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

Lantus®

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

Insulin with a long and steady blood-sugar-lowering action

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 100 units insulin glargine* (equivalent to 3.64 mg).

Lantus SoloStar 100 units/ml solution for injection in a pre-filled pen
Each pen contains 3 ml of solution for injection, equivalent to 300 units.
Excipients: Zinc chloride, m-cresol, glycerol, hydrochloric acid (for pH adjustment) sodium hydroxide (for pH adjustment), water for injections.

Insulin glargine is an insulin analogue produced by recombinant DNA technology using *Escherichia coli* (K 12 strains).

PHARMACEUTICAL FORM

Solution for injection.
Clear colourless solution.

THERAPEUTIC INDICATIONS

Treatment of diabetes mellitus in adults, adolescents and children aged 2 years and above.

POSOLOGY AND METHOD OF ADMINISTRATION

Lantus contains insulin glargine an insulin analogue with a prolonged duration of action. It should be administered once daily at any time but at the same time each day.
The dosage and timing of dose of Lantus 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.

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.

Paediatric population
Safety and efficacy of Lantus have been established in adolescents and children aged 2 years and older. Lantus has not been studied in children below the age of 2 years.

Change-over to Lantus

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

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 (100 units/ml) and insulin glargine 300 U/ml are not bioequivalent and are not directly interchangeable. When switching from Lantus XR to insulin glargine 100 units/ml, the dose should be reduced (approximately by 20%) to reduce the risk of hypoglycaemia.

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.

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

With improved metabolic control and resulting increase in insulin sensitivity a further adjustment in dosage 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.

Method of Administration
Lantus is administered by subcutaneous tissue injection.

Lantus is not intended for be intravenous administration. The prolonged duration of action of insulin glargine is dependent on injection into the subcutaneous space. 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 *Special warnings and precautions for use* and *Undesirable effects*).

Mixing, diluting
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 solution for injection in a 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 *Special warnings and precautions for use*).
Before using SoloStar, the instructions for use included in the package leaflet must be read carefully (see section *Special precautions for disposal and other handling)*

CONTRAINDICATIONS
Lantus must not be used in patients hypersensitive to insulin glargine or any of the excipient.

SPECIAL WARNING AND SPECIAL 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.

In case of insufficient glucose control or a tendency to hyper-or hypoglycaemic episodes, the patient's adherence to the prescribed treatment regimen, injection sites and proper injection technique and all other relevant factors must be reviewed before dose adjustment is considered.

Patients must be instructed in the skills necessary for the self-management of diabetes, such as blood sugar monitoring, proper injection technique, measures for recognising and managing reduced or increased blood sugar levels (**hypo**–or **hyperglycaemia**) as described below. In addition, they must learn how to handle special situations such as skipped, inadequate or increase insulin doses, inadequate food intake or missed meals. Moreover, patients and their relatives must learn how to recognize the signs and symptoms of hypo-or hyperglycaemia, what corrective actions need to be taken and when they must speak with their doctor.

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 *Posology and method of administration*). 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 *Special precautions for disposal and other handling*).

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.

Hypoglycaemia is more likely to occur at the start of insulin treatment, following transfer to a different insulin preparation, where metabolic control is unstable, or in severe kidney or liver diseases.

Symptoms that may indicate the onset of hypoglycaemia may be, e.g., sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heart beat, chest pain (angina pectoris). In many patients, these signs and symptoms often develop before those of a low sugar level in the brain. The latter include headache,, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesiae) numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after oneself, convulsions, and loss of consciousness.

The initial symptoms pointing to the onset of hypoglycaemia ("warning symptoms") may change be milder, or be entirely absent, e.g., in the following circumstances : markedly improved blood sugar control, slow-developing hypoglycaemia, advanced age, a certain type of nervous disease (autonomic neuropathy), long-standing diabetes, a psychiatric illness, or concurrent use of other medicines (see "Interactions"). In such circumstances severe hypoglycaemia (and even loss of consciousness) may develop without the patients noticing it. Affected patients should try to keep familiar at all times with their individual warning symptoms. More frequent blood sugar testing can help to identify mild hypoglycaemic episodes which otherwise might be overlooked. Patients not confident of recognizing their warning symptoms should avoid situations (e.g. driving a car) that might result in danger to themselves or others.

