PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

# TOUJEO™ SoloSTAR®

Insulin glargine (rDNA origin)
Solution for injection 300 U/mL

Antidiabetic Agent

Long-acting Recombinant Human Insulin Analogue

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## PART I: HEALTH PROFESSIONAL INFORMATION

### SUMMARY PRODUCT INFORMATION

| Route of Administration | Dosage Form / Strength | Clinically Relevant Nonmedicinal Ingredients |
|---|---|---|
| Subcutaneous | Solution for injection 300 U/mL<br>Disposable (pre-filled) pen (1.5 mL) | Glycerol 85%, m-cresol, zinc chloride, and water for injection.<br>Hydrochloric acid and sodium hydroxide for pH adjustment. |

### DESCRIPTION

TOUJEO [insulin glargine injection] is a long-acting human insulin analogue. TOUJEO is produced by recombinant DNA technology utilizing a non-pathogenic laboratory strain of *Escherichia coli* (K12) as the production organism. TOUJEO is supplied as a sterile solution containing 300 Units/mL of insulin glargine for subcutaneous injection.

Insulin glargine differs from natural human insulin in that the amino acid asparagine at position 21 of the A-chain is replaced by glycine and two arginines remain at the C-terminus of the B-chain (see PHARMACEUTICAL INFORMATION, Drug Substance).

### INDICATIONS AND CLINICAL USE

TOUJEO [insulin glargine injection (rDNA origin)] is indicated for once-daily subcutaneous administration in the treatment of adult patients (≥18 years) with Type 1 or Type 2 diabetes mellitus who require basal (long-acting) insulin for glycemic control.

**Pediatrics (< 18 years of age):**
The safety and effectiveness of TOUJEO have not been established in pediatric population.

Limitation of Use
Not recommended for treating diabetic ketoacidosis.

## CONTRAINDICATIONS

TOUJEO [insulin glargine injection (rDNA origin)] is contraindicated:

- In patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING.
- During episodes of hypoglycemia (see WARNINGS AND PRECAUTIONS).

## WARNINGS AND PRECAUTIONS

**Serious Warnings and Precautions**

- Hypoglycemia is the most common adverse effect of insulin, including TOUJEO (see WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hypoglycemia). As with all insulins, the timing of hypoglycemia may differ among various insulin formulations. Glucose monitoring is recommended for all patients with diabetes.
- Uncorrected hypoglycemic or hyperglycemic reactions can cause loss of consciousness, coma, or death.
- Any change of insulin should be made cautiously and only under medical supervision (see WARNINGS AND PRECAUTIONS, General).
- TOUJEO is not intended for intravenous or intramuscular administration. The prolonged duration of activity of insulin glargine is dependent on injection into subcutaneous tissue. Intravenous administration of the usual subcutaneous dose could result in severe hypoglycemia.
- **TOUJEO must not be mixed with any other insulin or diluted with any other solution**. If TOUJEO is diluted or mixed, the solution may become cloudy, and the pharmacokinetic/pharmacodynamic profile (e.g., onset of action, time to peak effect) of TOUJEO and/or the mixed insulin may be altered in an unpredictable manner (see DOSAGE AND ADMINISTRATION).
- This insulin product should not be used if it is not water-clear and colorless or if it has formed a deposit of solid particles on the wall of the vial or cartridge (see DOSAGE AND ADMINISTRATION).
- Medication errors have been reported in which other insulins, particularly short-acting insulins, have been accidentally administered instead of insulin glargine. Insulin label must always be checked before each injection to avoid medication errors between insulin glargine and other insulins. Patient must be instructed to not re-use needles and to never use a syringe to remove TOUJEO from the SoloSTAR pre-filled pen as regular insulin syringes are not graduated for TOUJEO (see WARNINGS AND PRECAUTIONS, DOSAGE AND ADMINISTRATION and PART III: PATIENT MEDICATION INFORMATION sections).

## General

When using TOUJEO in combination with oral anti-diabetic agents (OADs), please refer to the respective product monograph for OADs for their WARNINGS AND PRECAUTIONS Information.

The combination of Insulin, including TOUJEO, with a Thiazolidinediones (TZD) is not indicated for the treatment of Type 2 Diabetes Mellitus. Please refer to the respective TZD product monograph WARNINGS AND PRECAUTIONS information when the use of these drugs in combination with TOUJEO is contemplated.

Changes in insulin strength, manufacturer, type, or method of administration may affect glycemic control and predispose to hypoglycemia or hyperglycemia and may result in the need for a change in dosage (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION). 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.

***Insulin glargine, 100 U/mL (LANTUS) and insulin glargine 300 U/mL (TOUJEO) are not bioequivalent and are, therefore, not interchangeable without dose adjustment.***

On a unit to unit basis, the 24-hours exposure/activity AUC of TOUJEO is lower than LANTUS (see ACTION AND CLINICAL PHARMACOLOGY section). In clinical trials, patients who changed to TOUJEO from other basal insulins experienced higher average fasting plasma glucose levels in the first weeks of therapy compared to patients who were changed to LANTUS. To minimize the risk of hyperglycemia 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). Higher doses of TOUJEO were required to achieve similar levels of glucose control compared to LANTUS in clinical trials (see CLINICAL TRIALS).

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 and CLINICAL PHARMACOLOGY).

### Hypokalemia

Hypokalemia is among the potential clinical adverse effect associated with the use of all insulin therapies, particularly when given intravenously. However, TOUJEO should not be given intravenously (see DOSAGE AND ADMINISTRATION, General). If left untreated, hypokalemia may cause respiratory paralysis, ventricular arrhythmia, and death. This potential clinical adverse effect may be more relevant in patients who are at risk for hypokalemia (e.g., patient using potassium lowering drugs), patients taking medications sensitive to serum potassium concentrations, or patients losing potassium through other means (e.g. diarrhea). Monitor potassium levels in patients at risk for hypokalemia.

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

**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.

To avoid transmission of disease, the TOUJEO SoloSTAR pre-filled pen shall not be used by more than one person.

**Medication errors prevention**

**Insulin label must always be checked before each injection to avoid medication errors between TOUJEO and other insulins.** Medication errors have been reported in which other insulins, particularly short-acting insulins, have been accidentally administered instead of long-acting insulins (see PART III: PATIENT MEDICATION INFORMATION sections).

Patients must be informed that the dose pointer of 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 re-calculation is required** (see DOSAGE AND ADMINISTRATION, PART III: Patient Medication Information sections).

**To avoid dosing errors and potential overdose, the patients must also be instructed to never use a syringe to remove TOUJEO from the SoloSTAR pre-filled pen** as regular insulin syringes are not graduated for TOUJEO (see DOSAGE AND ADMINISTRATION, OVERDOSAGE and PART III: PATIENT MEDICATION INFORMATION sections).

**Patients must also be instructed to not re-use needles. 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. In the event of blocked needles, the patients must follow the instructions described in Step 3 of the TOUJEO SoloSTAR Instructions for Use (see DOSAGE AND ADMINISTRATION and PART III: PATIENT MEDICATION INFORMATION sections).

Like for all insulin pens, patients must visually verify the number of selected units on the dose counter of the pen. Patients who are blind or have poor vision must be instructed to get help/assistance from another person who has good vision and is trained in using the insulin device.

## Occupational Hazards

The patient's ability to concentrate and react may be impaired as a result of hypoglycemia or hyperglycemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery).

Patients should be advised to take precautions to avoid hypoglycemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycemia or have frequent episodes of hypoglycemia. It should be considered whether it is advisable to drive or operate machinery in these circumstances.

## Endocrine and Metabolism

### 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), or in patients who experience recurrent hypoglycemia.

Risk Factors for Hypoglycemia

The timing of hypoglycemia usually reflects the time-action profile of the administered insulin formulation. As with all insulin preparations, the glucose lowering effect time course of TOUJEO may vary in different individuals or at different times in the same individual and depends on many conditions, including the area of injection as well as the injection site blood supply and temperature (see ACTION AND CLINICAL PHARMACOLOGY). Other factors which may increase the risk of hypoglycemia include changes in meal pattern (e.g., macronutrient content or timing of meals), changes in level of physical activity, or changes to co-administered medication (see DRUG INTERACTIONS). Patients with renal or hepatic impairment may be at higher risk of hypoglycemia (see WARNINGS AND PRECAUTIONS, Hepatic/ Biliary/Pancreatic, Renal and Special Populations).

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.

**Hyperglycemia**

The use of too low insulin dosages or discontinuation of treatment, especially in Type 1 diabetes, may lead to hyperglycemia and diabetic ketoacidosis. Uncorrected hyperglycemic reactions can cause loss of consciousness, coma or death.

**Other**

The presence of diseases such as acromegaly, Cushing's syndrome, hyperthyroidism, and pheochromocytoma can complicate the control of diabetes mellitus.

**Hepatic/Biliary/Pancreas**

The effect of hepatic impairment on the pharmacokinetics of TOUJEO has not been studied. Frequent glucose monitoring and dose adjustment may be necessary for TOUJEO in patients with hepatic impairment (See WARNINGS AND PRECAUTIONS).

**Immune**

***Lipodystrophy and lipoatrophy***

As with any insulin therapy, lipodystrophy may occur at the injection site and delay insulin absorption.

Rarely, SC administration of insulin products can result in lipoatrophy (depression in the skin) or lipohypertrophy (enlargement or thickening of tissue). Patients should be advised to consult their doctor if they notice any of these conditions.

***Systemic 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). TOUJEO is contraindicated in patients who have had hypersensitivity reactions to insulin glargine or other of the excipients (see CONTRAINDICATIONS).

***Local Allergy at the injection site***

In TOUJEO clinical studies in adult patients, the incidence of overall injection site reactions was similar in TOUJEO-treated patients (2.5%) and LANTUS-treated patients (2.8%). Most minor reactions to insulins usually resolve in a few days to a few weeks (see CONTRAINDICATIONS and ADVERSE REACTIONS).

Other injection site reactions with insulin therapy include redness, pain, itching at the injection site, hives, swelling and inflammation. Continuous rotation of the injection site within a given

area may help to reduce or prevent these reactions. Most minor reactions to insulins usually resolve in a few days to a few weeks. They may occur if the injection is not properly made (irritants in the skin cleansing agent or poor injection technique) or if the patient is allergic to the insulin or any excipients (See ADVERSE REACTIONS section).

**Antibody Production**

Patients with human insulin antibodies may be hypersensitive to other insulins, with a risk of hypoglycemia and/or cross-reactivity.

Insulin administration including TOUJEO, may cause insulin antibodies to form. As with all insulins, the presence of such anti-insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyperglycemia or hypoglycemia (see ADVERSE REACTIONS, Antibody Production section).

**Intercurrent conditions**

Insulin requirements may be altered during intercurrent conditions such as infection or illness, emotional disturbances or stress.

Intercurrent illness requires intensified metabolic monitoring. In many cases urine tests for ketones are indicated, and often it is necessary to adjust the insulin dose. The insulin requirement is often increased. In patients with Type 1 diabetes, carbohydrate supplies must be maintained even if patients are able to eat only little or no food or are vomiting etc. In patients with Type 1 diabetes insulin, must never be omitted entirely.

**Ophthalmologic**

**Retinopathy**

A marked change in glycemic control may cause temporary visual impairment, due to temporary alteration in the turgidity and refractive index of the lens.

Long-term improved glycemic control decreases the risk of progression of diabetic retinopathy. However, as for all insulin regimens, intensification of insulin therapy with abrupt improvement in glycemic control may be associated with temporary worsening of diabetic retinopathy.

In patients with proliferative retinopathy, particularly if not treated with photocoagulation, severe hypoglycemic episodes may result in transient amaurosis (see ADVERSE REACTIONS, Insulin initiation and intensification of glucose control).

### Renal

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 renal impairment (see WARNINGS AND PRECAUTIONS).

## Special Populations

### Pregnant Women

Risk Summary

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

Human data

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

Animal data

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

### Nursing Women

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.

**Pediatrics (< 18 years of age)**

The safety and effectiveness of TOUJEO have not been established in pediatric patients (under 18 years of age).

**Geriatrics (> 65 years of age)**

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 6 (2.0 %) of the patients with type 1 and 37 (3.0%) of the patients with type 2 diabetes were ≥75 years of age. No overall difference in effectiveness and safety was observed between these patients and younger patients.

In elderly patients with diabetes, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemic reactions.

Hypoglycemia may be difficult to recognize in the elderly (see WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hypoglycemia). In the elderly, progressive deterioration of renal function may lead to steady decrease in insulin requirements. Careful glucose monitoring and dose adjustments of insulin or insulin analogues including TOUJEO may be necessary (see WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic and Renal).

## ADVERSE REACTIONS

### Adverse Drug Reaction Overview

The following adverse reactions were observed during clinical studies conducted with TOUJEO (see CLINICAL TRIALS section) and during clinical experience with LANTUS (insulin glargine 100 U/mL).

