## 1. NAME OF THE MEDICINAL PRODUCT

Toujeo 300 units/ml solution for injection in a pre-filled pen SoloStar
Toujeo 300 units/ml solution for injection in a pre-filled pen DoubleStar

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 300 units insulin glargine* (equivalent to 10.91 mg).

SoloStar pen
Each pen contains 1.5 ml of solution for injection, equivalent to 450 units.

DoubleStar pen
Each pen contains 3 ml of solution for injection, equivalent to 900 units.

* Insulin glargine is produced by recombinant DNA technology in *Escherichia coli*.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Solution for injection (injection).
Clear colourless solution.

Patient safety information guide and Guide for Healthcare Professionals

The marketing of Toujeo is subject to a risk management plan (RMP) including a 'Patient safety information guide' and “Guide for Healthcare Professionals”.

The 'Patient safety information guide', emphasizes important safety information that the patient should be aware of before and during treatment.
Please explain to the patient the need to review the guide before starting treatment.

Guide for Healthcare Professionals

This product is marketed with prescriber guide providing important safety information.
Please ensure you are familiar with this material as it contains important safety information.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Treatment of diabetes mellitus in adults, adolescents and children from the age of 6 years.

### 4.2 Posology and method of administration

Posology

Toujeo is a basal insulin for once-daily administration at any time of the day, preferably at the same time every day.

The dose regimen (dose and timing) should be adjusted according to individual response.

In type 1 diabetes mellitus, Toujeo must be combined with short-/rapid-acting insulin to cover mealtime insulin requirements.

In patients with type 2 diabetes mellitus, Toujeo can also be given together with other anti-hyperglycaemic medicinal products.

The potency of this medicinal product is stated in units. 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 (see section 5.1).

*Flexibility in dosing time*

When needed, patients can administer Toujeo up to 3 hours before or after their usual time of administration (see section 5.1).

Patients who forget a dose, should be advised to check their blood sugar, and then resume their usual once-daily dosing schedule. Patients should be informed not to inject a double dose to make up for a forgotten dose.

*Initiation*

*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 units/kg followed by individual dose adjustments.

*Switch between insulin glargine 100 units/ml and Toujeo*

Insulin glargine 100 units/ml and Toujeo are not bioequivalent and are not directly interchangeable.

- When switching from insulin glargine 100 units/ml to Toujeo, this can be done on a unit-to-unit basis, but a higher Toujeo dose (approximately 10-18%) may be needed to achieve target ranges for plasma glucose levels.
- When switching from Toujeo to insulin glargine 100 units/ml, the dose should be reduced (approximately by 20%) to reduce the risk of hypoglycaemia.

Close metabolic monitoring is recommended during the switch and in the initial weeks thereafter.

*Switch from other basal insulins to Toujeo*

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-hyperglycaemic treatment may need to be adjusted (dose and timing of additional regular insulins or fast-acting insulin analogues or the dose of non-insulin anti-hyperglycaemic medicinal products).

- Switching from once-daily basal insulins to once-daily Toujeo can be done unit-to-unit based on the previous 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.

Patients with high insulin doses because of antibodies to human insulin may experience an improved insulin response with Toujeo.

Close metabolic monitoring is recommended during the switch and in the initial weeks thereafter.

With improved metabolic control and resulting increase in insulin sensitivity a further adjustment in dose regimen may become necessary. Dose adjustment may also 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 hyperglycaemia (see section 4.4)

*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.

*Special populations*

Toujeo can be used in elderly people, renal and hepatic impaired patients, and children and adolescents from the age of 6 years.

*Elderly population (≥65 years old)*
In the elderly, progressive deterioration of renal function may lead to a steady decrease in insulin requirements (see section 4.8 and 5.1).

*Renal impairment*
In patients with renal impairment, insulin requirements may be diminished due to reduced insulin metabolism (see section 4.8).

*Hepatic impairment*
In patients with hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism.

*Paediatric population*
Toujeo can be used in adolescents and children from the age of 6 years based on the same principles as for adult patients (see sections 5.1and 5.2). When switching basal insulin to Toujeo, dose reduction of basal and bolus insulin needs to be considered on an individual basis, in order to mimimize the risk of hypoglycaemia (see section 4.4).
The safety and efficacy of Toujeo in children below 6 years of age have not been established. No data are available

Method of administration
Toujeo is for subcutaneous use only.
Toujeo is administered subcutaneously by injection in the abdominal wall, the deltoid or the thigh. Injection sites must be rotated within a given injection area from one injection to the next in order to reduce the risk of lipodystrophy and cutaneous amyloidosis (see section 4.4 and 4.8).

