What is Toujeo®?
Prescription Toujeo® is a long-acting insulin used to control blood sugar in adults with diabetes mellitus.

• Toujeo® contains 3 times as much insulin in 1 mL as standard insulin (100 Units/mL)
• Toujeo® is not for use to treat diabetic ketoacidosis
• Toujeo® should not be used in children

Important Safety Information for Toujeo®
Do not take Toujeo® if you have low blood sugar or if you are allergic to insulin or any of the ingredients in Toujeo®.

Please see Full Important Safety Information for Toujeo on pages 6 & 7.

Please click here or refer to the bottom of this document for the full Prescribing Information for Toujeo®.
Experience Toujeo® (insulin glargine injection) 300 Units/mL and see how it works for you

Work towards blood sugar control + stability
Whether you’re new to insulin or switching treatments, you may want to ask your doctor about Toujeo.

Toujeo provides proven significant A1C reduction.

Consider this
In studies, patients on Toujeo were required to stop taking one of their oral medications (sulfonylureas).
- Toujeo showed significant A1C reductions
- Do not change your medications without consulting with your doctor

Experience savings with a $0 copay if you are new to Toujeo
Talk to your doctor and see how Toujeo can work for you.
Your first 3 copays are on us, then get an additional year of copays for $10 each.
See full offer details on page 5.

Important Safety Information for Toujeo®
(insulin glargine injection) 300 Units/mL

Do NOT reuse needles or share insulin pens even if the needle has been changed.
Before starting Toujeo®, tell your doctor about all your medical conditions, including if you have liver or kidney problems, if you are pregnant or planning to become pregnant or if you are breastfeeding or planning to breastfeed.

Please see Full Important Safety Information for Toujeo on pages 6 & 7.
Please click here or refer to the bottom of this document for the full Prescribing Information for Toujeo®.

Important Safety Information for Toujeo®
(insulin glargine injection) 300 Units/mL

Heart failure can occur if you are taking insulin together with pills called TZDs (thiazolidinediones), even if you have never had heart failure or other heart problems. If you have heart failure, it may get worse while you take TZDs with Toujeo®. Your treatment with TZDs and Toujeo® may need to be changed or stopped by your doctor if you have new or worsening heart failure. Tell your doctor if you have any new or worsening symptoms, including:
- Shortness of breath
- Sudden weight gain
- Swelling of your ankles or feet

1American Diabetes Association.
Toujeo® comes from the makers of Lantus®

If your diabetes is changing, maybe it’s time for your treatment to change, as well. It is important to know your insulin.

Toujeo is the only 300 Units/mL long-acting insulin. All other long-acting insulins are available in 100 or 200 Units/mL.

See how Toujeo compares with Lantus, the most prescribed insulin.

<table>
<thead>
<tr>
<th>How Toujeo compares to Lantus, the most prescribed insulin¹:</th>
<th>Toujeo</th>
<th>Lantus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Once-daily, long-acting insulin</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Proven blood sugar control</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>More gradual release</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Smaller volume</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Less injection force‡</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>5 seconds hold time</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Longer storage outside the fridge once opened§</td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>

¹Based on TRx data from IMS Health, NPA™ monthly database, time period from May 2003 to September 2016.
²Study was performed in a laboratory setting. Doses were not delivered into tissue.
³Toujeo: 42 days  Lantus: 28 days

Copay Card Offer Terms

For patients new to Toujeo, the first three prescriptions will have a $0 copay. Thereafter, the copay will be $10 per script.

This offer is not valid for prescriptions covered by or submitted for reimbursement under Medicare, Medicaid, VA, DOD, TRICARE, or similar federal or state programs, including any state pharmaceutical programs.