### Clinical Trial Adverse Drug Reactions

*Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

### Type 1 and Type 2 diabetes in adults

The frequencies of adverse reactions reported during TOUJEO clinical trials in patients with Type 1 diabetes mellitus and Type 2 diabetes mellitus are listed in Table 1 and Table 2 below.

The most common adverse reactions (regardless of causality) in patients with Type 1 diabetes mellitus are summarized in Table 1.

Table 1 - Adverse reactions in two pooled clinical trials of 26 weeks and 16 weeks duration in adults with Type 1 diabetes (adverse reactions with incidence ≥1%)

| Preferred Term n(%) | TOUJEO (N=304) | LANTUS (N=304) |
|---|---|---|
| Nasopharyngitis | 39 (12.8%) | 33 (10.9%) |
| Upper respiratory tract infection | 29 (9.5%) | 23 (7.6%) |
| Headache | 14 (4.6%) | 14 (4.6%) |
| Influenza | 10 (3.3%) | 12 (3.9%) |
| Back pain | 9 (3.0%) | 7 (2.3%) |
| Hypoglycemia | 9 (3.0%) | 12 (3.9%) |
| Sinusitis | 9 (3.0%) | 5 (1.6%) |
| Nausea | 8 (2.6%) | 5 (1.6%) |
| Diarrhea | 7 (2.3%) | 6 (2.0%) |
| Fatigue | 7 (2.3%) | 7 (2.3%) |
| Bronchitis | 6 (2.0%) | 6 (2.0%) |
| Weight increased | 6 (2.0%) | 2 (0.7%) |
| Arthralgia | 5 (1.6%) | 3 (1.0%) |
| Gastroenteritis | 5 (1.6%) | 8 (2.6%) |
| Injection site bruising | 5 (1.6%) | 2 (0.7%) |
| Nasal congestion | 5 (1.6%) | 4 (1.3%) |
| Oedema peripheral | 5 (1.6%) | 5 (1.6%) |
| Pyrexia | 5 (1.6%) | 2 (0.7%) |
| Sinus congestion | 5 (1.6%) | 2 (0.7%) |
| Viral infection | 5 (1.6%) | 1 (0.3%) |
| Vomiting | 5 (1.6%) | 12 (3.9%) |
| Cough | 4 (1.3%) | 4 (1.3%) |
| Gastrointestinal viral infection | 4 (1.3%) | 0 |
| Malaise | 4 (1.3%) | 2 (0.7%) |
| Oropharyngeal pain | 4 (1.3%) | 7 (2.3%) |
| Urinary tract infection | 4 (1.3%) | 4 (1.3%) |
| Pharyngitis streptococcal | 3 (1.0%) | 5 (1.6%) |

The most common adverse reactions (regardless of causality) in patients with Type 2 diabetes mellitus are summarized in Table 2.

Table 2 - Adverse reactions in three pooled clinical trials of 26 weeks duration in adults with Type 2 diabetes (adverse reactions with incidence ≥1%)

| Preferred Term n(%) | TOUJEO (N=1242) | LANTUS (N=1246) |
|---|---|---|
| Nasopharyngitis | 88 (7.1%) | 72 (5.8%) |
| Upper respiratory tract infection | 71 (5.7%) | 67 (5.4%) |
| Headache | 61 (4.9%) | 47 (3.8%) |
| Diarrhea | 47 (3.8%) | 38 (3.0%) |
| Bronchitis | 41 (3.3%) | 42 (3.4%) |

| Preferred Term n(%) | TOUJEO (N=1242) | LANTUS (N=1246) |
|---|---|---|
| Nausea | 40 (3.2%) | 27 (2.2%) |
| Oedema peripheral | 34 (2.7%) | 36 (2.9%) |
| Back pain | 30 (2.4%) | 37 (3.0%) |
| Influenza | 30 (2.4%) | 33 (2.6%) |
| Hypertension | 29 (2.3%) | 24 (1.9%) |
| Urinary tract infection | 29 (2.3%) | 24 (1.9%) |
| Arthralgia | 26 (2.1%) | 33 (2.6%) |
| Fatigue | 26 (2.1%) | 20 (1.6%) |
| Sinusitis | 26 (2.1%) | 31 (2.5%) |
| Gastroenteritis viral | 22 (1.8%) | 13 (1.0%) |
| Vomiting | 21 (1.7%) | 24 (1.9%) |
| Dizziness | 20 (1.6%) | 19 (1.5%) |
| Cough | 19 (1.5%) | 25 (2.0%) |
| Pain in extremity | 19 (1.5%) | 19 (1.5%) |
| Anxiety | 18 (1.4%) | 5 (0.4%) |
| Muscle spasms | 18 (1.4%) | 15 (1.2%) |
| Gastroenteritis | 17 (1.4%) | 17 (1.4%) |
| Depression | 16 (1.3%) | 17 (1.4%) |
| Oropharyngeal pain | 16 (1.3%) | 12 (1.0%) |
| Insomnia | 15 (1.2%) | 14 (1.1%) |
| Constipation | 14 (1.1%) | 8 (0.6%) |
| Musculoskeletal pain | 14 (1.1%) | 13 (1.0%) |
| Dyspepsia | 13 (1.0%) | 9 (0.7%) |
| Weight increased | 13 (1.0%) | 7 (0.6%) |

**Less Common Clinical Trial Adverse Drug Reactions (<1%)**

**Type 1 diabetes**

**Eye disorders:** Eye irritation

**Gastrointestinal disorders:** Dry mouth, impaired gastric emptying

**General disorders and administration site conditions:** Fatigue, injection site bruising, injection site edema, injection site pain

**Infections and infestations:** Vulvovaginal mycotic infection

**Injury, poisoning and procedural complications:** Contusion, overdose, investigations, weight increased

**Metabolism and nutrition disorders:** Dehydration, increased appetite

**Nervous system disorders:** Headache, hypoesthesia, paresthesia, tremor

**Psychiatric disorders:** Insomnia, sleep disorder

**Skin and subcutaneous tissue disorders:** Lipohypertrophy, rash

**Type 2 diabetes**

**Blood and lymphatic system disorders:** Lymphadenopathy

**Cardiac disorders:** Palpitations

**Ear and labyrinth disorders:** Tinnitus

**Eye disorders:** Vision blurred, visual impairment

**Gastrointestinal disorders:** Abdominal discomfort, abdominal distension, abdominal pain lower, constipation, nausea, vomiting

**General disorders and administration site conditions:** Asthenia, fatigue, hunger, injection site bruising, injection site discomfort, injection site erythema, injection site hemorrhage, injection site inflammation, injection site irritation, injection site pain, injection site pruritus, injection site reaction, edema peripheral

**Infections and infestations:** Acute sinusitis, gastroenteritis viral

**Injury, poisoning and procedural complications:** Accidental overdose, injection related reaction, intentional overdose, overdose, toxicity to various agents

**Investigations:** Alanine aminotransferase increased, blood glucose decreased, blood glucose fluctuation, weight increased

**Metabolism and nutrition disorders:** Abnormal weight gain, hyperglycemia, increased appetite

**Musculoskeletal and connective tissue disorders:** Arthralgia, muscle spasms, myalgia

**Nervous system disorders:** Dizziness, dizziness postural, headache, hypoglycemic unconsciousness, sensory loss, tremor

**Psychiatric disorders:** Insomnia, restlessness

**Renal and urinary disorders:** Dysuria, renal impairment

**Respiratory, thoracic and mediastinal disorders:** Cough, dyspnea

**Skin and subcutaneous tissue disorders:** Alopecia, erythema, hyperhidrosis, night sweats

**Vascular disorders:** Flushing, hypotension

The adverse events most commonly associated with TOUJEO [insulin glargine injection (rDNA origin)] include the following:

Insulin initiation and intensification of glucose control

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

**Immune system disorders**

Allergic reactions (see WARNINGS AND PRECAUTIONS section).

Local Allergy at the injection site

As with any insulin therapy, such reactions include redness, pain, itching, hives, swelling, and inflammation. In TOUJEO clinical studies in adult patients, the incidence of overall **injection site reactions** was similar in TOUJEO-treated patients (2.5%) and LANTUS-treated patients (2.8%). Most minor reactions to insulins usually resolve in a few days to a few weeks.

Reports of injection site pain were similar in both treatment groups (0.8% TOUJEO versus 0.9% LANTUS).

Systemic Allergy

Immediate-type allergic reactions are rare. Such reactions to insulin (including insulin glargine) or the excipients may, for example, be associated with generalized skin reactions, angioedema, bronchospasm, hypotension and anaphylactic shock, and may be life threatening.

Antibodies production (see WARNINGS and PRECAUTIONS).

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

In a 6-month study of type 1 diabetes patients, 79% of patients in both TOUJEO and LANTUS groups were positive for anti-insulin antibodies (AIA) at least once during the study, including 62% for TOUJEO and 54% for LANTUS that were positive at baseline and 49% of patients who developed anti-drug antibody [i.e., anti-insulin glargine antibody (ADA)] for TOUJEO and 57% for LANTUS during the study. Seventy nine percent of the AIA positive patients on TOUJEO and 78% on LANTUS with antibody test at baseline, remained AIA positive at month 6.

In two 6-month studies in type 2 diabetes patients, 52% of patients in both groups were positive for AIA at least once during the study, including 42% for TOUJEO and 38% for LANTUS who were positive at baseline and 25% of patients for TOUJEO and 27% for LANTUS who developed ADA during the study. Seventy eight percent of the AIA positive patients on TOUJEO and 79% on LANTUS 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.

**Metabolism and nutrition disorders**

Hypoglycemia

Hypoglycemia is the most commonly observed adverse reaction in patients using insulin, including TOUJEO (see WARNINGS AND PRECAUTIONS).

In the TOUJEO program, severe hypoglycemia was defined as an event requiring assistance of another person to administer a resuscitative action. Documented symptomatic hypoglycemia was defined as an event with typical symptoms of hypoglycemia accompanied by a self-monitored plasma glucose value equal to or less than 3.9 mmol/L and are reported below.

**Type 1 diabetes** (EDITION IV)

**Severe hypoglycemia**

*Baseline to month 6*
The incidence of severe hypoglycemia in patients with type 1 diabetes receiving TOUJEO and LANTUS as part of a multiple daily injection regimen was 6.6% (n/N=18/274) and 9.5% (n/N=26/275) respectively. The event rate per patient-year in the TOUJEO group was 0.24 events per patient-year and in the LANTUS group 0.34 events per patient-year.

*Baseline to month 12*
The incidence of severe hypoglycemia was 9.1% (n/N=25/274) for TOUJEO and 11.3% (n/N= 31/275) for LANTUS. The event rate per patient-year in the TOUJEO group was 0.37 events per patient-year and in the LANTUS group 0.24 events per patient-year.

**Documented symptomatic hypoglycemia**

*Baseline to month 6*
The incidence of documented symptomatic hypoglycemia for TOUJEO and LANTUS was 85.0% (n/N=233/274) and 83.6% (n/N =233/274). The event rate per patient-year in the TOU-

JEO group was 42.46 events per patient-year and in the LANTUS group 38.93 events per patient-year.

*Baseline to month 12*
The incidence of documented symptomatic hypoglycemia for TOUJEO and LANTUS was 87.6 % (n/N= 240/274) and 86.5 % (n/N =238/275). The event rate per patient-year in the TOUJEO group was 39.09 events per patient-year and in the LANTUS group 35.06 events per patient-year.

**Type 2 diabetes**

**Severe hypoglycemia**

EDITION I (patients with type 2 diabetes, treated with basal insulin in combination with mealtime insulin)

*Baseline to month 6*
The incidence of severe hypoglycemia for TOUJEO was 5% (n/N =20/404) and 5.7% (n/N =23/402) for LANTUS. The event rate per patient-year in the TOUJEO group was 0.27 events per patient-year and in the LANTUS group 0.24 events per patient-year.

*Baseline to month 12*
The incidence of severe hypoglycemia for TOUJEO was 6.7 % (n/N =27 /404) and 7.5 % (n/N =30/402) for LANTUS. The event rate per patient-year in the TOUJEO group was 0.19 events per patient-year and in the LANTUS group 0.14 events per patient-year.

EDITION II and EDITION III (patients treated with basal insulin and anti-hyperglycemic agents)

*Baseline to month 6*
In the 2 studies, the incidence of severe hypoglycemia was 1.0% (n/N =8/838) for TOUJEO and 1.2% (n/N =10/844) for LANTUS. The event rate per patient-year in the TOUJEO group was 0.02 events per patient-year and in the LANTUS group 0.04 events per patient-year.

*Baseline to month 12*
In the 2 studies, the incidence of severe hypoglycemia was 1.6 % (n/N =13/838) for TOUJEO and 1.8 % (n/N =15/844) for LANTUS. The event rate per patient-year in the TOUJEO group was 0.02 events per patient-year and in the LANTUS group 0.03 events per patient-year.

