1. NAME OF THE MEDICINAL PRODUCT

Lantus SoloStar 100 units/ml solution for injection in a pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 100 units insulin glargine*(equivalent to 3.64 mg).
Each pen contains 3 ml of solution for injection, equivalent to 300 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 in a pre-filled pen SoloStar.
Lantus is a clear colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of adults, adolescents and children of 6 years or above with diabetes mellitus, where treatment with insulin is required.

4.2 Posology and method of administration

Posology

Lantus contains insulin glargine, an insulin analogue, and has a prolonged duration of action. Lantus should be administered once daily at any time but at the same time each day.

The Lantus dose regimen (dose and timing) should be individually adjusted. In patients with type 2 diabetes mellitus, Lantus can also be given together with orally active antidiabetic medicinal products. The potency of this medicinal product is stated in units. These units are exclusive to Lantus and are not the same as IU or the units used to express the potency of other insulin analogues (see section 5.1).

Special population

Elderly population (≥65 years old)

In the elderly, progressive deterioration of renal function may lead to a steady decrease in insulin requirements.

Renal impairment

In patients with renal impairment, insulin requirements may be diminished due to reduced insulin metabolism.

Hepatic impairment

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

Children

In children, efficacy and safety of Lantus have only been demonstrated when given in the evening. Due to limited experience, the efficacy and safety of Lantus have not been demonstrated in children below the age of 6 years.

Switch from other insulins to Lantus

When switching from a treatment regimen with an intermediate or long-acting insulin to a regimen with Lantus, a change of the dose of the basal insulin may be required and the concomitant antidiabetic treatment may need to be adjusted (dose and timing of additional regular insulins or fast-acting insulin analogues or the dose of oral antidiabetic medicinal products).

Switch from twice daily NPH insulin to Lantus

To reduce the risk of nocturnal and early morning hypoglycaemia, patients who are changing their

basal insulin regimen from a twice daily NPH insulin to a once daily regimen with Lantus should reduce their daily dose of basal insulin by 20-30% during the first weeks of treatment.

Switch from insulin glargine 300 units/ml to Lantus
Lantus and Toujeo (insulin glargine 300 units/ml) are not bioequivalent and are not directly interchangeable. To reduce the risk of hypoglycemia, patients who are changing their basal insulin regimen from an insulin regimen with once daily insulin glargine 300 units/ml to a once daily regimen with Lantus should reduce their dose by approximately 20%.

During the first weeks the reduction should, at least partially, be compensated by an increase in mealtime insulin, after this period the regimen should be adjusted individually.

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, change of timing of insulin dose or other circumstances arise that increase susceptibility to hypo-or hyperglycaemia (see section 4.4).

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

Method of administration
Lantus is administered subcutaneously.

Lantus should not be administered intravenously. The prolonged duration of action of Lantus is dependent on its injection into subcutaneous tissue. Intravenous administration of the usual subcutaneous dose could result in severe hypoglycaemia.

There are no clinically relevant differences in serum insulin or glucose levels after abdominal, deltoid or thigh administration of Lantus. Injection sites must be rotated within a given injection area from one injection to the next in order to reduce the risk of lipodystrophy and cutaneous amyloidosis (see section 4.4 and 4.8).

Lantus must not be mixed with any other insulin or diluted. Mixing or diluting can change its time/action profile and mixing can cause precipitation.

Lantus SoloStar 100 units/ml in pre-filled pen is only suitable for subcutaneous injections. If administration by syringe is necessary, a vial should be used (see section 4.4).
Before using SoloStar, the instructions for use included in the package leaflet must be read carefully (see section 6.6).

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

4.4 Special warnings and precautions for use
Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

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

Safety and efficacy of Lantus has been established in adolescents and children of 6 years and above. Due to limited experience the efficacy and safety of Lantus could not be assessed in children below 6

years of age, in patients with impaired liver function or in patients with moderate / severe renal impairment (see section “Posology and method of administration”).

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.

Transferring a patient to another type or brand of insulin 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.

