For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

This package insert is continually updated: Please read carefully before using a new pack

INSULIN GLARGINE INJECTION I.P. (r-DNA origin)

TOUJEO®

Active Ingredient
Insulin glargine I.P.

Recombinant human insulin analogue (21^{A}-Gly-30^{B}a-L-Arg-30^{B}b-L-Arg-human insulin or or 21^{A}-Gly-31^{B} -32^{B} -Di-Arg -human insulin)

Insulin glargine is produced by recombinant DNA technology utilizing *Escherichia coli* (K12 strain) as the production organism.

Therapeutic or Pharmacological Class
Antidiabetic agent, Long acting insulin analogue
Pharmacotherapeutic group: insulin and analogues, long acting.

Indication:
For the treatment of diabetes mellitus in adults.

Pharmaceutical Form(s)
Solution for injection

Composition
Active ingredient: Insulin glargine IP 300 U/mL
1 ml contains 10.91 mg Insulin glargine IP, corresponding to 300 U of Insulin glargine IP.
Excipients:
Cartridge Excipients (per mL): 90 µg zinc, 2.7 mg m-cresol, 20 mg glycerol 85%; hydrochloric acid and sodium hydroxide for pH adjustment, and water for injection.

The pH of the solution is 4.0.

Dosage And Administration

Insulin glargine Injection IP 300 U/mL is a long-acting recombinant human insulin analogue product.

These units are exclusive to Toujeo® and are not the same as IU or the units used to express the potency of other insulin analogues.

Toujeo® exhibits a more constant and prolonged glucose-lowering profile than LANTUS.

Toujeo® contains the same active ingredient, insulin glargine, as LANTUS.

Toujeo® is given subcutaneously.

Toujeo® is administered once daily, at any time during the day, preferably at the same time every day.

Toujeo® allows for flexibility in the once-daily time of administration. When needed, patients can administer their injections up to 3 hours before or after their usual time of administration.

The desired blood glucose levels as well as the doses and timing of anti-hyperglycemic medications must be determined and adjusted individually.

Dose adjustment may be required, for example, if the patient's weight or life-style changes, if there is a change in the timing of insulin dose or if other circumstances arise that increase susceptibility to hypo- or hyperglycemia (*see Section Warnings/ Precautions*). Any change of insulin dose should be made cautiously and only under medical supervision.

Toujeo® is not the insulin of choice for the treatment of diabetic ketoacidosis. An intravenous, short-acting insulin is the preferred treatment.

Blood glucose monitoring is recommended for all patients with diabetes.

Initiation of Toujeo®
Patients with type 1 diabetes mellitus
Toujeo® is to be used once-daily with meal-time insulin and requires individual dose adjustments.

Patients with type 2 diabetes mellitus
The recommended daily starting dose is 0.2 U/kg once daily followed by individual dosage adjustments.

Change from LANTUS (insulin glargine 100 U/ml) or other basal insulins to Toujeo®

When changing from a treatment regimen with an intermediate-acting or another long-acting insulin product to a regimen with Toujeo®, the amount and timing of short-acting insulin or fast-acting insulin analogue product or of the dose of any anti-hyperglycemic drug may need to be adjusted.

- Changing from once-daily basal insulin products to once-daily Toujeo® can be done unit-to-unit based on the previous basal insulin dose.
- Changing from twice-daily basal insulin products to once-daily Toujeo®, the recommended initial Toujeo® dose is 80% of the total daily dose of the basal insulin that is being discontinued.

A program of close metabolic monitoring under medical supervision is recommended during the change and in the initial weeks thereafter. As with all insulin analogues, this is particularly true for patients which, due to antibodies to human insulin, need high insulin doses and may experience a markedly improved insulin response with insulin glargine.

With improved metabolic control and resultant increase in insulin sensitivity (reduced insulin requirements) further adjustment of the doses of Toujeo® and other insulin products or non-insulin anti-hyperglycaemic drugs in the regimen may become necessary.

Change from Toujeo® to 100 U/ml basal insulins
Medical supervision with close metabolic monitoring is recommended during the change and in the initial weeks thereafter.
Please refer to the prescribing information of the product to which the patient is changing.

Mixing, 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 changes the time/action profile of Toujeo®.

SPECIAL POPULATIONS
Children
The safety and effectiveness of Toujeo® have not been established in paediatric patients (under 18 years of age) (*see Section Pharmacokinetics-Special Population*).

Elderly
Toujeo® can be used in elderly patients. Close glucose monitoring is recommended, and the insulin dose should be adjusted on an individual basis.

In the elderly patients, progressive deterioration of renal function may lead to a steady decrease in insulin requirements (*see Sections Warnings/Precautions, Clinical Efficacy/Clinical studies and Pharmacokinetics-Special Population*).

Renal impairment
Toujeo® can be used in patients with renal impairment. Close glucose monitoring is recommended and the insulin dose should be adjusted on an individual basis.

In patients with renal impairment, insulin requirements may be diminished due to reduced insulin metabolism (*see Sections Warnings/Precautions, Clinical Efficacy/Clinical studies and Pharmacokinetics-Special Population*).

Hepatic impairment
Toujeo® can be used in patients with hepatic impairment. Close glucose monitoring is recommended and the insulin dose should be adjusted on an individual basis.
In patients with hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism (*see Sections Warnings/Precautions, Clinical Efficacy/Clinical studies and Pharmacokinetics-Special Population*).

ADMINISTRATION
Toujeo® is administered by subcutaneous tissue injection.
As with all insulins, injection sites within an injection area (abdomen, thigh or deltoid) must be rotated from one injection to the next to reduce the risk of lipodystrophy and localized cutaneous amyloidosis. Do not inject into areas of lipodystrophy or localized cutaneous amyloidosis *(see Section Warnings/ Precautions and Adverse reactions).*

Toujeo® is not intended for intravenous administration.
The prolonged duration of activity of insulin glargine is dependent on injection into the subcutaneous tissue. Intravenous administration of the usual subcutaneous dose could result in severe hypoglycemia.

