TOUJEO® (insulin glargine injection) U-300, for subcutaneous use

INDICATIONS AND USAGE
TOUJEO is a long-acting human insulin analog indicated to improve glycemic control in adults with diabetes mellitus. (1)

CONTRAINDICATIONS
Injection: 300 units/mL insulin glargine in:

Dosage forms and strengths
TOUJEO is available in 2 disposable prefilled pens:

1.5 mL TOUJEO SoloStar disposable prefilled pen (3)
3 mL TOUJEO Max SoloStar disposable prefilled pen (3)

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

DOSE FORMS AND STRENGTHS
Injection: 300 units/mL insulin glargine in:
• 1.5 mL TOUJEO SoloStar disposable prefilled pen (3)
• 3 mL TOUJEO Max SoloStar disposable prefilled pen (3)

WARNINGS AND PRECAUTIONS
• Never share a TOUJEO SoloStar or TOUJEO Max SoloStar disposable prefilled pen between patients, even if the needle is changed. (5.1)
• Hyperglycemia or hypoglycemia with changes in insulin regimen: Carry out under close medical supervision. (5.2)
• Hypoglycemia: May be life-threatening, increased frequency of glucose monitoring with changes to insulin dosage, coadministered glucose-lowering medications, meal pattern, physical activity, and in patients with renal impairment or hepatic impairment or 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)
• Hypersensitivity reactions: Severe, life-threatening, generalized allergy, including anaphylaxis, can occur. Discontinue TOUJEO, 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 if heart failure occurs. (5.7)

ADVERSE REACTIONS
Adverse reactions commonly associated with TOUJEO (≥5%)
• Hypoglycemia, allergic reactions, injection site reaction, lipodystrophy, pruritus, rash, edema, and weight gain. (6.1, 6.2)

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 blood glucose. (7)
• Antidiuretic 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: 03/2019

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FULL PRESCRIBING INFORMATION
1

INDICATIONS AND USAGE
TOUJEO is indicated to improve glycemic control in adults with diabetes mellitus. Limitations of Use:

TOUJEO is not recommended for the treatment of diabetic ketoacidosis.

DOSE AND ADMINISTRATION
2

General Dosing Instructions
2.1

TOUJEO is available in 2 disposable prefilled pens:

- TOUJEO SoloStar contains 450 units of TOUJEO U-300. It delivers doses in 1 unit increments and can deliver up to 80 units in a single injection.
- TOUJEO Max SoloStar contains 900 units of TOUJEO U-300. It delivers doses in 2 unit increments and can deliver up to 160 units in a single injection. It is recommended for patients requiring at least 20 units per day.

Inject TOUJEO subcutaneously once a day into the abdominal area, thigh, or deltoid at the same time each day.

- Rotate injection sites within the same region from one injection to the next to reduce the risk of lipodystrophy [see Adverse Reactions (6.1)].
- Individualize and titrate the dosage of TOUJEO based on the individual’s metabolic needs, blood glucose monitoring results, and glycemic control goal.
- To minimize the risk of hypoglycemia, titrate the dose of TOUJEO no more frequently than every 3 to 4 days.
- Dosage adjustments may be needed with changes in physical activity, changes in meal patterns (i.e., macronutrient content or timing of food intake), changes in renal or hepatic function or during acute illness to minimize the risk of hypoglycemia or hyperglycemia [see Warnings and Precautions (5.2) and Use in Specific Populations (8.6, 8.7)].
- Use TOUJEO with caution in patients with visual impairment who may rely on audible clicks to dial their dose.
2.2 Starting Dose in Insulin-Naive Patients

Type 1 Diabetes
- The recommended starting dose of TOUJEO in insulin-naive patients with type 1 diabetes is approximately one-third to one-half of the total daily insulin dose. The remainder of the total daily insulin dose should be given as a short-acting insulin and divided between each daily meal.

Type 2 Diabetes
- The recommended starting dose of TOUJEO in insulin-naive patients with type 2 diabetes is 0.2 units per kilogram of body weight once daily. The dosage of other antidiabetic drugs may need to be adjusted when starting TOUJEO to minimize the risk of hypoglycemia.

