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

Limitations of Use:
Not recommended for treating diabetic ketoacidosis. (1)

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

Limitations of Use:
Not recommended for treating diabetic ketoacidosis. (1)

DOSE AND ADMINISTRATION

- 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:
- 2.5 mL TOUJEO SoloStar disposable prefilled pen (3)
- 3 mL TOUJEO Max SoloStar disposable prefilled pen (3)

CONTRAINDICATIONS
- During episodes of hypoglycemia (4)
- Hypersensitivity to TOUJEO or one of its excipients (4)

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

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. Increase 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, if possible. 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)

USE IN SPECIFIC POPULATIONS
- Pregnancy: Use during pregnancy only if the potential benefit justifies the potential risk to the fetus. (8.1)

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

Revised: 03/2018
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 clacks to dialle their dose.

2.2 Starting Dose in Insulin-Naïve Patients

Type 1 Diabetes

![Image]
The recommended starting dose of TOUJEO in insulin-naïve patients with type 1 diabetes is 0.2 units per kilogram of body weight once daily. The dosage of other anti-diabetic drugs may need to be adjusted when starting TOUJEO to minimize the risk of hypoglycemia [see Warnings and Precautions (5.3)].

The onset of action of TOUJEO develops over 6 hours following an injection. In type 1 diabetes patients and predispose to hypoglycemia. Changes in insulin strength, manufacturer, type, or method of administration may affect glycemic control [see Dosage and Administration (2.2) and Clinical Pharmacology (12.2)].

3.6 Hypokalemia

Hypokalemia may be a sign of heart failure. These are changes that 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 anti-diabetic products may be needed.

On a unit-to-unit basis, TOUJEO has a lower glucose lowering effect than LANTUS [see Clinical Pharmacology (12.2)]. In clinical trials, patients who changed to TOUJEO from other basal insulins experienced a fasting plasma glucose levels in the first weeks of therapy compared to patients who were changed to LANTUS. To minimize the risk of hypoglycemia when initiating TOUJEO monitor glucose daily, titrate TOUJEO according to labeling instructions, and adjust coadministered glucose-lowering therapies per standard of care [see Dosage and Administration (2.2, 2.3)]. Higher doses of TOUJEO compared to achieve similar levels of glucose control compared to LANTUS in clinical trials [see Clinical Studies (14.1)]

The onset of action of TOUJEO develops over 6 hours following an injection. In type 1 diabetes patients treated with IV insulin, consider the longer onset of action of TOUJEO before stopping IV insulin. The full glucose lowering effect may not be apparent for at least 5 days [see Dosage and Administration (2.2) and Clinical Pharmacology (12.2)].

5.3 Hypoglycemia

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

Risk Factors for Hypoglycemia

The timing of hypoglycemia usually reflects the time-action profile of the administered insulin formulation. As with all insulin preparations, the glucose lowering effect time course of TOUJEO may vary in different individuals or at different times in the same individual and depends on many conditions, including the area of injection as well as the injection site blood supply and temperature [see Clinical Pharmacology (12.2)]. Other factors which may increase the risk of hypoglycemia include changes in meal patterns (e.g., macronutrient content or timing of meals), changes in level of physical activity, or changes to coadministered medication [see Drug Interactions (7)]. Patients with renal or hepatic impairment may be at higher risk of hypoglycemia [see Use in Specific Populations (8.6, 8.7)].

Risk Mitigation Strategies for Hypoglycemia

Patients and caregivers must be educated to recognize and manage hypoglycemia. Self-monitoring of blood glucose plays an essential role in the prevention and management of hypoglycemia. In patients at higher risk for hypoglycemia and patients who have reduced symptomatic awareness of hypoglycemia, increased frequency of blood glucose monitoring is recommended. To minimize the risk of hypoglycemia do not administer TOUJEO intravenously, intramuscularly, or in an insulin pump, or dilute or mix TOUJEO with any other insulin products or solutions.