For the duration of the program, the Savings Card carries maximum savings up to:

- $500 per pack for all patients who are enrolled in a commercial insurance plan, whether Toujeo® or Lantus® is covered or not by your insurance
- $200 per pack of Toujeo® for patients not enrolled in a commercial insurance plan or in the Federal Employee Health Benefits (FEHB) Program
- $100 per pack of Lantus® for patients not enrolled in a commercial insurance plan or in the FEHB Program

This offer is valid for up to 3 packs per prescription. Savings may vary depending on patients’ out-of-pocket costs. Upon registration, patients receive all program details. Sanofi US reserves the right to change the maximum cap amount, rescind, revoke, or amend the program without notice.

Please note: the FEHB Program is not a federal or state government health care program for purposes of this savings program.

Void where prohibited by law.

Important Safety Information for Toujeo® (insulin glargine injection) 300 Units/mL

Tell your doctor about all the medications you take, including OTC medicines, vitamins, supplements, and herbal supplements.

Please see Full Important Safety Information for Toujeo on pages 6 & 7.

Please click here or refer to the bottom of this document for the full Prescribing Information for Toujeo®.
Tell your doctor about all the medications you take, including OTC medicines, vitamins, supplements, and herbal supplements.

Toujeo® should be taken at the same time once a day. Test your blood sugar levels daily while using insulin, including Toujeo®. Do not change your dose or type of insulin without talking to your doctor. Verify that you have the correct insulin before each injection. Do NOT use a syringe to remove Toujeo® from your SoloStar® pen. Your dose for Toujeo® may be different from other insulins you have taken. Any change of insulin should be made cautiously and only under medical supervision.

Do NOT dilute or mix Toujeo® with any other insulin or solution. It will not work as intended and you may lose blood sugar control, which could be serious. Use Toujeo® only if the solution is clear and colorless with no particles visible.

While using Toujeo®, do not drive or operate heavy machinery until you know how Toujeo® affects you. Don’t drink alcohol or use medicines that contain alcohol.

The most common side effect of any insulin, including Toujeo®, is low blood sugar (hypoglycemia), which may be serious and life-threatening. Severe hypoglycemia may cause harm to your heart or brain. Symptoms of serious low blood sugar may include shaking, sweating, fast heartbeat, and blurred vision.

Toujeo® may cause severe allergic reactions that can lead to death. Get medical help right away if you have:

- A rash over your whole body
- Shortness of breath
- Swelling of your face, tongue, or throat
- Extreme drowsiness, dizziness, or confusion
- Trouble breathing
- Fast heartbeat
- Sweating

Toujeo® may have additional side effects including swelling, weight gain, low potassium, and injection site reactions which may include change in fat tissue, skin thickening, redness, swelling, and itching.

Toujeo® SoloStar® is a disposable prefilled insulin pen. Talk to your doctor about proper injection technique and follow instructions in the Instruction Leaflet that comes with the pen.

Please click here or refer to the bottom of this document for the full Prescribing Information for Toujeo®.
HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TOUJEO safely and effectively. See full prescribing information for TOUJEO.

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

Initial U.S. Approval: 2015

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 the treatment of diabetic ketoacidosis. (1)

DOSEAGE AND ADMINISTRATION

Inject TOUJEO subcutaneously once daily into the abdominal area, thigh, or deltoid at the same time each day. (2.1)

Do not dilute or mix with any other insulin or solution. (2.1)

Never share a TOUJEO SoloStar® disposable prefilled pen between patients, even if the needle is changed (5.1)

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 (5.5, 6.1)

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)

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 resepine): Signs and symptoms of hypoglycemia may be reduced or absent (7.3, 7.4)

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)

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

Revised: 09/2015

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1. INDICATIONS AND USAGE

2. DOSAGE AND ADMINISTRATION

2.1 General Dosing Instructions

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

3. DOSAGE FORMS AND STRENGTHS

Injection: 300 units/mL insulin glargine in 1.5 mL SoloStar® disposable prefilled pen (3)

4. CONTRAINDICATIONS

• During episodes of hypoglycemia (4)

• Hypersensitivity to TOUJEO or one of its excipients (4)