Toujeo® is not intended to be administered via an insulin infusion pump.

Toujeo® is a clear solution, not a suspension. As such it does not require resuspension before use.

Toujeo® (Insulin glargine Injection IP 300 U/mL) is available in two disposable pre-filled pens. With Toujeo SoloStar® pre-filled pen, a dose of 1-80 units per injection, in steps of 1 unit, can be injected.

- The dose counter shows the number of units of Toujeo® units to be injected. The Toujeo SoloStar® pre-filled pen has been specifically designed for Toujeo®, therefore **no dose re- conversion** is required .

- Toujeo® must never be drawn from the cartridge of the pre-filled pen into a syringe *(see Sections Warnings/ Precautions)*

- 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. Using a new sterile needle for each injection also minimizes the risk of contamination and infection *(see Sections Warnings/ Precautions).*

CONTRAINDICATIONS
Toujeo® must not be used in patients hypersensitive to insulin glargine or any of the excipients.

WARNINGS/ PRECAUTIONS

General

Insulin therapy generally requires appropriate diabetes self-management skills, including glucose monitoring, proper injection technique, and hypo- and hyperglycemia management. Patients should be instructed on such self-management procedures. Additionally, patients must be instructed in how to handle special situations such as 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 must be instructed to perform continuous rotation of the injection site to reduce the risk of developing lipodystrophy and localized cutaneous amyloidosis. There is a potential risk of delayed insulin absorption and worsened glycemic control following insulin injections at sites with these reactions. A sudden change in the injection site to an unaffected area has been reported to result in hypoglycemia. Blood glucose monitoring is recommended after the change in the injection site, and dose adjustment of antidiabetic medications may be considered *(see Section Adverse Reactions)*.

Hypoglycemia

The time of occurrence of hypoglycemia depends on the action profiles of the insulin products used and may, therefore, change when the treatment regimen is changed.

As with all insulin products, particular caution should be exercised, and intensified blood glucose monitoring is advisable, in patients in whom sequelae of hypoglycemic episodes might be of particular clinical relevance. For example, these could be patients with significant stenoses of the coronary arteries or of the blood vessels supplying the brain (risk of cardiac or cerebral complications of hypoglycemia) as well as patients with proliferative retinopathy, particularly if not treated with photocoagulation (risk of transient amaurosis following hypoglycemia).

However, under certain conditions, as with all insulin products, the warning symptoms of hypoglycemia may be changed, be less pronounced or absent, for example:
- if glycemic control is markedly improved
- if hypoglycemia is developing gradually
- in elderly patients
- where an autonomic neuropathy is present
- in patients with a long history of diabetes
- in patients suffering from a psychiatric illness
- in patients receiving concurrent treatment with certain other drugs (see Interactions)

Such situations may result in severe hypoglycemia (and possibly, loss of consciousness) prior to patient's awareness of hypoglycemia.

The prolonged effect of subcutaneous Toujeo® may delay recovery from hypoglycemia.

If normal or decreased values for glycated haemoglobin are noted, the possibility of recurrent, unrecognized (especially nocturnal) episodes of hypoglycemia must be considered.

Compliance of the patient with the dosage and dietary regimen, correct insulin administration and awareness of hypoglycemia symptoms are essential to reduce the risk of hypoglycemia.

Presence of factors which increase the susceptibility to hypoglycemia requires particularly close monitoring and may necessitate dose adjustment. These factors include:
- change in the injection area,
- increase of insulin sensitivity (e.g. by removal of stress factors),
- unaccustomed, increased or prolonged physical exercise,
- intercurrent illness (e.g. vomiting, diarrhoea),
- inadequate food intake,
- alcohol consumption,
- certain uncompensated endocrine disorders,
- concomitant treatment with certain medications (*see Section Interactions*).

In patients with renal impairment, insulin requirements may be diminished due to reduced insulin metabolism (*see Sections Special Population*, *see Sections Warnings/Precautions, Clinical Efficacy/Clinical studies and Pharmacokinetics-Special Population*).

In the elderly, progressive deterioration of renal function may lead to steady decrease in insulin requirements (*see Sections Special Population*, *see Sections Warnings/Precautions, Clinical Efficacy/Clinical studies and Pharmacokinetics-Special Population*).

In patients with severe hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism (*see Sections Special Population*, *see Sections Warnings/Precautions, Clinical Efficacy/Clinical studies and Pharmacokinetics-Special Population*).

Hypoglycemia can generally be corrected by immediate carbohydrate intake. So that initial corrective action can be taken immediately, patients must carry a minimum of 20 grams of carbohydrates with them at all times.

Intercurrent illness
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.

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 Section Overdose).*

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 into a syringe *(see Sections Administration & Overdose).*

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 underdosing 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 Section Administration).*

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.

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

The following are examples of substances that may increase the blood glucose lowering effect and susceptibility to hypoglycemia: Anti-hyperglycemic products, ACE inhibitors, salicylates, disopyramide; fibrates; fluoxetine, MAO inhibitors; pentoxifylline; propoxyphene; sulfonamide antibiotics.

The following are examples of substances that may reduce the blood glucose lowering effect:
Corticosteroids; danazol; diazoxide; diuretics; sympathomimetic agents (such as epinephrine, salbutamol, terbutaline); glucagon; isoniazid; phenothiazine derivates; somatropin; thyroid hormones; estrogens, progestogens (e.g. in oral contraceptives), protease inhibitors and atypical antipsychotic medications (e.g. olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts and alcohol may either potentiate or weaken the blood glucose lowering effect of insulin. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation may be reduced or absent.

PREGNANCY
There are no randomized controlled clinical studies of the use of Toujeo® in pregnant women.

A large number (more than 1000 retrospective and prospective pregnancy outcomes with LANTUS) of exposed pregnancies from Post Marketing Surveillance indicate no specific adverse effects on pregnancy or on the health of the foetus and newborn child. Furthermore, a meta-analysis of eight observational clinical studies including 331 women using LANTUS and 371 women using insulin NPH was performed to assess the safety of insulin glargine and insulin NPH in gestational or pregestational diabetes. No significant differences in safety-related maternal or neonatal outcomes were seen between insulin glargine and insulin NPH during pregnancy.

