hypoglycemia); weight gain; allergic reactions, including reactions at your injection site; skin thickening or pits at the injection site (lipodystrophy).

These are not all the possible side effects of LANTUS. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of LANTUS.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use LANTUS for a condition for which it was not prescribed. It may harm them. This Patient Information 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 the website www.lantus.com.

What are the ingredients in LANTUS?

- **Active ingredient:** insulin glargine
- **3 ml SoloStar prefilled pen inactive ingredients:** zinc, m-cresol, glycerol and water for injection
Hydrochloric acid and sodium hydroxide may be added to adjust the pH.

Manufactured By: sanofi-aventis U.S. LLC Bridgewater, NJ 08807

This Patient Information has been approved by the U.S. Food and Drug Administration
Approved: July/2015

GLA-FPLR-SL-AUG15 Rx Only