5.4 Medication Errors

Accidental mix-ups between basal insulin products and other insulins, particularly rapid-acting insulins, have been reported. To avoid medication errors between TOUJEO and other insulins, instruct patients to always check the insulin label before each injection. To avoid dosing errors and potential overdose, never use a syringe to remove TOUJEO from the TOUJEO SoloStar or TOUJEO Max SoloStar prefilled pen into a syringe [see Dosage and Administration (2.4) and Warnings and Precautions (5.3)].

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. TOUJEO treatment should be discontinued for patients with a history of anaphylaxis, angioedema or urticaria; if these reactions occur, discontinue TOUJEO and monitor until symptoms and signs resolve. TOUJEO is contraindicated in patients who have had hypersensitivity reactions to insulin glargine or other excipients [see Contraindications (4)].

5.6 Hypokalemia

All insulin products, including TOUJEO, cause a shift in potassium from the extracellular to the 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, particularly when used in combination with insulin. Fluid retention may lead to 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)]
- Medication Errors [see Warnings and Precautions (5.4)]
- Hypersensitivity and allergic 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 the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug, and may not reflect the rates actually observed in clinical practice.

The data in Table 1 reflect the exposure of 1242 patients with type 1 diabetes to TOUJEO with mean exposure duration of 23 weeks. The type 1 diabetes population had the following characteristics: Mean age was 46 years and mean duration of diabetes was 21 years. Fifty-five percent were male, 86% were Caucasian, 5% were Black or African American, and 5% were Hispanic. At baseline, the mean eGFR was 82 mL/min/1.73 m² and 35% of patients had eGFR ≥ 90 mL/min/1.73 m². The mean BMI was 28 kg/m². HbA1c at baseline was greater or equal to 8% in 66% of patients.

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>TOUJEO + Mealtime Insulin, %</th>
<th>N=304</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngitis</td>
<td>12.8</td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>9.5</td>
<td></td>
</tr>
</tbody>
</table>

**‘mealtime insulin’ refers to insulin glulisine, insulin lispro, or insulin aspart.**

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 3: Clinically Significant Drug Interactions with TOUJEO (continued)

<table>
<thead>
<tr>
<th>Drugs That May Decrease the Blood Glucose Lowering Effect of TOUJEO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drugs</strong></td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td>Atypical antipsychotics (e.g., olanzapine and clozapine), corticosteroids, danazol, duretics, estragons, glucagon, isonizid, niacin, oral contraceptives, phenothiazines, progestogens (e.g., in oral contraceptives), protease inhibitors, somatropin, sympathomimetic agents (e.g., albuterol, ephrineph, terbutaline), and thyroid hormones.</td>
</tr>
</tbody>
</table>

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

All pregnancies have a background risk of birth defects, loss, or other adverse outcome regardless of drug exposure. This background risk is increased in pregnancies complicated by hyperglycemia and may be decreased with good metabolic control. It is essential for patients with diabetes or a history of gestational diabetes to maintain good metabolic control before conception and throughout pregnancy. In patients with diabetes or gestational diabetes, insulin requirements may decrease during the first trimester, generally increase during the second and third trimesters, and rapidly decline after delivery. Careful monitoring of glucose control is essential in these patients. Therefore, female patients should be advised to tell their physicians if they intend to become, or if they become, pregnant while taking TOUJEO.

Human data

There are no clinical studies of the use of TOUJEO in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal data

Subcutaneous reproduction and teratology studies have been performed with insulin glargine and regular human insulin in rats and Himalayan rabbits. Insulin glargine was given to female rats before mating, during mating, and throughout pregnancy at doses up to 0.36 mg/kg/day, which is approximately 50 times the recommended human subcutaneous starting dose of 0.2 Units/kg/day (0.007 mg/kg/day). In rabbits, doses of 0.072 mg/kg/day, which is approximately 10 times the recommended human subcutaneous starting dose of 0.2 Units/kg/day (0.007 mg/kg/day), were administered during organogenesis. The effects of insulin glargine did not generally differ from those observed with regular human insulin in rats or rabbits. However, in rabbits, five fetuses from two litters of the high-dose group exhibited dilation of the cerebral ventricles. Fertility and early embryonic development appeared normal.