Animal studies, with doses of insulin glargine 100 U/mL up to 6 to 40 times the human doses, do not indicate direct harmful effects on the pregnancy.

It is essential for patients with pre-existing or gestational diabetes to maintain good metabolic control throughout pregnancy to prevent adverse outcomes associated with hyperglycemia. Toujeo® can be used during pregnancy, if clinically needed.

Insulin requirements may decrease during the first trimester and generally increase during the second and third trimesters. Immediately after delivery, insulin requirements decline rapidly. Careful monitoring of glucose control is essential in such patients.

Patients with diabetes must inform their doctor if they are pregnant or are contemplating pregnancy.

LACTATION
Lactating women may require adjustments in insulin dose and diet.

DRIVING A VEHICLE OR PERFORMING HAZARDOUS TASKS
The patient's ability to concentrate and react may be impaired as a result of, for example, 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. The advisability of driving should be considered in these circumstances.

ADVERSE REACTIONS

The following CIOMS frequency rating is used, when applicable:
Very common ≥10%; Common ≥1 and <10%; Uncommon ≥0.1 and <1%;
Rare ≥0.01 and <0.1%; Very rare <0.01%, Not known (cannot be estimated from available data).

The following adverse reactions were observed during clinical studies conducted with Toujeo® *(see Section Clinical Efficacy/Clinical Studies)* and during clinical experience with insulin glargine 100 U/mL.

Hypoglycemia
Hypoglycemia, in general the most frequent adverse reaction of insulin therapy, may occur if the insulin dose is too high in relation to the insulin requirement.

As with all insulins, severe hypoglycemic attacks, especially if recurrent, may lead to neurological damage. Prolonged or severe hypoglycemic episodes may be life-threatening.

In many patients, the signs and symptoms of neuroglycopenia are preceded by signs of adrenergic counter-regulation. Generally, the greater and more rapid the decline in blood glucose, the more marked is the phenomenon of counter-regulation and its symptoms.

For hypoglycemia incidences from clinical trials, see table in Section Clinical Efficacy/Clinical Studies.

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

Long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy. However, as for all insulin regimens, intensification of insulin therapy with abrupt improvement in glycaemic 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 Section Clinical Efficacy/Clinical Studies for additional information regarding retinopathy study results.

Skin and subcutaneous tissue disorders
Lipodystrophy, as with any insulin therapy, may occur at the injection site and delay insulin absorption. In clinical studies, in regimens, which included insulin glargine, lipohypertrophy was observed in 1 to 2% of patients, whereas lipoatrophy was uncommon.

Localized cutaneous amyloidosis at the injection site has occurred with insulins. Hyperglycemia has been reported with repeated insulin injections into areas of cutaneous amyloidosis; hypoglycemia has been reported with a sudden change to an unaffected injection site.

Continuous rotation of the injection site within a given area may help to reduce or prevent these reactions *(See Section Warnings/Precautions)*

Allergic reactions
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.

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, and hypotension and anaphylactic shock, and may be life threatening.

Other reactions
Insulin administration may cause **anti- insulin antibodies** to form. In clinical studies comparing Toujeo® and LANTUS, anti-insulin antibodies were observed with similar frequencies in both treatment groups.

As with all insulins, in rare cases, 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 Section Clinical Efficacy/Clinical Studies)*.

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

Pediatric population
The safety profile for patients ≤18 years of age has not been established.

OVERDOSE

SIGNS AND SYMPTOMS
An excess of insulin, relative to food intake, energy expenditure or both, may lead to severe and sometimes prolonged and life-threatening hypoglycemia.

MANAGEMENT
Mild episodes of hypoglycemia can usually be treated with oral carbohydrates. Adjustments in drug dosage, meal patterns, or exercise may be needed.

More severe episodes culminating in 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.

INTERFERENCES WITH LABORATORY AND DIAGNOSTIC TEST
None known

ABUSE AND DEPENDENCE
No risk of abuse or dependence is likely to occur with Toujeo®

PHARMACODYNAMICS

MODE OF ACTION/PHARMACODYNAMIC CHARACTERISTICS
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.

Pharmacodynamic characteristics
Insulin glargine is a human insulin analog that has been designed to have low aqueous solubility at neutral pH. At pH 4, insulin glargine is completely soluble. After injection into the subcutaneous tissue, the acidic solution is neutralized, leading to formation of a precipitate from which small amounts of insulin glargine are continuously released.

In euglycaemic clamp studies in healthy subjects or in patients with type 1 diabetes, the onset of action of subcutaneous LANTUS was slower than with NPH insulin, its effect profile was smooth and peakless, and the duration of its effect was prolonged.

As observed in euglycemic clamp studies in patients with type 1 diabetes, the glucose lowering effect of Toujeo® was more constant and prolonged in comparison with LANTUS after subcutaneous injection.

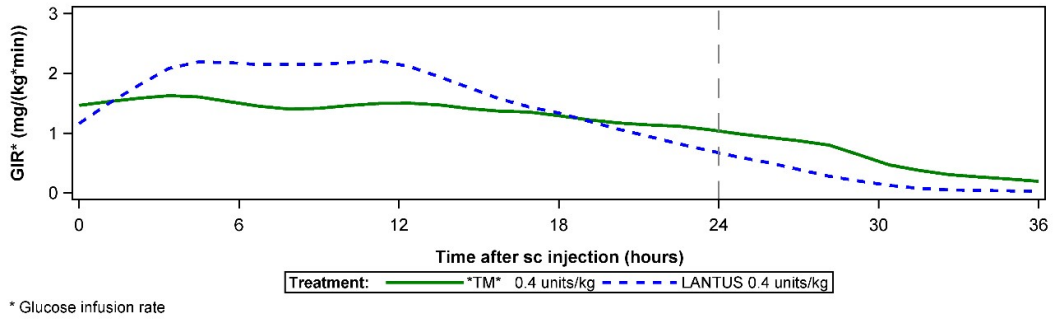
Figure 1 shows results from a cross-over study in 18 patients with type 1 diabetes conducted for a maximum of 36 hours after injection. The effect of Toujeo® was beyond 24 hours (up to 36 hours) at clinically relevant doses.