Patients must be instructed to perform continuous rotation of the injection site to reduce the risk of developing lipodystrophy and cutaneous amyloidosis. There is a potential risk of delayed insulin absorption and worsened glycaemic control following insulin injections at sites with these reactions. A sudden change in the injection site to an unaffected area has been reported to result in hypoglycaemia. Blood glucose monitoring is recommended after the change in the injection site, and dose adjustment of antidiabetic medications may be considered.

Hypoglycaemia
The time of occurrence of hypoglycaemia depends on the action profile of the insulins used and may, therefore, change when the treatment regimen is changed. Due to more sustained basal insulin supply with Lantus, less nocturnal but more early morning hypoglycaemia can be expected.

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 stenoses 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 subcutaneous 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 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).

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 (see section 5.1).

Handling of the SoloStar pre-filled pen
Lantus SoloStar 100 units/ml in pre-filled pen is only suitable for subcutaneous injections. If administration by syringe is necessary, a vial should be used (see section 4.2).
Before using SoloStar, the instructions for use included in the package leaflet must be read carefully. SoloStar has to be used as recommended in these instructions for use (see section 6.6).

Medication errors
Medication errors have been reported in which other insulins, particularly short-acting insulins, have been accidentally administered instead of insulin glargine. Insulin label must always be checked before each injection to avoid medication errors between insulin glargine and other insulins.

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 oral antidiabetic 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

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 1000 pregnancy outcomes) indicate no specific adverse effects of insulin glargine on pregnancy and no specific malformative nor feto/neonatal toxicity of insulin glargine. Animal data do not indicate reproductive toxicity.
The use of Lantus may be considered during pregnancy, if clinically needed.

It is essential for patients with pre-existing or gestational diabetes to maintain good metabolic control throughout pregnancy to prevent adverse outcomes associated with hyperglycemia. Insulin requirements may decrease during the first trimester and generally increase during the second and third trimesters. Immediately after delivery, insulin requirements decline rapidly (increased risk of hypoglycaemia). Careful monitoring of glucose control is essential.

Breast-feeding

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

Fertility

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

4.7 Effects on ability to drive and use machines

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

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

4.8 Undesirable effects

Summary of the safety profile

Hypoglycaemia (very common), 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 (see section 4.4).

Tabulated list of adverse reactions

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

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

MedDRA system organ classes	**Very common**	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not known**
Immune				Allergic		

system disorders				reactions		
Metabolism and nutrition disorders	Hypoglycae-mia					
Nervous system disorders					Dysgeusia	
Eyes disorders				Visual impairment Retinopathy		
Skin and subcutaneous tissue disorders		Lipohypertro-phy	Lipoatrophy			Cutaneous amyloidosis
Musculoskeletal and connective tissue disorders					Myalgia	
General disorders and administration site conditions		Injection site reactions		Oedema		

Description of selected adverse reactions

Metabolism and nutrition disorders

Severe hypoglycaemic attacks, especially if recurrent, may lead to neurological damage. Prolonged or severe hypoglycaemic episodes may be life-threatening.

In many patients, the signs and symptoms of neuroglycopenia are preceded by signs of adrenergic counter-regulation. Generally, the greater and more rapid the decline in blood glucose, the more marked is the phenomenon of counter-regulation and its symptoms (see section 4.4).

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.

Eyes disorders

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

Long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy. However, intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy. In patients with proliferative retinopathy, particularly if not treated with photocoagulation, severe hypoglycaemic episodes may result in transient amaurosis.

Skin and subcutaneous tissue disorders

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

General disorders and administration site conditions

Injection site reactions include redness, pain, itching, hives, swelling, or inflammation. Most minor

reactions to insulins at the injection site usually resolve in a few days to a few weeks.

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

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.

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
Insulin glargine is a human insulin analogue designed to have a low solubility at neutral pH. It is completely soluble at the acidic pH of the Lantus injection solution (pH 4). After injection into the subcutaneous tissue, the acidic solution is neutralised leading to formation of micro-precipitates from which small amounts of insulin glargine are continuously released, providing a smooth, peakless, predictable concentration/time profile with a prolonged duration of action.