8.3 Nursing Mothers

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

8.4 Pediatric Use

The safety and effectiveness of TOUJEO have not been established in pediatric patients.

8.5 Obstetric Use

In controlled clinical studies, 30 of 304 (9.8%) TOUJEO-treated patients with type 1 diabetes and 327 of 1242 (26.3%) TOUJEO-treated patients with type 2 diabetes were <18 years of age, among them 2.0% of the patients with type 1 and 3.0% of the patients with type 2 diabetes were ≥18 years of age.

8.6 Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of TOUJEO has not been studied. Frequent glucose monitoring and dose adjustment may be necessary for TOUJEO in patients with hepatic impairment [see Warnings and Precautions (5.3), Adverse Reactions (6), and Clinical Studies (14)].

8.7 Renal Impairment

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

8.8 Obesity

No new differences in effectiveness and safety were observed in subgroup analyses based on BMI.

10. OVERDOSAGE

Excess insulin administration may cause hypoglycemia and hypokalemia [see Warnings and Precautions (5.3, 5.6)]. Mild episodes of hypoglycemia can be treated with oral glucose. Adjustments in drug dosage, meal patterns, or physical activity level may be needed. More severe episodes of hypoglycemia with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose.

Sustained carbohydrate intake and observation may be necessary.

TOUJEO is not associated with the occurrence of diabetic ketoacidosis.

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>-----------</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>

7. DRUG INTERACTIONS

Table 3 includes clinically significant drug interactions with TOUJEO.

8.4 Pediatric Use

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Sustained carbohydrate intake and observation may be necessary because hypoglycemia may recur after apparent clinical recovery. Hypokalemia must be corrected appropriately.
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 C$_{24}$H$_{55}$N$_{13}$O$_{30}$S$_{2}$ and has a molecular weight of 6083. Insulin glargine has the following structural formula:

```
CH$_2$OH-CHOH-(CH$_2$)$_3$-Arg human insulin and has the empirical formula C$_{24}$H$_{55}$N$_{13}$O$_{30}$S$_{2}$.
```

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.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The primary activity of insulin, including insulin glargine, is regulation of glucose metabolism. Insulin and its analog 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 (GIR$_{max}$) and 24-hour glucose lowering effect (GIR-AUC$_{0–24}$) 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-AUC$_{0–24}$) 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), Warning and Precautions (5.2), and Clinical Pharmacology (12.3)].

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.

Figure 1: Glucose Infusion Rate in Patients with Type 1 Diabetes in Multiple-Dose Administration of TOUJEO

Glucose infusion rate: determined as amount of glucose infused to maintain constant plasma glucose levels.

12.3 Pharmacokinetics

Absorption and Bioavailability

The pharmacokinetic profiles 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. The median time to maximum serum insulin concentration was 12 (8–14), 12 (12–18), and 16 (12–20) hours, respectively. Mean serum insulin concentrations declined to the lower limit of quantitation of 5.02 µU/mL by 16, 28, and beyond 36 hours, respectively. Steady-state insulin concentrations are reached by at least 5 days of once-daily subcutaneous administration of 0.4 U/kg to 0.6 U/kg doses of TOUJEO over 8 days in patients with type 1 diabetes mellitus.

After subcutaneous injection of TOUJEO, the intra-subject variability, defined as the coefficient of variation for the insulin exposure during 24 hours was 21.0% at steady state.

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>TOUJEO + Mealtime Insulin</th>
<th>LANTUS + Mealtime Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects treated (mITT)</td>
<td>273</td>
<td>273</td>
</tr>
<tr>
<td>HbA1c</td>
<td>8.13</td>
<td>8.12</td>
</tr>
<tr>
<td>Adjusted Mean change from baseline</td>
<td>-0.40</td>
<td>-0.44</td>
</tr>
<tr>
<td>Adjusted Mean difference$^2$ [95% Confidence Interval]</td>
<td>0.04 [-0.10 to 0.18]</td>
<td></td>
</tr>
</tbody>
</table>

$^*$meatime insulin* refers to insulin glulisine, insulin lispro or insulin aspart.

