LANTUS® (insulin glargine) injection, for subcutaneous use

INDICATIONS AND USAGE
LANTUS is a long-acting human insulin analog indicated to improve glycemic control in adult and pediatric patients with diabetes mellitus. (1)

Limitations of Use
Not recommended for the treatment of diabetic ketoacidosis. (1)

DOSAGE AND ADMINISTRATION

DOSE AND ADMINISTRATION

• Individualize dosage based on metabolic needs, blood glucose monitoring, glycemic control, type of diabetes, and prior insulin use. (2.2)
• Administer subcutaneously into the abdominal area, thigh, or deltoid 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 risk of lipodystrophy and localized cutaneous amyloidosis. (2.1)
• See Full Prescribing Information for the recommended starting dosage in patients with type 2 diabetes (2.3) and how to change to LANTUS from other insulins (2.4)
• Closely monitor glucose when switching to LANTUS and during initial weeks thereafter. (2.4)

DOSE FORMS AND STRENGTHS

Injection: 100 units/mL (U-100) available as:
• 10 mL multiple-dose vial (3)
• 3 mL single-patient-use SoloStar prefilled pen (3)

CONTRAINDICATIONS

• During episodes of hypoglycemia (4)
• Hypersensitivity to insulin glargine or any of the excipients in LANTUS (4)

FULL PRESCRIBING INFORMATION: CONTENTS*

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WARNINGS AND PRECAUTIONS

Never share a LANTUS SoloStar prefilled pen, insulin syringe, or needle between patients, even if the needle is changed. (5.1)

Hypoglycemia or hypoglycemia with changes in insulin regimen: Make changes to a patient’s insulin regimen (e.g., insulin strength, manufacturer, type, injection site or method of administration) under close medical supervision with increased frequency of blood glucose monitoring. (5.2)

Hypoglycemia: May be life-threatening. Increase frequency of glucose monitoring with changes to: insulin dosage, concomitant drugs, meal pattern, physical activity; and in patients with renal or hepatic impairment and hypoglycemia unawareness. (5.3)

Hypoglycemia due to medication errors: Accidental mix-ups between insulin products can occur. Instruct patients to check insulin labels before injection. (5.4)

Hypersensitivity reactions: Severe, life-threatening, generalized allergy, including anaphylaxis, can occur. Discontinue LANTUS. Monitor and treat if indicated. (5.5)

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. (7)
• Antidabetic Drugs (e.g., beta-blockers, clonidine, guanethidine, and reserpine): Signs and symptoms of hypoglycemia may be reduced or absent. (7)

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

Revised: 06/2023
• Dosage adjustments may be needed with changes in physical activity, changes in meal patterns (i.e., receiving a different form 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)].

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

2.3 Initiation of LANTUS Therapy

Recommended Starting Dosage in Patients with Type 1 Diabetes

The recommended starting dosage of LANTUS in patients with type 1 diabetes is approximately one-third of the total daily insulin requirements. Use short-acting, premeal insulin to satisfy the remainder of the daily insulin requirements.

Recommended Starting Dosage in Patients with Type 2 Diabetes

The recommended starting dosage of LANTUS in patients with type 2 diabetes who are not currently treated with insulin is 0.5 to 1.0 units/mL or up to 10 units daily.

2.4 Switching from LANTUS to Other Insulin Therapies

Dosage adjustments are recommended to lower the risk of hypoglycemia when switching patients to LANTUS from other insulin therapies [see Warnings and Precautions (5.3)].

When switching:

• Once-daily TOUJEO (insulin glargine 300 units/mL) to once-daily LANTUS (100 units/mL), the recommended starting LANTUS dosage is 80% of the TOUJEO dosage that is being discontinued.

• Once-daily NPH insulin to once-daily LANTUS, the recommended starting LANTUS dosage is the same as the dosage of NPH that is being discontinued.

• Twice-daily NPH insulin to once-daily LANTUS, the recommended starting LANTUS dosage is 80% of the total NPH dosage that is being discontinued.

3 DOSAGE FORMS AND STRENGTHS

Injection: 100 units/mL (U-100) a clear and colorless solution available as:

• 10 mL multiple-dose vial

• 3 mL single-patient-use LANTUS SoloStar prefilled pen

4 CONTRAINDICATIONS

LANTUS is contraindicated:

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

• In patients with hyperinsulinemia [see Warnings and Precautions (5.3)]

5 WARNINGS AND PRECAUTIONS

5.1 Never Share a LANTUS SoloStar Prefilled Pen, Insulin 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 re-use or share needles or syringes with another person. Sharing poses a risk for transmission of blood-borne pathogens.

5.2 Hypoglycemia or Hyperglycemia with Changes in Insulin Regimen

Changes in an insulin regimen (e.g., insulin strength, manufacturer, type, injection site or method of administration) may affect glycemic control and predispose to hypoglycemia [see Warnings and Precautions (5.4)] or hyperglycemia. Repeated insulin injections into areas of lipodystrophy or localized cutaneous amyloidosis have been reported to result in hyperglycemia; and a sudden change in the injection site (to unaffected area) has been reported to result in hypoglycemia [see Adverse Reactions (6)].

Make any changes to a patient’s insulin regimen under close medical supervision with increased frequency of blood glucose monitoring. Advise patients who have repeatedly injected into areas of lipodystrophy or localized cutaneous amyloidosis to change the injection site to unaffected areas and closely monitor for hypoglycemia. For patients with type 2 diabetes, dosage adjustments of concomitant oral and antidiabetic products may be needed.

5.3 Hypoglycemia

Hypoglycemia is the most common adverse reaction associated with insulins, including LANTUS. Severe hypoglycemia can cause seizures, may be life-threatening or cause death. Hypoglycemia can happen suddenly, and symptoms may differ in each patient and change over time.