5. WARNINGS AND PRECAUTIONS

• Never share a TOUJEO SoloStar® disposable prefilled pen between patients, even if the needle is changed (5.1)

• Hyper- or hypoglycemia with changes in insulin regimen: Carry out under close medical supervision. (5.2)

6. ADVERSE REACTIONS

6.1 Clinical trial experience

6.2 Immunogenicity

6.3 Gastrointestinal (GI) symptoms

7. DRUG INTERACTIONS

7.1 Drugs That May Increase the Risk of Hypoglycemia

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

7.3 Drugs That May Increase or Decrease the Blood Glucose Lowering Effect of TOUJEO

7.4 Drugs That May Affect Signs and Symptoms of Hypoglycemia

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17.6 Pregnancy

17.7 FDA Approved Patient Labeling

*Sections or subsections omitted from the full prescribing information are not listed.
acute illness to minimize the risk of hypoglycemia or hyperglycemia [see Warnings and Precautions (5.2)].

- To minimize the risk of hypoglycemia, do not dilute or mix TOUJEO with any other insulin products or solutions.

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 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 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 Section (12.2)].

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 needle sticks and incomplete dosing.

- Patient should follow the Instructions for Use to correctly use the pen device and administer TOUJEO.

- Patients should be instructed 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 discoloration 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)].

- Refrigerate unopened (unopened) 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:

- 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 treated 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 higher average plasma glucose levels in the first week 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 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 (12.4)].

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. After the initiation of 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 physical activity, changes in sleep pattern, changes in level of physical activity, or changes to co-administered medication [see Drug Interactions (7)]. Patients with renal or hepatic impairment may be at higher risk of hypoglycemia [see Use in Specific Populations (8.5, 8.6)].

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.

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)]. TOUJEO is contraindicated in patients who have had hypersensitivity reactions to insulin glargine or one of the excipients [See Contraindications (4)].

5.6 Hypokalemia

All insulin products, including 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, 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)].

- 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 17% were Hispanic. At baseline, mean eGFR was 82 mL/min/1.73m² and 35% of patients had eGFR<60 mL/min/1.73m². The mean BMI was 28 kg/m² at baseline in 59% of patients.

The data in Table 2 reflect the exposure of 1242 patients with type 2 diabetes to TOUJEO with mean exposure duration of 25 weeks. The type 2 diabetes population had the following characteristics: Mean age was 59 years and mean duration of diabetes was 13 years. Fifty three percent were male, 86% were Caucasian, 7% were Black or African American and 17% were Hispanic. At baseline, mean eGFR was 79 mL/min/1.73m² and 27% of patients had an eGFR<60 mL/min/1.73m². The mean BMI was 35 kg/m². HbA1c at baseline was greater or equal to 8% in 66% of patients.

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. Hypoglycemia is discussed in a dedicated subsection below.

**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>

**“meatline 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 mealtime insulin
Hypoglycemia

Hypoglycemia is the most commonly observed adverse reaction in patients using insulin, including TOUJEO [see Warnings and Precautions (5.3)]. In the TOUJEO program, severe hypoglycemia was defined as an event requiring assistance of another person to administer a resuscitative action and documented symptomatic hypoglycemia was defined as an event with typical symptoms of hypoglycemia accompanied by a self-monitored or plasma glucose value equal to or less than 54 mg/dL.

The incidence of severe hypoglycemia in patients with type 1 diabetes receiving TOUJEO as part of a multiple daily injection regimen was 6.6% at 26 weeks. The incidence of documented symptomatic hypoglycemia was 69% at 26 weeks. There were no clinically important differences in hypoglycemia between TOUJEO and LANTUS among type 1 diabetes patients.