**Documented symptomatic hypoglycemia**

EDITION I (patients with type 2 diabetes, treated with basal insulin in combination with mealtime insulin)

*Baseline to month 6*
The incidence of documented symptomatic was 70.0% (n/N =283/404) and 77.9% (n/N =313/402) for TOUJEO and LANTUS respectively. The event rate per patient-year in the TOUJEO group was 13.48 events per patient-year and in the LANTUS group 14.76 events per patient-year.

*Baseline to month 12*
The incidence of documented symptomatic hypoglycemia was 74.8 % (n/N=302/404) and 82.8 % (n/N= 333/402) for TOUJEO and LANTUS respectively. The event rate per patient-year in the TOUJEO group was 12.07 events per patient-year and in the LANTUS group 11.70 events per patient-year.

EDITION II and EDITION III (patients treated with basal insulin and anti-hyperglycemic agents)

*Baseline to month 6*
In the 2 studies, the incidence of documented symptomatic hypoglycemia was 39.7% (n/N =333/838) for TOUJEO and 46.2% (n/N = 390/844) for LANTUS. The event rate per patient-year was 4.49 events per patient-year and in the LANTUS group 5.91 events per patient-year.

*Baseline to month 12*
In the 2 studies, the incidence of documented symptomatic hypoglycemia was 48.6 % (n/N =407/838) for TOUJEO and 53.3 % (n/N = 450/844) for LANTUS. The event rate per patient-year in the TOUJEO group was 4.20 events per patient-year and in the LANTUS group 4.73 events per patient-year.

Sodium retention and edema

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

**Skin and subcutaneous tissue disorders**

Lipodystrophy
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).

**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). MACE was defined as the composite of CV death, nonfatal myocardial infarction and nonfatal stroke. The incidence of MACE was similar between LANTUS and standard care in ORIGIN [Hazard Ratio (95% CI) for MACE; 1.02 (0.94, 1.11)].

**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 (see PART II, CLINICAL TRIALS, Study results).

## DRUG INTERACTIONS

A number of substances affect glucose metabolism and may require insulin dose adjustment and particularly close monitoring.

**Drug-Drug Interactions**

**Drugs That May Increase the Risk of Hypoglycemia**
The risk of hypoglycemia associated with TOUJEO use may be increased with antidiabetic agents, (ACE) inhibitors, angiotensin II receptor blocking agents, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, pentoxifylline, pramlintide, propoxyphene, salicylates, somatostatin analogs (e.g., octreotide), and sulfonamide antibiotics. Dose adjustment and increased frequency of glucose monitoring may be required when TOUJEO is coadministered with these drugs.

**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, danazol, diuretics, estrogens, glucagon, isonazid, 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.

**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.

**Drugs That May Affect Signs and Symptoms of Hypoglycemia**
The signs and symptoms of hypoglycemia (see WARNINGS AND PRECAUTIONS) may be blunted when beta-blockers, clonidine, guanethidine, and reserpine are co-administered with TOUJEO.

**Other:**

To avoid the risk of developing new or worsening heart failure, the use of TZDs in combination therapy with insulin is not indicated (see WARNINGS AND PRECAUTIONS).

**Drug-Food Interactions**
Interactions with food have not been established.

**Drug-Herb Interactions**
Interactions with herbal products have not been established.

**Drug-Laboratory Interactions**
Interactions with laboratory tests have not been established.

## DOSAGE AND ADMINISTRATION

### Dosing Considerations

#### General

Insulin glargine is a human insulin analogue designed to have low solubility at neutral pH. At pH 4, as in the TOUJEO injection solution, it is completely soluble. After injection into the subcutaneous tissue, the acidic solution is neutralized, leading to formation of a precipitate from which small amounts of insulin glargine are continuously released.

- Inject TOUJEO subcutaneously once a day into the abdominal area, thigh, buttock or deltoid at the same time each day.
- Rotate injection sites within the same region from one injection to the next to reduce the risk of lipodystrophy (see ADVERSE REACTIONS).
- Individualize and titrate the dosage of TOUJEO based on the individual's metabolic needs, blood glucose monitoring results, and glycemic control goal. The dosage of TOUJEO ranges from 1 to 80 units per one injection.
- Dosage adjustments may be needed with changes in physical activity, changes in meal patterns (i.e., macronutrient content or timing of food intake), changes in renal or hepatic func-

tion or during acute illness to minimize the risk of hypoglycemia or hyperglycemia (see WARNINGS AND PRECAUTIONS).

- To minimize the risk of hypoglycemia, do not administer TOUJEO intravenously, intramuscularly or in an insulin pump.
- TOUJEO must not be mixed or diluted with any other insulin products or solutions. Mixing or diluting can change its time/action profile and mixing can cause precipitation.

**Recommended Dose and Dosage Adjustment**

**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-third to one-half of the total daily insulin dose. The remainder of the total daily insulin dose should be given as a short-acting insulin and divided between each daily meal. 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.
- The maximum glucose lowering effect of a dose of TOUJEO may take five days to fully manifest and the first TOUJEO dose may be insufficient to cover metabolic needs in the first 24 hours of use (see CLINICAL PHARMACOLOGY). To minimize risks associated with insufficient insulinization when initiating TOUJEO, monitor glucose daily, titrate TOUJEO per instructions, and adjust co-administered glucose lowering therapies per standard of care.

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).

**Starting Dose in Patients with either Type 1 or Type 2 Diabetes Already on Insulin Therapy**

When switching from a treatment regimen with an intermediate or long-acting insulin to a regimen with TOUJEO, a change of the dose of the basal insulin may be required and the concomitant anti-hyperglycemic treatment may need to be adjusted.

*Switch from LANTUS 100 U/mL to Toujeo*

- Insulin glargine 100 units/mL and TOUJEO are not bioequivalent and are not directly interchangeable.
- When switching from LANTUS (insulin glargine 100 units/mL) to TOUJEO, the starting dose of TOUJEO can be the same as the LANTUS, but a higher daily TOUJEO dose may be needed to achieve target ranges for plasma glucose level.

*Switch from other basal insulins to Toujeo*

- Switching from once-daily basal insulins to once-daily TOUJEO, the starting dose of TOUJEO can be the same as the previous once-daily basal insulin dose.
- Switching from twice-daily basal insulins to once-daily TOUJEO, the recommended initial TOUJEO dose is 80% of the total daily dose of basal insulin that is being discontinued.

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 and ACTION AND CLINICAL PHARMACOLOGY).

*Switch from Toujeo to other basal insulins*

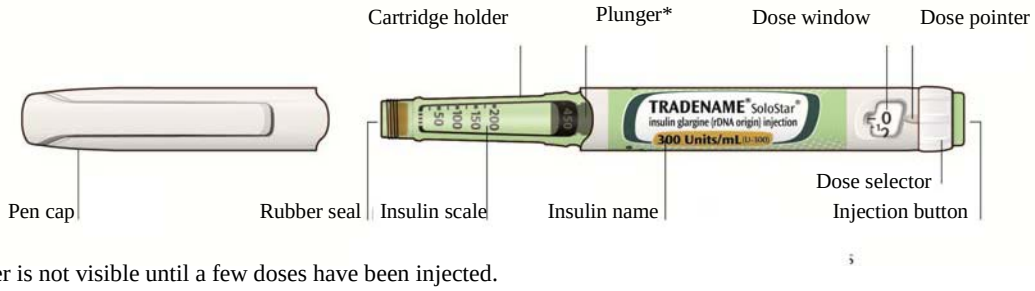
- Medical supervision with close metabolic monitoring is recommended during the switch and in the initial weeks thereafter.
- Please refer to the prescribing information of the medicinal product to which the patient is switching.

**Preparation and handling:**

TOUJEO is a clear solution, not a suspension, as such it does not require resuspension before use.

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, and if it is of water-like consistency. To minimize local irritation at the injection site, it is recommended to allow the insulin to reach room temperature before injection.

**TOUJEO SoloSTAR pre-filled pen**




* The plunger is not visible until a few doses have been injected.

**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.

With TOUJEO SoloSTAR pre-filled pen, a dose of 1–80 units per injection, in steps of 1 unit, can be injected.

- The dose pointer shows the number of TOUJEO units to be injected. The TOUJEO SoloSTAR pre-filled pen has been specifically designed for TOUJEO, therefore **no dose re-calculation is required**.
- **TOUJEO must never be drawn from the cartridge of the pre-filled pen into a syringe,** as regular insulin syringes are not graduated for TOUJEO.
- **Patients must also be instructed to not re-use needles**. A new sterile needle must be attached before each injection. Re-use of needles may increase the risk of blocked needles which may cause underdosing or overdosing. Using a new sterile needle for each injection also minimizes the risk of contamination and infection (See WARNINGS AND PRECAUTIONS and PART III: PATIENT MEDICATION INFORMATION section).
- 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.
- The injection pen is for single patient use only. The pen should not be shared with anyone including other family members. The pen should not be used on multiple patients.
- Refrigerate unused (unopened) TOUJEO SoloSTAR prefilled pens.

**Mixing and diluting**

**TOUJEO must not be mixed with any other insulin products.** Mixing changes the time/action profile of TOUJEO and causes precipitation**.**

**TOUJEO must not be diluted. Diluting can change the time/action profile of TOUJEO.**

## OVERDOSAGE

Excess insulin administration may cause hypoglycemia and hypokalemia [see WARNINGS AND PRECAUTIONS). Mild episodes of hypoglycemia can be treated with oral glucose. Adjustments in drug dosage, meal patterns, or physical activity level may be needed. More severe episodes of hypoglycemia with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycemia may recur after apparent clinical recovery. Hypokalemia must be corrected appropriately.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

## ACTION AND CLINICAL PHARMACOLOGY

### Mode of action

The primary activity of insulin, including insulin glargine, is regulation of glucose metabolism. Insulin and its analogues lower blood glucose levels by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin inhibits lipolysis in the adipocyte, inhibits proteolysis, and enhances protein synthesis.

### Pharmacodynamics

The pharmacodynamics for TOUJEO in patients with type 1 diabetes mellitus was evaluated in euglycemic clamp studies following single (0.4, 0.6, and 0.9 U/kg) or multiple daily doses (0.4, 0.6 U/kg). After the first subcutaneous injection of TOUJEO, the onset of action of TOUJEO develops over 6 hours post-dose. After multiple daily doses, once the steady state is achieved, the action of TOUJEO is constant throughout a 24-hour period. The time course of action of TOUJEO may vary between individuals and within the same individual.

**Comparing to Lantus:**

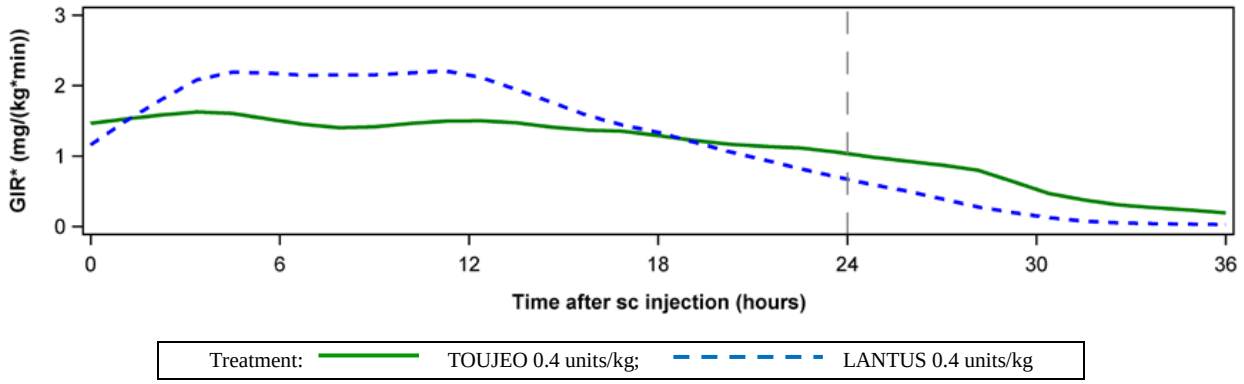
Following single SC dose:

TOUJEO takes more time to achieve steady state effect levels and therefore, after a single dose on a unit-to-unit basis, TOUJEO had a lower maximum ($GIR_{max}$) and 24 hour glucose lowering effect (GIR-$AUC_{0-24}$) compared to LANTUS. The overall glucose lowering effect (GIR-$AUC_{0-36}$) of TOUJEO 0.4 U/kg was only 12% of the glucose lowering effect of an equivalent dose of LANTUS. After a single dose of TOUJEO at 0.6 U/kg, the overall glucose lowering effect was about 33% of the effect of a single 0.4 U/kg dose of LANTUS.

Following once daily multiple SC dose:

The glucose lowering effect of TOUJEO increased with daily administration. The pharmacodynamics profile of TOUJEO and LANTUS after 8 days of once-daily subcutaneous injections of 0.4 U/kg in a euglycemic clamp study in 30 patients with type 1 diabetes is shown in Figure 2. At steady state, the maximum ($GIR_{max}$) and 24 hour glucose lowering effect (GIR-$AUC_{0-24}$) of TOUJEO 0.4 U/kg was approximately 19% and 27% lower, respectively, with a different distribution profile than that of an equivalent dose of LANTUS.