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 halfmaximal 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 Lantus therapy, are considerably lower than the pharmacological concentrations required to activate the IGF-1 pathway.

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,

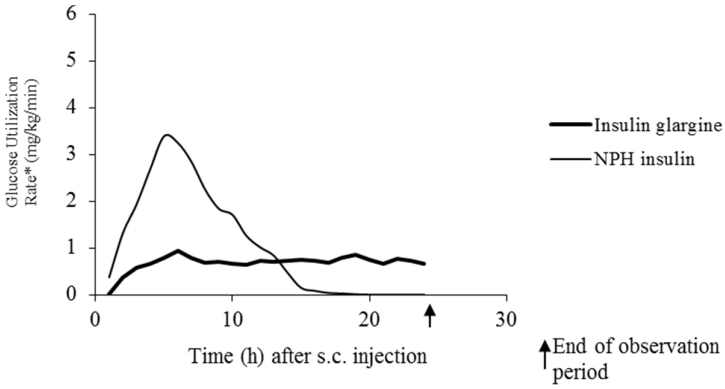
especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin inhibits lipolysis in the adipocyte, inhibits proteolysis and enhances protein synthesis.

In clinical pharmacology studies, 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.

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

The following graph shows the results from a study in patients:

Activity Profile in Patients with Type 1 Diabetes



*determined as amount of glucose infused to maintain constant plasma glucose levels (hourly mean values)

The longer duration of action of subcutaneous insulin glargine is directly related to its slower rate of absorption and supports once daily administration. The time course of action of insulin and insulin analogues such as insulin glargine may vary considerably in different individuals or within the same individual.

In a clinical study, symptoms of hypoglycaemia or counter-regulatory hormone responses were similar after intravenous insulin glargine and human insulin both in healthy volunteers and patients with type 1 diabetes.

In clinical studies, antibodies that cross-react with human insulin and insulin glargine were observed with the same frequency in both NPH-insulin and insulin glargine treatment groups.

Effects of insulin glargine (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 glargine was compared to NPH insulin.

The ORIGIN (Outcome Reduction with Initial Glargine INtervention) study was a multicenter, randomised, 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 randomised (1:1) to receive insulin glargine (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 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 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 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 and 0.30 for standard care group and the rates of confirmed non-severe hypoglycaemia were 7.71 for insulin glargine and 2.44 for standard care group. Over the course of this 6-year study, 42% of the insulin glargine 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 group and a mean decrease of 0.8 kg in the standard care group.

Paediatric population

In a randomised, controlled clinical study, paediatric patients (age range 6 to 15 years) with type 1 diabetes (n=349) were treated for 28 weeks with a basal-bolus insulin regimen where regular human insulin was used before each meal. Insulin glargine was administered once daily at bedtime and NPH human insulin was administered once or twice daily. Similar effects on glycohemoglobin and the incidence of symptomatic hypoglycemia were observed in both treatment groups, however fasting plasma glucose decreased more from baseline in the insulin glargine group than in the NPH group. There was less severe hypoglycaemia in the insulin glargine group as well. One hundred forty-three of the patients treated with insulin glargine in this study continued treatment with insulin glargine in an uncontrolled extension study with mean duration of follow-up of 2 years. No new safety signals were seen during this extended treatment with insulin glargine.

A crossover study comparing insulin glargine plus lispro insulin to NPH plus regular human insulin (each treatment administered for 16 weeks in random order) in 26 adolescent type 1 diabetic patients.

aged 12 to 18 years was also performed. As in the paediatric study described above, fasting plasma glucose reduction from baseline was greater in the insulin glargine group than in the NPH group. HbA1c changes from baseline were similar between treatment groups; however blood glucose values recorded overnight were significantly higher in the insulin glargine/ lispro group than the NPH/regular group, with a mean nadir of 5.4 mM versus 4.1 mM. Correspondingly, the incidences of nocturnal hypoglycaemia were 32% in the insulin glargine / lispro group versus 52% in the NPH / regular group.