In patients with type 1 diabetes, LANTUS must be used concomitantly with short-acting insulin. Adverse events related to fluid retention, 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 or Hypoglycemia with Changes in Insulin Regimen [see Warnings and Precautions (5.2)]

• Hyperglycemia [see Warnings and Precautions (5.3)]

• Hypoglycemia Due to Medication Errors [see Warnings and Precautions (5.4)]

• Hypersensitivity Reactions [see Warnings and Precautions (5.5)]

• Hypokalemia [see Warnings and Precautions (5.6)]

6.1 Clinical Trials 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 2,327 patients with type 1 diabetes to LANTUS or NPH in Studies A, B, C, and D [see Clinical Studies (14.2)]. The type 1 diabetes population had the following characteristics: the mean age was 39 years, 54% were male, and mean body mass index (BMI) was 25.1 kg/m². Ninety-seven percent were White, 2% were Black or African American and less than 1% were Asian. Approximately 3% of the patients in studies B and C were Hispanic.

In the data in Table 2, the percentage of patients with type 2 diabetes to LANTUS or NPH in Studies E, F, and G [see Clinical Studies (14.3)]. The type 2 diabetes population had the following characteristics: the mean age was 59 years, 56% were male, and mean BMI was 29.2 kg/m². Seventy-three percent were White, 8% were Black or African American and 3% were Asian. Approximately 9% of patients in Study F were Hispanic.

The frequency of adverse reactions during LANTUS clinical studies in patients with type 1 diabetes mellitus and type 2 diabetes mellitus is listed in the tables below (Tables 1, 2, 3, and 4).

Table 1: Adverse Reactions Occurring ≥5% in Pooled Clinical Studies up to 28 Weeks Duration in Adults with Type 1 Diabetes

<table>
<thead>
<tr>
<th>Reaction</th>
<th>LANTUS, % (n=1,257)</th>
<th>NPH, % (n=1,070)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchitis</td>
<td>15.2</td>
<td>14.1</td>
</tr>
<tr>
<td>Cataract</td>
<td>5.8</td>
<td>5.3</td>
</tr>
<tr>
<td>Cough</td>
<td>12.1</td>
<td>11.6</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>Lower respiratory tract infection</td>
<td>11.4</td>
<td>13.3</td>
</tr>
<tr>
<td>Malaria</td>
<td>4.7</td>
<td>4.7</td>
</tr>
<tr>
<td>Nausea</td>
<td>12.1</td>
<td>11.6</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>9.4</td>
<td>9.4</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>12.1</td>
<td>11.6</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>4.7</td>
<td>4.7</td>
</tr>
<tr>
<td>Retinal vascular disorder</td>
<td>5.8</td>
<td>7.4</td>
</tr>
</tbody>
</table>

*Body system not specified

Table 2: Adverse Reactions Occurring ≥5% in Pooled Clinical Studies up to 1 Year Duration in Adults with Type 2 Diabetes

<table>
<thead>
<tr>
<th>Reaction</th>
<th>LANTUS, % (n=849)</th>
<th>NPH, % (n=714)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchitis</td>
<td>15.2</td>
<td>14.1</td>
</tr>
<tr>
<td>Cataract</td>
<td>5.8</td>
<td>5.3</td>
</tr>
<tr>
<td>Cough</td>
<td>12.1</td>
<td>11.6</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>Lower respiratory tract infection</td>
<td>11.4</td>
<td>13.3</td>
</tr>
<tr>
<td>Malaria</td>
<td>4.7</td>
<td>4.7</td>
</tr>
<tr>
<td>Nausea</td>
<td>12.1</td>
<td>11.6</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>9.4</td>
<td>9.4</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>4.7</td>
<td>4.7</td>
</tr>
<tr>
<td>Retinal vascular disorder</td>
<td>5.8</td>
<td>7.4</td>
</tr>
</tbody>
</table>

*Body system not specified

Table 3: Adverse Reactions Occurring ≥10% in a 5-Year Study of Adults with Type 2 Diabetes

<table>
<thead>
<tr>
<th>Reaction</th>
<th>LANTUS, % (n=514)</th>
<th>NPH, % (n=932)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchitis</td>
<td>15.2</td>
<td>14.1</td>
</tr>
<tr>
<td>Cataract</td>
<td>18.1</td>
<td>15.9</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>

*Body system not specified

Table 4: Adverse Reactions Occurring ≥10% in a 1-Year Study of Adults with Type 2 Diabetes

<table>
<thead>
<tr>
<th>Reaction</th>
<th>LANTUS, % (n=714)</th>
<th>NPH, % (n=714)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchitis</td>
<td>15.2</td>
<td>14.1</td>
</tr>
<tr>
<td>Cataract</td>
<td>18.1</td>
<td>15.9</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>

*Body system not specified

5.4 Hypoglycemia Due to Medication Errors

Accidental mix-ups among insulin products 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)].

5.5 Hypersensitivity Reactions

Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulins, including LANTUS [see Adverse Reactions (6)]. If hypersensitivity reactions occur, discontinue LANTUS; treat per standard of care and monitor until symptoms and signs resolve. LANTUS is contraindicated in patients who have had hypersensitivity reactions to insulin glargine or one of the excipients.

5.6 Hypokalemia

All insulins, including LANTUS, cause a shift in potassium from the extracellular to intracellular space, possibly leading 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, 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.
Severe Hypoglycemia

Percentages of LANTUS-treated adult patients who experienced severe symptomatic hypoglycemia in the LANTUS clinical studies with type 1 diabetes had a higher incidence of severe symptomatic hypoglycemia in the two treatment groups compared to the adult studies with type 1 diabetes.