The prolonged glucose lowering effect of Toujeo® beyond 24 hours allows flexibility in the once-daily time of administration of Toujeo® *(see Sections General and Clinical Efficacy/Clinical Studies)*.

The difference of profile between Toujeo® and LANTUS is attributable to the modification of the release of insulin glargine from the precipitate.

For the same number of insulin glargine units injected, the injected volume of Toujeo® is one third that of LANTUS. This leads to a reduction of the precipitate surface area which provides a more sustained release of insulin glargine from the Toujeo® precipitate compared to LANTUS.

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



Glucose infusion rate: determined as amount of glucose infused to maintain constant plasma glucose levels (hourly mean values). The end of the observation was 36 hours.

In clinical pharmacology study, intravenous use of insulin glargine and human insulin has been shown to be equipotent when given at the same doses.

Insulin glargine is metabolized into 2 active metabolites M1 and M2 *(see Section Elimination)*.

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 slightly lower affinity compared to human insulin.

The total therapeutic insulin concentration (insulin glargine and its metabolites) found in type 1 diabetic patients was markedly lower than what would be required for a half maximal occupation of the IGF-1 receptor and the subsequent activation of the mitogenic-proliferative pathway initiated by the IGF-1 receptor. Physiological concentrations of endogenous IGF-1 may activate the mitogenic-proliferative pathway; however, the therapeutic concentrations found in insulin therapy, including in Toujeo® therapy, are considerably lower than the pharmacological concentrations required to activate the IGF-1 pathway.

CLINICAL EFFICACY/CLINICAL STUDIES

The overall efficacy and safety of Toujeo® once-daily on glycaemic control was compared to that of once-daily LANTUS in open-label, randomized, active-control, parallel studies of up to 26 weeks of duration, including 546 patients with type 1 diabetes mellitus (Table 1) and 2474 patients with type 2 diabetes mellitus (Table 2).

Results from all clinical trials with Toujeo® indicated that reductions in HbA1c from baseline to end of trial were non-inferior to LANTUS.

The proportion of patients who reached the target HbA1c value (below 7%) was similar in both treatment groups.

Plasma glucose reductions at the end of the trial with Toujeo® were similar to LANTUS with a more gradual reduction during the titration period with Toujeo®.

Glycaemic control was similar when Toujeo® was administered once daily in the morning or in the evening.

Flexible/ time of administration (within 3 hours before or after the patient's usual injection time) had no effect on glycaemic control.

Mean change in body weight of less than 1 kg at the end of the 6-month period was observed in Toujeo® treated patients.

Improvement in HbA1c was not affected by, gender, ethnicity, age, diabetes duration (<10 years and ≥10 years), HbA1c value at baseline (<8% or ≥8%) or baseline body mass index (BMI).

Type 1 Adult Diabetes (Table 1**)**. In an open-label, controlled study (Study A), patients with type 1 diabetes (n=546) were randomized to basal-bolus treatment with Toujeo® or LANTUS and treated for 26 weeks. Toujeo® and LANTUS were administered once daily in the morning (time period covering from pre-breakfast until pre-lunch) or in the evening (time period defined as prior to the evening meal until at bedtime). Fast-acting insulin analogue was administered before each meal.

Toujeo® had similar reduction in HbA1c as LANTUS.

Differences in timing of Toujeo® (morning or evening) administration had no effect on HbA1c

Table 1 Summary of Main Therapeutic Outcome of the Clinical Study in Type 1 Diabetes Mellitus

Study A	**Toujeo®**	**LANTUS**
Treatment duration	26 weeks	
Treatment in combination with	Fast-acting insulin analogue	
Number of subjects treated (mITT[a])	273	273
HbA1c[i]		
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]	
FPG[c] mmol/L[ii]		
Baseline mean	10.32	11.06
Adjusted Mean change from baseline	-0.95	-1.14
Adjusted Mean difference[b]	0.19	
[95% Confidence Interval]	[-0.536 to 0.919]	
Basal insulin dose[d] (U/kg)[iii]		
Baseline mean	0.32	0.32
Mean change from baseline	0.15	0.09
Total insulin dose[d] (U/kg)[iv]		
Baseline mean	0.64	0.64
Mean change from baseline	0.19	0.10
Body weight[e] (kg)[v]		
Baseline mean	81.89	81.80
Mean change from baseline	0.46	1.02

a mITT: Modified intention-to-treat

b Treatment difference: Toujeo®- LANTUS

c FPG: Fasting plasma glucose

d Change from baseline to Month 6 (observed case)

e Change from baseline to Last main 6-month on-treatment value

Type 2 Adult Diabetes

- **Studies of Toujeo® in combination with mealtime insulin+/- oral antidiabetic drugs, as background therapy (**Table 2**)**

In a 26-week open-label, controlled study (Study B, n=804), adults with type 2 diabetes were randomized to once daily treatment in the evening with either Toujeo® or LANTUS. Short-acting mealtime insulin analogues with or without metformin were also administered. Toujeo® was associated with a similar reduction in HbA1c as LANTUS.

- **Studies of Toujeo® in combination with non-insulin anti-hyperglycemic drugs, as background therapy (**Table 2**)**

In two open-label, controlled studies (n= 1670), adults with type 2 diabetes mellitus were randomized to Toujeo® or LANTUS once daily for 26 weeks as part of a regimen of combination therapy with non-

insulin anti-hyperglycemic agents. At the time of randomization, 808 patients were treated with basal insulin for more than 6 months (Study C) and 862 patients were insulin-naive (Study D).