A 24-week parallel group study was conducted in 125 children with type 1 diabetes mellitus aged 2 to 6 years, comparing insulin glargine given once daily in the morning to NPH insulin given once or twice daily as basal insulin. Both groups received bolus insulin before meals.
The primary aim of demonstrating non-inferiority of insulin glargine to NPH in all hypoglycaemia was not met and there was a trend to an increase of hypoglycemic events with insulin glargine [insulin glargine: NPH rate ratio (95% CI) = 1.18 (0.97-1.44)].
Glycohaemoglobin and glucose variabilities were comparable in both treatment groups. No new safety signals were observed in this study.

5.2 Pharmacokinetic properties

In healthy subjects and diabetic patients, insulin serum concentrations indicated a slower and much more prolonged absorption and showed a lack of a peak after subcutaneous injection of insulin glargine in comparison to human NPH insulin. Concentrations were thus consistent with the time profile of the pharmacodynamic activity of insulin glargine. The graph above shows the activity profiles over time of insulin glargine and NPH insulin.

Insulin glargine injected once daily will reach steady state levels in 2-4 days after the first dose. When given intravenously the elimination half-life of insulin glargine and human insulin were comparable.

After subcutaneous injection of Lantus in diabetic patients, insulin glargine is rapidly metabolized at the carboxyl terminus of the Beta chain with formation of two active metabolites M1. (21A-Gly-insulin) and M2 (21A-Gly-des-30B-Thr-insulin). In plasma, the principal circulating compound is the metabolite M1. The exposure to M1 increases with the administered dose of Lantus. The pharmacokinetic and pharmacodynamic findings indicate that the effect of the subcutaneous injection with Lantus 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 of Lantus.

In clinical studies, subgroup analyses based on age and gender did not indicate any difference in safety and efficacy in insulin glargine-treated patients compared to the entire study population.

Paediatric population

Pharmacokinetics in children aged 2 to less than 6 years with type 1 diabetes mellitus was assessed in one clinical study (see section 5.1). Plasma “trough” levels of insulin glargine and its main M1 and M2 metabolites were measured in children treated with insulin glargine, revealing plasma concentration patterns similar to adults, and providing no evidence for accumulation of insulin glargine or its metabolites with chronic dosing.

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

This medicinal product must not be mixed with other medicinal products.

6.3 Shelf-life

3 years.

Shelf life after first use of the pen

The medicinal product may be stored for a maximum of 4 weeks not above 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

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

In-use SoloStar pens
For storage conditions after first opening of this medicinal product, see section 6.3.

6.5 Nature and contents of container

Type 1 colourless glass cartridge with a black plunger (bromobutyl rubber) and a flanged cap (aluminium) with a stopper (bromobutyl or laminate of polyisoprene and bromobutyl rubber) containing 3 ml of solution. The cartridge is sealed in a disposable pen injector. Needles are not included in the pack. Packs of 1, 3, 4, 5, 6, 8, 9 and 10 SoloStar pre-filled pens are available. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Inspect Lantus 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 Lantus is a solution, it does not require resuspension before use.
Lantus must not be mixed with any other insulin or diluted. Mixing or diluting can change its time/action profile and mixing can cause precipitation.
Insulin label must always be checked before each injection to avoid medication errors between insulin glargine and other insulins (see section 4.4).

Lantus SoloStar 100 units/ml in pre filled pen is only suitable for subcutaneous injections. If administration by syringe is necessary, a vial should be used (see section 4.2 and 4.4).
Before first use, the pre-filled pen must be stored at room temperature for 1 to 2 hours.
Empty pre-filled pens must never be reused and must be properly discarded.
To prevent the possible transmission of disease, each pen must be used by one patient only.
Before using the pre-filled pen, the instructions for use included in the package leaflet must be read carefully.