2.3 Starting Dose in Patients with Either Type 1 or Type 2 Diabetes Already on Insulin Therapy
- To minimize the risk of hypoglycemia when changing patients from a once-daily long-acting or intermediate-acting insulin product to TOUJEO, the starting dose of TOUJEO can be the same as the once-daily long-acting dose. For patients controlled on LANTUS (insulin glargine, 100 units/mL), expect that a higher daily dose of TOUJEO will be needed to maintain the same level of glycemic control.
- To minimize the risk of hypoglycemia when changing patients from twice-daily NPH insulin to once-daily TOUJEO, the recommended starting TOUJEO dose is 80% of the total daily NPH dosage.
- To minimize the risk of hyperglycemia when changing patients to TOUJEO, monitor glucose frequently in the first weeks of therapy titrate the dose of TOUJEO per instructions and the dose of other glucose-lowering therapies per standard of care (see Warnings and Precautions (5.2) and Clinical Pharmacology).

2.4 Important Administration Instructions
- Always check insulin labels before administration (see Warnings and Precautions [5.4]).
- When changing between TOUJEO SoloStar or TOUJEO Max SoloStar, if the patient’s previous dose was an odd number, the dose should be increased or decreased by 1 unit.
- The dose counter of the TOUJEO SoloStar or TOUJEO Max SoloStar disposable prefilled pen shows the number of units of TOUJEO to be injected and no conversion is required.
- Instruct patients to visually inspect the TOUJEO solution for particulate matter and discoloration prior to administration. If the solution is not clear and colorless with no visibly stable particles, do not administer TOUJEO intravenously, intramuscularly, or in an insulin pump.
- Do not dilute or mix TOUJEO with any other insulin products or solutions.
- Never transfer TOUJEO from the cartridges of the TOUJEO SoloStar or TOUJEO Max SoloStar prefilled pen into a syringe for administration.

3 DOSAGE FORMS AND STRENGTHS
- Injection: 300 units per mL of insulin glargine available as a clear, colorless, solution in: 1.5 mL TOUJEO SoloStar disposable prefilled pen (450 units/1.5 mL). 3 mL TOUJEO Max SoloStar disposable prefilled pen (900 units/3 mL).

4 CONTRAINDICATIONS
- TOUJEO is contraindicated: during episodes of hypoglycemia, in patients with hypersensitivity to insulin glargine or one of its excipients, with concurrent use of an insulin sensitizing agent, and in patients with renal or hepatic impairment.

5 WARNINGS AND PRECAUTIONS
5.1 Severe Hypoglycemia
- Severe hypoglycemia has been reported. TOUJEO is contraindicated: in patients with hypersensitivity to insulin glargine or one of its excipients, with concurrent use of an insulin sensitizing agent, and in patients with renal or hepatic impairment.

5.2 Hyperglycemia 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 hyperglycemia. 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 antidiabetic products may be needed.

5.3 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 hyperglycemia. 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 antidiabetic products may be needed.

5.4 Medications
- Medications that block the sympathetic nervous system (e.g., beta-blockers) may need to be adjusted when starting TOUJEO to minimize the risk of hypoglycemia (see Drug Interactions [7]).

5.5 Hypersensitivity and Allergic Reactions
- Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products, including TOUJEO. If hypersensitivity reactions occur, discontinue TOUJEO, treat per standard of care and monitor until symptoms and signs resolve (see Adverse Reactions [6]).

5.6 Hypokalemia
- All insulin products, including TOUJEO, 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 concentration).

5.7 Fluid Retention and Heart Failure with Concomitant Use of PPAR-gamma Agonsists
- 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 mask or exacerbate heart failure. Patients treated with insulin, including TOUJEO, 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 responses (see Warnings and Precautions [5.5])
- Hypokalemia (see Warnings and Precautions [5.6])

6.1 Clinical Trials Experience

Common adverse reactions occurring for TOUJEO-treated subjects during clinical trials in patients with type 1 diabetes mellitus and type 2 diabetes mellitus are listed in Table 1 and Table 2, respectively.