Toujeo® was associated with a similar reduction in HbA1c as LANTUS

Table 2 Summary of Main Efficacy Results of the Clinical Study in Type 2 Diabetes Mellitus

	Study B		**Study C**		**Study D**	
Treatment duration	26 weeks		26 weeks		26 weeks	
Treatment in combination with	Mealtime insulin analog+/- metformin		Non-insulin anti-hyperglycemic agents			
	Toujeo®	LANTUS	Toujeo®	LANTUS	* Toujeo®	LANTUS
Number of subjects treated (mITT[a])	404	400	403	405	432	430
HbA1c[vi]						
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]	
FPG[c] (mmol/L)[vii]						
Baseline mean	8.74	8.90	8.25	7.90	9.93	10.21
Adjusted mean change from baseline	-1.63	-1.68	-1.03	-1.20	-3.41	-3.80
Adjusted mean difference[b]	0.05		0.17		0.39	
[95% Confidence interval]	[-0.293 to 0.386]		[-0.180 to 0.519]		[0.100 to 0.676]	
Basal insulin dose (U/kg)						
Baseline mean	0.67	0.67	0.64	0.66	0.19	0.19
Mean change from baseline	0.31	0.22	0.30	0.19	0.43	0.34
Total insulin dose (U/kg)						
Baseline mean	1.19	1.19	-	-	-	-
Mean change from baseline	0.35	0.27	-	-	-	-
Body weight (kg)						
Baseline mean	106.11	106.50	98.73	98.17	95.14	95.65
Mean change from baseline	0.93	0.90	0.08	0.66	0.50	0.71

a m-ITT population: Modified intention-to-treat population
b Treatment difference: - Toujeo® LANTUS
c Fasting plasma glucose
d Change from baseline to Month 6 (observed case)
e Change from baseline to Last main 6-month on-treatment value

The effect on the risk of hypoglycemia of Toujeo® was compared to that of LANTUS in clinical trials in patients with type 1 diabetes mellitus and type 2 diabetes mellitus (Table 3).

In patients with type 2 diabetes, results from clinical trials demonstrated that the incidence of severe and/or confirmed hypoglycemia and documented symptomatic hypoglycemia was lower in patients treated with Toujeo® compared to LANTUS-treated patients.

The superiority of Toujeo®over LANTUS in lowering the risk of severe and/or confirmed nocturnal hypoglycemia was shown in patients previously treated with either oral anti-hyperglycemic agents (23% risk reduction) or mealtime insulin (21% risk reduction) during the period from week 9 to end of the study period compared to LANTUS.

In insulin pre-treated patients as well as insulin naïve patients a reduction of hypoglycemia risk was observed and the reduction was greater during first 8 weeks of treatment (initiation period).

Overall, these effects on hypoglycemia risk were consistently observed whatever the age, gender, race, body mass index (BMI) and duration of diabetes (<10 years and ≥10 years) in Toujeo®-treated patients compared to LANTUS-treated patients.

In patients with type 1 diabetes, the incidence of hypoglycemia was similar in patients treated with Toujeo™ compared to LANTUS-treated patients. However, the incidence of nocturnal hypoglycemia was lower in patients treated with Toujeo® for all categories of hypoglycemia during the initiation period compared to LANTUS-treated patients.

Table 3 Summary of the hypoglycemic episodes of the clinical study in patients with type 1 and type 2 diabetes mellitus.

Diabetic population	**Type 1 diabetes mellitus Previously on basal insulin**		**Type 2 diabetes mellitus Previously on basal insulin**		**Type 2 diabetes mellitus Previously on basal insulin or insulin naive**	
Treatment in combination with	Mealtime insulin analog+/-oral anti-hyperglycemic agents		Mealtime insulin analog+/-metformin		Non-insulin anti-hyperglycemic agents	
	Toujeo®	**LANTUS**	**Toujeo®**	**LANTUS**	**Toujeo®**	**LANTUS**
Incidence (%) of severe[a] hypoglycemia (n/Total N)						
Entire study period[e]	6.6 (18/274)	9.5 (26/275)	5.0 (20/404)	5.7 (23/402)	1.0 (8/838)	1.2 (10/844)
	RR: 0.69 [0.39; 1.23]*		*RR: 0.87 [0.48; 1.55]*		*RR: 0.82 [0.33; 2.00]*	
Patients ≥65	0 (0/29)	11.3 (3/26)	6.3 (8/127)	8.4 (10/119)	1.0 (2/200)	1.9 (4/213)
	Not estimated		*RR: 0.74 [0.30; 1.80]*		*RR: 0.64 [0.16; 2.54]*	
Initiation period	3.3 (9/274)	5.1 (14/275)	1.5 (6/404)	2.7 (11/402)	0.2 (2/838)	0.5 (4/844)
	RR: 0.65 [0.29; 1.45]		*RR: 0.54 [0.20; 1.45]*		*RR: 0.60 [0.15; 2.52]*	
Incidence (%) of severe and/or confirmed[b] hypoglycemia (n/Total N)						
Entire study period	93.1 (255/274)	93.5 (257/275)	81.9 (331/404)	87.8 (353/402)	57.6 (483/838)	64.5 (544/844)
	RR: 1.00 [0.95;1.04]		*RR: 0.93 [0.88; 0.99]*		*RR: 0.89 [0.83; 0.96]*	
Patients ≥65	86.2 (25/29)	92.3 (24/26)	82.7 (105/127)	88.2 (105/119)	64.5 (129/200)	71.4 (152/213)
	RR: 0.91 [0.74;1.13]		*RR: 0.94 [0.85; 1.05]*		*RR: 0.92 [0.80; 1.04]*	
Initiation period	88.3 (242/274)	90.2 (248/275)	64.4 (260/404)	75.1 (302/402)	35.2 (295/838)	44.1 (372/844)
	RR: 0.98 [0.92;1.04]		*RR: 0.86 [0.78;0.94]*		*RR: 0.80 [0.71;0.90]*	