Toujeo must not be administered intravenously. The prolonged duration of action of Toujeo is dependent on its injection into subcutaneous tissue. Intravenous administration of the usual subcutaneous dose could result in severe hypoglycaemia.
Toujeo must not be used in insulin infusion pumps.

Toujeo is available in two pre-filled pens. The dose window shows the number of units of Toujeo to be injected. The Toujeo SoloStar and Toujeo DoubleStar pre-filled pens have been specifically designed for Toujeo and no dose re-calculation is required for either pen.

Before using Toujeo SoloStar pre-filled pen or Toujeo DoubleStar pre-filled pen, the instructions for use included in the package leaflet must be read carefully (see section 6.6).

With Toujeo SoloStar pre-filled pen, a dose of 1-80 units per single injection, in steps of 1 unit, can be injected. With Toujeo DoubleStar pre-filled pen a dose of 2-160 units per single injection, in steps of 2 units, can be injected.

When changing from Toujeo SoloStar to Toujeo DoubleStar, if the patient's previous dose was an odd number (e.g. 23 units) then the dose must be increased or decreased by 1 unit (e.g. 24 or 22 units).

Toujeo DoubleStar prefilled pen is recommended for patients requiring at least 20 units per day (see section 6.6).

Toujeo must not be drawn from the cartridge of the Toujeo SoloStar pre-filled pen or Toujeo DoubleStar pre-filled pen into a syringe or severe overdose can result (see section 4.4, 4.9 and 6.6).

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 (see section 4.4 and 6.6).

To prevent possible transmission of disease, insulin pens should never be used for more than one person, even when the needle is changed (see section 6.6).

## 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

## 4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the name of the administered product should be clearly recorded. It is recommended to record the batch number as well.

Toujeo is not the insulin of choice for the treatment of diabetic ketoacidosis. Instead, regular insulin administered intravenously is recommended in such cases.

In case of insufficient glucose control or a tendency to hyper- or hypoglycaemic episodes, the patient's adherence to the prescribed treatment regimen, injection sites and proper injection technique 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 cutaneous amyloidosis. There is a potential risk of delayed insulin absorption and worsened glycaemic 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 hypoglycaemia. Blood glucose monitoring is recommended after the change in the injection site, and dose adjustment of antidiabetic medications may be considered.

Hypoglycaemia
The time of occurrence of hypoglycaemia depends on the action profile of the insulins used and may, therefore, change when the treatment regimen is changed.

Particular caution should be exercised, and intensified blood glucose monitoring is advisable in patients in whom hypoglycaemic episodes might be of particular clinical relevance, such as in patients with significant stenosis of the coronary arteries or of the blood vessels supplying the brain (risk of cardiac or cerebral complications of hypoglycaemia) as well as in patients with proliferative retinopathy, particularly if not treated with photocoagulation (risk of transient amaurosis following hypoglycaemia).

Patients should be aware of circumstances where warning symptoms of hypoglycaemia are diminished. The warning symptoms of hypoglycaemia may be changed, be less pronounced or be absent in certain risk groups. These include patients:
- in whom glycaemic control is markedly improved,
- in whom hypoglycaemia develops gradually,
- who are elderly,
- after transfer from animal insulin to human insulin,
- in whom an autonomic neuropathy is present,
- with a long history of diabetes,
- suffering from a psychiatric illness,

- receiving concurrent treatment with certain other medicinal products (see section 4.5).

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

The prolonged effect of insulin glargine may delay recovery from hypoglycaemia.

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

Adherence of the patient to the dose and dietary regimen, correct insulin administration and awareness of hypoglycaemia symptoms are essential to reduce the risk of hypoglycaemia. Factors increasing the susceptibility to hypoglycaemia require particularly close monitoring and may necessitate dose adjustment. These factors include:
- change in the injection area,
- improved insulin sensitivity (e.g., by removal of stress factors),
- unaccustomed, increased or prolonged physical activity,
- intercurrent illness (e.g.vomiting, diarrhoea),
- inadequate food intake,
- missed meals,
- alcohol consumption,
- certain uncompensated endocrine disorders, (e.g. in hypothyroidism and in anterior pituitary or adrenocortical insufficiency),
- concomitant treatment with certain other medicinal products (see section 4.5).

Switch between insulin glargine 100 units/ml and Toujeo
Since insulin glargine 100 units/ml and Toujeo are not bioequivalent and are not interchangeable, switching may result in the need for a change in dose and should only be done under strict medical supervision (see section 4.2).