Table 1: Adverse Reactions in Two Pooled Clinical Trials of 26 Weeks and 16 Weeks Duration in Adults with Type 1 Diabetes (with incidence ≥5%)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngitis</td>
<td>12.8</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>9.5</td>
</tr>
</tbody>
</table>

["meatmeal insulin" refers to insulin glulisine, insulin lispro, or insulin aspart].
Table 3: Clinically Significant Drug Interactions with TOUJEO (continued)

<table>
<thead>
<tr>
<th>Drugs That May Increase or Decrease the Blood Glucose Lowering Effect of TOUJEO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drugs</strong></td>
</tr>
<tr>
<td>Alcohol, beta-blockers, clonidine, and lithium salts. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Intervention</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose adjustment and increased frequency of glucose monitoring may be required when TOUJEO is coadministered with these drugs.</td>
</tr>
</tbody>
</table>

Table 3: Clinically Significant Drug Interactions with TOUJEO

**Drugs That May Decrease the Risk of Hypoglycemia**

<table>
<thead>
<tr>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidiabetic agents, ACE inhibitors, angiotensin II receptor blocking agents; diacylglycerol, fibrates, fluoxetine, monoamine oxidase inhibitors, pentoxifylline, pramlintide, propoxyphene, salicylates, statin analogs (e.g., ocreotide), and sulfonylurea antibiotics, GLP-1 receptor agonists, DPP-4 inhibitors, and SGLT-2 inhibitors.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Intervention</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose reductions and increased frequency of glucose monitoring may be required when addition of TOUJEO to the insulin regimen is made.</td>
</tr>
</tbody>
</table>

**Drugs That May Decrease the Blood Glucose Lowering Effect of TOUJEO**

<table>
<thead>
<tr>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atypical antipsychotics (e.g., olanzapine and clozapine), corticosteroids, danazol, diuretics, estrogens, glucagon, iodinated, insulin, oral contraceptives, phenoxybenzamine, progestogens (e.g., in oral contraceptives), proton pump inhibitors, somatropin, sympathomimetic agents (e.g., albuterol, epinephrine, terbutaline), and thyroid hormones.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Intervention</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose increases and increased frequency of glucose monitoring may be required when TOUJEO is coadministered with these drugs.</td>
</tr>
</tbody>
</table>
Each milliliter of TOUJEO contains 300 units (10.91 mg) insulin glargine dissolved in a clear aqueous fluid. The 1.5 mL TOUJEO SoloStar disposable prefilled pen presentation contains the following inactive ingredients per mL: 90 mcg zinc, 2.7 mg m-cresol, 20 mg glycerol 85%, and water for injection. The 3 mL TOUJEO Max SoloStar disposable prefilled pen presentation contains the following inactive ingredients per mL: 90 mcg zinc, 2.7 mg m-cresol, 20 mg glycerol 85%, and water for injection. The pH is adjusted by addition of aqueous solutions of hydrochloric acid and sodium hydroxide. TOUJEO has a pH of approximately 4. At pH 4, insulin glargine is completely soluble. After injection into the subcutaneous tissue, the acidic solution is neutralized, leading to formation of a precipitate from which small amounts of insulin glargine are slowly released.

11 DESCRIPTION
TOUJEO (insulin glargine injection) is a long-acting insulin supplied as a sterile solution for subcutaneous injection containing 300 units/mL of insulin glargine. Insulin glargine is a human insulin analog produced by recombinant DNA technology utilizing a nonpathogenic laboratory strain of Escherichia coli (K12) as the production organism. Insulin glargine differs from human insulin in that the amino acid asparagine at position A21 is replaced by glycine and two arginines remain at the C-terminus of the B-chain. Chemically, insulin glargine is 21-Gly-31Thr.

