Certificate of a Medicinal Product[1]
Certificado de Medicamento[1]
Certificat de Médicament[1]

This Certificate conforms to the format recommended by the World Health Organization. (Explanatory notes attached) / El presente certificado se adapta al formato recomendado por la Organización Mundial de la Salud. (Se adjuntan notas explicativas) / Ce Certificat est conforme à la présentation recommandée par l'Organisation Mondiale de la Santé. (Voir notes explicatives ci-jointes)

No. of Certificate / N° de certificado / N° du certificat: ***06/19/137318***

Exporting (Certifying) region / Región exportadora (que certifica) / Région d'exportation (certificateur) :
European Union / Unión Europea / Union Européenne :

Belgium, Bulgaria, Czech Republic, Denmark, Germany, Estonia, Greece, Spain, France, Croatia, Ireland, Italy, Cyprus, Latvia, Lithuania, Luxembourg, Hungary, Malta, Netherlands, Austria, Poland, Portugal, Romania, Slovenia, Slovak Republic, Finland, Sweden and United Kingdom.

Bélgica, Bulgaria, República Checa, Dinamarca, Alemania, Estonia, Grecia, España, Francia, Croatie, Irlanda, Italia, Chipre, Letonia, Lituania, Luxemburgo, Hungría, Malta, Paises Bajos, Austria, Polonia, Portugal, Rumanía Eslovenia, República Eslovaca, Finlandia, Suecia y Reino Unido.

Belgique, Bulgarie, République tchèque, Danemark, Allemagne, Estonie, Grèce, Espagne, France, Croacia, Irlande, Italie, Chypre, Lettonie, Lituanie, Luxembourg, Hongrie, Malte, Pays-Bas, Autriche, Pologne, Portugal, Roumanie, Slovénie, Slovaquie, Finlande, Suède et Royaume-Uni.

Importing (requesting) country / País importador (solicitante) / Pays importateur (sollicitant):

CHILE

1 Name and pharmaceutical form of the product / Nombre y forma farmaceútica del medicamento / Dénomination et forme pharmaceutique du médicament:

TOUJEO Solution for injection

1.1 Active substance(s)[2] and amount(s) per unit dose or unit volume[3]:
Principio(s) activo(s)[2] y cantidad(es) por unidad de dosis o unidad de volumen[3]:
Substance(s) active(s)[2] et quantité(s) par unité de dose ou unité de volume[3]:

Insulin glargine; 300 Units/ml; 1, 3, 5, 10 pre-filled pens, 6 (2x3) or 9 (3x3) prefilled pens Multipack

For complete composition including excipients, see attached. [4]/ Para la composición completa incluidos los excipientes, véase información anexa. [4] / La composition complète du médicament, y compris les excipients, voir annexe. [4]

1.2 Is this product subject to a Community Marketing Authorisation? [5]
¿Está sujeto este medicamento a una autorización de comercialización comunitaria? [5]
Ce médicament fait-il l'objet d'une autorisation communautaire de mise sur le marché ? [5]

yes

Confidential

1.3 Is this product actually on the market in the exporting region?
¿Se encuentra este medicamento en el mercado de la región exportadora?
Ce médicament est- il actuellement commercialisé dans la région exportatrice?

yes

2.1 Number in the Community Register of Medicinal Products [7] and date of issue:
Número de autorización de comercialización comunitaria [7] y fecha de emisión:
Numéro au registre communautaire de mise sur le marché [7] et date de délivrance:

EU/1/00/133/033-041, 24.4.2015

2.2 Community Marketing Authorisation Holder (name and address):
Titular de la autorización de comercialización comunitaria (nombre y dirección):
Titulaire de l'autorisation communautaire de mise sur le marché (nom et adresse) :

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

2.3 Status of the Community Marketing Authorisation Holder: [8]
Estatus del titular de la autorización de comercialización comunitaria: [8]
Statut du titulaire de l'autorisation communautaire de mise sur le marché : [8]

a

2.3.1 For categories (b) and (c) the name and address of the manufacturer producing the pharmaceutical form is: [9]
Para las categorías (b) y (c), el nombre y dirección del fabricante que produce la forma farmaceútica es: [9]
Pour les catégories (b) et (c), nom et l'adresse du fabricant de la forme pharmaceutique considérée : [9]

Sanofi-Aventis Deutschland GmbH, Industriepark Höchst, Brüningstraße 50, D-65926 Frankfurt am Main, Germany (site also responsible for batch release in the EU, quality control, primary and secondary packaging).

2.4 Is the European Public Assessment Report (EPAR) appended? [10]
¿Se adjunta el informe europeo público de evaluación (EPAR)? [10]
Un rapport européen public d'evaluation (EPAR) est-il annexé ? [10]

no

2.5 Is the attached, officially approved product information included in the Community Marketing Authorisation?[11]
¿Se incluye la información sobre el medicamento adjunto en la autorización de comercialización comunitaria?[11]
L'information sur le médicament, officiellement approuvée, fait elle partie de l'autorisation communautaire de mise sur le marché ? [11]

yes

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2.6 Applicant for the Certificate, if different from the Community Marketing Authorisation Holder (name and address): [12]
Solicitante del Certificado, si es diferente del titular de la autorización de comercialización comunitaria (nombre y dirección): [12]
Demandeur du Certificat, s'il est autre que le titulaire de l'autorisation communautaire de mise sur le marché (nom et adresse) : [12]

3. Does the Certifying Authority arrange for periodic inspections of the manufacturing site in which the pharmaceutical form is produced?
¿La autoridad certificadora, dispone la inspección periódica de la planta de fabricación en que se produce la forma farmaceútica?
L'autorité certificatrice organise-t-elle des inspections périodiques de l'usine de production de la forme pharmaceutique?

yes

If no or not applicable, proceed to question 4 / Si no o no aplicable, pase a la pregunta 4 / Si la réponse est non ou sans objet, passer à la question 4.