Incidence (%) of severe and/or confirmed nocturnal[d] hypoglycemia (n/Total N)						
Entire study period	68.6 (188/274)	70.2 (193/275)	44.6 (180/404)	57.5 (231/402)	22.9 (192/838)	31.4 (265/844)
	RR: 0.98 [0.88;1.09]		*RR: 0.78 [0.68;0.89]*		*RR: 0.73 [0.62;0.85]*	
Patients ≥65	62.1 (18/29)	61.5 (16/26)	43.3 (55/127)	63.9 (76/119)	24.5 (49/200)	34.3 (73/213)
	RR: 0.99 [0.61;1.61]		*RR: 0.68 [0.53;0.86]*		*RR: 0.72 [0.53;0.98]*	
Initiation period	46.7 (128/274)	57.1 (157/275)	26.2 (106/404)	33.3 (134/402)	10.1 (85/838)	17.1 (144/844)
	RR: 0.82 [0.70;0.96]		*RR: 0.79 [0.64;0.98]*		*RR: 0.59 [0.46;0.76]*	
Incidence (%) of documented symptomatic[c] hypoglycemia (n/Total N)						
Entire study period	85.0 (233/274)	83.6 (230/275)	70.0 (283/404)	77.9 (313/402)	39.7 (333/838)	46.2 (390/844)
	RR: 1.02 [0.95;1.09]		*RR: 0.90 [0.83;0.98]*		*RR: 0.86 [0.77;0.96)*	
Initiation period	78.1 (214/274)	77.1 (212/275)	49.5 (200/404)	61.7 (248/402)	21.2 (178/838)	28.3 (239/844)
	RR: 1.01 [0.93 ; 1.11]		*RR: 0.80 [0.71;0.91]*		*RR: 0.75 [0.64;0.89]*	

[a] Severe hypoglycemia: Episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.

[b] Any severe hypoglycemia and/or hypoglycemia confirmed by plasma glucose value ≤70mg/dl (3.9 mmol/L).

[c] Any event during which typical symptoms of hypoglycemia were accompanied by a measured plasma glucose concentration of ≤70mg/dl (3.9 mmol/L).

[d] Nocturnal hypoglycemia: Episode that occurred between 00:00 and 05:59 hours

[e] 6-month treatment period

* RR estimated risk ratio

- **Flexibility in time of administration** (Table 4)

The safety and efficacy of Toujeo® administered with a fixed or flexible time of administration were also evaluated in 2 randomized, open-label clinical studies for 3 months. Type 2 diabetic patients (n=194) received Toujeo® once daily in the evening, either at the same time of the day (fixed time of administration) or within 3 hours before or after the usual time of administration (flexible time of administration). The flexible time of administration was used at least 2 days per week. The interval of time between 2 injections was as short as 18 to as long as 30 hours.

In both studies, once-daily administration of Toujeo®, with fixed or flexible time of administration had similar effects on HbA1c, FPG and average pre-injection SMPG. In addition, no difference in the incidence of hypoglycemia at any time of the day or nocturnal hypoglycemia was observed when Toujeo® was administered with a fixed or flexible time of administration.

Table 3 Adaptable time of administration in Type 2 Diabetes

Treatment	Toujeo®		Toujeo®	
Treatment in combination with	Mealtime insulin analog+/-metformin[viii ix x xi]		Non-insulin anti-hyperglycaemic agent	
Time of administration	Fixed (every 24 hours)	Flexible (every 24 hours ± 3 hours)	Fixed (every 24 hours)	Flexible(every 24 hours ± 3 hours)
Number of subjects treated (mITT[a] population)	53	55	42	44
HbA_{1c} (%)				
Baseline (mean)	7.17	7.21	7.47	7.41
Adjusted mean change from baseline	0.15	0.21	-0.25	-0.12
Adjusted mean difference *	0.05		0.13	
[95% confidence interval]	[-0.189 to 0.298]		[-0.152 to 0.415]	
FPG[b] (mmol/L)				
Baseline (mean)	6.71	7.33	7.13	7.08
Adjusted mean change from baseline	1.17	1.44	-0.25	-0.46
Adjusted mean difference*	0.27		-0.21	
[95% confidence interval]	[-0.590 to 1.128]		[-1.200 to 0.784]	
Pre-injection SMPG[c] (mmol/L)				
Baseline (mean)	8.51	8.60	10.53	9.98
Adjusted mean change from baseline	-0.45	-0.06	-1.33	-1.10
Adjusted mean difference*	0.39		0.23	
[95% confidence interval]	[-0.241 to 1.016]		[-0.576 to 1.039]	
Incidence (%) of any hypoglycemia[d] (n/Total N)				
At any time of the day	66.0 (33/53)	57.1 (32/56)	41.9 (18/43)	36.4 (16/44)
Nocturnal[e] hypoglycemia	22.6 (12/53)	26.8 (15/56)	23.3 (10/43)	15.9 (7/44)

* Treatment difference Toujeo®flexible versus fixed time of administration

a m-ITT: modified intention- to-treat

b FPG: Fasting plasma glucose

c Average Pre-injection SMPG: Self-monitored plasma Glucose was the plasma glucose measured by the patients within 30 minutes prior to injection of the basal insulin injection.

d Number (%) of patients with at least one hypoglycemia event during the 3-month study period.

e Nocturnal hypoglycemia was defined as hypoglycemia occurring between 00:00 and 05:59 hours.

Antibodies
Results from studies comparing Toujeo® and LANTUS did not indicate any difference in term of development of insulin antibodies, on efficacy, safety or dose of basal insulin between Toujeo® and LANTUS-treated patients (see Section Adverse Reactions).

• ORIGIN Trial (Study 4032)

The ORIGIN (Outcome Reduction with Initial Glargine Intervention) trial was a, international, multicenter, randomized, 2x2 factorial design study conducted in 12,537 participants with impaired fasting glucose (IFG), impaired glucose tolerance (IGT) or early type 2 diabetes mellitus and evidence of CV disease. Participants were randomized to receive LANTUS (insulin glargine 100 U/mL) (n=6264), titrated to a FPG of 95 mg/dL (5.3mM) or less, or Standard Care (n=6273). At baseline participants had a mean age of 63.5 years, mean duration of diabetes of 5.8 years in those with pre-existing diabetes, and median HbA1c of 6.4%. Median duration of follow-up was approximately 6.2 years.