Switch between other insulins and Toujeo
Switching a patient between another type or brand of insulin and Toujeo should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (regular, NPH, lente, long-acting, etc.), origin (animal, human, human insulin analogue) and/or method of manufacture may result in the need for a change in dose (see section 4.2).

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. Patients with type 1 diabetes must continue to consume at least a small amount of carbohydrates on a regular basis, even if they are able to eat only little or no food, or are vomiting etc. and they must never omit insulin entirely.

Insulin antibodies
Insulin administration may cause insulin antibodies to form. In rare cases, the presence of such insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyper-or hypoglycaemia.

Combination of Toujeo with pioglitazone
Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for development of cardiac heart failure. This should be kept in mind if treatment with the combination of pioglitazone and Toujeo is considered. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs.

Medication errors prevention
Medication errors have been reported in which other insulins, particularly rapid-acting insulins, have been accidentally administered instead of long-acting insulins. Insulin label must always be checked before each injection to avoid medication errors between Toujeo and other insulins (see section 6.6).

To avoid dosing errors and potential overdose, the patients must be instructed to never use a syringe to remove Toujeo (insulin glargine 300 units/ml) from the Toujeo SoloStar pre-filled pen or Toujeo DoubleStar pre-filled pen (see section 4.9 and 6.6).

A new sterile needle must be attached before each injection. Patients must also be instructed to not re-use needles. Re-use of needles increases the risk of blocked needles which may cause underdosing or overdosing. In the event of blocked needle, the patients must follow the instructions described in Step 3 of the Instructions for Use accompanying the package leaflet (see section 6.6).

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

See also section 4.2 under "Method of administration".

Excipients
This medicinal product contains less than 1 mmol (23 mg) sodium per dose, i.e. it is essentially 'sodium-free'.

## 4.5 Interaction with other medicinal products and other forms of interaction

A number of substances affect glucose metabolism and may require dose adjustment of insulin glargine.

Substances that may enhance the blood-glucose-lowering effect and increase susceptibility to hypoglycaemia include anti-hyperglycaemic medicinal products, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, pentoxifylline, propoxyphene, salicylates and sulfonamide antibiotics.

Substances that may reduce the blood-glucose-lowering effect include corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, oestrogens and progestogens, phenothiazine derivatives, somatropin, sympathomimetic medicinal products (e.g. epinephrine [adrenaline], salbutamol, terbutaline), thyroid hormones, atypical antipsychotic medicinal products (e.g. clozapine and olanzapine) and protease inhibitors.

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

## 4.6 Fertility, pregnancy and lactation

Pregnancy
There is no clinical experience with use of Toujeo in pregnant women.

For insulin glargine no clinical data on exposed pregnancies from controlled clinical studies are available. A large amount of data on pregnant women (more than 1,000 pregnancy outcomes with a medicinal product containing insulin glargine 100 units/ml) indicate no specific adverse effects on pregnancy and no specific malformative nor feto/neonatal toxicity of insulin glargine.
Animal data do not indicate reproductive toxicity.
The use of Toujeo may be considered during pregnancy, if clinically needed.

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. Insulin requirements may decrease during the first trimester and generally increase during the second and

third trimesters. Immediately after delivery, insulin requirements decline rapidly (increased risk of hypoglycaemia). Careful monitoring of glucose control is essential.

Breast-feeding
It is unknown whether insulin glargine is excreted in human milk. No metabolic effects of ingested insulin glargine on the breast-fed newborn/infant are anticipated since insulin glargine as a peptide is digested into amino acids in the human gastrointestinal tract.
Breast-feeding women may require adjustments in insulin dose and diet.

Fertility
Animal studies do not indicate direct harmful effects with respect to fertility.

## 4.7 Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia 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 using machines).

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

## 4.8 Undesirable effects

Summary of the safety profile
The following adverse reactions were observed during clinical studies conducted with Toujeo (see section 5.1) and during clinical experience with insulin glargine 100 units/ml.
Hypoglycaemia, 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.