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

12.2 Pharmacodynamics
Onset of Action
The pharmacodynamic profiles for TOUJEO given subcutaneously as a single dose of 0.4, 0.6, or 0.9 U/kg in a euglycemic clamp study in patients with type 1 diabetes showed that on average, the onset of action develops over 6 hours post dose for all three single doses of TOUJEO. Single-Dose Pharmacodynamics
The pharmacodynamics for single 0.4, 0.6, and 0.9 U/kg doses of TOUJEO in 24 patients with type 1 diabetes mellitus was evaluated in a euglycemic clamp study. On a unit-to-unit basis, TOUJEO had a lower maximum (GIRmax) and 24-hour glucose lowering effect (GIR[0-24h]) compared to LANTUS. The overall glucose lowering effect of TOUJEO 0.4 U/kg was 12% of the glucose lowering effect of an equivalent dose of LANTUS. Glucose lowering at least 30% of the effect of a single 0.4 U/kg dose of LANTUS was not observed until the single dose of TOUJEO exceeded 0.6 U/kg. Multiple Once-Daily Dose Pharmacodynamics
The pharmacodynamics of TOUJEO after 8 days of daily injection was evaluated in 30 patients with type 1 diabetes. At steady state, the 24-hour glucose lowering effect (GIR[AUC0-24h]) of TOUJEO 0.4 U/kg was approximately 27% lower with a different distribution profile than that of an equivalent dose of LANTUS [see Dosage and Administration (2), Warnings and Precautions (5.2), and Clinical Pharmacology (12.3)]. The glucose lowering effect of a TOUJEO dose increased with each daily administration. The pharmacodynamic profile for TOUJEO given subcutaneously as multiple once-daily subcutaneous injections of 0.4 U/kg in a euglycemic clamp study in patients with type 1 diabetes is shown in Figure 1.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
In mice and rats, standard two-year carcinogenicity studies with insulin glargine were performed at doses up to 0.455 mg/kg, which was for the rat approximately 65 times the recommended human subcutaneous starting dose of 0.2 Units/kg/day (0.007 mg/kg/day). The findings in female mice were not conclusive due to excessive mortality in all dose groups during the study. Histocytomas 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 different vehicles. 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 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 TOUJEO given once daily was compared to that of once-daily LANTUS in open-label, randomized, active-control, parallel studies of up to 26 weeks in patients with type 1 diabetes mellitus and patients with type 2 diabetes mellitus [Tables 4 and 5]. At trial end, the reduction of HbA1c was statistically significant and clinically meaningful compared to LANTUS. TOUJEO treated to goal was similar to that with LANTUS titrated to goal. At the end of the trial, depending on the patient population and concomitant therapy, patients were receiving a higher dose of TOUJEO than LANTUS.

14.2 Clinical Study in Adult Patients with Type 1 Diabetes
In an open-label, controlled study (Study A), patients with type 1 diabetes (n=549), were randomized to basal-bolus treatment with TOUJEO or LANTUS and treated for 26 weeks. TOUJEO and LANTUS were administered once daily in the morning (time period covering from pre-breakfast until pre-lunch) or in the evening (time period defined as prior to the evening meal until bedtime). A mealtime insulin analogue was administered before each meal. Mean age was 47.3 years and mean duration of diabetes was 21 years. Fifty-seven percent were male, 85.1% were Caucasian, 4.7% Black or African American, and 4.7% were Hispanic. 32.2% of patients had GFR >90 mL/min/1.73 m². The mean BMI was approximately 27.8 kg/m². At week 26, treatment with TOUJEO provided a mean reduction in HbA1c that met the prespecified noninferiority margin of 0.4% (Table 4). Patients treated with TOUJEO used 17.5% more basal insulin than patients treated with LANTUS. There were no clinically important differences in glycemic control when TOUJEO was administered once daily in the morning or in the evening. There were no clinically important differences in body weight between treatment groups.

Table 4: Type 1 Diabetes Mellitus – Adult (TOUJEO plus mealtime insulin versus LANTUS plus mealtime insulin)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Treatment duration</th>
<th>Number of subjects treated (miITT)</th>
<th>HbA1c</th>
<th>Adjusted Mean change from baseline</th>
<th>Adjusted Mean difference* [95% Confidence Interval]</th>
<th>Fasting Plasma Glucose mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOUJEO +</td>
<td>26 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mealtime</td>
<td>Treatment in combination</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>insulin analog</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LANTUS +</td>
<td>273</td>
<td>273</td>
<td></td>
<td>-0.4</td>
<td>-0.04 [-0.10 to 0.18]</td>
<td></td>
</tr>
<tr>
<td>Mealtime</td>
<td>8.13</td>
<td>8.12</td>
<td></td>
<td>-0.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>insulin</td>
<td></td>
<td></td>
<td></td>
<td>-0.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>*miITT: Modified intention-to-treat.</td>
<td></td>
<td></td>
<td></td>
<td>Treatment difference: TOUJEO – LANTUS.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

14.3 Clinical Studies in Adult Patients with Type 2 Diabetes
In a 26-week open-label, controlled study (study B, n=804), adults with type 2 diabetes were randomized to once-daily treatment in the evening with either TOUJEO or LANTUS. Short-acting mealtime insulin analogues with or without metformin were also administered. The average age was 60 years. The majority of patients were White (92.3%) and 52.9% were male; 20.3% of patients had GFR >90 mL/min/1.73 m². The mean BMI was approximately 36.6 kg/m². At week 26, treatment with TOUJEO provided a mean reduction in HbA1c that met the prespecified noninferiority margin of 0.4% compared to LANTUS (Table 5). Patients treated with TOUJEO used 11% more basal insulin than patients treated with LANTUS. There were no clinically important differences in body weight between treatment groups.