3.1 Periodicity of routine inspections: ***Frequency of inspections is determined on risk-based approach.***
Periodicidad de las inspecciones de rutina: ***La frecuencia de las inspecciones esta basada en función del riesgo.***
Périodicité des inspections de routine: ***L'évaluation du risque détermine la fréquence des inspections.***

3.2 Has the manufacture of this type of pharmaceutical form been inspected?
¿Se ha inspeccionado la fabricación de este tipo de forma farmaceútica?
La fabrication de ce type de forme pharmaceutique a-t-elle fait l'objet d'une inspection?

yes

3.3 Do the facilities and operations conform to GMP as recommended by the World Health Organization? [15]
¿Se adaptan las instalaciones y procedimientos a las GMP recomendadas por la Organización Mundial de la Salud? [15]
Est-ce que l'établissement pharmaceutique est conforme aux BPF recommandées par l'Organisation Mondiale de la Santé ? [15]

yes

4. Does the information submitted by the applicant satisfy the Certifying Authority on all aspects of the manufacture of the product undertaken by another party? [16]
¿La información presentada por el solicitante satisface a la autoridad de certificación en relación a todos los aspectos de la fabricación del medicamento realizada por terceros? [16]
Les informations fournies par le demandeur satisfont-elles aux exigences des autorités certificatrices sur tous les aspects de la fabrication du médicament pris en charge par une tierce partie ? [16]

yes

EUROPEAN MEDICINES AGENCY

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EUROPEAN MEDICINES AGENCY

Certificate: 06/19/137318
Request: 75710

Address of the Certifying Authority / Dirección de la autoridad certificadora / Adresse de l'autorité certificatrice :

European Medicines Agency
Domenico Scarlattilaan 6, 1083 HS Amsterdam, The Netherlands

Telephone / Teléfono / Téléphone: ***+31 (0)88 781 6000***
E-mail / Correo electrónico / Courrier électronique: ***certificate@ema.europa.eu***

Name of authorised person / Nombre de la persona autorizada / Nom de la personne autorisée:

Brendan Cuddy

Signature / Firma / Signature:

Stamp and date / Sello y fecha / Tampon et date: ***9.10.2019***

Declaration

The undersigned, Jan Hein Frederik Siemerink , LL.M., civil-law notary, officiating in Amsterdam, the Netherlands, herewith declares that the signature on the attached document resembles the signature of:
Brendan Cuddy
as shown on a signatory list, provided by the European Medicines Agency on the 4th of June 2019.

This statement explicitly contains no judgment as (i) to the contents of the attached document and (ii) the authority and/or the competence of the signatory of the attached document (iii) the issuing authority of the document.
The undersigned has not informed the signatory of the document on the contents of the attached document and the consequences which will result from the contents of the attached document. Any and all liability of the undersigned and KB notarissen B.V. is excluded.

EUROPEAN MEDICINES AGENCY

KB notarissen B.V.
Prinses Irenestraat 43
1077 WV Amsterdam
0031(0)20 5407070

Amsterdam, the Netherlands, 16th of October 2019

J.H.F. Siemerink, LL.M., *Civil-law notary*

mr. Jan Hein Frederik Siemerink * Notaris te Amsterdam *

Confidential

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Country: THE NETHERLANDS
   This public document
2. has been signed by **mr. J.H.F. Slemerink**
3. acting in the capacity of notary at Amsterdam
4. bears the seal/stamp of aforesaid notary

Certified

5. in Amsterdam 6. on 17-10-2019
7. by the registrar of the district court of Amsterdam
8. no. 051885
9. Seal/stamp: 10. Signature:

J. Hoogeveen

RECHTBANK AMSTERDAM

Explanatory notes

[1] This Certificate, which is in the format recommended by WHO, establishes the status of the medicinal product and of the applicant for the Certificate in the exporting region at the time of issue. It is for a single product at a given point in time since manufacturing arrangements and approved information for different pharmaceutical forms and different strengths can vary.

[2] Whenever possible, International Non-proprietary Names (INNs) or national non-proprietary names are used.

[3] The formula (complete composition) of the pharmaceutical form is appended.

[4] Provision of the details of quantitative composition is attached on request of the Community Marketing Authorisation Holder.

[5] When applicable, details are appended of any conditions or restrictions applied to the supply and use of the product that is entered into the Community Marketing Authorisation.

[6] Not applicable.

[7] Indicated, when applicable, if the Community Marketing Authorisation has been granted under exceptional circumstances, conditional approval or if the product has not yet been approved.

[8] The person responsible for placing the product on the market:
(a) manufactures the pharmaceutical form;
(b) packages and/or labels a pharmaceutical form manufactured by an independent company; or
(c) is involved in none of the above.

[9] This information can only be provided with the consent of the Community Marketing Authorisation Holder or, in the case of non-registered products, the applicant. Non-completion of this section (2.3.1) indicates that the party concerned has not agreed to inclusion of this information. It should be noted that information concerning the site of production is part of the Community Marketing Authorisation. If the production site is changed, the Community Marketing Authorisation has to be updated or it is no longer valid.

[10] This refers to the document that summarises the technical basis on which the product has been authorised.

[11] This refers to the product information which forms a part of the Community Marketing Authorisation, such as the Summary of Product Characteristics (SPC).

[12] In this circumstance, permission for issuing the Certificate is required from the Community Marketing Authorisation Holder. This permission has to be provided to the European Medicines Agency by the applicant.

[13] If applicable the reason why the medicinal product does not have a Community Marketing Authorisation, e.g.:
(a) the product has been developed exclusively for the treatment of conditions – particularly tropical diseases - not endemic in the exporting region;
(b) the product has been reformulated with a view to improving its stability under tropical conditions;
(c) the product has been reformulated to exclude excipients not approved for use in medicinal products in the country of import;
(d) the product has been reformulated to meet a different maximum dosage limit for an active substance;
(e) any other reason, as specified.

[14] "Not applicable" means the manufacture is taking place in a region other than that issuing the Certificate and inspection is conducted under the aegis of the country of manufacture.

[15] The requirements for good practices in the manufacture and quality control of medicinal products referred to in the Certificate are those included in the thirty-second report of the Expert Committee on Specifications for Pharmaceutical Preparations (WHO Technical Report Series No 823, 1992, Annex 1). Recommendations specifically applicable to biological products have been formulated by the WHO Expert Committee on Biological Standardization (WHO Technical Report Series, No 822, 1992, Annex 1).