Tabulated list of adverse reactions
The following related adverse reactions from clinical investigations are listed below by system organ class and in order of decreasing incidence (very common: ≥1/10; common: ≥1/100 to <1/10; uncommon: ≥1/1,000 to <1/100; rare: ≥1/10,000 to <1/1,000; very rare: <1/10,000; not known: cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

| **MedDRA system organ classes** | **Very common** | **Common** | **Uncommon** | **Rare** | **Very rare** | **Not known** |
|---|---|---|---|---|---|---|
| Immune system disorders | | | | Allergic reactions | | |
| Metabolism and nutrition disorders | Hypoglycaemia | | | | | |
| Nervous system disorders | | | | | Dysgeusia | |

| **MedDRA system organ classes** | **Very common** | **Common** | **Uncommon** | **Rare** | **Very rare** | **Not known** |
|---|---|---|---|---|---|---|
| Eyes disorders | | | | Visual impairment<br><br>Retinopathy | | |
| Skin and subcutaneous tissue disorders | | Lipohypertro-phy | Lipoatrophy | | | Cutaneous amyloidosis |
| Musculoskeletal and connective tissue disorders | | | | | Myalgia | |
| General disorders and administration site conditions | | Injection site reactions | | Oedema | | |

Description of selected adverse reactions

*Metabolism and nutrition disorders*

Severe hypoglycaemic attacks, especially if recurrent, may lead to neurological damage. Prolonged or severe hypoglycaemic 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.

*Immune system disorders*

Immediate-type allergic reactions to insulin are rare. Such reactions to insulin (including insulin glargine) or the excipients may, for example, be associated with generalised skin reactions, angio-oedema, bronchospasm, hypotension and shock, and may be life-threatening. In Toujeo clinical studies in adult patients, the incidence of allergic reactions was similar in Toujeo-treated patients (5.3%) and insulin glargine 100 units/ml-treated patients (4.5%).

*Eyes disorders*

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, 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 hypoglycaemic episodes may result in transient amaurosis.

*Skin and subcutaneous tissue disorders*

Lipodystrophy and cutaneous amyloidosis may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions (see section 4.4).

*General disorders and administration site conditions*

Injection site reactions include redness, pain, itching, hives, swelling, or inflammation. Most minor reactions to insulins at the injection site usually resolve in a few days to a few weeks. In Toujeo clinical studies in adult patients, the incidence of injection site reactions was similar in Toujeo-treated patients (2.5%) and insulin glargine 100 units/ml-treated patients (2.8%).

Rarely, insulin may cause oedema particularly if previously poor metabolic control is improved by intensified insulin therapy.

Paediatric population
Safety and efficacy of Toujeo have been demonstrated in a study in children aged 6 to less than 18 years. The frequency, type and severity of adverse reactions in the paediatric population do not indicate differences to the experience in the general diabetes population (see section 5.1).
Clinical study safety data are not available for children under 6 years.

Other special populations
Based on the results from clinical studies, the safety profile of Toujeo in elderly patients and in patients with renal impairment was similar to that of the overall population (see section 5.1).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form at https://sideeffects.health.gov.il/.

## 4.9 Overdose

Symptoms
Insulin overdose may lead to severe and sometimes long-term and life-threatening hypoglycaemia.

Management
Mild episodes of hypoglycaemia can usually be treated with oral carbohydrates. Adjustments in dose of the medicinal product, meal patterns, or physical activity may be needed.

More severe episodes 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 hypoglycaemia may recur after apparent clinical recovery.

# 5. PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, insulins and analogues for injection, long-acting.
ATC Code: A10A E04.

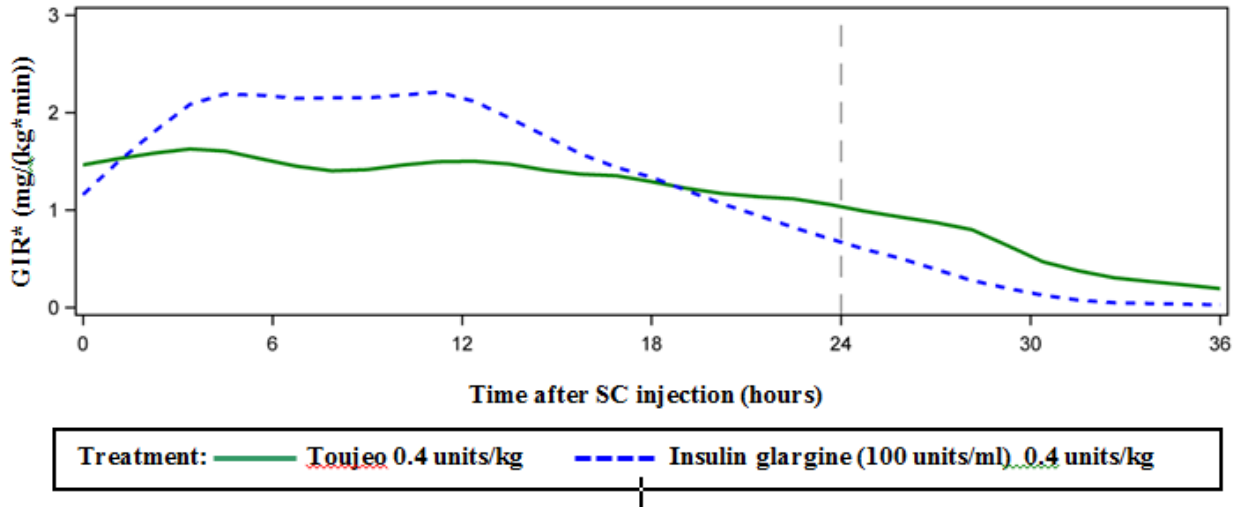
Mechanism of action
The primary activity of insulin, including insulin glargine, is regulation of glucose metabolism. Insulin and its analogues lower blood glucose levels by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin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