Table 3: Adverse Reactions Occurring ≥10% in a 5-Year Study of Adults with Type 2 Diabetes (continued)

<table>
<thead>
<tr>
<th>Event</th>
<th>LANTUS, % (n=614)</th>
<th>NPH, % (n=503)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>10.7</td>
<td>10.3</td>
</tr>
<tr>
<td>Depression</td>
<td>10.5</td>
<td>9.7</td>
</tr>
<tr>
<td>Headache</td>
<td>10.3</td>
<td>9.3</td>
</tr>
</tbody>
</table>

*Body system not specified

Severe hypoglycemia requiring the assistance of another person and associated with either a blood glucose below 50 mg/dL (≤5.6 mmol/L) in the 5-year study and ≤38 mg/dL (≤2.1 mmol/L) in the ORIGIN study or prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration.

Table 4: Adverse Reactions Occurring ≥5% in a 28-Week Clinical Study in Pediatric Patients with Type 1 Diabetes

<table>
<thead>
<tr>
<th>Event</th>
<th>LANTUS, % (n=174)</th>
<th>NPH, % (n=175)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>13.8</td>
<td>17.7</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>13.8</td>
<td>16.0</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>7.5</td>
<td>8.6</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>5.2</td>
<td>5.1</td>
</tr>
</tbody>
</table>

Severe Hypoglycemia

Hypoglycemia was the most commonly observed adverse reaction in patients treated with LANTUS. Tables 5, 6, and 7 summarize the incidence of severe hypoglycemia in the LANTUS clinical studies. Severe symptomatic hypoglycemia was defined as an event with symptoms consistent with hypoglycemia requiring the assistance of another person and associated with a blood glucose below 50 mg/dL (≤5.6 mmol/L) in the 5-year study or prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration.

Percentages of LANTUS-treated adult patients who experienced severe symptomatic hypoglycemia in the LANTUS clinical studies (see Clinical Studies (14)] were comparable to percentages of NPH-treated patients for all treatment regimens (see Tables 5 and 6). In the pediatric clinical study, pediatric patients with type 1 diabetes had a higher incidence of severe symptomatic hypoglycemia in the two treatment groups compared to the adults with type 1 diabetes.

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

<table>
<thead>
<tr>
<th>Study A: Type 1 Diabetes Adults 28 weeks in combination with regular insulin</th>
<th>Study B: Type 1 Diabetes Adults 28 weeks in combination with regular insulin</th>
<th>Study C: Type 1 Diabetes Adults 16 weeks in combination with insulin lispro</th>
<th>Study D: Type 1 Diabetes Pediatrics 26 weeks in combination with regular insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>LANTUS N=292</td>
<td>NPH N=293</td>
<td>LANTUS N=264</td>
<td>NPH N=270</td>
</tr>
<tr>
<td>Percent of patients</td>
<td>10.6</td>
<td>15.0</td>
<td>8.7</td>
</tr>
<tr>
<td></td>
<td>6.5</td>
<td>23.0</td>
<td>20.8</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Study E: Type 2 Diabetes Adults 52 weeks in combination with oral agents</th>
<th>Study F: Type 2 Diabetes Adults 28 weeks in combination with regular insulin</th>
<th>Study G: Type 2 Diabetes Adults 5 years in combination with regular insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>LANTUS N=269</td>
<td>NPH N=261</td>
<td>LANTUS N=259</td>
</tr>
<tr>
<td>Percent of patients</td>
<td>1.7</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td>7.8</td>
<td>11.9</td>
</tr>
</tbody>
</table>

Table 7 displays the proportion of patients who experienced severe symptomatic hypoglycemia in the LANTUS and Standard Care groups in the ORIGIN study (see Clinical Studies [14]).

Table 7: Severe Symptomatic Hypoglycemia in the ORIGIN Study

<table>
<thead>
<tr>
<th>ORIGIN Study Median duration of follow-up: 6.2 years</th>
<th>LANTUS N=5231</th>
<th>Standard Care N=5273</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent of patients</td>
<td>5.6</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 was improved by intensified insulin therapy.

Table 8: Clinically Significant Drug Interactions with LANTUS

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Antidiabetic agents, ACE inhibitors, angiotensin II receptor blocking agents, diopyridamide, furosemide, fluoxetine, monoamine oxidase inhibitors, pentoxifylline, pramlintide, salicylates, somatostatin analogs (e.g., octreotide), sulfonamide antibiotics: GLP-1 receptor agonists, DPP-4 inhibitors, and SGLT-2 inhibitors.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Dosage reductions and increased frequency of glucose monitoring may be required when LANTUS is coadministered with these drugs.</td>
</tr>
</tbody>
</table>

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. 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 clinical studies of LANTUS, increases in titers of antibodies to insulin were observed in NPH insulin and LANTUS treatment groups with similar incidences.

6.3 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of LANTUS. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Medsication errors have been reported in which rapid-acting insulin similar to insulin and other insulin, have been accidentally administered instead of LANTUS.

Localized cutaneous amyloidosis at the injection site has occurred. Hypoglycemia has been reported with repeated insulin injections into areas of localized cutaneous amyloidosis; hypoglycemia has been reported with a sudden change to an unaffected injection site.

7. DRUG INTERACTIONS

Table 8 includes clinically significant drug interactions with LANTUS.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Published studies with use of insulin glargine during pregnancy have not reported a clear association with insulin glargine and adverse developmental outcomes (see Data). There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy (see Clinical Considerations). Rats and rabbits were exposed to insulin glargine in animal reproduction studies during organogenesis, respectively 50 times and 10 times the human subcutaneous dosage of 0.2 units/kg/day. Overall, the effects of insulin glargine did not generally differ from those observed with regular human insulin (see Data). In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. The estimated background risk of major birth defects is 6% to 10% in women with pregestational diabetes with a
Insulin glargine is a long-acting human insulin analog produced by recombinant DNA technology. It is administered by subcutaneous injection and is used exclusively for once-daily basal insulin treatment. Over time, subcutaneous insulin glargine accumulates in the subcutaneous depot to form two active metabolites with glucose-lowering activity.