The incidence of severe hypoglycemia in patients with type 2 diabetes receiving TOUJEO as part of a multiple daily injection regimen was 5% at 26 weeks in patients receiving TOUJEO as part of a multiple daily injection regimen. The incidence of documented symptomatic hypoglycemia in patients with type 2 diabetes receiving TOUJEO ranged from 8% to 37% at 26 weeks and the highest risk was again seen in patients receiving TOUJEO as part of a multiple daily injection regimen.

Insulin initiation and intensification of glucose control

Intensification or rapid improvement in glucose control has been associated with a transient, reversible ophthalmo-optic neuropathy, worsening of diabetic retinopathy, and acute painful peripheral neuropathy. However, long-term glycemic control decreases the risk of diabetic retinopathy and neuropathy.

Peripheral Edema

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

Lipoatrophy

Long-term use of insulin, including TOUJEO, can cause lipoatrophy (depression in the skin) or lipohypertrophy (enlargement or thickening of tissue) in some patients and may affect insulin absorption [see Dosage and Administration (2.1)].

Weight gain

Weight gain has occurred with some insulin therapies including TOUJEO and has been attributed to the anabolic effects of insulin and the decrease in glucosuria.

Allergic Reactions

Some patients taking insulin therapy, including TOUJEO have experienced urticaria, local edema, and pruritus at the injection site. These conditions were usually self-limited. Severe cases of generalized allergy (anaphylaxis) have been reported [see Warnings and Precautions (5.5)].

Cardiovascular Safety

No clinical studies to establish the cardiovascular safety of TOUJEO have been conducted. A cardiovascular outcomes trial, ORIGIN, has been conducted with LANTUS. It is unknown whether the results of ORIGIN can be applied to TOUJEO.

The Outcome Reduction with Initial Glargine Intervention trial (i.e., ORIGIN) was an open-label, randomized, 12,537 patient study that compared LANTUS to standard care on the time to first occurrence of a major adverse cardiovascular event (MACE). MAC was defined as the composite of CV death, MI, and non-fatal stroke. The incidence of MAC was similar between LANTUS and standard care in ORIGIN (Hazard Ratio (95% CI) for MACE. 1.02 (0.94, 1.11)). In the ORIGIN trial, the overall incidence of cancer (all types combined) (Hazard Ratio (95% CI); 0.99 (0.88, 1.11)) or death from cancer (Hazard Ratio (95% CI); 0.94 (0.77, 1.15)) was also similar between treatment groups.

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity.

In a 6-month study of type 1 diabetes patients, 79% of patients who received TOUJEO once daily were positive for anti-insulin antibodies (AIA) at least once during the study, including 62% that were positive at baseline. In a 6- to 12-month study of patients with AIs that developed anti-drug antibody [i.e., anti-insulin glargine antibody (ADA)] during the study. Eighty percent of the AIA positive patients on TOUJEO with antibody test at baseline, remained AIA positive at month 6.

In two 6-month studies in type 2 diabetes patients, 25% of patients who received TOUJEO once daily were positive for AIA at least once during the study, including 42%, who were positive at baseline and 20% of patients who developed ADA during the study. Ninety percent of the AIA positive patients on TOUJEO with antibody test at baseline, remained AIA positive at month 6.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay and may be influenced by several factors such as: assay methodology, sample handling, timing of sample collection, concomitant medication, and underlying disease. For these reasons, comparison of the incidence of antibodies to TOUJEO with the incidence of antibodies in other studies or to other products, may be misleading.

7. Drug Interactions

7.1 Drugs That May Increase the Risk of Hypoglycemia

The risk of hypoglycemia associated with TOUJEO use may be increased with antidepressant agents, (ACE) inhibitors, angiotensin II receptor blocking agents, diacytamide, fibrates, flavonoids, monamine oxidase inhibitors, pentoxifylline, pramipexile, propylphenazone, salicylates, somatostatin analogs (e.g., octreotide), and sulfonamide antibiotics. Dose adjustment and increased frequency of glucose monitoring may be required when TOUJEO is co-administered with these drugs.