$^*$mITT: Modified intention-to-treat.

$^?$Treatment difference: TOUJEO – LANTUS.

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 68 years. The majority of patients were White (92.3%) and 52.9% were male; 39.3% of patients had GFR >90 mL/min/1.73 m$^2$. The mean BMI was approximately 30.8 kg/m$^2$. 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 glycaemic 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)
with noninsulin antidiabetic drugs. At the time of randomization, 808 patients were treated with basal insulin in more than 6 months (study C) and 862 patients were insulin-naive (study D). In study C, the average age was 58.2 years, 45.9% were male; 32.8% of patients had GFR >90 mL/min/1.73 m². The mean BMI was approximately 34.8 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 (78%) and 45.9% 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 duration</th>
<th>Study B</th>
<th>Study C</th>
<th>Study D</th>
</tr>
</thead>
<tbody>
<tr>
<td>26 weeks</td>
<td>404</td>
<td>400</td>
<td>403</td>
</tr>
<tr>
<td>26 weeks</td>
<td>404</td>
<td>400</td>
<td>403</td>
</tr>
<tr>
<td>26 weeks</td>
<td>404</td>
<td>400</td>
<td>403</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment in combination with</th>
<th>Mealtime insulin analog ± metformin</th>
<th>Noninsulin antidiabetic drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOUJEO</td>
<td>LANTUS</td>
<td>TOUJEO LANTUS</td>
</tr>
<tr>
<td>Number of patients treated</td>
<td>404</td>
<td>400</td>
</tr>
<tr>
<td>HbA1c Baseline mean</td>
<td>8.13</td>
<td>8.14</td>
</tr>
<tr>
<td>Adjusted mean change from baseline</td>
<td>-0.90</td>
<td>-0.87</td>
</tr>
<tr>
<td>Adjusted mean difference†</td>
<td>[-0.14 to 0.08]</td>
<td>[-0.17 to 0.10]</td>
</tr>
<tr>
<td>[95% Confidence interval]</td>
<td>[-0.09 to 0.17]</td>
<td></td>
</tr>
<tr>
<td>Fasting Plasma Glucose (mg/dL)</td>
<td>157</td>
<td>160</td>
</tr>
<tr>
<td>Baseline mean</td>
<td>149</td>
<td>142</td>
</tr>
<tr>
<td>Adjusted mean change from baseline</td>
<td>-29</td>
<td>-30</td>
</tr>
<tr>
<td>Adjusted mean difference†</td>
<td>[5 to 7]</td>
<td>[-3 to 9]</td>
</tr>
<tr>
<td>[95% Confidence interval]</td>
<td>[2 to 12]</td>
<td></td>
</tr>
</tbody>
</table>

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.

Storage conditions are summarized in the following table:

<table>
<thead>
<tr>
<th>Not in-use (unopened)</th>
<th>In-use (opened)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refrigerated</td>
<td>Room temperature only</td>
</tr>
<tr>
<td>36°F–46°F (2°C–8°C)</td>
<td>(Do not refrigerate)</td>
</tr>
<tr>
<td>Below 89°F (30°C)</td>
<td>42 days</td>
</tr>
</tbody>
</table>

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

16 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.

17 Patient Counseling Information
Advises patients 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.

[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 to never use a syringe to remove TOUJEO from the TOUJEO SoloStar or TOUJEO Max SoloStar disposable prefilled pen.

Inform 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 recalculation 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 not to 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.

Pregnancy

Advise patients to inform their health care professional if they are pregnant or are contemplating pregnancy.
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:
• 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. Re-using 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 each 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:
  - a rash over your whole body, trouble breathing, a fast heartbeat, or sweating
- **low potassium in your blood (hypokalemia).**
- **heart failure.** Taking certain diabetes pills called TZDs (thiazolidinediones) with 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.