[16] This section is to be completed when the Community Marketing Authorisation Holder or applicant conforms to status (b) or (c) as described in note 8 above. It is of particular importance when foreign contractors are involved in the manufacture of the product. In these circumstances the applicant should supply the Certifying Authority with information to identify the contracting parties responsible for each stage of manufacture of the pharmaceutical form, and the extent and nature of any controls exercised over each of these parties.

STATEMENT OF QUANTITATIVE COMPOSITION
DECLARACIÓN DE COMPOSICIÓN CUANTITATIVA
ÉNONCÉ DE LA COMPOSITION QUANTITATIVE

1. Name and pharmaceutical form of the Medicinal Product:

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

2. Number(s) in the Community Register of Medicinal Products:

EU/1/00/133/033
EU/1/00/133/034
EU/1/00/133/035
EU/1/00/133/036
EU/1/00/133/037
EU/1/00/133/038
EU/1/00/133/039
EU/1/00/133/040
EU/1/00/133/041

3. Qualitative and quantitative composition of the Medicinal Product:
Composición cualitativa y cuantitativa del medicamento:
Composition qualitative et quantitative du médicament:

Active ingredient(s)[a]:	Quantities and units:					
	Percentage (%)	**Per mL (mg)**	**Per unit (1.5mL cartridge) (mg)**	**Per unit (3mL cartridge) (mg)**	**Function**	**Reference to standards[b]**
Insulin glargine [equivalent to U (units) of insulin glargine]	1.1	10.91 [300]	16.37 [450]	32.74 [900]	Drug substance	In-house
Other ingredient(s)[a]:	Quantities and units:					
Metacresol[c]	0.27	2.70	4.05	8.10	Antimicrobial preservative	Ph.Eur., USP
Zinc Chloride[d]	0.02	0.19	0.29	0.58	Stabilizing agent	Ph.Eur., USP
Glycerol (85 per cent)	2.0	20.00	30.00	60.00	Tonicity agent	Ph.Eur.
Sodium hydroxide	----	q.s. pH 4.0	q.s. pH 4.0	q.s. pH 4.0	Alkalizing agent	Ph.Eur., NF
Hydrochloric acid, concentrated [hydrochloric acid]	----	q.s. pH 4.0	q.s. pH 4.0	q.s. pH 4.0	Acidifying agent	Ph.Eur., NF

Water for injection	q.s. 100	q.s. 1.0 mL	q.s. 1.5mL	q.s. 3mL	Solvent	Ph.Eur.,
Nitrogen	Process aid for filtration					Ph.Eur.,

a Components are listed according to their pharmacopoeial names. If more than one monograph exists, other names are given in brackets, along with the compendial origin.
b Reference is made to the current edition of the Pharmacopoeia.
c For metacresol, the common chemical name "m-cresol" is also used within this document.
d Composition gives total zinc chloride amount from drug substance and from the manufacturing of the drug product.

SUMMARY OF PRODUCT CHARACTERISTICS

as relevant example

1. NAME OF THE MEDICINAL PRODUCT

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

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.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of diabetes mellitus in adults.

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.

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
The safety and efficacy of Toujeo in children and adolescents below 18 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 (see section 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

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.

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 hyperglycaemia. 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 aminoacids 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
Immune system disorders				Allergic reactions	
Metabolism and nutrition disorders	Hypoglycaemia				
Nervous system disorders					Dysgeusia
Eyes disorders				Visual impairment Retinopathy	
Skin and subcutaneous tissue disorders		Lipohypertrophy	Lipoatrophy		
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 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.

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
No clinical studies with Toujeo have been conducted in the paediatric population. Therefore, the safety profile of Toujeo has not been established.

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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.

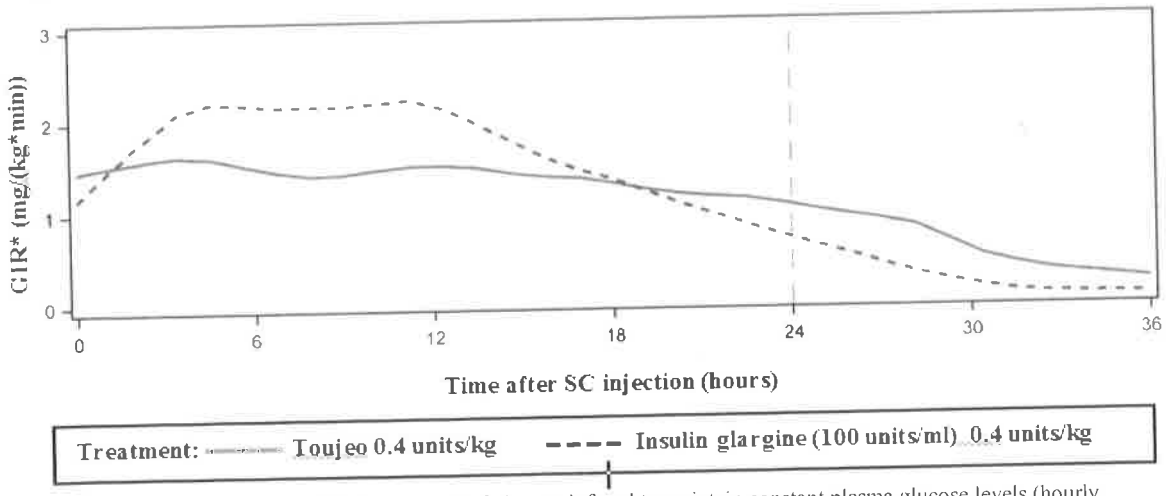
Mechanism of action
The primary activity of insulin, including insulin glargine, is regulation of glucose metabolism. Insulin and its analogues lower blood glucose levels by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin 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 euglycaemic 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 hypoglycaemia 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]*	
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.

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

Toujeo SoloStar
30 months.

Toujeo DoubleStar
24 months.