As with all insulins, particular caution should be exercised, and intensified blood glucose monitoring is advisable, in patients in whom hypoglycaemic episodes might be of particular clinical relevance. For example these could be patients with significant stenoses of the coronary arteries or of the blood vessels supplying the brain (risk of cardiac or cerebral complications of 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.

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, unrecognized (especially nocturnal) episodes of hypoglycaemia must be considered.

Adherence of the patient to the dosage and dietary regimen, correct insulin administration and awareness of hypoglycaemia symptoms are essential to reduce the risk of hypoglycaemia. Presence of 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 (by e.g., 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.

A hypoglycaemic attack can be corrected by immediately taking sugar, e.g., in the form of glucose, sugar cubes or sugar-sweetened beverages. In this regard, please note that food or beverages containing artificial sweeteners (e.g. diet foods and drinks) are not suitable. Subsequently, some food having a long-acting blood-sugar-raising effect (e.g. bread) should be taken. The long action of Lantus may delay recovery from hypoglycaemia. If hypoglycaemia recurs, another 10 to 20 g of sugar should be taken. If a hypoglycaemia attack cannot be corrected or if it recurs, speak to a doctor immediately.

Carry at least 20 grams of sugar with you at all times, together with some information identifying you as a diabetic. Inability to swallow or unconsciousness will make necessary injections of glucose solution or glucagons (a medicine increasing blood sugar), even where the presence of hypoglycaemia is uncertain. Following intake of glucose, hypoglycaemia should be conformed by means of blood sugar testing.

Please inform your doctor in the event of intercurrent illness, since this situation necessitates intensified metabolic monitoring and, possibly, further special measures (e.g,. dose adjustment, urine tests for ketones).

Hyperglycaemia may occur under certain circumstances. These include:

- omission or reduction of injections or decrease in insulin effectiveness (e.g. due to incorrect storage)
- pen malfunction
- decreased physical activity, stress situations (emotional distress, excitement), injuries, operations, feverish illnesses or certain other diseases
- concurrent use of other medicines (see "Interactions")

Thirst, increased need to pass water, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat and high concentrations of sugar and ketone bodies in the urine may be signs of hyperglycaemia. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious metabolic condition (ketoacidosis) resulting from lack of insulin. Blood sugar testing or tests for ketones in urine must be carried out as soon as any such symptoms occur. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

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 *Pharmacodynamic properties*)

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'.

INTERACTION

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

Substances that may enhance the blood-glucose-lowering effect and increase susceptibility to hypoglycaemia include: oral antidiabetic agents, ACE inhibitors, disopyramide, fibrates, fluoxetine, MAO inhibitors, pentoxifylline, propoxyphene, salicylates and sulfonamide antibiotics.

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

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.

PREGNANCY
There are no randomized controlled clinical studies of the use of insulin glargine in pregnant women.

A large number (more than 1000 retrospective and prospective pregnancy outcomes) of exposed pregnancies from Post Marketing Surveillance indicate no specific adverse effects of insulin glargine on pregnancy or on the health of the foetus and newborn child. Furthermore a meta-analysis of eight observational clinical studies including 331 women using insulin glargine and 371 women using insulin NPH was performed to assess the safety of insulin glargine and insulin NPH in gestational or pregestational diabetes. No significant differences in safety-related maternal or neonatal outcomes were seen between insulin glargine and insulin NPH during pregnancy.
Animal studies, with doses up to 6 to 40 times the human doses, do not indicate direct harmful effects on the pregnancy.

The use of Lantus may be considered during pregnancy, if necessary.
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 in such patients.
Patients with diabetes must inform their doctor if they are pregnant or are contemplating pregnancy.

LACTATION
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.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
The patients' ability to concentrate and react may be impaired as a result of, for example 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 operating machinery).

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 operate machinery in these circumstances.

UNDESIRABLE EFFECTS
Summary of the safety profile
Hypoglycaemia (very common), in general the most frequent undesirable effect of insulin therapy, may occur if the insulin dose is too high in relation to the insulin requirement (see section *Special warnings and precautions for use*).