### Pharmacokinetics

**Metabolism**

After subcutaneous injection of LANTUS in healthy subjects and in patients with diabetes, the insulin concentration/time profile over 24 hours with no pronounced peak in comparison to NPH insulin.侯

**Absorption**

Subcutaneous insulin glargine has been shown to be rapidly absorbed after subcutaneous injection, with peak concentration occurring within 2-3 hours. The terminal half-life is approximately 24 hours, allowing for once-daily administration.

### Clinical Studies

**12.2 Pharmacodynamics**

In clinical studies, the glucose-lowering effect on a molar basis (i.e., when given at the same doses) of intravenous LANTUS is approximately the same as that for human insulin. Figure 1 shows results from a study in patients with type 1 diabetes conducted for a maximum of 24 hours after subcutaneous injection of LANTUS or NPH insulin. The median time between subcutaneous injection and the end of glucose-lowering effect was 14.2 hours (range: 5.5 to 19.3 hours) for NPH insulin, and 24 hours for LANTUS.

**12.3 Pharmacokinetics**

Absorption

After subcutaneous injection of LANTUS in healthy subjects and in patients with diabetes, the insulin concentration/time profile over 24 hours with no pronounced peak in comparison to NPH insulin.

**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 0.45 mg/kg, which was for the rat approximately 65 times the recommended human subcutaneous starting dosage of 0.2 units/kg/day (0.007 mg/kg/day) on a mg/kg basis. Histocytomas were found at injection sites in male rats and mice in acid vehicle containing groups and are considered a response to chronic tissue irritation and inflammation in rodents. These tumors were not found in female animals, in saline control, or insulin comparator groups using a different vehicle.

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 50 times the recommended human subcutaneous starting dose of 0.2 units/kg/day (0.007 mg/kg/day) 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**

14.1 Overview of Clinical Studies

The safety and effectiveness of LANTUS given once-daily at bedtime was compared to that of insulin lispro before each meal. LANTUS was administered at bedtime. NPH insulin was administered at bedtime.

In a combined study in pediatric patients (n=349), subgroup analyses based on age, race, BMI, and gender did not show differences in safety and efficacy between LANTUS and NPH insulin (see Clinical Studies 14.1).

14.2 Clinical Studies in Adult and Pediatric Patients with Type 1 Diabetes

**Adult Patients with Type 1 Diabetes**

In two clinical studies (Studies A and B), adult patients with type 1 diabetes (Study A, n=1465; 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.

In Study A, the average age was 39 years. The majority of patients were White (96%) and 56% were female. The mean BMI was approximately 24.9 kg/m². The mean duration of diabetes was 16 years. In Study B, the average age was 39 years. The majority of patients were White (95%) and 51% were male. The mean BMI was approximately 25.8 kg/m². The mean duration of diabetes was 17 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.

### Lactation

The safety and effectiveness of LANTUS to improve glycemic control in pediatric patients with diabetes mellitus has been established. Use of LANTUS for this indication is supported by evidence from an open-label, randomized, active-controlled, parallel studies in children with type 2 diabetes mellitus (see Clinical Pharmacology 12.3, Clinical Studies 14.2). In the pediatric clinical study, pediatric patients with type 1 diabetes had a higher incidence of severe symptomatic hypoglycemia compared to the adults in studies with type 1 diabetes (see Adverse Reactions 6.2).

**8.7 Hepatic Impairment**

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

**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% (n=316) were ≥65 years of age and 2% (n=42) were ≥75 years of age. No overall differences in safety or effectiveness of LANTUS have been observed between patients 65 years of age and older and younger adult patients. Nevertheless, caution should be exercised when LANTUS is administered to geriatric patients. In geriatric patients with diabetes, the initial dosing, dosage increments, and maintenance dosage should be conservative to avoid hypoglycemic reactions. Hypoglycemia may be difficult to recognize in geriatric patients.

**8.6 Renal Impairment**

The effect of kidney 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 dosage adjustment may be necessary for LANTUS in patients with kidney impairment [see Warnings and Precautions (5.3)].

**8.4 Pediatric Use**

Effect of age, race, body mass index, and gender on breastfed infant, or the effects on milk production. Endogenous insulin is present in human milk. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia-related morbidity. Data

**8.2 Lactation**

The safety and effectiveness of LANTUS to improve glycemic control in pediatric patients with diabetes mellitus has been established. Use of LANTUS for this indication is supported by evidence from an open-label, randomized, active-controlled, parallel studies in children with type 2 diabetes mellitus (see Clinical Pharmacology 12.3, Clinical Studies 14.2). In the pediatric clinical study, pediatric patients with type 1 diabetes had a higher incidence of severe symptomatic hypoglycemia compared to the adults in studies with type 1 diabetes (see Adverse Reactions 6.2).

**8.5 Geriatric Use**

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**8.6 Renal Impairment**

The effect of kidney 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 dosage adjustment may be necessary for LANTUS in patients with kidney impairment [see Warnings and Precautions (5.3)].

**8.7 Hepatic Impairment**

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

**10 OVERDOSAGE**

Excess insulin administration may cause hypoglycemia and hypokalemia [see Warnings and Precautions (5.3)].