**Figure 1 - Activity Profile in Patients with T1DM in a 36-hour Euglycemic Clamp Study**




*Glucose infusion rate

## Pharmacokinetics

### Absorption and Bioavailability

The pharmacokinetic profiles of TOUJEO was evaluated in euglycemic clamp studies following single 0.4, 0.6, and 0.9 U/kg doses (N = 24) or once daily of 0.4 U/kg and 0.6 U/kg doses for 8 days (N = 30) in patients with type 1 diabetes mellitus. The median time to maximum serum insulin concentration was 12 (8-14), 12 (12-18), and 16 (12-20) hours, respectively. Mean serum insulin concentrations declined to the lower limit of quantitation of 5.02 μU/mL by 16, 28, and beyond 36 hours, respectively.

Steady state insulin concentrations are reached by approximately 4 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 about 17% (90% confidence interval 15 – 21%).

### Metabolism and Elimination

After subcutaneous injection of TOUJEO in healthy subjects and diabetic patients, insulin glargine is metabolized at the carboxyl terminus of the Beta chain with formation of two active metabolites M1 (21A-Gly-insulin) and M2 (21A-Gly-des-30B-Thr-insulin). The mean half-life of M1, the major circulating metabolite of insulin glargine, ranged 21 to 24 hours following TOUJEO administration in patients with type 1 diabetes mellitus.

## Special Populations and Conditions

*Age (Geriatric Population and Pediatric Population), Gender, race:* Effect of age, race, and gender on the pharmacokinetics of TOUJEO has not been evaluated.

*Pediatric patients*: The pharmacokinetics of TOUJEO has not been established in pediatric patients.

*Renal impairment:* The effect of renal impairment on the pharmacokinetics of TOUJEO has not been studied. However, some studies with human insulin have shown increased circulating levels of insulin in patients with renal failure. Careful glucose monitoring is recommended and the insulin dose should be adjusted on an individual basis (see WARNINGS AND PRECAUTIONS, Renal impairment and CLINICAL TRIALS sections).

*Hepatic Impairment*: The effect of hepatic impairment on the pharmacokinetics of TOUJEO has not been studied. However, some studies with human insulin have shown increased circulating levels of insulin in patients with liver failure. Careful glucose monitoring is recommended and the insulin dose should be adjusted on an individual basis (see WARNINGS AND PRECAUTIONS, Hepatic/ Biliary/ Pancreatic impairment and CLINICAL TRIALS sections).

*Pregnancy:* The effect of pregnancy on the pharmacokinetics and pharmacodynamics of TOUJEO has not been studied (see WARNINGS AND PRECAUTIONS, Special Populations).

*Obesity and Smoking:* Effect of BMI and smoking on the pharmacokinetics of TOUJEO has not been evaluated.

## STORAGE AND STABILITY

### TOUJEO™ SoloSTAR®

**Unopened/not in use pre-filled pen**

TOUJEO SoloSTAR pen must be stored between +2°C and +8 °C (in a refrigerator) and protected from light. Do not allow the insulin to freeze, discard if frozen.

Do not put TOUJEO SoloSTAR pen next to the freezer compartment or a freezer pack.

**Opened/in use**

Do not allow the insulin to freeze, discard if frozen.

Opened pre-filled pen must be discarded after 42 days (6 weeks) from the first use. The open pre-filled pen of TOUJEO should be kept away from direct heat and light, at room temperature (15 - 30°C), below 30°C.

These storage conditions are summarized in the following table:

| | Not in-use (unopened) | In-use (opened) |
|---|---|---|
| Pre-filled pen | Until expiration date (Refrigerate) | 42 days (6 weeks) Room temperature only (Do not refrigerate) |

As with all medications and devices, keep out of reach of children.

## SPECIAL HANDLING INSTRUCTIONS

Information to be provided to the Patient

TOUJEO must only be used if the solution is clear and colorless with no particles visible (see DOSAGE AND ADMINISTRATION, Important ~~a~~dministration Instructions). TOUJEO is a clear solution, not a suspension.

TOUJEO can be confused with other insulin types.
Medication errors have been reported in which other insulins, particularly short-acting insulins, have been accidentally administered instead of insulin glargine.

To avoid medication errors between TOUJEO and other insulins, instruct patients to always check the insulin label before each injection.

Patient must be instructed to not re-use needles and to never use a syringe to remove TOUJEO from the SoloSTAR pre-filled pen as regular insulin syringes are not graduated for TOUJEO (see WARNINGS AND PRECAUTIONS, DOSAGE AND ADMINISTRATION and PART III: PATIENT MEDICATION INFORMATION sections).

It is not necessary to shake or rotate the TOUJEO SoloSTAR before use. Patients must be advised that TOUJEO must not be mixed with any other insulin or diluted with any other solution (see WARNINGS AND PRECAUTIONS).

Patients should be instructed on self-management procedures including glucose monitoring, proper injection technique, and hypoglycemia and hyperglycemia management. 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 or skipped meals. The extent of patient participation in his/her diabetes management is variable and is generally determined by the physician.

Insulin treatment requires constant alertness to the possibility of hyper- and hypoglycemia. Patients and their relatives must know what steps to take if hyperglycemia or hypoglycemia occurs or is suspected, and they must know when to inform a physician.

In case of insufficient glucose control or a tendency to hyper- or hypoglycemic episodes, patient's compliance with the prescribed insulin regimen, injection sites and proper injection techniques, the handling of injection devices and all other relevant factors must be reviewed before dose adjustment is considered.

Patients with diabetes should be advised to inform their doctor if they are pregnant or are contemplating pregnancy.

See also PART III: PATIENT MEDICATION INFORMATION. Refer patients to the TOUJEO SoloSTAR Instructions for Use for additional information on use of the pen.

## DOSAGE FORMS, COMPOSITION AND PACKAGING

Active ingredient

The TOUJEO SoloSTAR pen contains a sterile solution of insulin glargine for use as an injection. TOUJEO [insulin glargine injection (rDNA origin)] consists of insulin glargine dissolved in a clear aqueous fluid.

Each milliliter of TOUJEO (insulin glargine injection) contains insulin glargine 300 units. 1 mL contains 10.91 mg insulin glargine, corresponding to 300 U of insulin glargine.

Non-medicinal ingredients

Cartridge excipient (per mL): Each milliliter also contains excipients: 0.19 mg zinc chloride, 2.7 mg m-cresol, 20 mg glycerol 85%; hydrochloric acid and sodium hydroxide for pH adjustment, and water for injection. TOUJEO has a pH of approximately 4.0.

TOUJEO [insulin glargine (rDNA origin)] 300 units per mL (U 300) is available in the following package sizes:

- 1.5-mL TOUJEO SoloSTAR disposable pre-filled pen (450 U/1.5 mL), package of 3 or 5.

## PART II: SCIENTIFIC INFORMATION

## PHARMACEUTICAL INFORMATION

### Drug Substance

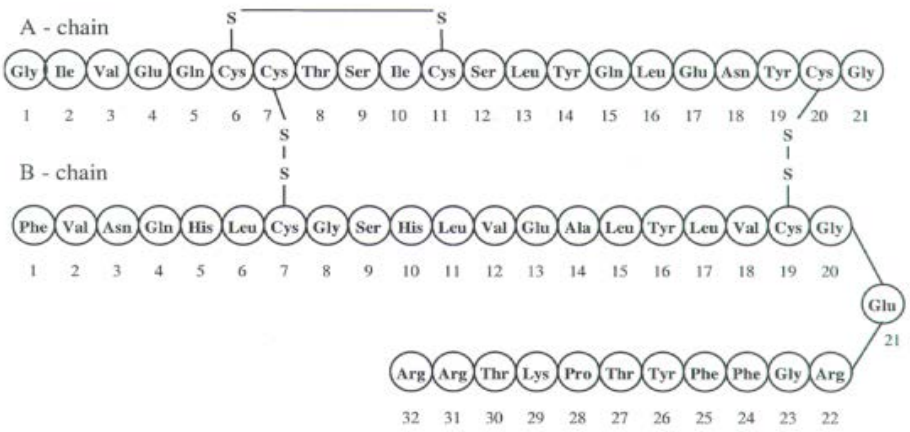
Proper name: insulin glargine (rDNA origin)

Chemical name: $21^{A}$-Gly-$30^{B}$a-L-Arg-$30^{B}$b-L-Arg-human insulin
Recombinant human insulin analogue.

Molecular formula: $C_{267}H_{404}N_{72}O_{78}S_6$

Molecular weight: 6063 daltons

Structural formula:




Physical Form: fine white powder

Solubility: 3 to 7 µg/mL at pH 7
at least 10 mg/mL at pH 5,
greater than 100 mg/mL at pH 2

## CLINICAL TRIALS

### TOUJEO

The safety and efficacy of TOUJEO is based on the assessment of data from four pivotal multinational Phase 3 clinical studies in patients with type 1 diabetes mellitus (EFC12456) and patients with type 2 diabetes mellitus (EFC11628, EFC11629 and EFC12347) (Tables 3 and 5).

### Type 1 Adult Diabetes

### Clinical Study in Adult Patients with Type 1 Diabetes

The efficacy assessment of TOUJEO once daily injection is based on Study EFC12456 (EDITION IV). The purpose of this phase 3, randomized, open-label, 4-arm parallel-group study was to evaluate the effects on glycemic control of TOUJEO in comparison to LANTUS (overall, regardless the injection time) in terms of change of HbA1c from baseline to endpoint (scheduled Month 6) in patients with Type 1 diabetes mellitus (T1DM).

EFC12456 enrolled patients with T1DM who had been on a basal plus mealtime insulin regimen for at least 1 year.

The recommended target range for the fasting (pre-breakfast) SMPG was 4.4 to 7.2 mmol/L. Glycemic targets were adapted for individual patients, if deemed necessary.

Study duration was 6 month with a 6-month safety extension period. Randomization was stratified by HbA1c obtained at the screening visit (<8.0% versus ≥8.0%) and geographical region (Non-Japan; Japan). Overall, 549 patients were randomized to 1 of 4 treatment groups (morning vs. evening).

The primary outcome measure was testing non-inferiority of TOUJEO compared to Lantus in terms of a change in HbA1c from baseline to endpoint (at Month6; non-inferiority margin 0.4%).

The demographic and baseline characteristics were generally comparable between the 2 treatment groups. The mean age of the randomized population was 47.3 years; 55 of 549 (10.0%) patients were ≥65 years. 85.1%-of patients were Caucasian. 8.6% of patients were Asian/Oriental (8.4% of patients were from Japan). 64.1% of the patients were from North America. The mean BMI at baseline was 27.6 $kg/m^2$ in both treatment groups. 27.9% of patients had a BMI ≥30 $kg/m^2$, 2.9% had a BMI ≥40 $kg/m^2$. 12.2% had renal impairment with an estimated glomerular filtration rate (GFR) ≤60 mL/min/1.73 $m^2$.

The mean duration of T1DM was 21 years. Number (%) of patients with prior use of LANTUS (taken within 3 months before randomization) was 220 (80.3%) in the TOUJEO group and 203 (73.8%) in the Lantus group.

The trial design and patient demographics for this study are summarized in Table 3.

**Table 3 - Summary of Trial Design and Patient Demographics for Clinical trial of TOUJEO in T1DM.**

| Study # | Trial design | Dosage, route of administration and duration | Study subjects (n=number) | Mean age (Range) | Gender (M/F) |
|---|---|---|---|---|---|
| EFC12456<br>(Edition IV) | Randomized, open-label, 4-arm parallel-group, multicenter study<br>Active control | TOUJEO (insulin glargine 300 U/mL solution)<br>Once daily SC injection either in the morning or in the evening.<br>Dosage titrated to reach and maintain the target self-measured, fasting (prebreakfast), plasma glucose (SMPG; target range; 4.4-7.2 mmol/L, also taking into account other preprandial SMPG and the presence of hypoglycemia<br><br>Lantus® (insulin glargine 100 U/mL solution)<br>Once daily SC injection either in the morning or in the evening.<br>Dosage titrated to reach and maintain the target self-measured, fasting (prebreakfast), plasma glucose (SMPG; target range; 4.4-7.2 mmol/L), also taking into account other preprandial SMPG and the presence of hypoglycemia<br><br>Duration: 6-month on-treatment period | Total = 549<br><br>TOUJEO morning : 136<br><br>TOUJEO evening : 138<br><br>Lantus morning : 137<br><br>Lantus evening : 138 | 47.3 ± 13.7 (18-86) | 313/236 |

## Study results

At week 26, treatment with TOUJEO provided a mean reduction in HbA1c that met the pre-specified non-inferiority margin of 0.4% (Table 4) in comparison with LANTUS. There were no clinically important differences in glycemic control when TOUJEO was administered once daily on the morning or in the evening. The mean fasting plasma glucose (FPG) at baseline was

10.32 mmol/L for TOUJEO and 11.06 mmol/L for LANTUS. The adjusted mean change from baseline were -0.95 mmol/L and -1.14 mmol/L for TOUJEO and LANTUS respectively. Patients treated with TOUJEO used 17.5% more basal insulin than patients treated with LANTUS. There were no clinically important differences in body weight between treatment groups.