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

Revision: Nov 2020 (CCDS V20)

Lantus® SoloStar® Solution for injection in a pre-filled pen

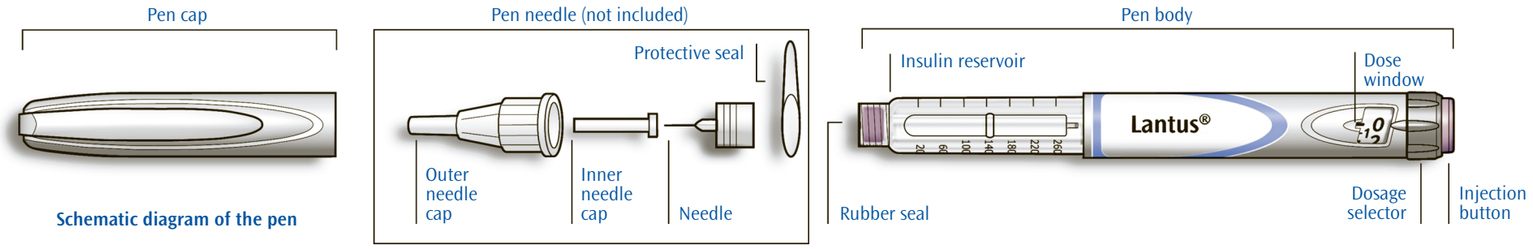
SANOFI

INSTRUCTIONS FOR USE

SoloStar is a pre-filled pen for the injection of insulin. Your doctor has decided that SoloStar is appropriate for you based on your ability to handle SoloStar. Talk with your doctor, pharmacist or nurse about proper injection technique before using SoloStar.
Read these instructions carefully before using your SoloStar. If you are not able to use SoloStar or follow all the instructions completely on your own, you must use SoloStar only if you have help from a person who is able to follow the instructions completely. Hold the pen as shown in this leaflet. To ensure that you read the dose correctly, hold the pen horizontally, with the needle on the left and the dosage selector to the right as shown in the illustrations below. You can set doses from 1 to 80 units in steps of 1 unit. Each pen contains multiple doses.

Keep this leaflet for future reference.

If you have any questions about SoloStar or about diabetes, ask your healthcare professional or call the local sanofi-aventis number.



Schematic diagram of the pen

Important information for use of SoloStar:

- Always attach a new needle before each use. Only use needles that are compatible for use with SoloStar.
- Do not select a dose and/or press the injection button without a needle attached.
- Always perform the safety test before each injection (see Step 3).
- This pen is only for your use. Do not share it with anyone else.
- If your injection is given by another person, special caution must be taken by this person to avoid accidental needle injury and transmission of infection.
- Never use SoloStar if it is damaged or if you are not sure that it is working properly.
- Always have a spare SoloStar in case your SoloStar is lost or damaged.

Step 1. Check the insulin

A. Check the label on your SoloStar to make sure you have the correct insulin. The Lantus SoloStar is grey with a purple injection button.

B. Take off the pen cap.

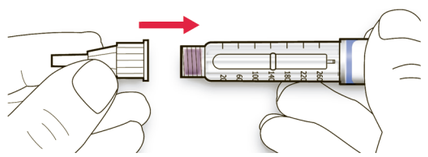
C. Check the appearance of your insulin. Lantus is a clear insulin. Do not use this SoloStar if the insulin is cloudy, coloured or has particles.

Step 2. Attach the needle

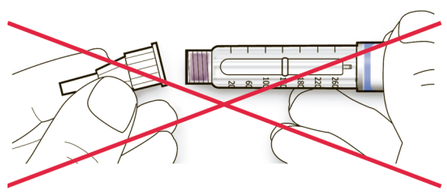
Always use a new sterile needle for each injection. This helps prevent contamination, and potential needle blocks.

A. Remove the protective seal from a new needle.

B. Line up the needle with the pen, and keep it straight as you attach it (screw or push on, depending on the needle type).