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, 5 and 10 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 1, 3, 6 (2 packs of 3), 9 (3 packs of 3) and 10 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 or Toujeo DoubleStar pre-filled pen, the Instructions for Use included in the package leaflet must be read carefully. Toujeo pre-filled pens 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 clear 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.
    - To 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-Aventis Deutschland GmbH, D-65926 Frankfurt am Main, Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/133/033
EU/1/00/133/034
EU/1/00/133/035
EU/1/00/133/036
EU/1/00/133/037
EU/1/00/133/038
EU/1/00/133/039
EU/1/00/133/040
EU/1/00/133/041

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27 June 2000
Date of latest renewal: 17 February 2015

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

LABELLING

as relevant example

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 300 units (10.91 mg) insulin glargine.
SoloStar pen:
Each pen contains 1.5 ml of solution, equivalent to 450 units.
DoubleStar pen:
Each pen contains 3 ml of solution, equivalent to 900 units.

3. LIST OF EXCIPIENTS

Zinc chloride, metacresol, glycerol, hydrochloric acid / sodium hydroxide (for pH adjustment), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in a pre-filled pen.
SoloStar pen:
1 pen
3 pens
5 pens
10 pens
DoubleStar pen:
1 pen
3 pens
10 pens

5. METHOD AND ROUTE(S) OF ADMINISTRATION

SoloStar pen
1 step=1 unit
DoubleStar pen:
1 step= 2 units
Read the package leaflet before use.
Open here
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Use only in this pen or severe overdose can result.
Always use a new needle for each injection.
For single patient use only.
Use only clear and colourless solutions.
450 units per pen (SoloStar pen)
900 units per pen (DoubleStar pen)

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Before first use
Store in a refrigerator.
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
The product may be stored for a maximum of 6 weeks below 30°C. Do not refrigerate. Put the pen cap back on the pen after each injection in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/133/033 1 pen (SoloStar)
EU/1/00/133/034 3 pens (SoloStar)
EU/1/00/133/035 5 pens (SoloStar)
EU/1/00/133/036 10 pens (SoloStar)
EU/1/00/133/037 1 pen (DoubleStar)
EU/1/00/133/038 3 pens (DoubleStar)
EU/1/00/133/041 10 pens (DoubleStar)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Toujeo 300 SoloStar
Toujeo 300 DoubleStar

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PEN LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Toujeo 300 units/ml SoloStar injection
Toujeo 300 units/ml DoubleStar injection
insulin glargine
Subcutaneous use

2. METHOD OF ADMINISTRATION

Use only in this pen or severe overdose can result.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1.5 ml **(SoloStar)**
3 ml (DoubleStar)

6. OTHER

SoloStar pen1 step=1 unit
DoubleStar pen
1 step=2 units

PACKAGE LEAFLET

as relevant example

Package leaflet: information for the user

Toujeo 300 units/ml SoloStar solution for injection in a pre-filled pen
Insulin glargine
Each SoloStar pen delivers 1-80 units in steps of 1 unit.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Toujeo is and what it is used for

Toujeo contains insulin called "insulin glargine". This is a modified insulin, very similar to human insulin.

Toujeo contains 3 times more insulin in 1 ml than standard insulin, which contains 100 unit/ml.

It is used to treat diabetes mellitus in adults. Diabetes mellitus is an illness where your body does not make enough insulin to control your blood sugar.

Toujeo lowers your blood sugar steadily over a long period of time. It is used for once daily dosing. You can change the time of your injection if you need to. This is because this medicine lowers your blood sugar over a long period of time (for more information, see section 3).

2. What you need to know before you use Toujeo

Do not use Toujeo
- If you are allergic to insulin glargine or to any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using Toujeo.

Follow closely the instructions for dose, monitoring (blood and urine tests), diet and physical activity (physical work and exercise) and injection technique, as discussed with your doctor.

Be especially aware of the following:
- Too low blood sugar (hypoglycaemia). If your blood sugar is too low, follow the guidance for hypoglycaemia (see information in the box at the end of this leaflet).
- If you switch from another type, brand or manufacturer of insulin your insulin dose may need to be changed.
- Pioglitazone. See "Pioglitazone used together with insulin".
- Ensure to use the right insulin. Medication errors due to mix-up between insulins, particularly between long-acting insulins and rapid-acting insulins have been reported. You must always check the insulin label before each injection to avoid mix-ups between Toujeo and other insulins.
- Never use a syringe to remove Toujeo from your SoloStar pre-filled pen. This is to avoid dosing errors and potential overdose which may lead to low blood sugar. Please, see also section 3.
- If you are blind or have poor eye sight, do not use the pre-filled pen without help. This is because you will not be able to read the dose window on the pen. Get help from a person with good eye sight who is trained in using the pen. If you have poor eyesight, please see section 3.

Illnesses and injuries
In the following situations, the management of your diabetes may require extra care (for example, blood and urine tests):
- If you are ill or have a major injury. Your blood sugar level may increase (hyperglycaemia).
- If you are not eating enough. Your blood sugar level may become too low (hypoglycaemia).

In most cases you will talk to a doctor. Contact a doctor as soon as you feel ill or get an injury.

If you have "Type 1" diabetes and you have an illness or injury:
- Do not stop your insulin
- Keep eating enough carbohydrates.

Always tell people who are caring or treating you, that you have diabetes.

Insulin treatment can cause the body to produce antibodies to insulin (substances that act against insulin). However, only very rarely, this will require a change to your insulin dose.

Travel
Talk to your doctor before travelling. You may need to talk about:
- If your type of insulin is available in the country you are visiting.
- How to arrange the supply of insulin, needles and other items.
- How to correctly store your insulin while travelling.
- The time you eat meals and use your insulin.
- The possible effects of changing to different time zones.
- Any health risks in the countries you will visit.
- What you should do in an emergency situation if you feel unwell or become ill.

Children and adolescents
This medicine should not be used in children or adolescents under 18 years of age. This is because there is no experience with Toujeo in this age group.

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

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

Your blood sugar level may fall (hypoglycaemia) if you take:
- Any other medicine to treat diabetes.
- Disopyramide – for some heart problems.