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

The glucose lowering effect of TOUJEO may be decreased when co-administered with atypical antipsychotics (e.g., olanzapine and clozapine), corticosteroids, diazepam, diuretics, estrogens, glucagon, isoniazid, niacin, oral contraceptives, phenothiazines, progestogens (e.g., in oral contraceptives), protease inhibitors, somatropin, sympathomimetic agents (e.g., albuterol, epinephrine, terbutaline) and thyroid hormones. Dose adjustment and increased frequency of glucose monitoring may be required when TOUJEO is co-administered with these drugs.

7.3 Drugs That May Increase or Decrease the Blood Glucose Lowering Effect of TOUJEO

The glucose lowering effect of TOUJEO may be increased or decreased when co-administered with alcohol, beta-blockers, clonidine, and lithium salts. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia. Dose adjustment and increased frequency of glucose monitoring may be required when TOUJEO is co-administered with these drugs.

7.4 Drugs That May Affect Signs and Symptoms of Hypoglycemia

The signs and symptoms of hypoglycemia [see Warnings and Precautions (5.5)] may be blunted when beta-blockers, clonidine, guanethidine, and reserpine are co-administered with TOUJEO.

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 have not been performed in animals, it is unknown whether TOUJEO can cause fetal harm when administered to a pregnant woman. Use of TOUJEO is compatible with breastfeeding, but women with diabetes who are lactating may require adjustments of their insulin doses.

8.2 Pediatric Use

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

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

8.5 Geriatric Use

In controlled clinical studies, 30 of 304 (9.8%) TOUJEO treated patients with type 1 diabetes and 327 of 1242 (26.5%) 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 patients with type 2 diabetes were ≥75 years of age.

No overall differences in effectiveness and safety were observed in the 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 dose, dose increments, and maintenance dosage should be conservative to avoid hypoglycemia [see Warnings and Precautions (5.3)].

8.6 Renal Impairment

The effect of renal 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)].

8.7 Renal Failure

The effect of renal failure 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.

8.8 Obesity

In the ORIGIN trial, the overall incidence of cancer (all types combined) [Hazard Ratio (95% CI); 0.99 (0.88, 1.11)] or death from cancer [Hazard Ratio (95% CI); 0.94 (0.77, 1.15)] was also similar between LANTUS and standard care in ORIGIN [Hazard Ratio (95% CI) for MACE. 1.02 (0.94, 1.11)].

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 two arginines remain at the C-term of the B-chain. Chemically, insulin glargine is 21-Gly31-32-D-Arg-human insulin and has the empirical formula C63H125N25O25S2 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 zinc, 2.7 mg m-cresol, 20 mg glycerol, 0.01% and 0.07% metformin. The pH is adjusted by addition of aqueous solutions of hydrochloric acid and sodium hydroxide.

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. 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 3: Type 1 Diabetes Mellitus – Adult (TOUJEO plus Mealtime insulin versus LANTUS plus Mealtime insulin)

<table>
<thead>
<tr>
<th>Treatment duration</th>
<th>Number of subjects treated (mITT)</th>
<th>Treatment in combination</th>
<th>Fast-acting insulin analogue</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOUJEO +mealtime insulin</td>
<td>273</td>
<td>273</td>
<td></td>
</tr>
<tr>
<td>LANTUS +mealtime insulin</td>
<td>273</td>
<td>273</td>
<td></td>
</tr>
<tr>
<td>HbA1c</td>
<td>8.13</td>
<td>8.12</td>
<td></td>
</tr>
<tr>
<td>Adjusted Mean change from baseline</td>
<td>-0.40</td>
<td>-0.44</td>
<td></td>
</tr>
<tr>
<td>Adjusted Mean difference</td>
<td>0.04</td>
<td>[-0.10 to 0.18]</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fasting Plasma Glucose mg/dL</th>
<th>Baseline mean</th>
<th>Adjusted Mean change from baseline</th>
<th>Adjusted Mean difference</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>treatment</td>
<td>186</td>
<td>-17</td>
<td>-20</td>
<td></td>
</tr>
</tbody>
</table>