At the end of the trial 81% of participants randomized to take insulin glargine 100 U/mL were still on treatment.

Median on-treatment HbA1c values ranged from 5.9 to 6.4 % in the insulin glargine 100 U/mL group, and 6.2% to 6.6% in the Standard Care group throughout the duration of follow-up. Median FPG in the insulin glargine 100U/mL group was at target (≤95mg/dL) following dose titration for the duration of the study.

The rates of severe hypoglycemia (affected participants per 100 participant years of exposure) were 1.05 for insulin glargine 100U/mL and 0.30 for Standard Care group. Overall, severe hypoglycemia was reported for 3.7% of these participants over the course of this 6 year study (approximately 0.6% per participant-year). The median of the change in body weight from baseline to the last on-treatment visit was 2.2 kg greater in the insulin glargine 100 units/ml group than in the Standard Care group.

The primary objective of this trial was to examine the effect of insulin glargine 100 U/mL on two co-primary composite efficacy outcomes. The first one was the time to the first occurrence of CV death, nonfatal myocardial infarction (MI), or nonfatal stroke, and the second one was the time to the first occurrence of any of the first co-primary events, or revascularization procedure (cardiac, carotid, or peripheral), or hospitalization for heart failure.

Secondary endpoints were:
• all-cause mortality
• a composite microvascular outcome
• development of type 2 diabetes, in participants with IGT and/or IFG at baseline

The primary and secondary outcome results, as well as the results for each component of the coprimary outcomes, are displayed in the two tables (Table 5 for the time-to-event analyses, and, for the non-time-to-event analysis of development of diabetes, Table 6) below.

Table 4 ORIGIN: Time to Onset of each Primary and Secondary Endpoint

	***Insulin glargine 100 U/mL* N=6264**	**Standard care N=6273**	***Insulin glargine 100 U/mL* vs Standard care**
	Participants with Events N (%)	Participants with Events N (%)	Hazard Ratio (95% CI)
Primary endpoints			
CV death, nonfatal myocardial infarction (MI), or nonfatal stroke	1041 (16.6)	1013 (16.1)	1.02 (0.94, 1.11)
CV death, nonfatal myocardial infarction (MI), or nonfatal stroke, or hospitalization for heart failure or revascularization procedure	1792 (28.6)	1727 (27.5)	1.04 (0.97, 1.11)
Secondary endpoints			
All-cause mortality	951 (15.2)	965 (15.4)	0.98 (0.90, 1.08)
Composite microvascular outcome*	1323 (21.1)	1363 (21.7)	0.97 (0.90, 1.05)
Components of coprimary endpoint			
CV death	580 (9.3)	576 (9.2)	1.00 (0.89, 1.13)
MI (fatal or non-fatal)	336 (5.4)	326 (5.2)	1.03 (0.88, 1.19)
Stroke (fatal or non-fatal)	331 (5.3)	319 (5.1)	1.03 (0.89, 1.21)
Revascularizations	908 (14.5)	860 (13.7)	1.06 (0.96, 1.16)
Hospitalization for heart failure	310 (4.9)	343 (5.5)	0.90 0.77, 1.05)

*with components of: laser photocoagulation or vitrectomy or blindness for diabetic retinopathy; progression in albuminuria; or doubling of serum creatinine or development of the need for renal replacement therapy.

Table 5 Incidence Rate of Diabetes by end of study OGTT[a]:

Treatment (N)	*Insulin glargine 100 U/mL* (6264)	Standard Care (6273)
Number of Participants**	737	719
# participants who developed diabetes (%)	182 (24.7)	224 (31.2)
Odds Ratio (95% CI)	0.72 (0.58 to 0.91)	

*End of study OGTT was performed 3-4 weeks after discontinuing Insulin glargine 100 units/mL

**Participants with prediabetes (IFG or IGT) at baseline, based on an OGTT performed then;

There were no statistical significant differences between treatment groups in the overall incidence of cancer (all types combined) or death from cancer. The time to first event of any cancer or new cancer during the study was similar between the two treatment groups with respective hazard ratios of 0.99 (0.88, 1.11) and 0.96 (0.85, 1.09).

Participation in ORIGIN for a median of approximately 6.2 years showed that treatment with insulin glargine 100 U/mL did not alter the risk for cardiovascular outcomes, all-cause mortality or cancer, when compared to standard glucose lowering therapy. In addition, metabolic control was maintained at a lower level of glycemia, with a decrease in the percentage of participants developing diabetes, at a cost of a modest increase in hypoglycemia and weight gain.

- **Diabetic Retinopathy**:

Effects of insulin glargine 100 U/mL on diabetic retinopathy were evaluated in a large 5-year NPH-controlled study in which progression of retinopathy was investigated by fundus photography using a grading protocol derived from the Early Treatment Diabetic Retinopathy Study (ETDRS). The primary outcome in this study was progression by 3 or more steps on the ETDRS scale at study endpoint. The results of this analysis are shown in the table below for both the per-protocol (primary) and Intent-to-Treat (ITT) populations, and indicate non inferiority of insulin glargine 100 U/mL to NPH in the progression of diabetic retinopathy as assessed by this outcome (Table 7).

Table 6 Number (%) of patients with 3 or more step progression on ETDRS scale at endpoint

	Insulin glargine 100 units/mL (%)	NPH (%)	Difference[a],[b] (SE)	95% CI for difference
Per-protocol	53/374 (14.2%)	57/363 (15.7%)	-1.98% (2.57%)	-7.02% to 3.06%
Intent-to-Treat	63/502 (12.5%)	71/487 (14.6%)	- 2.10% (2.14%)	-6.29% to 2.09%

a: Difference = insulin glargine 100 units/mL – NPH

b: using a generalized linear model (SAS GENMOD) with treatment and baseline HbA1c strata as the classified independent variables, and with binomial distribution and identity link function

- **Special populations**

Gender, race: In controlled clinical trials in adults (n= 3096, safety population), subgroup analysis based on gender and race did not indicate any difference in efficacy and safety between Toujeo® and LANTUS *(see Section Special Population).*

Elderly patients: In controlled clinical trials, a total of 716 patients (23% of the safety population) with type 1 and type 2 diabetes patients were ≥65 years of age and 97 (3%) 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. Close glucose monitoring is recommended, and the insulin dose should be adjusted on an individual basis *(see Sections Special Population, Precautions)*

Renal impairment: In controlled clinical studies (n=3096, safety population), subgroup analyses based on renal function status (baseline estimated glomerular filtration rate categories <60 or ≥60 ml/min/1.73m^2) did not indicate difference in safety and efficacy between Toujeo® and LANTUS. Close glucose monitoring is recommended and the insulin dose should be adjusted on an individual basis *(see Sections Special Population, Precautions)*

Obesity: In clinical trials subgroup analysis based on BMI (up to 63 kg/m^2) showed no differences in efficacy and safety between Toujeo® and LANTUS.