- Fluoxetine – for depression.
- Sulfonamide antibiotics.
- Fibrates – for lowering high levels of blood fats.
- Monoamine oxidase inhibitors (MAOIs) – for depression.
- Angiotensin converting enzyme (ACE) inhibitors – for heart problems or high blood pressure.
- Medicines to relieve pain and lower fever, such as pentoxifylline, propoxyphene and salicylates (such as acetylsalicylic acid).
- Pentamidine – for some infections caused by parasites. This may cause too low blood sugar which is sometimes followed by too high blood sugar.

Your blood sugar level may rise (hyperglycaemia) if you take:
- Corticosteroids such as cortisone – for inflammation.
- Danazol – for endometriosis.
- Diazoxide – for high blood pressure.
- Protease inhibitors- for HIV.
- Diuretics – for high blood pressure or fluid retention.
- Glucagon – for very low blood sugar.
- Isoniazid – for tuberculosis.
- Somatropin – a growth hormone.
- Thyroid hormones – for thyroid gland problems.
- Oestrogens and progestogens – such as in the contraceptive pill for birth control.
- Clozapine, olanzapine and phenothiazine derivatives – for mental health problems.
- Sympathomimetic medicines such as epinephrine (adrenaline), salbutamol and terbutaline – for asthma.

Your blood sugar level may either rise or fall if you take:
- Beta-blockers or clonidine – for high blood pressure.
- Lithium salts – for mental health problems.

Beta-blockers
Beta-blockers like other "Sympatholytic medicines" (such as clonidine, guanethidine, reserpine – for high blood pressure) may make it harder to recognise warning signs of your blood sugar being too low (hypoglycaemia). It can even hide or stop the first signs that your blood sugar is too low.

Pioglitazone used together with insulin
Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. If you experience signs of heart failure such as unusual shortness of breath, a rapid increase in weight or localised swelling (oedema). Inform your doctor as soon as possible.

If any of the above apply to you (or you are not sure), talk to your doctor, pharmacist or nurse before using Toujeo.

Toujeo with alcohol
Your blood sugar level may either rise or fall if you drink alcohol. You should check your blood sugar level more than usual.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you might be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine. Your insulin dose may need to be changed during pregnancy and after giving birth. For the health of your baby, it is particularly important to carefully control your diabetes and to prevent hypoglycaemia.
If you are breast-feeding, talk to your doctor, as your insulin doses and your diet might need to be changed.

Driving and using machines
Having too low or too high blood sugar or sight problems can affect your ability to drive and use tools or machines. Your concentration may be affected. This could be dangerous to yourself and others.

Ask your doctor whether you can drive if:
- Your blood sugar is often too low.
- You find it hard to recognise when your blood sugar is too low.

Important information about some of the ingredients of Toujeo
This medicine contains less than 1 mmol (23 mg) sodium per dose. This means it is essentially 'sodium-free'.

3. How to use Toujeo

Always use this medicine exactly as your doctor has told you. Check with your doctor, pharmacist or nurse if you are not sure.

Although Toujeo contains the same active substance as insulin glargine 100 units/ml, these medicines are not interchangeable. The switch from one insulin therapy to another requires medical prescription, medical supervision and blood glucose monitoring. Please, consult your doctor for further information.

How much to use
The Toujeo SoloStar pre-filled pen can provide a dose of 1 to 80 units in one injection, in steps of 1 unit.
The dose window of the SoloStar pen shows the number of units of Toujeo to be injected. Do not make any dose re-calculation.

Based on your lifestyle, your blood sugar tests and your previous insulin use, your doctor will tell you:
- How much Toujeo you need each day and at what time.
- When to check your blood sugar level and if you need to carry out urine tests.
- When you may need a higher or lower dose.

Toujeo is a long-acting insulin. Your doctor may tell you to use it with a short-acting insulin, or with other medicines for high blood sugar.

If you use more than one insulin always ensure you use the right insulin by checking the insulin label before each injection. Medication errors due to mix-up between insulins, particularly between long-acting insulins and rapid-acting insulins have been reported. The strength "300" is highlighted in honey gold on the label of your Toujeo SoloStar pre-filled pen. Ask your doctor or pharmacist if you are not sure.

Many factors may affect your blood sugar level. You should know these factors so that you can take the right action if your blood sugar level changes and help step it becoming too high or too low. See the box at the end of this leaflet for more information.

Flexibility in time of administration
- Use Toujeo once a day, preferably at the same time every day.
- When needed, you can inject it up to 3 hours before or after the usual time that you use it.

Use in elderly patients (65 years and over)
If you are 65 years or older, talk to your doctor as you may need a lower dose.

If you have kidney or liver problems
If you have kidney or liver problems, talk to your doctor as you may need a lower dose.

Before injecting Toujeo
- Read the instructions for use that come with this package leaflet.
- If you do not follow all of these instructions, you may get too much or too little insulin.

How to inject
- Toujeo is injected under the skin (subcutaneous use or "SC").
- Inject it into the front of your thighs, upper arms or the front of your waist (abdomen).
- Change the place within the area you inject each day. This will reduce the risk of skin shrinking or thickening (for more information, see "Other side effects" in section 4).

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

Always attach a new sterile needle before each injection. Never re-use needles. If you re-use a needle this increases the risk of it becoming blocked and of you getting too much or too little insulin.

Throw away the used needle in a puncture resistant container, or as told by your pharmacist or local authority.

Do not use Toujeo
- In a vein. This will change the way it works and may cause your blood sugar to become too low.
- In an insulin infusion pump.
- If there are particles in the insulin. The solution should be clear, colourless and water-like.

Never use a syringe to remove Toujeo from your SoloStar pen or severe overdose can result. Please, see also section 2.

If the SoloStar pen is damaged, has not been stored correctly, if you are not sure that it is working properly or you notice that your blood sugar control is unexpectedly getting worse:
- Throw the pen away and use a new one.
- Talk to your doctor, pharmacist or nurse if you think you have problem with your pen.

If you use more Toujeo than you should
If you have injected too much of this medicine, your blood sugar level may become too low. Check your blood sugar and eat more food to prevent you blood sugar getting too low. If your blood sugar gets too low, see the advice in the box at the end of this leaflet.

If you forget to use Toujeo
When needed, Toujeo can be injected up to 3 hours before or after the time you usually inject it.

