TOUJEO is indicated to improve glycemic control in adults with diabetes mellitus. 

INDICATIONS AND USAGE
TOUJEO is not recommended for the treatment of diabetic ketoacidosis.

Dosage 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)
- Administer subcutaneously once daily. (2.4)

Contraindications
- Never share a TOUJEO SoloStar® disposable prefilled pen between patients, even if the needle is changed. (5.1)
- Hypersensitivity to TOUJEO or one of its excipients. (4)

Warnings and Precautions
- Never share a TOUJEO SoloStar® disposable prefilled pen between patients, even if the needle is changed. (5.1)
- Hypo- or hyperglycemia with changes in insulin regimen: Carry out under close medical supervision. (5.2)

Adverse Reactions
- Hypoglycemia: May be life-threatening. Increase frequency of glucose monitoring with changes to insulin dosage, co-administered glucose lowering medications, meal pattern, physical activity; and in patients with renal 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)

Full Prescribing Information: Contents
1. Indications and Usage
2. Dosage and Administration
- General Dosing Instructions
- Starting Dose in Insulin-Naive Patients
- Starting Dose in Patients with Either Type 1 or Type 2 Diabetes Already on Insulin Therapy
- Important Administration Instructions
3. Dosage Forms and Strengths
4. Contraindications
5. Warnings and Precautions
- Never Share a TOUJEO SoloStar® disposable prefilled pen between patients, even if the needle is changed. (5.1)
- Hypo- or hyperglycemia with changes in insulin regimen: Carry out under close medical supervision. (5.2)
- Fluid retention and heart failure with concomitant use of PPAR-gamma Agonists
6. Adverse Reactions
- Hypoglycemia: May be life-threatening. Increase frequency of glucose monitoring with changes to insulin dosage, co-administered glucose lowering medications, meal pattern, physical activity; and in patients with renal 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%): are:
- 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. (7.1, 7.2, 7.3)
- Anti-Adrenergic Drugs (e.g., beta-blockers, clonidine, guanethidine, and reserpine): Signs and symptoms of hypoglycemia may be reduced or absent. (7.3, 7.4)

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: 09/2015
2.2 Starting Dose in Insulin-Naïve Patients

Type 1 Diabetes:
The recommended starting dose of TOUJEO in insulin naïve patients with type 1 diabetes is approximately 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. As a general rule, 0.2 to 0.4 units of insulin per kilogram of body weight can be used to calculate the initial total daily insulin dose in insulin naïve patients with type 1 diabetes.

Type 2 Diabetes:
The recommended starting dose of TOUJEO in insulin naïve patients with type 2 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)].

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 [See Clinical Pharmacology (12.2) and Clinical Studies (14.1)].

To minimize the risk of hypoglycemia when changing from twice-daily NPH insulin to once-daily TOUJEO, the recommended starting dose of TOUJEO is 80% of the total daily NPH dosage.

To minimize the risk of hyperglycemia when changing to TOUJEO, monitor glucose frequently in the first weeks of therapy titrate the dose of TOUJEO per instructions and adjust co-administered glucose lowering therapies per standard of care.

2.4 Important Administration Instructions

- Prior to initiation of TOUJEO, patients should be trained by their healthcare professional on proper use and injection technique. Training reduces the risk of administration errors such as needlesticks and incomplete dosing.
- Patient should follow the Instructions for Use for correctly use the pen device and administer TOUJEO.
- Patients should be informed that the dose counter of the TOUJEO SoloStar disposable prefilled pen shows the number of units of TOUJEO to be injected. The TOUJEO SoloStar prefilled pen has been specifically designed for TOUJEO, therefore no dose conversion is required [Patient counseling (17.1)].
- Patients should be instructed to visually inspect the TOUJEO solution for particulate matter and discolaration prior to administration and only use if the solution is clear and colorless with no visible particles.
- For single patient use only [See Warnings and Precautions (5.1)].
- Recondition and reheater TOUJEO SoloStar prefilled pens.