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

As observed in euglycemic clamp studies in patients with type 1 diabetes, the glucose lowering effect of Toujeo was more stable and prolonged in comparison with insulin glargine 100 units/ml 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 more sustained release of insulin glargine from the Toujeo precipitate compared to insulin glargine 100 units/ml is attributable to the reduction of the injection volume by two thirds that results in a smaller precipitate surface area.

Figure 1: Activity profile at steady state in patients with type 1 diabetes in a 36-hour euglycaemic clamp study




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

Insulin glargine is metabolised into 2 active metabolites M1 and M2 (see section 5.2).

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.

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

As with all insulins, the time course of action of insulin glargine may be affected by physical activity and other variables.

Clinical efficacy and safety

The overall efficacy and safety of Toujeo (insulin glargine 300 units/ml) once-daily on glycaemic control was compared to that of once-daily insulin glargine 100 units/ml in open-label, randomised, active-control, parallel studies of up to 26 weeks of duration, including 546 patients with type 1 diabetes mellitus and 2,474 patients with type 2 diabetes mellitus (Table 1 and 2).
Results from all clinical trials with Toujeo indicated that reductions in HbA1c from baseline to end of trial were non-inferior to insulin glargine 100 units/ml. Plasma glucose reductions at the end of the trial with Toujeo were similar to insulin glargine 100 units/ml 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.
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).
At the end of these treat-to-target trials, depending on the patient population and concomitant therapy, a 10-18% higher dose was observed in the Toujeo group than in the comparator group (Table 1 and 2).

Results from clinical trials demonstrated that the incidence of confirmed hypoglycaemia (at any time of the day and nocturnal) was lower in patients treated with Toujeo compared to insulin glargine 100 units/ml-treated patients, in patients with type 2 diabetes treated in combination with either non-insulin anti-hyperglycaemic medicinal product or mealtime insulin.
The superiority of Toujeo over insulin glargine 100 units/ml in lowering the risk of confirmed nocturnal hypoglycemia was shown in patients with type 2 diabetes treated with basal insulin in combination with either non-insulin anti-hyperglycaemic medicinal product (18% risk reduction) or mealtime insulin (21% risk reduction) during the period from week 9 to end of study period.
Overall, these effects on hypoglycaemia risk were consistently observed whatever the age, gender, BMI and duration of diabetes (<10 years and ≥10 years) in Toujeo-treated patients compared to insulin glargine 100 units/ml-treated patients.

In patients with type 1 diabetes, the incidence of hypoglycaemia was similar in patients treated with Toujeo compared to insulin glargine 100 units/ml-treated patients (Table 3).

Table 1: Results from clinical trials in type 1 diabetes mellitus

| **26 weeks of treatment** | | |
|---|---|---|
| | **Toujeo** | **IGlar** |
| Treatment in combination with | Meal-time insulin analogue | |
| Number of subjects treated (mITT[a]) | 273 | 273 |
| **HbA1c** | | |
| Baseline mean | 8.13 | 8.12 |
| Adjusted Mean change from baseline | -0.40 | -0.44 |
| Adjusted Mean difference[b] | 0.04 [-0.098 to 0.185] | |
| **Basal insulin dose[c] (U/kg)** | | |
| Baseline mean | 0.32 | 0.32 |
| Mean change from baseline | 0.15 | 0.09 |
| **Body weight[d] (kg)** | | |
| Baseline mean | 81.89 | 81.80 |
| Mean change from baseline | 0.46 | 1.02 |