### Hypoglycemia

- **11 DESCRIPTION**
- **12 CLINICAL PHARMACOLOGY**
- **12.1 Mechanism of Action**
- **12.2 Pharmacodynamics**
- **12.3 Pharmacokinetics**
- **13 NONCLINICAL TOXICOLOGY**
- **14 CLINICAL STUDIES**

### LACTATION

The safety and effectiveness of LANTUS to improve glycemic control in pediatric patients with diabetes mellitus has been established. Use of LANTUS for this indication is supported by evidence from an open-label, randomized, active-controlled, parallel studies in children with type 2 diabetes mellitus (see Clinical Pharmacology 12.3, Clinical Studies 14.2). In the pediatric clinical study, pediatric patients with type 1 diabetes had a higher incidence of severe symptomatic hypoglycemia compared to the adults in studies with type 1 diabetes (see Adverse Reactions 6.2).

**8.5 Geriatric Use**

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**8.6 Renal Impairment**

The effect of kidney 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 dosage adjustment may be necessary for LANTUS in patients with kidney impairment [see Warnings and Precautions (5.3)].

**8.7 Hepatic Impairment**

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

**10 OVERDOSAGE**

Excess insulin administration may cause hypoglycemia and hypokalemia [see Warnings and Precautions (5.3)].
**Table 9: Type 1 Diabetes Mellitus – Adults**

<table>
<thead>
<tr>
<th>Treatment duration</th>
<th>Treatment in combination with</th>
<th>Study A 28 weeks Regular insulin</th>
<th>Study B 28 weeks Regular insulin</th>
<th>Study C 16 weeks Insulin lispro</th>
</tr>
</thead>
<tbody>
<tr>
<td>LANTUS</td>
<td>NPH</td>
<td>LANTUS</td>
<td>NPH</td>
<td>LANTUS</td>
</tr>
<tr>
<td>Number of subjects treated</td>
<td>292</td>
<td>293</td>
<td>264</td>
<td>270</td>
</tr>
<tr>
<td><strong>HbA1c</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline HbA1c</td>
<td>8.0</td>
<td>8.0</td>
<td>7.7</td>
<td>7.7</td>
</tr>
<tr>
<td>Adjusted mean change at study end</td>
<td>+0.2</td>
<td>-0.1</td>
<td>-0.2</td>
<td>-0.1</td>
</tr>
<tr>
<td>Treatment Difference (95% CI)</td>
<td>-0.1 (0.0; +0.2)</td>
<td>+0.1 (-0.1; +0.2)</td>
<td>0.0 (-0.1; +0.1)</td>
<td></td>
</tr>
<tr>
<td><strong>Basal insulin dose</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline mean</td>
<td>21</td>
<td>23</td>
<td>29</td>
<td>29</td>
</tr>
<tr>
<td>Mean change from baseline</td>
<td>-2</td>
<td>0</td>
<td>-4</td>
<td>+2</td>
</tr>
<tr>
<td><strong>Total insulin dose</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline mean</td>
<td>48</td>
<td>52</td>
<td>50</td>
<td>51</td>
</tr>
<tr>
<td>Mean change from baseline</td>
<td>-1</td>
<td>0</td>
<td>0</td>
<td>+4</td>
</tr>
<tr>
<td><strong>Fasting blood glucose (mg/dL)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline mean</td>
<td>167</td>
<td>166</td>
<td>166</td>
<td>175</td>
</tr>
<tr>
<td>Adj. mean change from baseline</td>
<td>-21</td>
<td>-16</td>
<td>-20</td>
<td>-17</td>
</tr>
<tr>
<td><strong>Body weight (kg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline mean</td>
<td>73.2</td>
<td>74.8</td>
<td>75.5</td>
<td>75.0</td>
</tr>
<tr>
<td>Mean change from baseline</td>
<td>0.1</td>
<td>-0.0</td>
<td>0.7</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Pediatric Patients with Type 1 Diabetes

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 (97%) and 52% were male. The mean BMI was approximately 18.9 kg/m². The mean duration of diabetes was 5 years. Similar effects on HbA1c (Table 10) were observed in both treatment groups [see Adverse Reactions (6.1)].

**Table 10: Type 1 Diabetes Mellitus – Pediatric Patients**

<table>
<thead>
<tr>
<th>Treatment duration</th>
<th>Treatment in combination with</th>
<th>Study D 28 weeks Regular insulin</th>
<th>Study E 52 weeks Oral agents</th>
<th>Study F 28 weeks Regular insulin</th>
<th>Study G 5 years Regular insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>LANTUS</td>
<td>NPH</td>
<td>LANTUS</td>
<td>NPH</td>
<td>LANTUS</td>
<td>NPH</td>
</tr>
<tr>
<td>Number of subjects treated</td>
<td>289</td>
<td>281</td>
<td>269</td>
<td>259</td>
<td>513</td>
</tr>
<tr>
<td><strong>HbA1c</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline mean</td>
<td>9.0</td>
<td>8.9</td>
<td>8.6</td>
<td>8.5</td>
<td>8.4</td>
</tr>
<tr>
<td>Adjusted mean change from baseline</td>
<td>-0.5</td>
<td>-0.4</td>
<td>-0.4</td>
<td>-0.6</td>
<td>-0.6</td>
</tr>
<tr>
<td>95% CI for Treatment difference</td>
<td>(-0.3; +0.1)</td>
<td>(0.0; +0.4)</td>
<td>(+0.1; +0.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Basal insulin dose</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline mean</td>
<td>14</td>
<td>15</td>
<td>44.1</td>
<td>45.5</td>
<td>39</td>
</tr>
<tr>
<td>Mean change from baseline</td>
<td>+12</td>
<td>+9</td>
<td>-1</td>
<td>+7</td>
<td>+23</td>
</tr>
<tr>
<td><strong>Total insulin dose</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline mean</td>
<td>14</td>
<td>15</td>
<td>64</td>
<td>67</td>
<td>48</td>
</tr>
<tr>
<td>Mean change from baseline</td>
<td>+12</td>
<td>+9</td>
<td>+10</td>
<td>+13</td>
<td>+41</td>
</tr>
</tbody>
</table>

14.3 Clinical Studies in Adults with Type 2 Diabetes

In a randomized, controlled clinical study (Study E) in 570 adults with type 2 diabetes, LANTUS was evaluated for 28 weeks in combination with oral antidiabetic 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 years. The majority of patients were White (81%) and 60% were male. The mean BMI was approximately 30.5 kg/m². The mean duration of diabetes was 14 years. LANTUS had similar effectiveness as either once- or twice-daily NPH insulin in reducing HbA1c and fasting glucose (Table 11). The rate of severe symptomatic hypoglycemia was similar in LANTUS and NPH insulin treated patients [see Adverse Reactions (6.1)].