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

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

MedDRA system organ classes	Very common	Common	Uncommon	Rare	Very rare	Not known
Immune system disorders				Allergic reactions		
Metabolism and nutrition disorders	Hypoglycaemia					
Nervous system disorders					Dysgeusia	
Eyes disorders				Visual impairment Retinopathy		
Skin and subcutaneous tissue disorders		Lipohypertrophy	Lipoatrophy			Cutaneous amyloidosis
Musculoskeletal and connective tissue disorders					Myalgia	
General disorders and administration site conditions		Injection site reactions		Oedema		

Description of selected adverse reactions

Metabolism and nutrition disorders

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

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

Immune system disorders

Immediate-type allergic reactions to insulin are rare. Such reactions to insulin (including insulin glargine) or the excipients may, for example, be associated with generalized 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 decrease 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.

General disorders and administration site conditions

Such 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.

Paediatric population
In general, the safety profile for children and adolescents (≤18 years of age) is similar to the safety profile for adults.
The adverse reaction reports received from post marketing surveillance included relatively more frequent injection site reactions (injection site pain, injection site reaction) and skin reactions (rash, urticaria) in children and adolescents (≤18 years of age) than in adults.
Clinical study safety data are not available for children under 2 years.

Reporting adverse reaction
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 reaction via farmakovigilans@kalventis.com and Pusat Farmakovigilans/MESO Nasional Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika, Psikotropika, Prekursor dan Zat Adiktif Badan Pengawas Obat dan Makanan. Jl. Percetakan Negara No. 23, Jakarta Pusat, 10560
Email: pvcenter@pom.go.id
Phone: +62-21-4244691 Ext.1079
Website: https://e-meso.pom.go.id/

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.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
Pharmacotherapeutic group: Drugs used in diabetes, Insulin and analogues, 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 neutralized 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.
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 Lantus therapy, are considerably lower than the pharmacological concentrations required to activate the IGF-1 pathway.

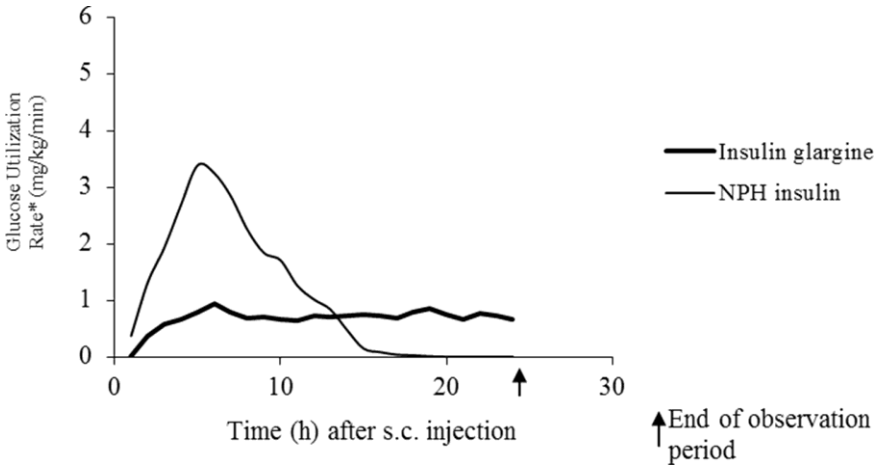
The primary activity of insulin, including insulin glargine, is regulation of glucose metabolism. Insulin and

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.
After subcutaneous injection of 0.3 IU/kg insulin glargine in diabetic patients, a flat concentration-time profile has been demonstrated.

The following graph shows the results from a study in patients:
The median time between injection of the drug and the end of its pharmacological effect was 14.5 hours for NPH insulin while the median time for insulin glargine was 24 hours (the end of the observation period).

Figure 1. Activity Profile in Patients with Type 1 Diabetes



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

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.

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

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

	Lantus (%)	NPH (%)	Difference[a,b](SE)	95% Cl for difference
Per-protocol	53/374 (14.2%)	57/363 (15,7%)	-1.98 (2.57%)	-7.02% to 3.06%
Intend–to-Treat	63/502 (12.5%)	71/487 (14.6%)	-2.10% (2.14%)	-6.29% to 2.09%

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

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 (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 randomized, 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 vs 4.1 mM. Correspondingly, the incidences of nocturnal hypoglycaemia were 32% in the insulin glargine / lispro group vs 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.

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.