*mealtime insulin* refers to insulin glulisine, insulin lispro or insulin aspart from mITT. Modified intention-to-treat

†Treatment difference: TOUJEO – LANTUS

14. 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 (time period covering from pre-breakfast until bedtime). A mealtime insulin analogues with or without metformin were also administered. The average age was 58 years. The majority of patients were White (93.8%) and 45.9% were Hispanic. 32.2 percent of patients had HbA1c>9.0% (7.0 mmol/l or lower limit of quantitation). The mean BMI was approximately 37 kg/m². 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 (93.8%) and 45.7% were Hispanic. 32.8 percent of patients had HbA1c>9.0% (7.0 mmol/l or lower limit of quantitation). The mean BMI was approximately 34.8 kg/m². 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 D, the average age was 57.7 years. The majority of patients were White (78%) and 57.7% were ethnic minorities. 29.3 percent of patients had HbA1c>9.0% (7.0 mmol/l or lower limit of quantitation). The mean BMI was approximately 33 kg/m². At week 26, treatment with TOUJEO provided a mean reduction in HbA1c that met the pre-specified non-inferiority margin compared to LANTUS (Table 4). 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 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>Mealtime insulin analog/°-metformin</td>
<td>Non-insulin anti-diabetic drugs</td>
<td></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</td>
<td>-0.03</td>
<td>-0.03</td>
<td>0.04</td>
</tr>
<tr>
<td>Baseline mean</td>
<td>[-0.14 to 0.08]</td>
<td>[-0.17 to 0.10]</td>
<td></td>
</tr>
<tr>
<td>Adjusted mean change from baseline</td>
<td>[-0.3 to 0.0]</td>
<td>[0 to 0.1]</td>
<td>[-0.09 to 0.17]</td>
</tr>
<tr>
<td>Fasting Plasma Glucose (mg/dL)</td>
<td>157</td>
<td>160</td>
<td>149</td>
</tr>
<tr>
<td>Baseline mean</td>
<td>-29</td>
<td>-30</td>
<td>0.8</td>
</tr>
<tr>
<td>Adjusted mean change from baseline</td>
<td>121</td>
<td>129</td>
<td>3</td>
</tr>
<tr>
<td>Adjusted mean difference* [95% Confidence interval]</td>
<td>[-5 to 7]</td>
<td>[0 to 1]</td>
<td>[2 to 12]</td>
</tr>
<tr>
<td>1.5 mL SoloStar disposable prefilled pen</td>
<td>Refrigerated</td>
<td>Until expiration date</td>
<td></td>
</tr>
<tr>
<td>In-use (opened)</td>
<td>Room temperature only</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(See Temperature Below)</td>
<td>(Do not refrigerate)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1.5 mL SoloStar disposable prefilled pen must be discarded 42 days after being opened. These storage conditions are summarized in the following 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 overdosing. Using a new sterile needle for each injection also minimizes the risk of contamination and infection. 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° F – 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.
Patient Information

TOUJEO (Too-Jay-o) (insulin glargine injection) for subcutaneous use, 300 Units/mL (U-300)

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.
- 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

6
What are the possible side effects of TOUJEO?

TOUJEQ 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 TOUJEQ 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 TOUJEQ. Your healthcare provider should monitor you closely while you are taking TZDs with TOUJEQ. 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 TOUJEQ 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 TOUJEQ 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 TOUJEQ. 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 TOUJEQ.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use TOUJEQ for a condition for which it was not prescribed. Do not give TOUJEQ 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 TOUJEQ. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about TOUJEQ that is written for health professionals. For more information, go to www.TOUJEQ.com or call 1-800-633-1610.

What are the ingredients in TOUJEQ?
- 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
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Revised September 2015

GLR-FPLR-SL-SEP15 Rx Only