**Table 4 - Type 1 Diabetes mellitus- Adult (TOUJEO plus Mealtime Insulin versus LANTUS plus Mealtime Insulin).**

| | TOUJEO | LANTUS |
|---|---|---|
| Treatment duration | 26 weeks | |
| Treatment in combination with | Fast-acting insulin analogue | |
| Number of subjects treated (mITT[a]) | 273 | 273 |
| $HbA1_C$ | | |
| Baseline mean | 8.13 | 8.12 |
| Adjusted Mean change from baseline | -0.40 | -0.44 |
| Adjusted Mean difference[b] | 0.04 | |
| [95% Confidence Interval] | [-0.098 to 0.185] | |

*a* mITT: Modified intention-to-treat

*b* Treatment difference: (TOUJEO – LANTUS) using a Mixed model for repeated measurements (MMRM) with randomized groups (TOUJEO Morning injection TOUJEO Evening injection, Lantus Morning injection and Lantus Evening injection), randomization strata of screening HbA1c (<8.0, ≥8.0%), randomization strata of geographical region (Non Japan; Japan), visit (Week 12, Month 6) and visit-by-randomized groups interaction as fixed categorical effects as well as baseline HbA1c value and baseline HbA1c-by-visit interaction as continuous fixed covariates.

## Type 2 Adult Diabetes

### General

Within all EDITION trials in Type 2 diabetes mellitus, the dose of TOUJEO or LANTUS was adjusted once weekly, but no more often than every 3 days to achieve fasting self-measured plasma glucose (SMPG) targets of 4.4 to 5.6 mmol/L. Dose was reduced if occurrence of hypoglycemia.

The same dosing schedule was applied for TOUJEO or LANTUS. Changes in the LANTUS or TOUJEO dose were based on the fasting SMPG measurements.

Lifestyle and diet counseling were continued during the study and were consistent with the recommendations of international or local guidelines for patients with Type 2 diabetes mellitus.

Compliance with diet and lifestyle recommendations was discussed with the patients throughout the study, and more specifically in case of insufficient glucose control.

**Study Demographics and design of Trials.**

**Study of TOUJEO in combination with mealtime insulin with or without metformin (EFC11628)**

In a 26-week open-label, controlled study (EFC11628, n=807), adults with Type 2 diabetes who have been treated with basal insulin plus mealtime insulin for at least one year were randomized to once daily treatment in the evening with either TOUJEO or LANTUS. Mealtime insulin analogues with or without metformin were also continued.

The mean age of the randomized study population was 60.0 years; 246/807 (30.5%) patients were ≥65 years. 52.9% of the patients were male. The majority of patients were Caucasian (92.3%). 20.3% of patients had GFR≥90mL/min/1.73m$^2$. At baseline, the mean BMI was 36.6 kg/m$^2$ for both treatment groups, and 86.6% of patients had a BMI ≥30 kg/m$^2$.

**Studies of TOUJEO in combination with non-insulin anti-hyperglycemic drugs (EFC11629 and EFC12347)**

In two 26-week, open-label, controlled studies (n= 1670), adults with Type 2 diabetes mellitus were randomized to TOUJEO or LANTUS once daily in the evening in combination with non-insulin antihyperglycemic agents. At the time of randomization, 811 patients had been treated with basal insulin for more than 6 months (EFC11629) and 878 patients were insulin-naïve (EFC12347).

In EFC11629, the average age was 58.2 years. 190/ 811 (23.4%) patients were ≥65 years, and 22 (2.7%) were ≥75 years of age. The majority of patients were white (93.8%) and 45.9% were male. 32.8% of patients had GFR≥90mL/min/1.73m$^2$. The mean BMI was 34.8 kg/m$^2$.

In EFC12347, the average age was 57.7 years. 226 of 878 (25.7%) patients were ≥65 years and 36 (4.1%) ≥75 years of age. The majority of patients were white (78%) and 57.7% were male. 29% of patients had GFR≥90mL/min/1.73m$^2$. The mean BMI was 33.0 kg/m$^2$.

**Table 5 - Summary of Trial Design and Patient Demographics for Clinical Trials of TOUJEO in T2DM.**

| Study # | Trial design | Dosage, route of administration and duration | Study subjects (n=number) | Mean age (Range) | Gender (M/F) |
|---|---|---|---|---|---|
| EFC11628<br>(Edition I) | Randomized, open-label, 2-arm parallel-group, multicenter trial<br>Active control | TOUJEO (insulin glargine 300 U/mL solution)<br>Once SC daily injection in the evening. Dosage titrated to reach and maintain the target selfmeasured, fasting (pre-breakfast) plasma glucose (SMPG; target range of 4.4 to 5.6 mmol/L without hypoglycemia)<br><br>Lantus® (insulin glargine 100 U/mL solution)<br>Once daily SC injection in the evening. Dosage titrated to reach and maintain the target selfmeasured, fasting (pre-breakfast), plasma glucose (SMPG; target range 4.4-5.6 mmol/L, without hypoglycemia)<br><br>Duration: 6-month on-treatment period | Total = 807<br><br>TOUJEO: 404<br><br>Lantus: 403 | 60 ± 8.6<br>(28-86) | 427/380 |

| Study # | Trial design | Dosage, route of administration and duration | Study subjects (n=number) | Mean age (Range) | Gender (M/F) |
|---|---|---|---|---|---|
| EFC11629<br>(Edition II) | Randomized, open-label, 2-arm parallel-group multicenter trial<br>Active control | TOUJEO (insulin glargine 300 U/mL solution)<br>Once SC daily injection in the evening. Dosage titrated to reach and maintain the target selfmeasured, fasting (pre-breakfast) plasma glucose (SMPG; target range of 4.4 to 5.6 mmol/L without hypoglycemia)<br><br>Lantus® (insulin glargine 100 U/mL solution)<br>Once daily SC injection in the evening. Dosage titrated to reach and maintain the target selfmeasured, fasting (pre-breakfast), plasma glucose (SMPG; target range 4.4-5.6 mmol/L, without hypoglycemia)<br><br>Duration: 6-month on-treatment period | Total = 811<br><br>TOUJEO :<br>404<br><br>Lantus<br>407 | 58.2 ± 9.2<br>(24-84) | 372/439 |

| Study # | Trial design | Dosage, route of administration and duration | Study subjects (n=number) | Mean age (Range) | Gender (M/F) |
|---|---|---|---|---|---|
| EFC12347<br>(Edition III) | Randomized, open-label, 2-arm parallel-group multicenter trial<br>Active control | TOUJEO (insulin glargine 300 U/mL solution)<br>Once SC daily injection in the evening. Dosage titrated to reach and maintain the target selfmeasured, fasting (pre-breakfast) plasma glucose (SMPG; target range of 4.4 to 5.6 mmol/L without hypoglycemia)<br><br>Lantus® (insulin glargine 100 U/mL solution)<br>Once daily SC injection in the evening. Dosage titrated to reach and maintain the target selfmeasured, fasting (pre-breakfast), plasma glucose (SMPG; target range 4.45.6 mmol/L, without hypoglycemia)<br><br>Duration: 6-month on-treatment period | Total = 878<br><br>TOUJEO: 439<br><br>Lantus : 439 | 57.7 ± 10.1 (26-87) | 507/371 |

**Study results**

In the three studies in patients with T2DM, the primary endpoint was the change in HbA1c from baseline to month 6. At month 6, treatment with TOUJEO provided a mean reduction in HbA1c that met the pre-specified non-inferiority margin of 0.4% compared to LANTUS in the three studies (Table 6). The mean fasting plasma glucose at baseline varied from 8.25 -9. 93 mmol/L for TOUJEO and from 7.90-10.21 mmol/L for LANTUS. The adjusted mean change from baseline varied from -1.03 mmol/L to -3.41 mmol/L for TOUJEO and from -1.20 mmol/L to -3.80 mmol/L for LANTUS. At month 6, and depending on the patient population and concomitant therapy, patients treated with TOUJEO used 11%-15% more basal insulin than patients treated with LANTUS. The mean change from baseline for the body weight was 0.93 kg for TOUJEO and 0.90 kg for LANTUS in EDITION I; 0.08 kg for TOUJEO and 0.66 kg for LANTUS in EDITION II and 0.50 kg for TOUJEO and 0.71 kg in EDITION III.

**Table 6 - Type 2 Diabetes mellitus- Adult**

| | EFC11628 (EDITION I) | | EFC11629 (EDITION II) | | EFC12347 (EDITION III) | |
|---|---|---|---|---|---|---|
| Treatment duration | 6 months | | 6 months | | 6 months | |
| Treatment in combination with | Mealtime insulin analog+/- metformin | | Non-insulin anti-hyperglycemic agents | | | |
| | TOUJEO | LANTUS | TOUJEO | LANTUS | TOUJEO | LANTUS |
| Number of patients treated[a] | 404 | 400 | 403 | 405 | 432 | 430 |
| HbA1c | | | | | | |
| Baseline mean | 8.13 | 8.14 | 8.27 | 8.22 | 8.49 | 8.58 |
| Adjusted mean change from baseline | -0.90 | -0.87 | -0.73 | -0.70 | -1.42 | -1.46 |
| Adjusted mean difference[b] | -0.03 | | -0.03 | | 0.04 | |
| [95% Confidence interval] | [-0.144 to 0.083] | | [-0.168 to 0.099] | | [-0.090 to 0.174] | |

[a] m-ITT population: Modified intention-to-treat population

[b] Treatment difference: (TOUJEO – LANTUS) using a MMRM with treatment, randomization strata of screening HbA1c, world region (or randomization strata of geographical region for EFC12347), visit and visit-by-treatment interaction as fixed categorical effects, baseline value and baseline-by-visit interaction as fixed continuous covariates.

Note: For all patients rescued during the 6-month period (EFC11629 and EFC12347), only the post-baseline HbA1c measurements before rescue and during the 6-month on-treatment period are considered in the analysis.

### Antibodies

In studies in type 2 diabetes patients, in both TOUJEO and LANTUS groups, the percentages of patients reporting any TEAEs in the anti-insulin antibody (AIA)-positive groups were: TOUJEO 43%; LANTUS 40%, and in the AIA-negative groups were: TOUJEO 37%; LANTUS 36% (see also ADVERSE REACTIONS).

## DETAILED PHARMACOLOGY

Insulin glargine is metabolized into 2 active metabolites M1 and M2.

Insulin receptor binding: *In vitro* studies indicate that the affinity of insulin glargine and its metabolites M1 and M2 for the human insulin receptor is similar to the one of human insulin.

IGF-1 receptor binding: The affinity of insulin glargine for the human IGF-1 receptor is approximately 5 to 8-fold greater than that of human insulin (but approximately 70 to 80-fold lower than the one of IGF-1), whereas M1 and M2 bind the IGF-1 receptor with lower affinity compared to human insulin.

## TOXICOLOGY

**Acute toxicity:** The acute toxicity of i.v. and s.c. administration of insulin glargine was tested in mice and rats. The LD50 in each species was in the range of greater than or equal to 1000 IU/kg.

**Chronic toxicity:** In repeated subcutaneous dose toxicity studies of insulin glargine in mice, rats, and dogs only expected pharmacodynamic results were observed.

**Carcinogenesis:** The carcinogenic potential of insulin glargine was evaluated in mice and rats at three different dose levels. These two-year carcinogenicity studies were performed in mice and rats.

In mice and rats, standard two-year carcinogenicity studies with insulin glargine were performed at doses up to 0.455 mg/kg, which is for the rat approximately 65 times the recommended human subcutaneous starting dose of 0.2 U/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. Histiocytomas 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.

**Mutagenesis:** Insulin glargine was not mutagenic in tests for detection of gene mutations in bacteria and mammalian cells (Ames- and HGPRT-test) and in tests for detection of chromosomal aberrations (cytogenetics *in vitro* in V79 cells and *in vivo* in Chinese hamsters).

**Reproduction Toxicity and Impairment of Fertility:**

**Teratogenicity**

In an embryotoxicity study in rats, hypoglycemia, but no maternal toxicity, occurred.

In an embryotoxicity study in rabbits, maternal (hypoglycemic shock, intrauterine deaths) and embryo-fetal hypoglycemia-induced toxicity, including single anomalies in the middle- and high-dose groups, were observed. Similar effects were observed with NPH human insulin.

**Impairment of fertility**

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 is approximately 50 times the recommended human subcutaneous starting dose of 0.2 U/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 human insulin.

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**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE**
**PART III: PATIENT MEDICATION INFORMATION**

# TOUJEO™ (Too-Jay-o) SoloSTAR®
## Insulin glargine (rDNA origin)
## 300 units/mL solution for subcutaneous injection in a pre-filled pen (SoloSTAR®)

Read this carefully before you start taking TOUJEO and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about TOUJEO.