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

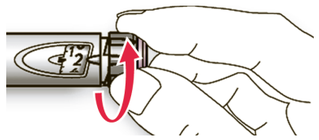


Step 3. Perform a Safety test

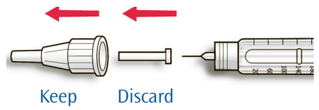
Always perform the safety test before each injection. This ensures that you get an accurate dose by:

- ensuring that pen and needle work properly
- removing air bubbles

A. Select a dose of 2 units by turning the dosage selector.



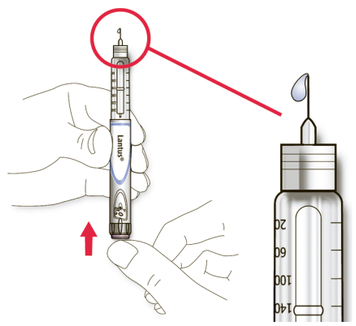
B. Take off the outer needle cap and keep it to remove the used needle after injection
Take off the inner needle cap and discard it.



C. Hold the pen with the needle pointing upwards.

D. Tap the insulin reservoir so that any air bubbles rise up towards the needle.

E. Press the injection button all the way in. Check if insulin comes out of the needle tip.



You may have to perform the safety test several times before insulin is seen.

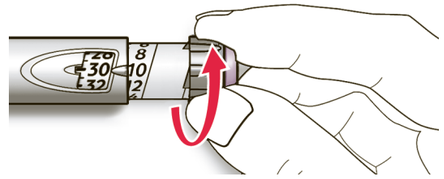
- If no insulin comes out, check for air bubbles and repeat the safety test two more times to remove them.
- If still no insulin comes out, the needle may be blocked. Change the needle and try again.
- If no insulin comes out after changing the needle, your SoloStar may be damaged. Do not use this SoloStar.

Step 4. Select the dose

You can set the dose in steps of 1 unit, from a minimum of 1 unit to a maximum of 80 units. If you need a dose greater than 80 units, you should give it as two or more injections.

A. Check that the dose window shows "0" following the safety test.

B. Select your required dose (in the example below, the selected dose is 30 units).
If you turn past your dose, you can turn back down.

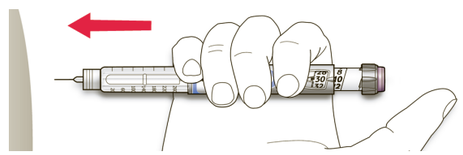


- Do not push the injection button while turning, as insulin will come out.
- You cannot turn the dosage selector past the number of units left in the pen. Do not force the dosage selector to turn. In this case, either you can inject what is remaining in the pen and complete your dose with a new SoloStar or use a new SoloStar for your full dose.

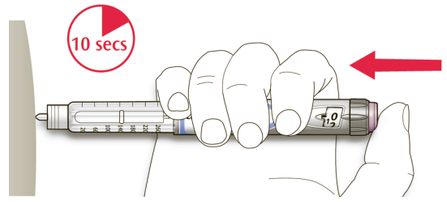
Step 5. Inject the dose

A. Use the injection method as instructed by your healthcare professional.

B. Insert the needle into the skin.



C. Deliver the dose by pressing the injection button in all the way. The number in the dose window will return to "0" as you inject.



D. Keep the injection button pressed all the way in. Slowly count to 10 before you withdraw the needle from the skin. This ensures that the full dose will be delivered.
The pen plunger moves with each dose. The plunger will reach the end of the cartridge when the total of 300 units of insulin has been used.

Step 6. Remove and discard the needle

Always remove the needle after each injection and store SoloStar without a needle attached.

This helps prevent:

- Contamination and/or infection,
- Entry of air into the insulin reservoir and leakage of insulin, which can cause inaccurate dosing.

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 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. Dispose of the needle safely, as instructed by your healthcare professional.

C. Always put the pen cap back on the pen, then store the pen until your next injection.

Storage Instructions

See the reverse (insulin) side of this leaflet for instructions on how to store SoloStar.

If your SoloStar is in cool storage, take it out 1 to 2 hours before you inject to allow it to warm up. Cold insulin is more painful to inject.

Discard your used SoloStar as required by your local authorities.

Maintenance

Protect your SoloStar from dust and dirt.

You can clean the outside of your SoloStar by wiping it with a damp cloth.

Do not soak, wash or lubricate the pen as this may damage it.

It should be handled with care. Avoid situations where SoloStar might be damaged. If you are concerned that your SoloStar may be damaged, use a new one.

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