If you have missed a dose of Toujeo or if you have not injected enough insulin, your blood sugar level may become too high (hyperglycaemia):
- Do not inject a double dose to make up for a forgotten dose.
- Check your blood sugar and then inject your next dose at the usual time.
- For information on the treatment of hyperglycaemia, see the box at the end of this leaflet.

<u>If you stop using Toujeo</u>
Do not stop using this medicine without talking to your doctor. If you do, it could lead to very high blood sugar and a build-up of acid in the blood (ketoacidosis).

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If you notice signs of your blood sugar being too low (hypoglycaemia), take action to increase your blood sugar level straight away (see the box at the end of this leaflet).
Hypoglycaemia can be very serious and is very common with insulin treatment (may affect more than 1 in 10 people).
Low blood sugar means that there is not enough sugar in your blood.
If your blood sugar falls too low, you may pass out (become unconscious).
Serious low blood sugar may cause brain damage and may be life-threatening.
For more information, see the box at the end of this leaflet.

Severe allergic reactions (rare, may affect up to 1 in 1,000 people).The signs may include rash and itching all over the body, swelling of skin or mouth, shortness of breath, feeling faint (a fall in blood pressure) with fast heart beat and sweating. Severe allergic reactions may become life-threatening.
Tell a doctor straight away if you notice signs of a severe allergic reaction.

Other side effects
Tell your doctor, pharmacist or nurse if you notice any of the following side effects:

Common: may affect up to 1 in 10 people

- Skin changes where the injection is given: If you inject insulin too often at the same place, the skin may either shrink (lipoatrophy) or thicken (lipohypertrophy). The insulin may not work very well. Change the injection site with each injection to help prevent these skin changes.
- Skin and allergic reactions at the injection site: The signs may include reddening, unusually intense pain when injecting, itching, hives, swelling or inflammation. This can spread around the injection site. Most minor reactions to insulins usually disappear in a few days to a few weeks.

Rare: may affect up to 1 in 1,000 people

- Eye reactions: A big change in your blood sugar control (getting better or worse) can disturb your vision. If you have an eye disorder related to diabetes called "proliferative retinopathy", very low blood sugar attack may cause temporary loss of vision.
- Swelling in the calves and ankles, caused by temporary build-up of water in the body.

Very rare: may affect up to 1 in 10,000 people

- Changes in taste (dysgeusia).
- Muscular pain (myalgia).

Tell your doctor, pharmacist or nurse if you notice any of the side effects above.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via **the national reporting system listed in Appendix V**. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Toujeo

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the label of the pen after "EXP". The expiry date refers to the last day of that month.

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 pen in the outer carton in order to protect from light.

After first use or if carried as a spare
Do not store the pen in a refrigerator. The pen may be stored for a maximum of 6 weeks below 30°C and away from direct heat or direct light. Discard the pen after this time period. Do not leave your insulin in a car on an exceptionally warm or cold day. Always keep the cap on the pen when you are not using it in order to protect from light.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer used. These measures will help protect the environment.

6. Contents of the pack and other information

What Toujeo contains
- The active substance is insulin glargine. Each ml of the solution contains 300 units of insulin glargine (equivalent to 10.91 mg). Each pen contains 1.5 ml of solution for injection, equivalent to 450 units.
- The other ingredients are: zinc chloride, metacresol, glycerol, water for injections, and sodium hydroxide (see section 2 "Important information about some of the ingredients of Toujeo") and hydrochloric acid (for pH adjustment).

What Toujeo looks like and contents of the pack
Toujeo is a clear and colourless solution.
Each pen contains 1.5 ml of solution for injection (equivalent to 450 units).
Packs of 1, 3, 5 and 10 pre-filled pens.
Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Sanofi-Aventis Deutschland GmbH, D-65926 Frankfurt am Main, Germany.

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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This leaflet was last revised in

Other source of information
Detailed information on this medicine is available on the European Medicines Agency web site:
http://www.ema.europa.eu/

HYPERGLYCAEMIA AND HYPOGLYCAEMIA

If you take insulin, you should always carry the following things with you:

- Sugar (at least 20 grams).
- Information so that others know you have diabetes.

Hyperglycaemia (high blood sugar levels)

If your blood sugar is too high (hyperglycaemia), you may not have injected enough insulin.

Reasons why hyperglycaemia may happen:
Examples include:

- You have not injected your insulin or not injected enough.
- Your insulin has become less effective – for example because it was not stored properly.
- Your insulin pen does not work properly.
- You are doing less exercise than usual.
- You are under stress – such as emotional distress or excitement.
- You have an injury, infection or fever or have had an operation.
- You are taking or have taken certain other medicines (see section 2, "Other medicines and Toujeo").

Warning signs of hyperglycaemia
Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat, and glucose and ketone bodies in urine. Stomach pain, fast and deep breathing, feeling sleepy or passing out (becoming unconscious) may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

What to do if you experience hyperglycaemia

- Test your blood sugar level and your urine for ketones as soon as you notice any of the above signs
- Contact your doctor straight away if you have severe hyperglycaemia or ketoacidosis. This must always be treated by a doctor, normally in a hospital.

Hypoglycaemia (low blood sugar levels)

If your blood sugar level falls too much you may pass out (become unconscious). Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. You should learn to recognise the signs when your blood sugar is falling – so you can take action to stop it getting worse.

Reasons why hypoglycaemia may happen:
Examples include:

- You inject too much insulin.
- You miss meals or delay them.
- You do not eat enough, or eat food containing less sugar (carbohydrate) than normal – artificial sweeteners are not carbohydrates.
- You drink alcohol – especially when you have not eaten much.
- You lose carbohydrates from being sick (vomiting) or diarrhoea.
- You are doing more exercise than usual or a different type of physical activity.
- You are recovering from an injury, operation or other stress.
- You are recovering from an illness or from fever.
- You are taking or have stopped taking certain other medicines (see section 2, "Other medicines and Toujeo").

Hypoglycaemia is also more likely to happen if:

- You have just started insulin treatment or changed to another insulin – if low blood sugar occurs, it may be more likely to happen in the morning.
- Your blood sugar levels are almost normal or are unstable.
- You change the area of skin where you inject insulin. For example from the thigh to the upper arm.
- You have severe kidney or liver disease, or some other disease such as hypothyroidism.