**Serious Warnings and Precautions**

- Hypoglycemia is the most common adverse effect of insulin, including TOUJEO.
- Glucose monitoring is recommended for all patients with diabetes.
- Uncorrected hypoglycemic or hyperglycemic reactions can cause loss of consciousness, coma, or death.
- Any change of insulin should be made cautiously and only under medical supervision.
- TOUJEO is not intended for intravenous or intramuscular administration.
- TOUJEO **must not be mixed with any other insulin or diluted with any other solution because it might not work as intended.**
- This insulin product should not be used if it is not water-clear and colorless or if it has formed a deposit of solid particles on the wall of the vial or cartridge.
- Medication errors have been reported in which other insulins, particularly short-acting insulins, have been accidentally administered instead of insulin glargine. Insulin label must always be checked before each injection to avoid medication errors between insulin glargine and other insulins. Do not re-use needles and never use a syringe to remove TOUJEO from the SoloSTAR pre-filled pen as regular insulin syringes are not graduated for TOUJEO.

## What is TOUJEO used for?

- TOUJEO is a long-acting man-made insulin used to control high blood sugar in adults (≥18 years of age) 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 (<18 years of age).

## How does TOUJEO work?

Diabetes is a disease in which the body does not produce or not enough insulin to control the level of blood glucose. TOUJEO is a long-acting human insulin analogue which lowers your blood glucose level.

**What are the ingredients in TOUJEO?**

Medicinal ingredients: The active ingredient in TOUJEO is insulin glargine (rDNA origin).

Non-medicinal ingredients in the 1.5 mL SoloSTAR are: glycerol 85%, m-cresol, water, zinc chloride, hydrochloric acid and sodium hydroxide for pH adjustment.

**TOUJEO comes in the following dosage form:**

TOUJEO is a solution for injection (300 U/mL) and is available in the following package size:

- 1.5 mL SoloSTAR (pre-filled disposable pen), package of 3 or 5.

**Do not use TOUJEO:**

- If you are allergic to this drug or to any ingredient in the formulation or component of the container;
- If you have diabetes ketoacidosis;
- If you are having an episode of low blood sugar (hypoglycemia);
- For intravenous or intramuscular injections.

**To help avoid side effects and ensure proper use, talk to your healthcare professional before you take TOUJEO. Talk about any health conditions or problems you may have, including if you:**

- Have renal or hepatic impairment;
- Have any endocrine disease such as: acromegaly (too much growth hormone), Cushing's syndrome (too much of the adrenal hormones or long-time use of cortisone-type drugs), hyperthyroidism (hyperfunction of the thyroid gland), pheochromocytoma (tumor of the adrenal gland);
- Have any psychiatric disease;
- Have any blood vessels disease, such as narrowing of the heart blood vessels (coronary arteries) or of the blood vessels supplying the brain;
- Have an eye disease called proliferative retinopathy;
- Are currently consuming alcohol;
- Are currently taking any medicine, including other types of insulins;
- 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 planning to have a baby, are pregnant or are nursing a baby. 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.***

**Other warnings you should know about:**

TOUJEO (300 U/mL) and LANTUS (100 U/mL) contain the same active ingredient. Although TOUJEO contains the same active substance as insulin glargine 100 U/mL (LANTUS), these drugs are not interchangeable. The switch from one insulin therapy to another requires medical prescription, medical supervision and blood glucose monitoring. Please, consult your doctor for further information.

Concomitant oral antidiabetic treatment may need to be adjusted.

**High blood sugar (hyperglycemia) or Low blood sugar (hypoglycemia) with Changes in Insulin Regimen.**

**Never Share a TOUJEO SoloSTAR pen Between Patients.**

**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.

**Edema**, particularly if previously poor metabolic control is improved by intensified insulin therapy.

**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.

The combination of Insulin, including TOUJEO, with a TZD is not indicated for the treatment of Type 2 Diabetes Mellitus.

Hypokalemia (low potassium) is a possible side effect with all insulins. You might be more at risk if you are using potassium lowering drugs or losing potassium through other means (e.g. diarrhea). Symptoms of hypokalemia may include: Fatigue, muscle weakness or spasms, constipation, tingling or numbness, feeling of skipped heart beats or palpitations.

If you have diabetic retinopathy (condition affecting the retina of the eye) and you have a marked change in blood glucose levels, the retinopathy may temporary get worse. Ask your doctor about this.

Accidental mix-ups between insulin glargine and other insulins, particularly short-acting insulins, have been reported. To avoid medication errors between insulin glargine and other insulins, check your insulin labels before every injection.

**Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.**

**The following may interact with TOUJEO:**

Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines.

Some medicines can change your blood sugar level. This may mean your insulin dose has to change. So, before taking a medicine ask your doctor if it will affect your blood sugar and what action, if any, you need to take. You also need to be careful when you stop taking a medicine.

Your blood sugar level may fall (hypoglycemia) if you take:

- any other medicine to treat diabetes;
- medicines used to treat high blood pressure and/or heart problems, such as: angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blocking (ARB) agents, disopyramide;
- sulfonamide antibiotics;
- fibrates (medicines used for lowering high levels of blood fats);
- monoamine oxidase inhibitors (MAOIs) (medicines used to treat depression);
- medicines used to relieve pain and lower fever, such as pentoxifylline, propoxyphene and salicylates (such as acetylsalicylic acid);
- somatostatin analogs, such as octreotide.

Your blood sugar level may rise (hyperglycemia) if you take:

- medicines used to treat mental health problems, such as: olanzapine, clozapine;
- hormones, such as: estrogens and/or progesterone (alone or as contraceptive pills), somatotropin, thyroid hormones, glucagon;
- corticosteroids, such as cortisone;
- danazol (a medicine used to treat endometriosis);

- protease inhibitors (used to treat HIV injection);
- diuretics (also called water pills), used to treat high blood pressure or fluid retention;
- isoniazid (used to treat tuberculosis);
- some medicines used to treat asthma, such as albuterol, epinephrine, terbutaline.

Your blood sugar level may either rise or fall if you take:

- high blood pressure medicines, such as: beta-blockers or clonidine;
- some medicines used to treat mental health problems, such as: lithium salts;
- alcohol;
- a medicine used to treat some parasitic infections, called pentamidine. This may cause too low blood sugar which is sometimes followed by too high blood sugar.

Some medicines may make harder to recognize the warning signs of your blood sugar being too low (hypoglycemia). Such medicines include: beta-blockers medicines, clonidine, guanethidine, or reserpine.

Do not use insulin together with medicines used to treat type 2 diabetes belonging to a class called Thiazolidinediones (TZDs). The use of these medicines together may increase your risk of developing heart failure.

**How to take 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 to. Your healthcare provider should tell you how much TOUJEO to use and when to use it.

- 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;
- TOUJEO is injected under your skin (subcutaneously);
- Change (rotate) your injection sites within the area you chose with each dose;
- **Do not** use the exact spot for each injection;
- **Do not** use TOUJEO in an insulin pump or inject TOUJEO into your vein (intravenously);
- **Do not** mix TOUJEO with any other type of insulin or liquid medicine;
- **Keep TOUJEO and all medicines out of the reach of children.**

TOUJEO is a clear solution and looks like some short-acting insulins. Always check for the name of the insulin on your carton and your TOUJEO SoloSTAR pen label when you pick it up from the pharmacy to make sure it is the same as what your doctor recommended.

**CAREFULLY FOLLOW THE DIRECTIONS SUPPLIED BY YOUR HEALTH PROFESSIONAL ON THE CORRECT USE OF YOUR TOUJEO SoloSTAR PEN TO:**

- **HELP AVOID CONTAMINATION AND POSSIBLE INFECTION**
- **OBTAIN AN ACCURATE DOSE**

× The injection pen is for single patient use. Do not share it with anyone including other family members. Do not use on multiple patients.
×Never use your pen if it is damaged or if you are not sure that it is working properly.
✓Always perform a safety test.
✓Always carry a spare pen and spare needles in case they got lost or stop working.

The dose counter of the pen shows the number of units of TOUJEO to be injected. **No dose recalculation is required.** The TOUJEO pen delivers doses of 1-80 units per injection, in steps of 1 unit.

As with all insulins, if patients are blind or have poor eyesight and cannot read the dose counter on the pen, they should get help from a person with good eyesight who is trained to use the insulin device.

**Never use a syringe to remove TOUJEO from the pen** as regular insulin syringes are not graduated for TOUJEO.

**Do not re-use the needle.** A new sterile needle must be attached before each injection. Re-use of needles may increase the risk of blocked needles which may cause inaccurate dose delivery. Using a new sterile needle for each injection also minimizes the risk of contamination and infection.

Carefully read the "TOUJEO SoloSTAR pre-filled pen Instructions for Use" included in the package and use the pen as described. If you do not follow all of these instructions, you may get too much or too little insulin.

**Preparing the Dose**

1. **Take the new pen out of the fridge at least 1 hour before you inject.** Make sure the insulin is at room temperature to minimize local irritation at the injection site, cold insulin is more painful to inject.
2. **Check the name and expiration date on the label of your pen.** To avoid medication errors between TOUJEO and other insulins, Check the label on your TOUJEO SoloSTAR pen to make sure you have the correct insulin before every injection. Never use your pen after the expiration date.
3. **Check that the insulin is clear.** TOUJEO should be a clear and colorless solution with no visible particles. Do not use the pen if you notice anything unusual in the appearance of the solution.
4. **Wash your hands**.
5. **It is not necessary to shake or rotate the TOUJEO SoloSTAR pen before use.**

6. **Always attach a new needle.** Follow the TOUJEO SoloSTAR Instructions for Use for attaching and changing the needle.
7. **Pull off the protective cap and set it aside for later.**
8. **Do a safety test.** Always do a safety test before each injection to ensure your pen and needle are working correctly and to make sure that you get the correct insulin dose.
    - You may see air bubbles in the insulin – this is normal, they will not harm you.
9. **Select the correct dose.** Follow the steps included in your TOUJEO SoloSTAR Instructions for Use to ensure the correct dose of TOUJEO is selected.
    - Never select a dose or press the injection button without a needle attached – this may damage your pen.
10. **Choose a place to inject – upper arms, stomach, buttock or thighs.** There is no relevant difference in absorption of TOUJEO between your abdominal, thigh, buttock or upper arm subcutaneous injection areas.
    - Injection sites within an injection area (abdomen, thigh, buttock or upper arm) MUST be rotated from one injection to the next.
11. **Cleanse the skin with alcohol where the injection is to be made.**
12. **Push the needle into your skin as shown by your health provider.** Do not touch the injection button yet.
13. **Place your thumb on the injection button – press all the way in and hold.** Do not press at an angle – your thumb could block the dose selector from turning.
14. **Keep the injection button held in and when you see "0" in the dose window, slowly count to 5.** This will make sure you get your full dose. DO NOT RUB THE AREA.
15. **Remove the needle immediately after each injection**. Follow the steps included in your TOUJEO SoloSTAR Instructions for Use – do not re-use the needle.
    - Always take care when handling needles – this is to prevent injury and cross-infection. Never put the inner needle cap back on.
16. **Dispose of your needle appropriately.** Throw away the used needle in a puncture-resistant container or as instructed by your health provider or local authority.
17. **Put the pen cap back on.** Do not put the pen back in the fridge.

Hypo- or hyperglycemia can result from injecting insulin in the wrong site or incorrectly. Hypoglycemia can result from injection directly into a blood vessel and if not recognized or treated may be followed by hyperglycemia since there was no deposition for long-term absorption.

**Usual dose:**

**Dosage**

- The dosage of TOUJEO should be individualized and determined based on your health professional's advice in accordance with your needs. Your healthcare provider should tell you how much TOUJEO to use and when to use it.
- Use TOUJEO exactly as your healthcare provider tells you to.
- TOUJEO should be used 1 time each day and at the same time each day.
- **Do not** change the amount of TOUJEO you use unless your healthcare provider tells you to.
- **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.
- **Check your blood sugar levels.** Ask your healthcare provider what your blood sugar should be and when you should check your blood sugar levels.

**Overdose:**
If you **have injected too much TOUJEO**, your blood sugar level may become too low (hypoglycemia). Check your blood sugar frequently. **If your blood sugar gets too low, take action to increase your blood sugar level straight away. See advice "What to do if you experience hypoglycemia?" below.**

| |
|---|
| If you think you have taken too much TOUJEO, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms. |

**Missed Dose:**

If you **have missed a dose of TOUJEO** or if you **have not injected enough insulin,** your blood sugar level may become too high (hyperglycemia). Check your blood sugar frequently. For information on the treatment of hyperglycemia, see "What to do if you experience hyperglycemia" below.

Do not take a double dose to make up for a forgotten dose.

**What are possible side effects from using TOUJEO?**

These are not all the possible side effects you may feel when taking TOUJEO. If you experience any side effects not listed here, contact your healthcare professional. Please also see Warnings and Precautions.