In two open-label, controlled studies (n=1670), adults with type 2 diabetes mellitus were randomized to either TOUJEO or LANTUS once daily for 26 weeks as part of a regimen of combination therapy
with noninsulin antidiabetic drugs. At the time of randomization, 808 patients were treated with basal insulin for more than 6 months (study C) and 862 patients were insulin-naive (study D). In Study C, the average age was 58.2 years. The majority of patients were White (93.6%) and 45.9% were male; 32.8% of patients had GFR >90 mL/min/1.73 m². The mean BMI was approximately 34 kg/m². At week 26, treatment with TOUJEO provided a mean reduction in HbA1c that met the prespecified noninferiority margin of 0.4% compared to LANTUS (Table 5). Patients treated with TOUJEO used 12% more basal insulin than patients treated with LANTUS. There were no clinically important differences in body weight between treatment groups. In Study D, the average age was 57.7 years. The majority of patients were White (76%) and 57.7% were male; 29% of patients had GFR >90 mL/min/1.73 m². The mean BMI was approximately 33 kg/m². At week 26, treatment with TOUJEO provided a mean reduction in HbA1c that met the prespecified noninferiority margin compared to LANTUS (Table 5). Patients treated with TOUJEO used 15% more basal insulin than patients treated with LANTUS. There were no clinically important differences in body weight between treatment groups.

### Table 5: Type 2 Diabetes Mellitus – Adult

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Study B</th>
<th>Study C</th>
<th>Study D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration</td>
<td>26 weeks</td>
<td>26 weeks</td>
<td>26 weeks</td>
</tr>
<tr>
<td>In combination with</td>
<td>Mealtime insulin analog ± metformin</td>
<td>Noninsulin antidiabetic drugs</td>
<td></td>
</tr>
<tr>
<td>TOUJEO</td>
<td>LANTUS</td>
<td>TOUJEO</td>
<td>LANTUS</td>
</tr>
<tr>
<td>Number of patients treated</td>
<td>404</td>
<td>400</td>
<td>403</td>
</tr>
<tr>
<td>HbA1c Baseline mean</td>
<td>8.13</td>
<td>8.14</td>
<td>8.27</td>
</tr>
<tr>
<td>Adjusted mean change from baseline</td>
<td>-0.90</td>
<td>-0.87</td>
<td>-0.73</td>
</tr>
<tr>
<td>Adjusted mean difference</td>
<td>-0.03</td>
<td>-0.03</td>
<td>0.04</td>
</tr>
<tr>
<td>[95% Confidence interval]</td>
<td>[-0.14 to 0.08]</td>
<td>[-0.17 to 0.10]</td>
<td>[-0.09 to 0.17]</td>
</tr>
<tr>
<td>Fasting Plasma Glucose (mg/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline mean</td>
<td>157</td>
<td>160</td>
<td>149</td>
</tr>
<tr>
<td>Adjusted mean change from baseline</td>
<td>-29</td>
<td>-30</td>
<td>-18</td>
</tr>
<tr>
<td>Adjusted mean difference</td>
<td>0.8</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>[95% Confidence interval]</td>
<td>[-5 to 7]</td>
<td>[-3 to 9]</td>
<td>[2 to 12]</td>
</tr>
</tbody>
</table>

†Treatment difference: TOUJEO – LANTUS. 