Warning signs of hypoglycaemia

The first signs may be in your body generally. Examples of signs that your blood sugar level is falling too much or too fast include: sweating, clammy skin, feeling anxious, fast or irregular heart beat, high blood pressure and palpitations. These signs often develop before the signs of a low sugar level in the brain.

Signs in your brain include: headaches, feeling very hungry, feeling sick (nausea) or being sick (vomiting), feeling tired, sleepy, restless, sleeping problems, aggressive behaviour, difficulty concentrating, slow reactions, depression, feeling confused, difficulty speaking (sometimes total loss of speech), changes in your sight, trembling, being unable to move (paralysis), tingling in the hands or arms, feeling numb and tingling often around the mouth, feeling dizzy, loss of self-control, being unable to look after yourself, fits, passing out.

When the signs of hypoglycaemia may be less clear:

The first warning signs of hypoglycaemia may change, be weaker or missing altogether if:

- You are elderly.
- You have had diabetes for a long time.
- You have a certain type of nervous disease (called "diabetic autonomic neuropathy").
- You have recently had too low blood sugar (for example the day before).
- Your low blood sugar comes on slowly.
- Your low blood sugar is always around "normal" or your blood sugar has got much better.
- You have recently changed from an animal insulin to a human insulin, like Toujeo.
- You are taking or have taken certain other medicines (see section 2, "Other medicines and Toujeo").

In such cases, you may develop severe hypoglycaemia (and even pass out) before you know what is happening. Be familiar with your warning signs. If necessary, you might need to test your blood sugar more often. This can help to spot mild hypoglycaemic episodes. If you find it difficult to recognise your warning signs, you should avoid situations (such as driving a car) in which you or others would be put at risk by hypoglycaemia.

What to do if you experience hypoglycaemia?

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

What other people should do if you have hypoglycaemia

Tell your relatives, friends and close colleagues to get medical help straight away if you are not able to swallow or if you pass out (become unconscious).

You will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections should be given even if it is not certain that you have hypoglycaemia.

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

Toujeo 300 units/ml solution for injection in a pre-filled pen (SoloStar)
INSTRUCTIONS FOR USE

Read this first

Toujeo SoloStar contains 300 units/ml insulin glargine in a 1.5 ml disposable prefilled pen

- **Never re-use needles.** If you do you might not get your dose (underdosing) or get too much (overdosing) as the needle could block.
- **Never use a syringe to remove insulin from your pen.** If you do you will get too much insulin. The scale on most syringes is made for non-concentrated insulin only.

Important information

✗ Never share your pen – it is only for you.
✗ Never use your pen if it is damaged or if you are not sure that it is working properly.
✓ Always perform a safety test
✓ Always carry a spare pen and spare needles in case they got lost or stop working.

Learn to inject

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

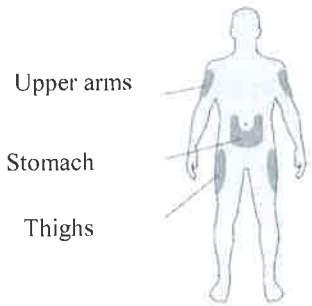
Need help?

If you have any questions about your pen or about diabetes, ask your doctor, pharmacist or nurse or call sanofi-aventis number on the front of this leaflet.

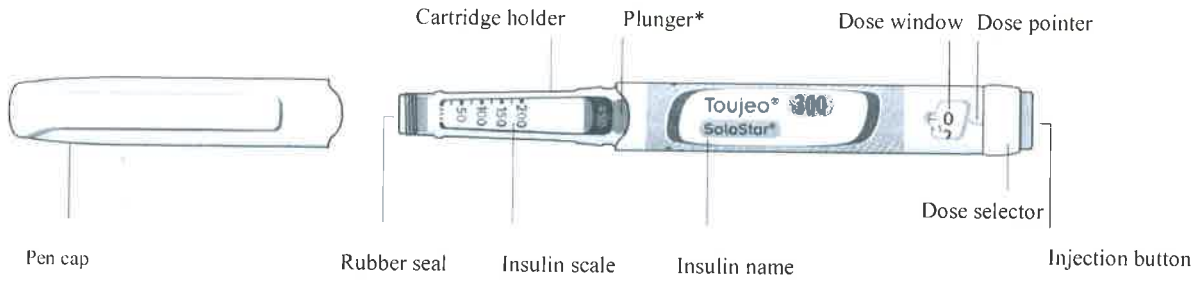
Extra items you will need:

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

Places to inject



Get to know your pen



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

STEP 1: Check your pen

Take a new pen out of the fridge at least 1 hour before you inject. Cold insulin is more painful to inject.

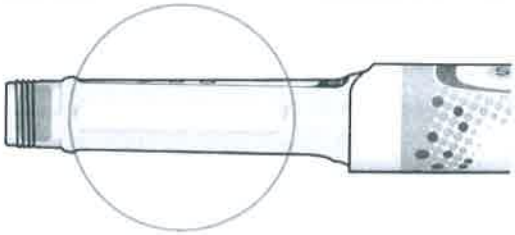
A Check the name and expiration date on the label of your pen.

- Make sure you have the correct insulin. This is especially important if you have other injector pens.
- Never use your pen after the expiration date.

B Pull off the pen cap.

C Check that the insulin is clear.

- Do not use the pen if the insulin looks cloudy, coloured or contains particles.



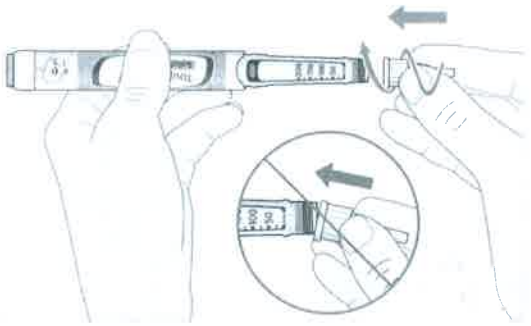
STEP 2: Attach a new needle

✓ Always use a new sterile needle for each injection. This helps stop blocked needles, contamination and infection.