IGlar: Insulin glargine 100 units/ml
*a* mITT: Modified intention-to-treat
*b* Treatment difference: Toujeo– insulin glargine 100 units/ml; [95% Confidence Interval]
*c* Change from baseline to Month 6 (observed case)
*d* Change from baseline to Last main 6-month on-treatment value

Table 2: Results from clinical trials in type 2 diabetes mellitus

| **26 weeks of treatment** | | | | | | |
|---|---|---|---|---|---|---|
| | **Patients previously treated with basal insulin** | | **Patients previously treated with basal insulin** | | **Previously insulin naive patients** | |
| Treatment in combination with | Meal-time insulin analog+/-metformin | | Non-insulin anti-hyperglycaemic medicinal products | | | |
| | **Toujeo** | **IGlar** | **Toujeo** | **IGlar** | **Toujeo** | **IGlar** |
| 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 [-0.144 to 0.083] | | -0.03 [-0.168 to 0.099] | | 0.04 [-0.090 to 0.174] | |
| **Basal insulin dose[c] (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 |
| **Body weight[d] (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 |

IGlar: Insulin glargine 100 units/ml

*a* mITT: Modified intention-to-treat

*b* Treatment difference: Toujeo– insulin glargine 100 units/ml; [95% Confidence Interval]

*c* Change from baseline to Month 6 (observed case)

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

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

| ***Diabetic population*** | ***Type 1 diabetes mellitus*** **Patients previously treated with basal insulin** | | ***Type 2 diabetes mellitus*** **Patients previously treated with basal insulin** | | ***Type2 diabetes mellitus*** ***Patients previously Insulin naive or on basal insulin*** | |
|---|---|---|---|---|---|---|
| Treatment in combination with | Meal-time insulin analog | | Meal-time insulin analog+/-metformin | | Non-insulin anti-hyperglycaemic medicinal products | |
| | **Toujeo** | **IGlar** | **Toujeo** | **IGlar** | **Toujeo** | **IGlar** |
| **Incidence (%) of severe[a] hypoglycaemia (n/Total N)** | | | | | | |
| Entire study period[d] | 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]* | |

| ***Diabetic population*** | ***Type 1 diabetes mellitus*** **Patients previously treated with basal insulin** | | ***Type 2 diabetes mellitus*** **Patients previously treated with basal insulin** | | ***Type2 diabetes mellitus*** ***Patients previously Insulin naive or on basal insulin*** | |
|---|---|---|---|---|---|---|
| Treatment in combination with | Meal-time insulin analog | | Meal-time insulin analog+/-metformin | | Non-insulin anti-hyperglycaemic medicinal products | |
| | **Toujeo** | **IGlar** | **Toujeo** | **IGlar** | **Toujeo** | **IGlar** |
| **Incidence (%) of confirmed[b] hypoglycaemia (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]* | |
| **Incidence (%) of confirmed nocturnal[c] hypoglycaemia (n/Total N)** | | | | | | |
| From week 9 to end of study period | 59.3 (162/273) | 56.0 (153/273) | 36.1 (146/404) | 46.0 (184/400) | 18.4 (154/835) | 22.5 (188/835) |
| | *RR: 1.06 [0.92;1.23]* | | *RR: 0.79 [0.67;0.93]* | | *RR: 0.82 [0.68;0.99]* | |

IGlar: Insulin glargine 100 units/ml

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

[b] Confirmed hypoglycaemia: Any severe hypoglycaemia and/or hypoglycaemia confirmed by plasma glucose value ≤3.9 mmol/l.

[c] Nocturnal hypoglycaemia: Episode that occurred between 00:00 and 05:59 hours

[d] 6-month treatment period

*RR: estimated risk ratio; [95% Confidence Interval]

*Flexibility in dosing time*

The safety and efficacy of Toujeo administered with a fixed or flexible dosing time 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 dosing time). Administration with a flexible dosing time had no effect on glycaemic control and the incidence of hypoglycaemia.

*Antibodies*

Results from studies comparing Toujeo and insulin glargine 100 units/ml did not indicate any difference in term of development of anti-insulin antibodies, on efficacy, safety or dose of basal insulin between Toujeo and insulin glargine 100 units/ml.

*Body weight*

Mean change in body weight of less than 1 kg at the end of the 6-month period was observed in Toujeo-treated patients (see Table 1 and 2).

*Results from a study on progression of diabetic retinopathy*

Effects of insulin glargine 100 units/ml (once daily) on diabetic retinopathy were evaluated in an open-label 5 year NPH-controlled study (NPH given bid) in 1024 type 2 diabetic patients in which progression of retinopathy by 3 or more steps on the Early Treatment Diabetic Retinopathy Study (ETDRS) scale was investigated by fundus photography. No significant difference was seen in the progression of diabetic retinopathy when insulin glargine100 units/ml was compared to NPH insulin.