3. DOSAGE FORMS AND STRENGTHS

Injection: 300 units per mL of insulin glargine available as a clear, colorless, solution in a 1.5 mL TOUJEO SoloStar disposable prefilled pen (450 Units/1.5 mL).

4. CONTRAINDICATIONS

TOUJEO is contraindicated in:

- During episodes of hypoglycemia [See Warnings and Precautions (5.3)].
- In patients with hypersensitivity to insulin glargine or one of its excipients [See Warnings and Precautions (5.5)].

5. WARNINGS AND PRECAUTIONS

5.1 Never Share a TOUJEO SoloStar pen Between Patients

TOUJEO SoloStar disposable prefilled pens must never be shared between patients, even if the needle is changed. Pen sharing poses a risk for transmission of blood-borne pathogens.

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 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 lower 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 co-administered glucose lowering therapies per standard of care [See Dosage and Administration (2.2, 2.3)]. Higher doses of TOUJEO were required 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 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 and ability to react in 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 hypothalamic nervous system, e.g., beta-blockers) [See Drug Interactions (7)], or in patients who experience recurrent hypoglycemia.

5.4 Medication Errors

Accidental mix-ups between basal insulin products and other insulin, 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.

5.5 Hypersensitivity and Allergic Reactions

Severe, life-threatening, generalised 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)]. TOUJEO is contraindicated in patients who have had hypersensitivity reactions to insulin glargine or other of the excipients [See Contraindications (4)].

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 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, are associated with a dose-related increased risk of 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)].
- Hypersensitivity and allergic reactions [See Warnings and Precautions (5.5)].
- Hypokalemia [See Warnings and Precautions (5.6)].

6.1 Clinical trial experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in 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 304 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, mean eGFR was 82 mL/min/1.73m² and 35% of patients had eGFR 90 mL/min/1.73m². The mean BMI was 28 kg/m² at baseline and 35% of patients had eGFR ≥ 90 mL/min/1.73m². Patients with renal or hepatic impairment may be 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 mix TOUJEO with any other insulin products or solutions.

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>

[“meatime insulin” refers to insulin glulisine, insulin lispro, or insulin aspart]

Table 2: Adverse reactions in three pooled clinical trials of 26 weeks duration in adults with type 2 diabetes (with incidence ≥5%)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngitis</td>
<td>7.1</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>5.7</td>
</tr>
</tbody>
</table>

*one of the trials in type 2 diabetes included meatime insulin
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 pregnant, 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

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

8.5 Geriatric 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 ≥65 years of age, among them 2.0% of patients with type 1 and 3.0% of the patient sample with type 2 diabetes were ≥75 years of age.

No overall differences in effectiveness and safety were observed in subgroup analyses across the age groups.

Nevertheless, caution should be exercised when TOUJEO is administered to geriatric patients. In elderly patients with diabetes, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemia.

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.

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.

8.8 Obesity

There are no 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), Adverse reactions (6) and Clinical Studies (14)].

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 non-pathogenic laboratory strain of Escherichia coli (K12) as the production organism. Insulin glargine differs from human insulin in that the amino acid asparagine at position A21 is replaced by glycine and a molecular weight of 6063. Insulin glargine has the following structural formula.

Each milliliter of TOUJEO contains 300 Units (10.91 mg) insulin glargine dissolved in a clear aqueous fluid.
The 1.5 mL SoloStar disposable prefilled pen presentation contains the following inactive ingredients per mL: 30 mg of zinc, 27 mg of croscMC, 20 mg of glycine, 0.05%, and 0.01% 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 the 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 analogs lower blood glucose by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin inhibits lipolysis and protein synthesis.

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$\text{max}$) and 24 hour glucose lowering effect (GIR-AUC$_{24h}$) 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-AUC$_{24h}$) 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), Warning 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.

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 3.02 µU/mL by 16, 26, 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.