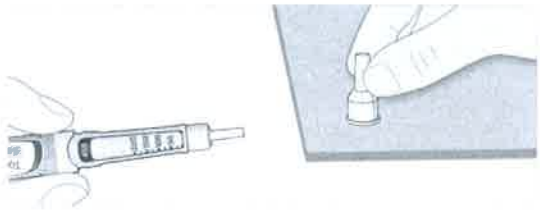
✓ Only use needles that are compatible for use with Toujeo (e.g. needles from BD, Ypsomed, Artsana or Owen Mumford).

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

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



C Pull off the outer needle cap. Keep this for later.



D Pull off the inner needle cap and throw away.

Handling needles

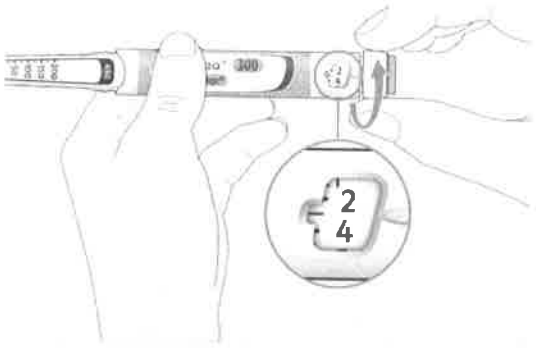
- Take care when handling needles – this is to prevent needle injury and cross-infection.

STEP 3: Do a safety test

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

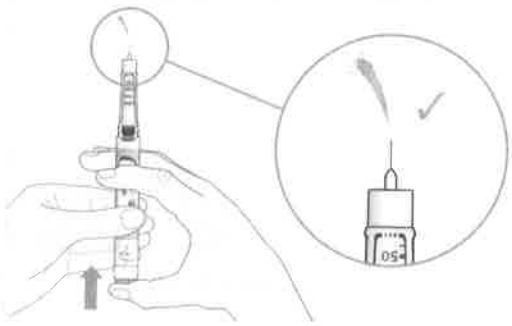
- check your pen and the needle are working properly.
- make sure that you get the correct insulin dose.

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



B Press the injection button all the way in.

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



If no insulin appears:

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

If you see air bubbles

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

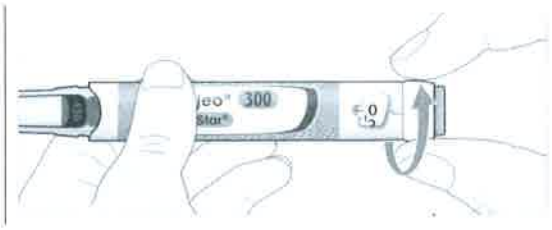
STEP 4: Select the dose

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

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

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

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



How to read the dose window

Even numbers are shown in line with the dose pointer:

30 units selected

Odd numbers are shown as a line between even numbers:

29 units selected

Units of insulin in your pen

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

STEP 5: Inject your dose

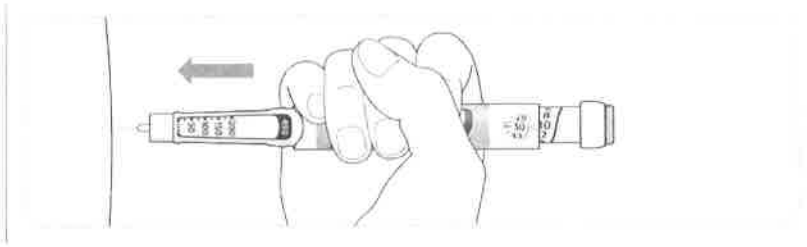
✗

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

A Choose a place to inject as shown in the picture

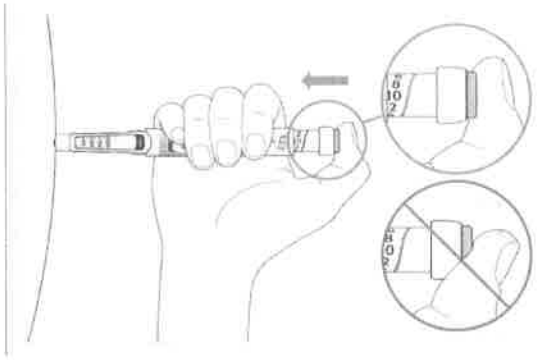
B Push the needle into your skin as shown by your doctor, pharmacist or nurse.

- Do not touch the injection button yet.



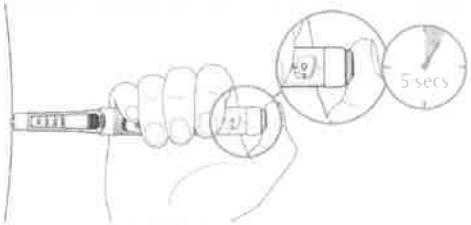
C Place your thumb on the injection button. Then press all the way in and hold.

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



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

- This will make sure you get your full dose.



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

If you find it hard to press the button in:

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

STEP 6: Remove the needle

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

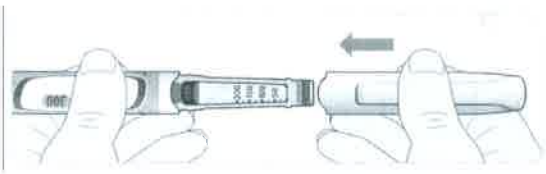
A Put the outer needle cap back on the needle, and use it to unscrew the needle from the pen.

- To reduce the risk of accidental needle injury, never replace the inner needle cap.
- If your injection is given by another person, or if you are giving an injection to another person, special caution must be taken by this person when removing and disposing of the needle.
- Follow recommended safety measures for removal and disposal of needles (contact your doctor, pharmacist or nurse) in order to reduce the risk of accidental needle injury and transmission of infectious diseases.

B Throw away the used needle in a puncture resistant container, or as told by your pharmacist or local authority.

C Put the pen cap back on.

- Do not put the pen back in the fridge.



Use by

- Only use your pen for up to 6 weeks after its first use.

How to store your pen

Before first use

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

After first use

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

How to care for your pen

Handle your pen with care

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

Protect your pen from dust and dirt

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

Throwing your pen away

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