In a randomized, controlled clinical study (Study F), in adult patients with type 2 diabetes not using oral antidiabetic 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 years. The majority of patients were White (81%) and 60% were male. The mean BMI was approximately 30.5 kg/m². The mean duration of diabetes was 14 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), adult 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 dosage 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 dosage that was 80% of the total previous NPH insulin dosage. The primary endpoint for this study was 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 dosages to a target fasting plasma glucose ≤100 mg/dL. After the LANTUS or NPH insulin dosage was adjusted, other antidiabetic agents, including premeal insulin were to be adjusted or added. The average age was 55 years. The majority of patients were White (85%) and 54% were male. The mean BMI was approximately 34.3 kg/m². The mean duration of diabetes was 11 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 11: Type 2 Diabetes Mellitus – Adults**

<table>
<thead>
<tr>
<th>Treatment duration</th>
<th>Treatment in combination with</th>
<th>Study D 28 weeks Regular insulin</th>
<th>Study E 52 weeks Oral agents</th>
<th>Study F 28 weeks Regular insulin</th>
<th>Study G 5 years Regular insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>LANTUS</td>
<td>NPH</td>
<td>LANTUS</td>
<td>NPH</td>
<td>LANTUS</td>
<td>NPH</td>
</tr>
<tr>
<td>Number of subjects treated</td>
<td>289</td>
<td>281</td>
<td>269</td>
<td>259</td>
<td>513</td>
</tr>
<tr>
<td><strong>HbA1c</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline mean</td>
<td>9.0</td>
<td>8.9</td>
<td>8.6</td>
<td>8.5</td>
<td>8.4</td>
</tr>
<tr>
<td>Adjusted mean change from baseline</td>
<td>-0.5</td>
<td>-0.4</td>
<td>-0.4</td>
<td>-0.6</td>
<td>-0.6</td>
</tr>
<tr>
<td>95% CI for Treatment difference</td>
<td>(-0.3; +0.1)</td>
<td>(0.0; +0.4)</td>
<td>(+0.1; +0.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Basal insulin dose</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline mean</td>
<td>14</td>
<td>15</td>
<td>44.1</td>
<td>45.5</td>
<td>39</td>
</tr>
<tr>
<td>Mean change from baseline</td>
<td>+12</td>
<td>+9</td>
<td>-1</td>
<td>+7</td>
<td>+23</td>
</tr>
<tr>
<td><strong>Total insulin dose</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline mean</td>
<td>14</td>
<td>15</td>
<td>64</td>
<td>67</td>
<td>48</td>
</tr>
<tr>
<td>Mean change from baseline</td>
<td>+12</td>
<td>+9</td>
<td>+10</td>
<td>+13</td>
<td>+41</td>
</tr>
</tbody>
</table>

LANTUS was administered once daily at bedtime and NPH insulin was administered once or twice daily. The average age was 59 years. The majority of patients were White (81%) and 52% were male. The mean BMI was approximately 25.6 kg/m². The mean duration of diabetes was 19 years. In these 3 adult 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)].
Progression of Retinopathy Evaluation in Adults with Diabetes Type 1 and Diabetes Type 2

The safety and efficacy of once daily LANTUS administered either at pre-breakfast, pre-dinner, or at bedtime were evaluated in a randomized, controlled clinical study in adult patients with type 1 diabetes (Study H, n=378). Patients were also treated with insulin lispro at mealtime. The average age was 41 years. All patients were White (100%) and 54% were male. The mean BMI was approximately 25.3 kg/m². Progression of Retinopathy Evaluation in Adults with Diabetes Type 1 and Diabetes Type 2

The safety and efficacy of once daily 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. The objective of the study was to demonstrate that LANTUS use could significantly lower the risk of major adverse cardiovascular (CV) outcomes defined as the composite of CV death, nonfatal myocardial infarction, and nonfatal stroke. The second coprimary endpoint was the time to the first occurrence of a major adverse CV event defined as a combination of CV death, nonfatal myocardial infarction, and nonfatal stroke. Patients were randomized to either LANTUS (N=3,624) straited to a goal fasting plasma glucose of <100 mg/dL or to standard care (N=6,273). Anthropometric and disease characteristics were balanced at baseline. The mean age was 64 years and 8% of patients were 75 years of age or older. The majority of patients had a prior CV event and 39% had documented coronary artery disease or other CV risk factors. Established CV disease or CV risk factors at baseline. The mean HbA1c (SD) at baseline was 6.5% (1.0). Fifty-nine percent of the patients had abnormal glucose levels (i.e., impaired fasting glucose [IFG] and/or impaired glucose tolerance [IGT]) or early type 2 diabetes mellitus and 39% had documented coronary artery disease or other CV risk factors. 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 the patients had a prior CV event and 39% had documented coronary artery disease or other CV risk factors. Vital status was available for 99.9% and 99.8% of patients randomized to LANTUS and standard care respectively at end of study. 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 study 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 study 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 CV outcomes was similar between groups (see Table 14). All-cause mortality was also similar between groups.