Elimination
After subcutaneous injection of TOUJEO in diabetic patients, insulin glargine is metabolized at the carboxyl terminus of the B-chain with formation of two active metabolites M1 (21A-Gly-insulin) and M2 (21A-Gly-des-30B-Thr-insulin). The in vitro activity of M1 and M2 were similar to that of human insulin.

Specific Populations
Age (Geriatric Population and Pediatric Population), Race, and Sex: Effect of age, race, and sex on the pharmacokinetics of TOUJEO has not been evaluated.

Obesity: Effect of BMI on the pharmacokinetics of TOUJEO has not been evaluated.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
In mice and rats, standard two-year carcinogenicity studies with insulin glargine were performed at doses up to 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 a different vehicle. The relevance of these findings to humans is unknown.

Insulin glargine was not mutagenic in tests for detection of gene mutations in bacteria and mammalian cells (Ames test and HGPRT-test) and in 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 3 and 4). At trial end, the reduction in glycated hemoglobin (HbA1c) and fasting plasma glucose with TOUJEO titrated 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=546), 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. 57% were male. 85.1% were Caucasian, 4.7% Black or African American. 4.7% were Hispanic. 32.2 percent of patients had GFR<90 mL/min/1.73m$^2$. The mean BMI was approximately 27.6 kg/m$^2$. At week 26, treatment with TOUJEO provided a mean reduction in HbA1c that met the pre-specified non-inferiority margin of 0.4% (Table 3). 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 3: Type 1 Diabetes Mellitus – Adult (TOUJEO plus Mealtime insulin versus LANTUS plus Mealtime Insulin)

<table>
<thead>
<tr>
<th>Treatment duration</th>
<th>Treatment in combination</th>
<th>Number of subjects treated (mITT) $^1$</th>
<th>HbA1c $^2$</th>
<th>Fasting Plasma Glucose mg/dL $^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOUJEO +mealtime insulin</td>
<td>Fast-acting insulin analogue</td>
<td>273</td>
<td>8.13</td>
<td>186</td>
</tr>
<tr>
<td>LANTUS +mealtime insulin</td>
<td></td>
<td>273</td>
<td>8.12</td>
<td>199</td>
</tr>
</tbody>
</table>

$^1$mITT: Modified intention-to-treat

$^2$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 60 years. The majority of patients were White (92.3%) and 52.9% were male. 20.3 percent of patients had GFR<90 mL/min/1.73m$^2$. The mean BMI was approximately 36.6 kg/m$^2$. At week 26, treatment with TOUJEO provided a mean reduction in HbA1c that met the pre-specified non-inferiority margin of 0.4% compared to LANTUS (Table 4). 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=1,670), 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 non-insulin anti-diabetic drugs. At the time of randomization, 868 patients were treated with basal insulin for more than 6 months (study C) and 862 patients were insulin-naïve (study D). In Study C, the average age was 58.2 years. The majority of patients were White (39.8%) and 45.9% were female. 32.8 percent of patients had GFR<90 mL/min/1.73m$^2$. The mean BMI was approximately 34.8 kg/m$^2$. At week 26, treatment with TOUJEO provided a mean reduction in HbA1c that met the pre-specified non-inferiority margin of 0.4% compared to LANTUS (Table 4). 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 C, the average age was 57.7 years. The majority of patients were White (78%) and 57.7% were male. 29 percent of patients had GFR<90 mL/min/1.73m$^2$. The mean BMI was approximately 33 kg/m$^2$. At week 26, treatment with TOUJEO provided a mean reduction in HbA1c that met the pre-specified non-inferiority margin of 0.4% compared to LANTUS (Table 4). 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.
Table 4: 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></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mealtime insulin analog + metformin</td>
<td>Non-insulin anti-diabetic drugs</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of patients treated</th>
<th>TOUJEO</th>
<th>LANTUS</th>
<th>TOUJEO</th>
<th>LANTUS</th>
<th>TOUJEO</th>
<th>LANTUS</th>
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<tbody>
<tr>
<td>404</td>
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<td>403</td>
<td>405</td>
<td>432</td>
<td>430</td>
<td></td>
</tr>
</tbody>
</table>