*Long term efficacy and safety outcome study*

The ORIGIN (Outcome Reduction with Initial Glargine INtervention) study was a multicenter, randomized, 2x2 factorial design study conducted in 12,537 participants at high cardiovascular (CV) risk with impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) (12% of participants) or type 2 diabetes mellitus (treated with ≤1 antidiabetic oral agent) (88% of participants). Participants were randomized (1:1) to receive insulin glargine 100 units/ml (n=6264), titrated to reach FPG ≤95 mg/dl (5.3 mM), or standard care (n=6273).
The first co-primary efficacy outcome was the time to the first occurrence of CV death, nonfatal myocardial infarction (MI), or nonfatal stroke, and the second co-primary efficacy outcome was the time to the first occurrence of any of the first co-primary events, or revascularisation procedure (coronary, carotid, or peripheral), or hospitalisation for heart failure.

Secondary endpoints included all-cause mortality and a composite microvascular outcome.

Insulin glargine 100 units/ml did not alter the relative risk for CV disease and CV mortality when compared to standard of care. There were no differences between insulin glargine and standard care for the two co-primary outcomes; for any component endpoint comprising these outcomes; for all-cause mortality; or for the composite microvascular outcome.
Mean dose of insulin glargine 100 units/ml by study end was 0.42 U/kg. At baseline, participants had a median HbA1c value of 6.4% and median on-treatment HbA1c values ranged from 5.9 to 6.4% in the insulin glargine 100 units/ml group, and 6.2% to 6.6% in the standard care group throughout the duration of follow-up.
The rates of severe hypoglycaemia (affected participants per 100 participant years of exposure) were 1.05 for insulin glargine 100 units/ml and 0.30 for standard care group and the rates of confirmed non-severe hypoglycaemia were 7.71 for insulin glargine 100 units/ml and 2.44 for standard care group. Over the course of this 6-year study, 42% of the insulin glargine 100 units/ml group did not experience any hypoglycaemia.

At the last on-treatment visit, there was a mean increase in body weight from baseline of 1.4 kg in the insulin glargine 100 units/ml group and a mean decrease of 0.8 kg in the standard care group.

Pediatric population
The efficacy and safety of Toujeo have been studied in a 1:1 randomized controlled open label clinical trial in children and adolescents with type 1 diabetes mellitus for a period of 26 weeks (n=463). Patients in the Toujeo arm included 73 children aged < 12 years and 160 children aged ≥12 years. Toujeo dosed once daily showed similar reduction in HbA1c and FPG from baseline to week 26 compared to insulin glargine 100 units/mL.

The dose-response analysis showed that following the initial titration phase, the body weight adjusted doses in pediatric patients are higher than in adult patients at steady state.

Overall the incidence of hypoglycaemia in patients in any category was similar in both treatment groups, with 97.9% of patients in the Toujeo group and 98.2% in the insulin glargine 100 units/mL group reporting at least one event. Similarly, nocturnal hypoglycaemia was comparable in the Toujeo and insulin glargine 100 units/mL treatment groups. The percentage of patients reporting severe hypoglycaemia was lower in patients in the Toujeo group as compared to patients in the insulin glargine 100 units/mL group, 6% and 8.8% respectively. The percentage of patients with hyperglycaemic episodes with ketosis was lower for Toujeo versus insulin glargine 100 units/mL, 6.4% and 11.8%, respectively. No safety issues were identified with Toujeo with respect to adverse events and standard safety parameters. Antibody development was sparse and had no clinical impact. Efficacy and safety data for paediatric patients with type 2 diabetes mellitus have been extrapolated from data for adolescent and adult patients with type 1 diabetes mellitus and adult patients with type 2 diabetes mellitus. Results support the use of Toujeo in paediatric patients with type 2 diabetes mellitus.

## 5.2 Pharmacokinetic properties

Absorption and distribution
In healthy subjects and diabetic patients, insulin serum concentrations indicated a slower and more prolonged absorption resulting in a flatter time-concentration profile after subcutaneous injection of Toujeo in comparison to insulin glargine 100 units/ml.

Pharmacokinetic profiles were consistent with 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%).

Biotransformation
After subcutaneous injection of insulin glargine, 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 insulin glargine. The pharmacokinetic and pharmacodynamic findings indicate that the effect of the subcutaneous injection with insulin glargine 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
When given intravenously the elimination half-life of insulin glargine and human insulin were comparable.