### 16 HOW SUPPLIED/STORAGE AND HANDLING

#### 16.1 How Supplied

TOUJEO SoloStar is supplied as a clear and colorless solution containing 300 units per mL (U-300) of insulin glargine and is available in 2 disposable prefilled pen presentations:

<table>
<thead>
<tr>
<th>TOUJEO</th>
<th>Total volume</th>
<th>Concentration</th>
<th>Total units available in presentation</th>
<th>Max dose per injection</th>
<th>Dose increment</th>
<th>NDC number</th>
<th>Package size</th>
</tr>
</thead>
<tbody>
<tr>
<td>SoloStar disposable prefilled pen</td>
<td>1.5 mL</td>
<td>300 units/mL</td>
<td>450 units</td>
<td>80 units</td>
<td>1 unit</td>
<td>0024-5869-03</td>
<td>3 pens/pack</td>
</tr>
<tr>
<td>Max SoloStar disposable prefilled pen</td>
<td>3 mL</td>
<td>300 units/mL</td>
<td>900 units</td>
<td>160 units</td>
<td>2 units</td>
<td>0024-5871-02</td>
<td>2 pens/pack</td>
</tr>
</tbody>
</table>

Needles are not included in the packs of TOUJEO SoloStar or TOUJEO Max SoloStar disposable prefilled pen.

BD (such as BD Ultra-Fine®), Ypsomed (such as Clickfine®) or Owen Mumford (such as Unifine® Penlets®) needles† can be used in conjunction with TOUJEO SoloStar or TOUJEO Max SoloStar disposable prefilled pen and are sold separately. A new sterile needle must be attached before each injection. TOUJEO SoloStar or TOUJEO Max SoloStar disposable prefilled pens must never be shared between patients, even if the needle is changed.

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

#### 16.2 Storage

TOUJEO SoloStar or TOUJEO Max SoloStar disposable prefilled pen should not be stored in the freezer and should not be allowed to freeze. Discard TOUJEO disposable prefilled pen if it has been frozen. Protect TOUJEO SoloStar/TOUJEO Max SoloStar from direct heat and light.

Storage conditions are summarized in the following table:

<table>
<thead>
<tr>
<th>Storage condition</th>
<th>Temperature</th>
<th>Shelf life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not in-use (unopened)</td>
<td>Refrigerated 36°F–46°F (2°C–8°C)</td>
<td>Until expiration date</td>
</tr>
<tr>
<td>In-use (opened)</td>
<td>Room temperature only (Do not refrigerate) below 86°F (30°C)</td>
<td>56 days</td>
</tr>
</tbody>
</table>

To prevent degradation, always store the prefilled pens with the cap on during in-use period.

#### 17 PATIENT COUNSELING INFORMATION

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

Never share a TOUJEO SoloStar or TOUJEO Max SoloStar Pen Between Patients

[See Warnings and Precautions (5.1)].

Advise patients that they must never share TOUJEO SoloStar or TOUJEO Max SoloStar pen with another person even if the needle is changed. Pen sharing poses a risk for transmission of blood-borne pathogens.

Hyperglycemia or Hypoglycemia

[See Warnings and Precautions (5.2, 5.3)]. Inform patients that hypoglycemia 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 hyperglycemia or hypoglycemia. Advise patients that changes in insulin regimen should be made under close medical supervision. Inform patients that if they change to TOUJEO from other basal insulins they may experience higher average fasting plasma glucose levels in the first weeks of therapy. Advise patients to monitor glucose daily when initiating TOUJEO.

Medication Errors

[See Warnings and Precautions (5.4)].

Instruct patients to always check the insulin label before each injection. The “300 units/mL (U-300)” is highlighted in honey gold on the labels of TOUJEO and TOUJEO Max SoloStar disposable prefilled pens. Inform patients that TOUJEO (insulin glargine injection) 300 units/mL contains 3 times as much insulin in 1 mL as standard insulin (100 units/mL). To avoid dosing errors and potential overdose, instruct patients not to use a syringe to remove TOUJEO from the TOUJEO SoloStar or TOUJEO Max SoloStar disposable prefilled pen. Instruct patients that TOUJEO (insulin glargine injection) 300 units/mL is available in two disposable prefilled pens. The dose counter of TOUJEO SoloStar or TOUJEO Max SoloStar disposable prefilled pen shows the number of units of TOUJEO to be injected and no dose recalibration is required. Instruct patients to follow the instructions for Use and perform a safety test as described in Step 3 of the Instructions for Use. Failure to perform this step may result in not receiving the full dose. If this occurs, patients should increase the frequency of checking their blood glucose levels and might need to administer additional insulin.