In studies in type 1 and in type 2 diabetes mellitus patients, the overall efficacy of once-daily insulin glargine on metabolic control was compared to that of once-daily and twice-daily NPH human insulin.

In general, insulin glargine maintained or improved the level of glycaemic control as measured by glycohaemoglobin and fasting glucose. In addition, fewer patients using insulin glargine reported a hypoglycaemic episode compared to patients using NPH human 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.

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

STORAGE CONDITIONS AND SHELF-LIFE

Shelf life
Lantus SoloStar 100 units/ml solution for injection in a pre-filled pen
3 years.

Unopened/not in use Solostar pen
Lantus must be stored between +2°C and +8 °C (e.g. in a refrigerator) and protected from light. Do not allow the insulin to freeze, discard if frozen.
Do not put Lantus 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.

Opened/in use:
Do not allow the insulin to freeze, discard if frozen.
If a cartridge is placed in a pen, it must not be put in the refrigerator**.**

PATIENT INFORMATION
Accidental mix-ups between insulin glargine and other insulins, particularly short-acting insulins, have been reported. To avoid medication errors between insulin glargine and other insulins, patients should be instructed to always check the insulin label before each injection.

NATURE AND CONTENTS OF CONTAINER
Lantus SoloStar 100 units/ml solution for injection in a pre-filled pen
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.

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 *Special warnings and precautions for use*).

Lantus SoloStar 100 units/ml solution for injection in a 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 *Posology and method of administration* and *Special warnings and precautions for use*).
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.

Keep medicines out of the reach of children

Presentation
Solution for injection

Lantus SoloStar pre-filled pen
Box contains: 5 SoloStar Injection Pens with Cartridges
Reg. No. : DKI0259201443A5

HARUS DENGAN RESEP DOKTER ON MEDICAL
PRESCRIPTION ONLY

Manufactured by:
Sanofi Aventis Deutschland GmbH, Frankfurt (Main), Germany

Registered by:
PT. Kalventis Sinergi Farma, Jakarta, Indonesia

Approval date: Based on approval BPOM dated xxx - Standar Informasi Obat

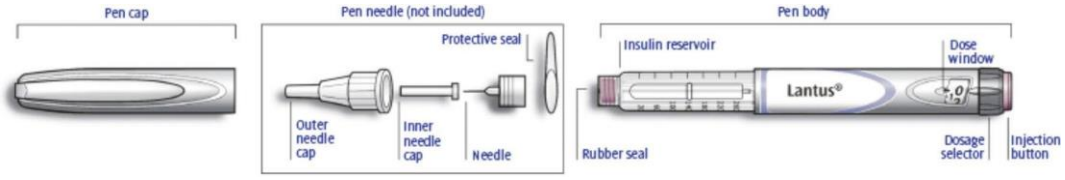
SoloStar®

Instruction Leaflet

SoloStar® is a prefilled pen for the injection of insulin. Your healthcare provider has decided that SoloStar is appropriate for you, based on your ability to handle SoloStar. Talk with your healthcare provider about proper injection technique before using SoloStar.

Read these instructions carefully before using your SoloStar. If you are not able to use SoloStar or to 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 provider or call sanofi-aventis at 1800 818 806 (Australia) or 0800 283 684 (New Zealand).



Important information for use of SoloStar:

- Always attach a new needle before each use. Only use needles that have been approved 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, colored 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.

Before use of needle, carefully read the "Instructions for Use" accompanying the needles.

Please note: The needles shown are for illustrative purposes only.

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.

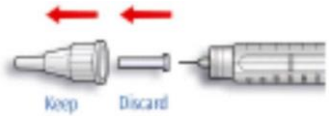
Step 3. Perform a safety test

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

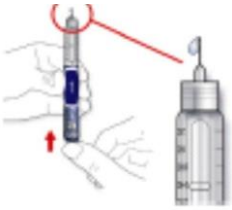
- ensuring that pen and needle work properly
- removing air bubbles

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.

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, 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 (e.g. contact your healthcare provider) in order to reduce the risk of accidental needle injury and transmission of infectious diseases.

B. Dispose of the needle safely
C. Always put the pen cap back on the pen, then store the pen until your next injection.

Storage Instructions
Please check 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.
Your SoloStar is designed to work accurately and safely. 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.