The following side effects may be observed while taking TOUJEO:

- Common (may affect up to 1 in 10 people)
    - hypoglycemia (see also Hypoglycemia section below);
- Rare (may affect up to 1 in 1,000 people)
    - hyperglycemia (see also Hyperglycemia section below);
    - skin changes and reactions at the injection site (see also Injection site reactions section below);
    - allergic reactions (see also Allergic reactions section below);
    - swelling in the calves and ankles (due to built-up of water in the body);
    - vision changes.

Weight gain has occurred with some insulin therapies including TOUJEO.

**Hypoglycemia (low blood sugar level)**

Hypoglycemia (too little glucose in the blood) is one of the most frequent adverse events experienced by insulin users. It can be brought on by situations such as:

- intercurrent conditions (illness, stress, or emotional disturbances);
- accidental injection of an increased insulin dose;
- malfunction and/or misuse of medical devices;
- too-low food intake, or skipped meals;
- an increase in exercise;
- a new insulin type or schedule;
- some new medications, including prescriptions, over-the counter medication, herbs, vitamins and street drugs.

Symptoms of mild to moderate hypoglycemia may occur suddenly and can include:

- abnormal behavior (anxiety, irritability, restlessness, trouble concentrating, personality changes, mood changes, confusion or nervousness);
- fatigue;
- tingling in your hands, feet, lips, or tongue;
- tremor (shaking);
- unsteady gait (walking);
- dizziness, light-headedness, or drowsiness;
- headache;
- blurred vision;
- slurred speech;
- palpitations (rapid heartbeat);
- cold sweat;
- pale skin;
- nightmares or trouble sleeping;

- nausea;
- hunger.

Mild to moderate hypoglycemia may be treated by consuming foods or drinks that contain sugar. Patients should always carry a quick source of sugar, such as candy, juice or glucose tablets, prominently labelled for rescuers. Contact your health-professional about appropriate proportions of carbohydrates.

Signs of severe hypoglycemia can include:
- disorientation;
- convulsions;
- loss of consciousness, coma;
- seizures.

Severe hypoglycemia may require the assistance of another person. Patients who are unable to take sugar orally or who are unconscious may require an injection of glucagon or should be treated with intravenous administration of glucose by medical personnel. Without immediate medical help, serious reactions, even death, may occur.

**The early warning symptoms of hypoglycemia may be changed, less pronounced, or even absent**, for example, in patients whose sugar levels are markedly improved, elderly patients, patients with diabetic nerve disease, patients with a long history of diabetes or patients receiving treatment with certain other drugs. Such situations may result in severe hypoglycemia (and possibly loss of consciousness) before a patient exhibits any symptoms.

Some people may not recognize when their blood sugar drops too low. Often the first sign of this is confusion of loss of consciousness. Educational and behavioural programs, including blood glucose awareness training, may help improve your ability to detect hypoglycemia and reduce the frequency of severe hypoglycemia.

Without recognition of early warning symptoms, you may not be able to take steps to avoid more serious hypoglycemia. Be alert for all of the various types of symptoms that may indicate hypoglycemia. Patients who experience hypoglycemia without early warning symptoms should monitor their blood glucose frequently, especially prior to activities such as driving a car or use mechanical equipment. If the blood glucose is below your normal fasting glucose, you should consider eating or drinking sugar-containing foods to treat your hypoglycemia.

Other people may develop hypoglycemia during the night – this is called nocturnal hypoglycemia. It is fairly common and lasts over 4 hours. Because the person is usually asleep when it occurs, nocturnal hypoglycemia can go undetected, resulting an increased risk of severe hypoglycemia compared to the daytime. To help reduce your risk of asymptomatic nocturnal hypoglycemia, your doctor may ask you to periodically monitor your overnight blood glucose levels.

If you have frequent episodes of hypoglycemia, experience difficulty in recognizing the symptoms, or if your diabetes is getting worse, you should consult your health professional to discuss possible changes in therapy, meal plans, and/or exercise programs to help you avoid hypoglycemia.

**What to do if you experience hypoglycemia?**

- Do not inject insulin. Take about 10 to 20 grams sugar straight away - such as glucose, sugar cubes or a sugary-drink. Do not drink or eat foods that contain artificial sweeteners (such as diet drinks). They do not help treat low blood sugar.
- Eat something (such as bread or pasta) that will raise your blood sugar over a longer time. Ask your doctor or nurse if you are not sure which foods you should eat. With TOUJEO, it may take longer to recover from low blood sugar because it is long-acting.
- Speak to a doctor straight away if you are not able to control the hypoglycemia, or it comes back again.

  **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.

  **What other people should do if you have hypoglycemia**
  Tell your relatives, friends and close colleagues to get medical help straight away if you are not able to swallow or if you pass out (become unconscious).

  You should test your blood sugar straight away after taking glucose to check that you really have hypoglycemia.

**Hyperglycemia**

Hyperglycemia (too much glucose in the blood) may develop if your body has too little insulin.

Hyperglycemia can be brought about by:

- intercurrent conditions (illness, stress, or emotional disturbances);
- not taking your insulin or taking less than recommended by your health professional;
- malfunction and/or misuse of medical devices;
- eating significantly more than your meal plan suggests;
- a new insulin type or schedule;
- some new medications, including prescriptions, over-the counter medication, herbs, vitamins and street drugs.

Symptoms of hyperglycemia include:

- confusion or drowsiness;
- increased thirst;
- decreased appetite, nausea, or vomiting;

- rapid heart rate;
- increased urination and dehydration (too little fluid in your body);
- blurred vision;
- flushed dry skin;
- acetone odour of breath.

Hyperglycemia can be mild or severe. It can **progress to high glucose levels, diabetic ketoacidosis (DKA), and result in unconsciousness and death.**

**What to do if you experience hyperglycemia**

- Test your blood sugar level and your urine for ketones as soon as you notice any of the above signs;
- Contact your doctor straight away if you have severe hyperglycemia or ketoacidosis.

**Diabetic ketoacidosis (DKA)**

The first symptoms of diabetic ketoacidosis usually come on over a period of hours or days. With ketoacidosis, urine tests show large amounts of glucose and acetone.

Symptoms of diabetic ketoacidosis include:

First symptoms:

- Drowsiness;
- flushed face;
- thirst;
- loss of appetite;
- fruity smelling breath;
- rapid, deep breathing;
- abdominal (stomach area) pain.

Severe symptoms:

- heavy breathing;
- rapid pulse.

Prolonged hyperglycemia or diabetic ketoacidosis can lead to:

- nausea;
- vomiting;
- dehydration;
- loss of consciousness;
- death.

**Severe or continuing hyperglycemia or DKA requires prompt evaluation and treatment by your health professional.** TOUJEO should not be used to treat DKA, and the persons treating you should be advised you are taking a long-acting insulin and about your regimen.

**Allergic reactions**

A patient may be allergic to an insulin product **including TOUJEO**. Severe insulin allergies may be life-threatening. If you **have any signs or symptoms of severe allergic reactions,** seek medical help immediately.

Signs of **severe** allergy include:

- a rash all over your body;
- shortness of breath;
- wheezing (trouble breathing);
- a fast pulse;
- sweating;
- low blood pressure.

**Injection site reactions**

Injecting insulin **including TOUJEO** can cause the following reactions on the skin at the injection site:

- a little depression in the skin (lipoatrophy);
- skin thickening (lipohypertrophy);
- redness, pain, swelling, itching, hives, or inflammation at injection site.

You can reduce the chance of getting an injection site reaction if you change the injection site each time. If you have local injection site reactions, contact your health-professional.

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

| **Serious side effects and what to do about them** | | | |
|---|---|---|---|
| Symptom/effect | Talk to your healthcare professional | | Stop taking drug and get immediate medical help |
| | Only if severe | In all cases | |
| **COMMON** (may affect up to 1 in 10 people) | | | |
| Severe hypoglycemia | | | ✓ |
| **RARE** (may affect up to 1 in 1,000 people) | | | |
| Allergic reactions | | | ✓ |

| Serious side effects and what to do about them | | | |
|---|---|---|---|
| Symptom/effect | Talk to your healthcare professional | | Stop taking drug and get immediate medical help |
| | Only if severe | In all cases | |
| Hyperglycemia | | ✓ | |
| Vision changes | | ✓ | |

**Reporting Side Effects**
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
**3 ways to report**:

- Online at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

    Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php).

*NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

**Storage:**

**Before first use**

- Keep new TOUJEO SoloSTAR pens in a fridge, between 2°C to 8°C;
- Do not freeze. If TOUJEO SoloSTAR freezes or overheats, discard it immediately.

**After first use**

- Keep your opened TOUJEO SoloSTAR pen at room temperature (15 - 30°C), below 30°C;
- Never put your pen back in the fridge;
- Never store your pen with the needle attached;
- Store your pen with the cap on;
- Your pen can be stored for up to 42 days (6 weeks) away from direct heat and light, as long as the temperature is not greater than 30°C. If the TOUJEO SoloSTAR overheats or if there is any remaining insulin after 42 days, discard it.

Opened TOUJEO SoloSTAR should not be stored in the freezer and should not be allowed to freeze. If TOUJEO SoloSTAR freezes, discard it.

Do not use a TOUJEO SoloSTAR after the expiration date stamped on the label or if it is cloudy or if you see particles.

As with all medications and devices, keep out of reach and sight of children.

**If you want more information about TOUJEO:**

- Talk to your healthcare professional;
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (http://hc-sc.gc.ca/index-eng.php); sanofi-aventis Canada Inc.'s website (www.sanofi.ca), or by calling 1-888-852-6887.

This document is available in large print format by contacting the sponsor, sanofi-aventis Canada Inc., at: 1-888-852-6887.

The size of the large print can be further enlarged if needed.

sanofi-aventis Canada Inc.
Laval, Québec
H7V 0A3

This leaflet was prepared by sanofi-aventis Canada Inc.

Last revised: May 28, 2015

**Instructions For Use**

# Toujeo™ SoloSTAR®

Read this first

**Toujeo contains 300 U/mL insulin glargine**

- **Never re-use needles.** If you do you might not get your dose or get an overdose as the needle could block.
- **Never use a syringe to remove insulin from your pen** as regular insulin syringes are not graduated for TOUJEO. If you do you will get too much insulin.

## Important information

✗ The injection pen is for single patient use. Do not share it with anyone including other family members. Do not use on multiple patients.
✗ Never use your pen if it is damaged or if you are not sure that it is working properly.
✓ Always perform a safety test
✓ Always carry a spare pen and spare needles in case they got lost or stop working.

**Learn to inject**

- Talk with your healthcare provider about how to inject, before using your pen.
- Ask for help if you have problems handling the pen, for example if you have problems with your sight.
- Read all of these instructions before using your pen. If you do not follow all of these instructions, you may get too much or too little insulin.

**Need help?**

If you have any questions about your Toujeo SoloSTAR pen or about diabetes, ask your healthcare provider, go to **www.sanofi.ca** or call sanofi-aventis at.

**Extra items you will need:**

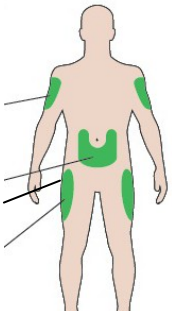
- a new sterile needle (see STEP 2).
- an alcohol swab.
- a puncture resistant container for used needles and pens.

**Places to inject**

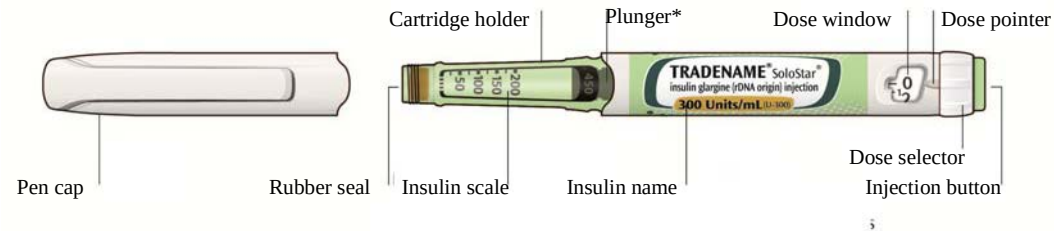
Upper arms

Stomach

Buttock
Thighs



**Get to know your pen**




* You will not see the plunger until you have injected a few doses.

## STEP 1: Check your pen

✓ Take a new pen out of the fridge at least 1 hour before you inject. Make sure the insulin is at room temperature to minimize local irritation at the injection site; cold insulin is more painful to inject.

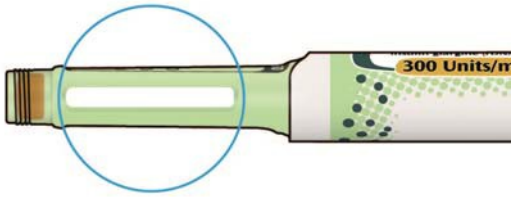
**A Check the name and expiration date on the label of your pen.**

- Check the label on your Toujeo SoloSTAR to make sure you have the correct insulin.
- Never use your pen after the expiration date.