TOUJEO SoloStar Prefilled Pen

TOUJEO SoloStar prefilled pen contains 450 units of TOUJEO. It delivers 1 to 80 units in a single injection. The dose can be adjusted by 1 unit at a time.

TOUJEO Max SoloStar Prefilled Pen

TOUJEO Max SoloStar prefilled pen contains 900 units of TOUJEO. It delivers 2 to 160 units in a single injection. The dose can be adjusted by 2 units at a time.

If safety tests are not performed before first use of a new pen, insulin underdose can occur. To reduce potential underdose, this pen is recommended for patients requiring at least 20 units per day.

Instruct patients to not re-use needles. A new needle must be attached before each injection. Re-use of needles increases the risk of blocked needles which may cause underdosing or overdosing. In the event of blocked needle, the patients must follow the instructions described in Step 3 of the Instructions for Use.

Administration

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

Sanofi-aventis U.S. LLC

Bridgewater, NJ 08807

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Patient Information
TOUJEO® (Too-Jay-o) (insulin glargine injection)
300 units/mL (U-300)
for subcutaneous use

Do not share your TOUJEO SoloStar® or TOUJEO Max 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 TOUJEO?
- TOUJEO is a long-acting man-made insulin used to control high blood sugar in adults with diabetes mellitus.
- TOUJEO is not for use to treat diabetic ketoacidosis.
- It is not known if TOUJEO is safe and effective in children.

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

What should I tell my healthcare provider before using TOUJEO?
Before using TOUJEO, 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 TOUJEO.
- are pregnant, planning to become pregnant, or are breastfeeding. It is not known if TOUJEO may harm your unborn 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 TOUJEO, talk to your healthcare provider about low blood sugar and how to manage it.

How should I use TOUJEO?
- TOUJEO is available in two disposable prefilled pens: TOUJEO SoloStar and TOUJEO Max SoloStar. Your healthcare provider will tell you which TOUJEO Pen is right for you.
- Read the detailed Instructions for Use that come with your TOUJEO SoloStar or TOUJEO Max SoloStar disposable prefilled pen.
- Use TOUJEO exactly as your healthcare provider tells you to. Your healthcare provider should tell you how much TOUJEO to use and when to use it.
- Know the amount of TOUJEO you use. Do not change the amount of TOUJEO 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 use a syringe to remove TOUJEO from your TOUJEO SoloStar or TOUJEO Max SoloStar disposable prefilled pen. This can cause you to give yourself too much insulin. TOUJEO has 3 times as much insulin in 1 mL compared to other standard insulin pens.
- Do not re-use needles. Always use a new needle for each injection. Reusing needles increases your chance of having blocked needles, which can cause you to get the wrong dose of TOUJEO. Using a new needle for each injection also lowers your risk of getting an infection. If your needle is blocked, follow the instructions in Step 3 of the Instructions for Use.
- TOUJEO should be used 1 time each day and at the same time every day.
- TOUJEO is injected under your skin (subcutaneously). Do not use TOUJEO in an insulin pump or inject TOUJEO into your vein (intravenously).
- Change (rotate) your injection sites within the area you choose with each dose. Do not use the exact spot for each injection.
- Do not mix TOUJEO 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 TOUJEO and all medicines out of the reach of children.

Your dose of TOUJEO 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 other medicines you take.

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

What are the possible side effects of TOUJEO?
TOUJEO 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:
  - 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 TOUJEO 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 TOUJEO. Your healthcare provider should monitor you closely while you are taking TZDs with TOUJEO. 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 TOUJEO 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 TOUJEO include:
- low blood sugar (hypoglycemia), weight gain, itching, rash, swelling, 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 TOUJEO. 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 TOUJEO.
Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use TOUJEO for a condition for which it was not prescribed. Do not give TOUJEO 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 TOUJEO. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about TOUJEO that is written for health professionals.

What are the ingredients in TOUJEO?
- Active ingredient: insulin glargine
- Inactive ingredients: zinc, m-cresol, glycerol, and water for injection. Hydrochloric acid and sodium hydroxide may be added to adjust the pH.

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For more information, go to www.TOUJEO.com or call 1-800-633-1610.

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: March 2018

GLR-FPLR-SL-MAR19 Rx Only