Pediatric: no data

PHARMACOKINETICS

ABSORPTION, DISTRIBUTION

After subcutaneous injection of Toujeo® in healthy subjects and diabetic patients, the insulin serum concentrations indicated a slower and more prolonged absorption resulting in an even flatter time-concentration profile for up to 36 hours in comparison to LANTUS. Concentrations were consistent with the time profile of the pharmacodynamic activity of Toujeo®.

Steady state level within the therapeutic range is reached after 3-4 days of daily Toujeo® administration.
After subcutaneous injection of Toujeo®, the intra-subject variability, defined as the coefficient of variation for the insulin exposure during 24 hours was low at steady state (17.4%).

METABOLISM

After subcutaneous injection of Toujeo®in healthy subjects and diabetic patients, insulin glargine is rapidly 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). In plasma, the principal circulating compound is the metabolite M1. The exposure to M1 increases with the administered dose of Toujeo®. The pharmacokinetic and pharmacodynamic findings indicate that the effect of the subcutaneous injection with Toujeo® is principally based on exposure to M1. Insulin glargine and the metabolite M2 were not detectable in the vast majority of subjects and, when they were detectable their concentration was independent of the administered dose and formulation of insulin glargine.

ELIMINATION

The half-life of M1, the predominant metabolite of Toujeo® after subcutaneous injection is 18-19 hours independent of dose.

SPECIAL POPULATIONS

Gender, race: Information on the effect of gender or race on the pharmacokinetics of insulin glargine is unavailable *(see Section Clinical Efficacy/Clinical studies).*

Elderly patients: The effect of age on the pharmacokinetics of Toujeo® has not been studied. 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. Close glucose monitoring is recommended and the insulin dose should be adjusted on an individual basis *(see Sections Special Population, Adverse Reactions and Clinical Efficacy/Clinical studies).*

Pediatric patients: The pharmacokinetics of Toujeo® has not been established in paediatric 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. Close glucose monitoring is recommended and the insulin dose should be adjusted on an individual basis *(see Sections Special Population, Adverse Reactions and Clinical Efficacy/Clinical studies).*

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. Close glucose monitoring is recommended and the insulin dose should be adjusted on an individual basis *(see Section Special Population and Adverse reactions).*

NON CLINICAL SAFETY DATA

SINGLE DOSE TOXICITY

The acute toxicity of intravenous and subcutaneous administration of insulin glargine was tested in mice and rats. The LD50 in each species was in the range of ≥1000 IU/kg.

REPEAT DOSE TOXICITY

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

CARCINOGENICITY
Two-year carcinogenicity studies were performed in rats and mice. The results do not indicate a risk to humans.

GENOTOXICITY
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).

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY
• Teratogenicity
In an embryotoxicity study in rats, hypoglycemia but no maternal toxicity occurred. Insulin glargine was not embryotoxic and not teratogenic.

In an embryotoxicity study in rabbits, maternal (hypoglycemic shock, intrauterine deaths) and embryo-foetal toxicity, due to hypoglycemia, was observed, including single anomalies in the middle- and high-dose groups. Similar effects were obtained with an intermediate acting marketed insulin.

• Impairment of fertility
In a combined fertility and pre- and postnatal study in rats, maternal toxicity due to dose-dependent hypoglycemia was observed. Some deaths, and consequently a reduction of the rearing rate, occurred in the high-dose group only. Similar effects were obtained with an intermediate acting marketed insulin.

OTHER TOXICITY STUDIES

LOCAL TOLERANCE
Local tolerability studies with subcutaneous, intramuscular, intravenous and paravenous administration in rabbits gave no indication of risk for the use of insulin glargine in man.

IMMUNOGENICITY
Standard immunogenicity studies performed in pigs, rabbits and guinea pigs indicated a similar or lower immunogenic potential for insulin glargine than for human insulin in these species.

INCOMPATIBILITIES / COMPATIBILITIES
See under dosage

STORAGE CONDITIONS AND SHELF-LIFE
Unopened/not in use pre-filled pen:
Toujeo® must be stored between +2°C (36°F) and +8°C (46°F) (in a refrigerator) and protected from light. Do not allow the insulin to freeze, discard if frozen.
Do not put Toujeo® 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 (below 30°C (86°F)).

Presentation
1.5 mL cartridges

Shelf life
Refer outer carton

PREPARATION AND HANDLING
Inspect Toujeo® before use. Toujeo® must only be used if the solution is clear, colorless, with no solid particles visible, and if it is of water-like consistency.

Manufactured by: Sanofi-Aventis Deutschland GmbH, Industriepark Hoechst, 65926 Frankfurt am Main, Germany.

Importer: Sanofi Healthcare India Private Limited, Gala No. 4, Ground Floor, Building No. B1, Citylink Warehousing Complex, S No.121/10/A,121/10/B & 69, NH3, Vadape, Tal: Bhiwandi-16, (THANE-Z5), State: Maharashtra; Pin 421302.

Marketed by*:* Sanofi India Limited, Sanofi House, CTS No. 117-B, L & T Business Park, Saki Vihar Road, Powai, Mumbai-400072.

Updated: Nov 2024

Source*:* CCDS v5 dated 10th Sept 2020