Table 12: Study of Different Times of Once Daily LANTUS 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</th>
<th>Study I</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LANTUS before breakfast</td>
<td>LANTUS before dinner</td>
<td>LANTUS bedtime</td>
</tr>
<tr>
<td></td>
<td>LANTUS before breakfast</td>
<td>LANTUS before dinner</td>
<td>LANTUS bedtime</td>
</tr>
<tr>
<td></td>
<td>LANTUS before breakfast</td>
<td>LANTUS before dinner</td>
<td>LANTUS bedtime</td>
</tr>
<tr>
<td></td>
<td>NPH before breakfast</td>
<td>NPH before dinner</td>
<td>NPH bedtime</td>
</tr>
<tr>
<td>Number of subjects treated</td>
<td>112 124 128 234 226 227</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal insulin dose (Units)</td>
<td>-0.2 -0.1 0.0 -1.3 -1.0 -0.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal mean</td>
<td>22 23 21 19 20 19</td>
<td>7.6 7.5 7.6 9.1 9.1 9.1</td>
<td></td>
</tr>
<tr>
<td>Mean change from baseline</td>
<td>5 2 2 11 18 18</td>
<td>7.6 7.5 7.6 9.1 9.1 9.1</td>
<td></td>
</tr>
<tr>
<td>Total insulin dose (Units)</td>
<td>– – – NA¹ NA¹ NA¹</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal mean</td>
<td>52 52 49 – – –</td>
<td>52 52 49 – – –</td>
<td></td>
</tr>
<tr>
<td>Mean change from baseline</td>
<td>2 3 2 – – –</td>
<td>2 3 2 – – –</td>
<td></td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>77.1 77.8 74.5 80.7 82 81</td>
<td>77.1 77.8 74.5 80.7 82 81</td>
<td></td>
</tr>
</tbody>
</table>

Table 13: Number (%) of Patients with 3 or More Step Progression on ETDRS Scale at Endpoint

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>LANTUS (%)</th>
<th>NPH (%)</th>
<th>Difference¹</th>
<th>95% CI for difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per-protocol</td>
<td>53/374 (14.2%)</td>
<td>57/363 (15.7%)</td>
<td>-0.2% (2.6%)</td>
<td>-7.0% to +3.1%</td>
</tr>
<tr>
<td>Intent-to-Treat</td>
<td>63/502 (12.5%)</td>
<td>71/467 (14.6%)</td>
<td>-2.1% (2.1%)</td>
<td>-6.3% to +2.1%</td>
</tr>
</tbody>
</table>

¹Difference = LANTUS – NPH

*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

The ORIGIN Study of Major Cardiovascular Outcomes in Patients with Established CV Disease or CV Risk Factors

The Objective Reduction with Initial Glargine Intervention study (i.e., ORIGIN) was an open-label, factorial-designed, multicenter trial conducted in 12,537 adults ≥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
- Established CV disease or CV risk factors at baseline.

The objective of the study was to demonstrate that LANTUS use could significantly lower the risk of major CV outcomes compared to standard care. There were two coprimary composite CV endpoints:

- The first coprimary endpoint was the time to first occurrence of a major adverse CV event defined as the composite of CV death, nonfatal myocardial infarction, and nonfatal stroke.
- The second coprimary 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.

Patients were randomized to either LANTUS (N=6,244) or straited to a goal fasting plasma glucose of <95 mg/dL or to standard care (N=6,273). Anthropometric and disease characteristics were balanced at baseline. The mean age was 64 years and 8% of patients were 75 years of age or older. The majority of patients had a prior CV event and 39% had documented coronary artery disease or other CV risk factors. Vital status was available for 99.9% and 99.8% of patients randomized to LANTUS and standard care respectively at end of study. The median duration of follow-up was 6.2 years (range: 8 days to 7.9 years). The mean HbA1c (SD) at baseline was 6.5% (1.0). Fifty-nine percent of the patients had a prior CV event and 39% had documented coronary artery disease or other CV risk factors. Vital status was available for 99.9% and 99.8% of patients randomized to LANTUS and standard care respectively at end of study. 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 study 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 study 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 CV outcomes was similar between groups (see Table 14). All-cause mortality was also similar between groups.

Table 14: Cardiovascular Outcomes in ORIGIN in Patients with Established CV Disease or CV Risk Factors – Time to First Event Analyses

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>LANTUS vs Standard Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death</td>
<td>1041 (2.9) 1013 (2.9) 1.02 (0.94, 1.11)</td>
</tr>
<tr>
<td>Myocardial infarction, nonfatal stroke</td>
<td>1792 (5.5) 1727 (5.3) 1.04 (0.97, 1.11)</td>
</tr>
<tr>
<td>Myocardial infarction, fatal or nonfatal</td>
<td>336 326 1.03 (0.88, 1.19)</td>
</tr>
<tr>
<td>Stroke, fatal or nonfatal</td>
<td>331 319 1.03 (0.89, 1.21)</td>
</tr>
<tr>
<td>Revascularizations</td>
<td>908 890 1.06 (0.96, 1.16)</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>310 343 0.90 (0.77, 1.05)</td>
</tr>
</tbody>
</table>

*Intent-to-treat
†Not applicable
In the ORIGIN study, 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>Cancer endpoints</th>
<th>LANTUS N=6,264</th>
<th>Standard Care N=6,273</th>
<th>LANTUS vs Standard Care Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any cancer event (new or recurrent)</td>
<td>559 (1.56)</td>
<td>561 (1.56)</td>
<td>0.99 (0.86, 1.1)</td>
</tr>
<tr>
<td>New cancer events</td>
<td>524 (1.46)</td>
<td>535 (1.49)</td>
<td>0.96 (0.85, 1.09)</td>
</tr>
<tr>
<td>Death due to Cancer</td>
<td>189 (0.51)</td>
<td>201 (0.54)</td>
<td>0.94 (0.77, 1.15)</td>
</tr>
</tbody>
</table>