HbA1c

<table>
<thead>
<tr>
<th>Baseline mean</th>
<th>TOUJEO</th>
<th>LANTUS</th>
<th>TOUJEO</th>
<th>LANTUS</th>
</tr>
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<tbody>
<tr>
<td>8.13</td>
<td>8.14</td>
<td>8.27</td>
<td>8.22</td>
<td>8.49</td>
</tr>
</tbody>
</table>

Adjusted mean change from baseline

<table>
<thead>
<tr>
<th>TOUJEO</th>
<th>LANTUS</th>
<th>TOUJEO</th>
<th>LANTUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>-0.90</td>
<td>-0.87</td>
<td>-0.73</td>
<td>-0.70</td>
</tr>
</tbody>
</table>

Adjusted mean difference\(^\d\) [95\% Confidence interval]

<table>
<thead>
<tr>
<th>TOUJEO</th>
<th>LANTUS</th>
<th>TOUJEO</th>
<th>LANTUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>-0.03</td>
<td>-0.03</td>
<td>[0.04]</td>
<td>[0.04]</td>
</tr>
</tbody>
</table>

Fasting Plasma Glucose (mg/dL)

<table>
<thead>
<tr>
<th>Baseline mean</th>
<th>TOUJEO</th>
<th>LANTUS</th>
<th>TOUJEO</th>
<th>LANTUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>157</td>
<td>160</td>
<td>149</td>
<td>142</td>
<td>179</td>
</tr>
</tbody>
</table>

Adjusted mean change from baseline

<table>
<thead>
<tr>
<th>TOUJEO</th>
<th>LANTUS</th>
<th>TOUJEO</th>
<th>LANTUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>-29</td>
<td>-30</td>
<td>-18</td>
<td>-22</td>
</tr>
</tbody>
</table>

Adjusted mean difference\(^\d\) [95\% Confidence interval]

<table>
<thead>
<tr>
<th>TOUJEO</th>
<th>LANTUS</th>
<th>TOUJEO</th>
<th>LANTUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.8</td>
<td>3</td>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>

1.5 mL SoloStar disposable prefilled pen: Until expiration date

<table>
<thead>
<tr>
<th>1.5 mL SoloStar disposable prefilled pen (300 Units/mL)</th>
<th>Package of 3</th>
<th>0024-5869-03</th>
</tr>
</thead>
</table>

1.5 mL SoloStar disposable prefilled pen: Room temperature only (Do not refrigerate)

<table>
<thead>
<tr>
<th>1.5 mL SoloStar disposable prefilled pen (300 Units/mL)</th>
<th>Package of 5</th>
<th>0024-5869-05</th>
</tr>
</thead>
</table>

Needles are not included in the packs of TOUJEO SoloStar disposable prefilled pen. BD Ultra-Fine™ needles\(^\d\) to be used in conjunction with TOUJEO SoloStar disposable prefilled pen are sold separately and are manufactured by BD.

\(^\d\) The brands listed are the registered trademarks of their respective owners and are not trademarks of sanofi-aventis U.S. LLC.

16. HOW SUPPLIED/STORAGE AND HANDLING

16.1 How supplied

TOUJEO (insulin glargine injection) is supplied as a solution containing 300 units per mL (U-300) of insulin glargine and is available in:

<table>
<thead>
<tr>
<th>Dosage Unit/Strength</th>
<th>Package size</th>
<th>NDC #</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5 mL SoloStar disposable prefilled pen (300 Units/mL)</td>
<td>Package of 3</td>
<td>0024-5869-03</td>
</tr>
<tr>
<td>1.5 mL SoloStar disposable prefilled pen (300 Units/mL)</td>
<td>Package of 5</td>
<td>0024-5869-05</td>
</tr>
</tbody>
</table>

16.2 Storage

TOUJEO SoloStar disposable prefilled pen should not be stored in the freezer and should not be allowed to freeze. Discard TOUJEO SoloStar disposable prefilled pen if it has been frozen.