The half-life after subcutaneous administration of Toujeo is determined by the rate of absorption from the subcutaneous tissue. The half-life of Toujeo after subcutaneous injection is 18-19 hours independent of dose.

## 5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

# 6. PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Zinc chloride
Metacresol
Glycerol
Hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Water for injections.

## 6.2 Incompatibilities

Toujeo must not be mixed or diluted with any other insulin or other medicinal products.
Mixing or diluting Toujeo changes its time/action profile and mixing causes precipitation.

## 6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

Shelf life after first use of the pen
The medicinal product may be stored for a maximum of 6 weeks below 30°C and away from direct heat or direct light. Pens in use must not be stored in the refrigerator. The pen cap must be put back on the pen after each injection in order to protect from light.

## 6.4 Special precautions for storage

Before first use
Store in a refrigerator (2°C-8°C).
Do not freeze or place next to the freezer compartment or a freezer pack.
Keep the pre-filled pen in the outer carton in order to protect from light.

After first use or if carried as a spare
For storage conditions after first opening of this medicinal product, see section 6.3.

## 6.5 Nature and contents of container

SoloStar pen
Cartridge (type 1 colourless glass) with a grey plunger (bromobutyl rubber) and a flanged cap (aluminium) with a stopper (laminate of isoprene and bromobutyl rubber).
The cartridge is sealed in a disposable pen injector. Each cartridge contains 1.5 ml solution.

Packs of 1, 3 and 5 pens are available. Not all pack sizes may be marketed. Needles are not included in the pack.

DoubleStar pen Cartridge (type 1 colourless glass) with a black plunger (bromobutyl rubber) and a flanged cap (aluminium) with a stopper (laminate of isoprene and bromobutyl rubber).
The cartridge is sealed in a disposable pen injector. Each cartridge contains 3 ml solution.

Packs of 3 pens are available. Not all pack sizes may be marketed. Needles are not included in the pack.

## 6.6 Special precautions for disposal and other handling

Before first use, the pen must be stored at room temperature at least 1 hour before use.

Before using Toujeo SoloStar pre-filled pen or Toujeo DoubleStar pre-filled pen, the Instructions for Use included in the package leaflet must be read carefully. Toujeo SoloStar pre-filled pen have to be used as recommended in these Instructions for Use (see section 4.2). Instruct patients to perform a safety test as described in Step 3 of the Instructions for Use. If they don't, the full dose might not be delivered. If this occurs, patients should increase the frequency of checking their blood glucose levels and might need to administer additional insulin.

The cartridge should be inspected before use. It must only be used if the solution is clear, colourless, with no solid particles visible, and if it is of water-like consistency. Since Toujeo is a solution, it does not require resuspension before use.

Insulin label must always be checked before each injection to avoid medication errors between Toujeo and other insulins. The strength"300" is highlighted in honey gold on the label (see section 4.4).

Patients should be informed that the dose counter of Toujeo SoloStar or Toujeo DoubleStar pre-filled pen shows the number of units of Toujeo to be injected. No dose re-calculation is required.

- The Toujeo SoloStar pen contains 450 units of Toujeo. It delivers doses of 1-80 units per injection, in steps of 1 unit.
- The Toujeo DoubleStar pen contains 900 units of Toujeo. It delivers doses of 2-160 units per injection, in steps of 2 units.
    - o Tow reduce potential underdose, Toujeo DoubleStar is recommended for patients requiring at least 20 units per day.
- If safety tests are not performed before the first use of a new pen, insulin underdose can occur.

A syringe must never be used to withdraw Toujeo from the cartridge of the pre-filled pen or severe overdose can result (see section 4.2, 4.4 and 4.9).

A new sterile needle must be attached before each injection. Needles must be discarded immediately after use. Needles must not be re-used. Re-use of needles increases 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. In the event of blocked needle, the patients must follow the instructions described in Step 3 of the Instructions for Use accompanying the package leaflet (see section 4.2 and 4.4).
Used needles should be thrown away in a puncture resistant container or disposed of in accordance with local requirements.

Empty pens must never be reused and must be properly discarded.

To prevent possible transmission of disease, insulin pen should never be used by for more than one person, even when the needle is changed (see section 4.2).

## 7. MARKETING AUTHORISATION HOLDER

Sanofi israel ltd, Greenwork Park P.O. box 47, Yakum

## 8. MANUFACTURER

Sanofi-Aventis Deutschland GmbH, D-65926 Frankfurt am Main, Germany.

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