### 16 HOW SUPPLIED/STORAGE AND HANDLING

#### 16.1 How Supplied

LANTUS (insulin glargine) injection is supplied as a clear and colorless solution containing 100 units/mL (U-100) available as follows:

<table>
<thead>
<tr>
<th>LANTUS</th>
<th>NDC number</th>
<th>Package size</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mL Multiple-dose vial</td>
<td>0088-2220-33</td>
<td>1 vial per carton</td>
</tr>
<tr>
<td>3 mL SoloStar single-patient-use prefilled pen</td>
<td>0088-2219-05</td>
<td>5 pens per carton</td>
</tr>
</tbody>
</table>

Additional Information about LANTUS Solostar:
- The LANTUS SoloStar prefilled pen dials in 1 unit increments.
- Needles are not included in the packs. Use BD Ultra-Fine® needles with the SoloStar prefilled pens (these BD manufactured needles are sold separately).

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

#### 16.2 Storage

Dispense in the original sealed carton with the enclosed Instructions for Use. Store unused LANTUS in a refrigerator between 36°F and 46°F (2°C and 8°C). Do not freeze. Discard LANTUS if it has been frozen. Protect LANTUS from direct heat and light.

Storage conditions are summarized in the following table.

<table>
<thead>
<tr>
<th>Not in-use (unopened)</th>
<th>Not in-use (unopened)</th>
<th>In-use (opened)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(36°F–46°F)</td>
<td>(up to 86°F [30°C])</td>
<td>(see temperature below)</td>
</tr>
<tr>
<td>Refrigerated (2°C–8°C)</td>
<td></td>
<td>28 days Refrigerated or room temperature</td>
</tr>
<tr>
<td>Room Temperature only</td>
<td></td>
<td>28 days Room temperature</td>
</tr>
</tbody>
</table>

- 10 mL multiple-dose vial: Until expiration date
- 3 mL single-patient-use SoloStar prefilled pen: Until expiration date

### 17 PATIENT COUNSELING INFORMATION

Advises the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use). There are separate Instructions for Use for the Vial and LANTUS SoloStar Pen.

Never Share a LANTUS SoloStar Prefilled Pen or Insulin Syringe Between Patients

Advises patients that they must never share a LANTUS SoloStar pen with another person, even if the needle is changed. Advising patients using LANTUS vials not to re-use or share needles or insulin syringes with another person. Sharing carries a risk for transmission of blood-borne pathogens [see Warnings and Precautions (5.1)].

**Hyperglycemia or Hypoglycemia**

Inform patients that hypoglycemia is the most common adverse reaction with insulin. Inform patients of the symptoms of hypoglycemia (e.g., impaired ability to concentrate and react). This may present a risk in situations where these abilities are especially important, such as driving or operating other machinery. Advising patients who have frequent hypoglycemia or reduced or absent warning signs of hypoglycemia to use caution when driving or operating machinery [see Warnings and Precautions (5.3)].

Advises patients that changes in insulin regimen can predispose to hyperglycemia or hypoglycemia and that changes in insulin regimen should be made under close medical supervision [see Warnings and Precautions (5.2)].

**Hypoglycemia Due to Medications Errors**

Instruct patients to always check the insulin label before each injection to reduce the risk of a medication error [see Warnings and Precautions (5.4)].

**Hypersensitivity Reactions**

Advises patients that hypersensitivity reactions have occurred with LANTUS. Inform patients about the symptoms of hypersensitivity reactions [see Warnings and Precautions (5.5)].

Manufactured by: sanofi-aventis U.S. LLC

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**PATIENT INFORMATION**

**LANTUS® (LAN-tus)**

(insulin glargine)

injection, for subcutaneous use

**VIAL: 100 units/mL (U-100)**

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.

**What is LANTUS?**

LANTUS is a long-acting man-made insulin used to control high blood sugar in adults and children with diabetes mellitus. LANTUS is not for use to treat diabetic ketoacidosis.

**Who should not use LANTUS?**

Do not use LANTUS if you:
- have an episode of low blood sugar (hypoglycemia).
- have an allergy to insulin glargine or any of the 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.**

**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 the skin (subcutaneously) of your upper legs (thighs), upper arms, or stomach area (abdomen).
• 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 to reduce your risk of getting lipodystrophy (pits in skin or thickened skin) and localized cutaneous amyloidosis (skin with lumps) at the injection sites.
  o Do not use the exact same spot for each injection.
  o Do not inject where the skin has pits, is thickened, or has lumps.
  o Do not inject where the skin is tender, bruised, scaly or hard, or into scars or damaged skin.
• 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 swelling.
• 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. Do not give LANTUS to other people, even if they have the same symptoms that you have. 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: glycerol 85%, m-cresol, polysorbate 20, zinc, and Water for Injection, USP. Hydrochloric acid and sodium hydroxide may be added to adjust the pH.

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This Patient Information has been approved by the U.S. Food and Drug Administration.
Revised: June 2023
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How should I use LANTUS SoloStar?

- Read the detailed Instructions for Use that come with your LANTUS SoloStar single-patient-use prefilled pen.
- 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.
- The dose counter on your SoloStar pen shows your dose of LANTUS. Do not make any dose changes unless your healthcare provider tells you to.
- Do not use a syringe to remove LANTUS from your SoloStar disposable prefilled pen.
- 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. If your needle is blocked, follow the instructions in Step 3 of the Instructions for Use.
- You may take LANTUS at any time during the day but you must take it at the same time every day.
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- low blood sugar (hypoglycemia); weight gain; allergic reactions, including reactions at your injection site; skin thickening or pits at the injection site (lipodystrophy).

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