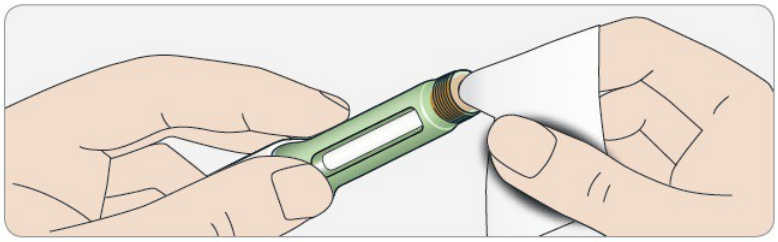
**B Pull off the pen cap.**

**C Check that the insulin is clear.**

- TOUJEO should be a clear and colorless solution with no visible particles. Do not use this SoloSTAR pen if you notice anything unusual in the appearance of the solution.




**D Wipe the rubber seal with an alcohol swab.**



**If you have other injector pens**

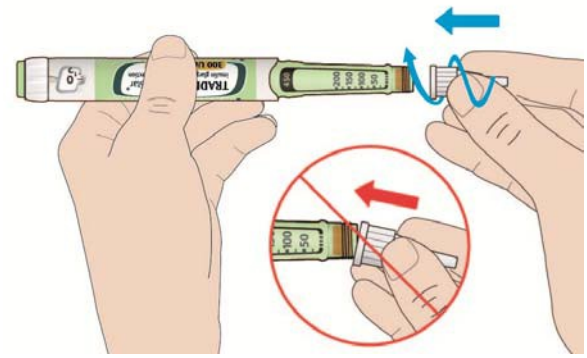
- Making sure you have the correct medication is especially important if you have other injector pens.

## STEP 2: Attach a new needle

- ✓ Always use a new sterile needle for each injection. This helps stop blocked needles, contamination and infection.
- ✓ Always use needles from BD, Ypsomed or Owen Mumford.

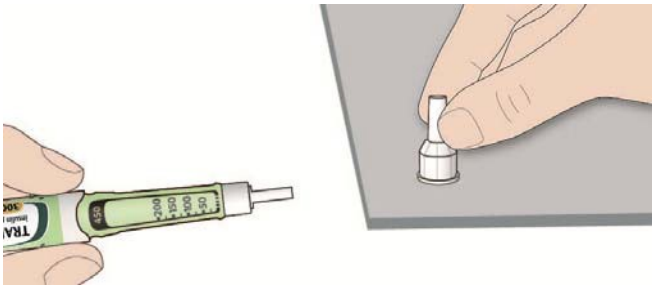
**A Take a new needle and peel off the protective seal.**

**B Keep the needle straight and screw it onto the pen until fixed. Do not overtighten.**

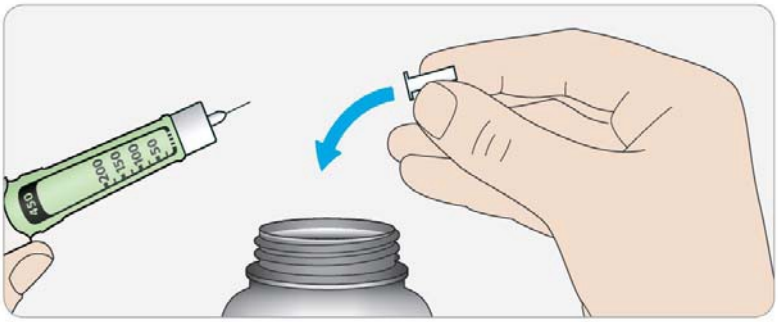


If the needle is not kept straight while you attach it, it can damage the rubber seal and cause leakage, or break the needle.

**C Pull off the outer needle cap and keep it to remove the used needle after injection. Keep this for later.**



**D Pull off the inner needle cap and throw away.**



**Handling needles**

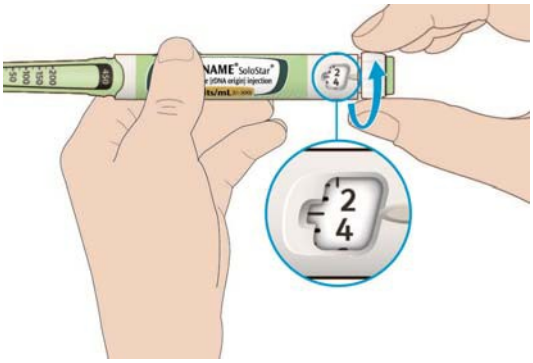
- Take care when handling needles – this is to prevent needle injury and cross-infection.

## STEP 3: Do a safety test

✓ Always do a safety test before each injection – this is to:

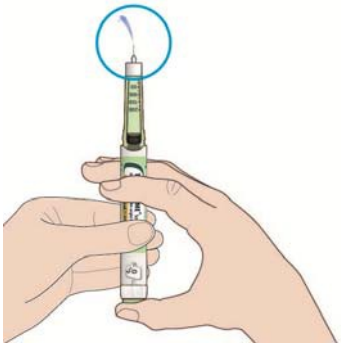
- check your pen and the needle are working properly.
- make sure that you get the correct insulin dose.

**A Select 3 UNITS by turning the dose selector until the dose pointer is at the mark between 2 and 4.**



**B Press the injection button all the way in.**

- When insulin comes out of the needle tip, your pen is working correctly.



**If no insulin appears:**

- You may need to repeat this step up to 3 times before seeing insulin.
- If no insulin comes out after the third time, the needle may be blocked. If this happens:
  - change the needle (see STEP 6 and STEP 2),
  - then repeat the safety test (STEP 3).
- Do not use your pen if there is still no insulin coming out of the needle tip. Use a new pen.
- Never use a syringe to remove insulin from the TOUJEO SoloSTAR pre-filled pen as regular insulin syringes are not graduated for TOUJEO.

**If you see air bubbles**

- You may see air bubbles in the insulin. This is normal, they will not harm you.

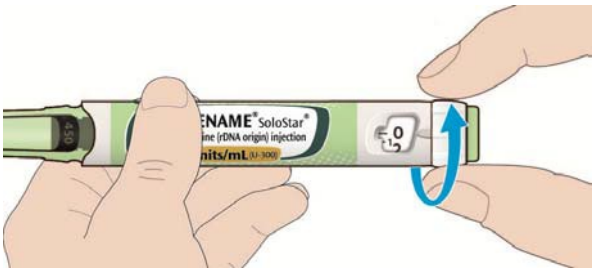
## STEP 4: Select the dose

✗ Never select a dose or press the injection button without a needle attached. This may damage your pen.

**A Make sure a needle is attached and the dose is set to '0'.**


**B Turn the dose selector until the dose pointer lines up with your dose.**

- If you turn past your dose, you can turn back down.
- If there are not enough units left in your pen for your dose, the dose selector will stop at the number of units left.
- If you cannot select your full prescribed dose, split the dose into two injections or use a new pen.



**How to read the dose window**

Even numbers are shown in line with the dose pointer:


**30 units selected**

Odd numbers are shown as a line between even numbers:


**29 units selected**

**Units of insulin in your pen**

- Your pen contains a total of 450 units of insulin. You can select doses from 1 to 80 units in steps of 1 unit. Each pen contains more than one dose.
- You can see roughly how many units of insulin are left by looking at where the plunger is on the insulin scale.

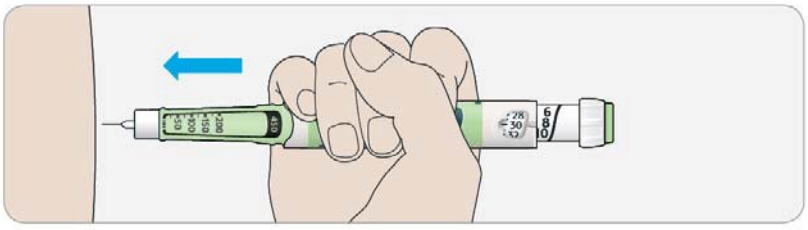
## STEP 5: Inject your dose

If you find it hard to press the injection button in, do not force it as this may break your pen. See the section below for help.

**A Choose a place to inject as shown in the picture above.**

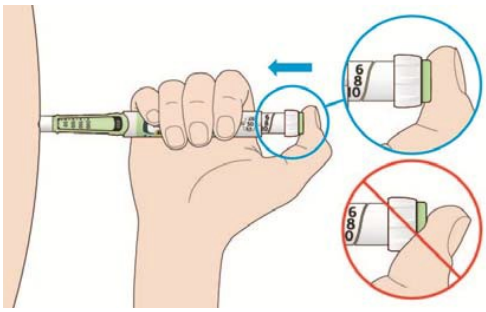
**B Push the needle into your skin as shown by your healthcare provider.**

- Do not touch the injection button yet.



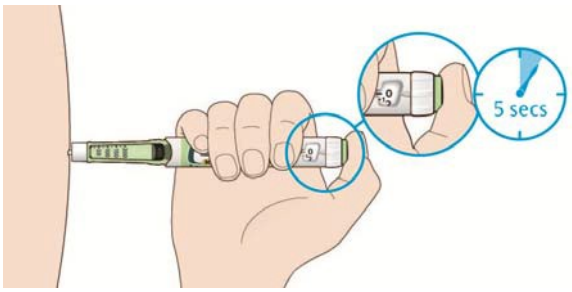
**C Place your thumb on the injection button. Then press all the way in and hold.**

- Do not press at an angle – your thumb could block the dose selector from turning.



**D** **Keep the injection button held in and when you see "0" in the dose window, slowly count to 5.**

- This will make sure you get your full dose.




**E** **After holding and slowly counting to 5, release the injection button. Then remove the needle from your skin.**

**If you find it hard to press the button in:**

- Change the needle (see STEP 6 and STEP 2) then do a safety test (see STEP 3).
- If you still find it hard to press in, get a new pen.
- Never use a syringe to remove insulin from your pen.

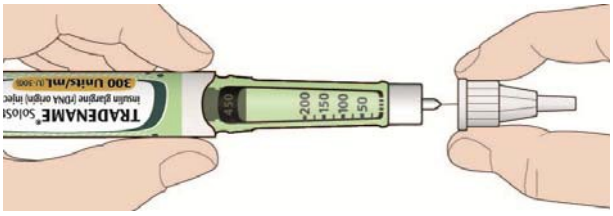
## STEP 6: Remove the needle

✓ Take care when handling needles – this is to prevent needle injury and cross-infection.
✗ Never put the inner needle cap back on.

**A** **Grip the widest part of the outer needle cap. Keep the needle straight and guide it into the outer needle cap.**

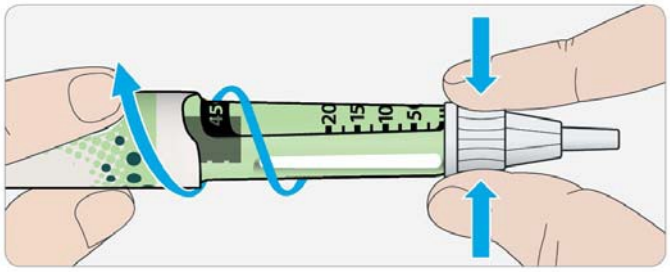
**Then push firmly on.**

- The needle can puncture the cap if it is recapped at an angle.



**B** **Grip and squeeze the widest part of the outer needle cap. Turn your pen several times with your other hand to remove the needle.**

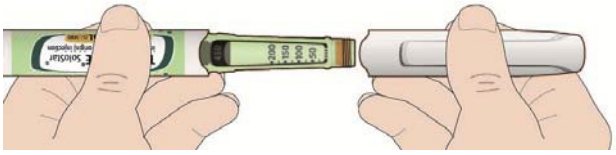
- Try again if the needle does not come off the first time.



**C** **Throw away the used needle in a puncture resistant container, or as told by your healthcare provider or local authority.**

**D** **Put the pen cap back on.**

- Do not put the pen back in the fridge.



## Use by

- Only use your pen for up to 42 days (6 weeks) after its first use.

## How to store your pen

**Before first use**

- Keep new pens in a fridge, at 2°C to 8°C.
- Do not freeze.

**After first use**

- Keep your pen at room temperature (15 and 30°C) and below 30°C.
- Never put your pen back in the fridge.
- Never store your pen with the needle attached.
- Store your pen with the pen cap on.

## How to care for your pen

**Handle your pen with care**

- Do not drop your pen or knock it against hard surfaces.
- If you think that your pen may be damaged, do not try to repair it, use a new one.

**Protect your pen from dust and dirt**

- You can clean the outside of your pen by wiping it with a damp cloth. Do not soak, wash or lubricate your pen – this may damage it.

## Throwing your pen away

- Remove the needle before throwing your pen away.
- Throw away your used pen as told by your healthcare provider or local authority.

Revision date: May 28, 2015

**Distributed by:**
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