Unopened SoloStar disposable prefilled pen:

Unopened TOUJEO SoloStar disposable prefilled pen should be stored in a refrigerator, 36°C – 46°F (2°C – 8°C). Discard after the expiration date.

Open (In-Use) SoloStar disposable prefilled pen:

The opened (in-use) TOUJEO SoloStar disposable prefilled pen should NOT be refrigerated but should be kept at room temperature (below 86°F [30°C]) away from direct heat and light. The opened (in-use) TOUJEO SoloStar disposable prefilled pen must be discarded 42 days after being opened. These 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>Refrigarated</td>
<td>(See Temperature Below)</td>
</tr>
</tbody>
</table>

16.3 Preparation and handling

Parenteral drug products should be inspected visually prior to administration whenever the solution and the container permit. TOUJEO must only be used if the solution is clear and colorless with no particles visible [See Dosage and Administration (2.4)].

Mixing and diluting: TOUJEO MUST NOT be diluted or mixed with any other insulin or solution [See Dosage and Administration (2.1)].

If TOUJEO SoloStar disposable prefilled pen, malfunctions, TOUJEO must not be drawn from the TOUJEO pen into any syringe and injected.

Needles must not be re-used. A new sterile needle must be attached before each injection. Re-use of needles increases the risk of blocked needles which may cause under-dosing or overdose. Using a new sterile needle for each injection also minimizes the risk of contamination and infection.

17. PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Instruction Leaflet)

General Counseling Information—Prior to treatment, patients should fully understand the risks and benefits of TOUJEO. Ensure that all patients receive the Instruction Leaflet prior to initiating TOUJEO therapy.

17.1 Never Share a TOUJEO SoloStar Pen Between Patients

[see Warnings and Precautions (5.1)]

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

17.2 Hypoglycemia 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 hyper- 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.

17.3 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 label of TOUJEO SoloStar disposable prefilled pen. Inform patients that TOUJEO (insulin glargine 300 U/mL) contains 3 times as much insulin in 1 mL as standard insulin (100 U/mL).

Inform patients that the dose counter of TOUJEO SoloStar disposable prefilled pen shows the number of units of TOUJEO to be injected. No dose re-calculation is required.

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 under-dosing or overdosing. In the event of blocked needle, the patients must follow the instructions described in Step 3 of the Instructions for Use.

Instruct Patients to never use a syringe to remove TOUJEO from the SoloStar disposable insulin prefilled pen.

17.4 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.

17.5 Management of Hypoglycemia and Handling of Special Situations

Patients should be instructed on self-management procedures including glucose monitoring, proper injection technique, and management of hypoglycemia and hyperglycemia. Patients must be instructed on handling of special situations such as intercurrent conditions (illness, stress, or emotional disturbances), an inadequate or skipped insulin dose, inadvertent administration of an increased insulin dose, inadequate food intake, and skipped meals.

17.6 Pregnancy

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

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

17.7 FDA Approved Patient Labeling

See attached document at end of Full Prescribing Information.

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

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LANTUS, TOUJEO and SoloStar are registered trademarks of sanofi-aventis U.S. LLC.
Do not share your TOUJEO 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 contains 3 times as much insulin in 1 mL as standard insulin (100 U/mL).
- 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?
- Read the detailed Instructions for Use that come with your TOUJEO SoloStar disposable prefilled pen.
- Use TOUJEO exactly as your healthcare provider tells you. 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.
- TOUJEO comes in a SoloStar disposable prefilled pen that you must use to give your TOUJEO. The dose counter on your pen shows your dose of TOUJEO. Do not make any dose changes unless your healthcare provider tells you to.
- Do not use a syringe to remove TOUJEO 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 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 chose 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

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

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.

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

This Patient Information has been approved by the U.S. Food and Drug Administration

Approved: February 2015

Revised September 2015

GLR-FPLR-SL-SEP15 Rx Only