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

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

INSULIN GLARGINE INJECTION I.P.

LANTUS®

Active Ingredient
Insulin glargine I.P.

Recombinant human insulin analogue (21A-Gly-30Ba-L-Arg-30Bb-L-Arg-human insulin)

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

Therapeutic or Pharmacological Class
Antidiabetic agent, Long acting insulin analogue
ATC Code: A 10 A E04 (insulin and analogues, long acting)

Indication:
For the treatment of diabetes mellitus in adults, adolescents and children aged 2 years and above.

Pharmaceutical Form(s)
Solution for injection

Composition
1 ml contains 3.6378 mg insulin glargine I.P, corresponding to 100 IU human insulin.

10 ml Vial Excipients (per ml):
30 µg zinc, 2.7 mg m-cresol, 20 mg glycerol 85%, 20 µg polysorbate 20; hydrochloric acid and sodium hydroxide for pH adjustment, and water for injection.

Cartridge Excipients (per ml):
30 µg zinc, 2.7 mg m-cresol, 20 mg glycerol 85%; hydrochloric acid and sodium hydroxide for pH adjustment, and water for injection.

The pH of the solution is 4.0.

Dosage And Administration
General
Insulin glargine is a novel recombinant human insulin analogue, equipotent to human insulin. It exhibits a peakless glucose-lowering profile with a prolonged duration of action.

Lantus® is given subcutaneously once a day. It may be administered at any time during the day, however, at the same time every day.

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

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

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

In basal bolus injection regimens, usually 40 to 60% of the daily dose is administered as insulin glargine to cover basal insulin requirements.

In a clinical study with patients with type 2 diabetes on oral antidiabetic agents, combination therapy was started with a dose of 10 IU insulin glargine once daily and the treatment regimen subsequently adjusted individually.

Blood glucose monitoring is recommended for all patients with diabetes.

- **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.

To reduce the risk of hypoglycemia, when patients are transferred from once daily insulin glargine 300U/mL to once daily Lantus®, the recommended initial Lantus® dose is 80% of the insulin glargine 300U/mL dose that is being discontinued.

In clinical studies when patients were transferred from once daily NPH or ultralente insulin to once daily Lantus®, the initial dose was usually not changed (i.e. amount of International Units, IU, of Lantus® per day equal to IU of NPH insulin).

In studies when patients were transferred from twice daily NPH insulin to once daily Lantus® at bedtime, to reduce the risk of hypoglycaemia, the initial dose (IU), was usually reduced by approximately 20% (compared to total daily IU of NPH insulin) and then adjusted based on patient response.

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 resultant increase in insulin sensitivity (reduced insulin requirements) further adjustment of the doses of Lantus® and other insulins or oral antidiabetic drugs in the regimen may become necessary.

- **Mixing, diluting**

Lantus® must not be mixed with any other insulin. Mixing can change the time/action profile of Lantus® and cause precipitation.
Lantus® must not be diluted. Diluting can change the time/action profile of Lantus®.

Special Populations

- **Children**

Lantus® can be administrated to children ≥ 2 years of age. Administration to children < 2 year has not been studied.

- **Elderly**

In elderly patients with diabetes, it is recommended that the initial dosing, dose increments, and maintenance dosage be conservative to avoid hypoglycaemic reactions. Hypoglycaemia may be difficult to recognize in the elderly (See section Precautions).

Administration

Lantus® is administered by subcutaneous tissue injection.
Lantus® is not intended for intravenous administration.

The prolonged duration of activity of insulin glargine is dependent on injection into the subcutaneous space. Intravenous administration of the usual subcutaneous dose could result in severe hypoglycaemia.
As with all insulins, injection sites within an injection area (abdomen, thigh or deltoid) must be rotated from one injection to the next.

Absorption of insulin glargine is not different between abdominal, thigh or deltoid subcutaneous injection area. As for all insulins, the rate of absorption and consequently the onset and duration of action may be affected by exercise and other variables.

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

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

Precautions

- **General**

Insulin therapy generally requires appropriate diabetes self-management skills, including glucose monitoring, proper injection technique, and hypo- and hyperglycaemia management. Patients should be instructed on such self-management procedures. Additionally, patients must be instructed on handling of special situations such as an inadequate or skipped insulin dose, inadvertent administration of an increased insulin dose, inadequate food intake or skipped meals. The extent of patient participation in his/her diabetes management is variable and is generally determined by the physician.

Insulin treatment requires constant alertness to the possibility of hyper- and hypoglycaemia. Patients and their relatives must know what steps to take if hyperglycaemia or hypoglycaemia occurs or is suspected, and they must know when to inform a physician.

In case of insufficient glucose control or a tendency to hyper- or hypoglycaemic episodes, patient's compliance with the prescribed insulin regimen, injection sites and proper injection techniques, the handling of injection devices and all other relevant factors must to 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.

As with all insulins, particular caution should be exercised, and intensified blood glucose monitoring is advisable, in patients in whom sequelae of 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 patients with proliferative retinopathy, particularly if not treated with photocoagulation (risk of transient amaurosis following hypoglycaemia).

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.

However, under certain conditions, as with all insulins, the warning symptoms of hypoglycaemia may be changed, be less pronounced or absent, for example:

- if glycaemic control is markedly improved
- if hypoglycaemia is developing gradually
- in elderly patients
- where an autonomic neuropathy is present
- in patients with a long history of diabetes
- in patients suffering from a psychiatric illness
- in patients receiving concurrent treatment with certain other drugs (see under 'Interactions')

Such situations may result in severe hypoglycaemia (and possibly, loss of consciousness) prior to 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.

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

Presence of factors which increase the susceptibility to hypoglycaemia requires particularly close monitoring and may necessitate dose adjustment include:

- change in the injection area,
- increase of insulin sensitivity (e.g. by removal of stress factors),
- unaccustomed, increased or prolonged physical exercise,
- intercurrent illness (e.g. vomiting, diarrhoea),
- inadequate food intake,
- alcohol consumption,
- certain uncompensated endocrine disorders,
- concomitant treatment with certain medications.

In patients with renal impairment, insulin requirements may be diminished due to reduced insulin metabolism. In the elderly, progressive deterioration of renal function may lead to steady decrease in insulin requirements.

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

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

- **Intercurrent illness**

Intercurrent illness requires intensified metabolic monitoring. In many cases urine tests for ketones are indicated, and often it is necessary to adjust the insulin dose. The insulin requirement is often increased. In patients with type 1 diabetes, carbohydrate supplies must be maintained even if patients are able to eat only little or no food, or are vomiting etc.; in patients with type 1 diabetes insulin must never be omitted entirely.

- **Pens to be used with Lantus cartridges**

Lantus cartridges should be used with Allstar pen and should not be used with any other reusable pen as the dosing accuracy has only been established with the listed pens.

Driving a Vehicle or Performing other Hazardous Tasks

The patient's 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. The advisability of driving should be considered in these circumstances.

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

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

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

Beta-blockers, clonidine, lithium salts and alcohol may either potentiate or weaken the blood glucose lowering effect of insulin. Pentamidine may cause 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.

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. Lantus can be used during pregnancy, if clinically needed.

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

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

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

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

- **Hypoglycaemia:** 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.

As with all insulins, 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.

- **Eyes:** A marked change in glycaemic control may cause temporary visual impairment, due to temporary alteration in the turgidity and refractive index of the lens.
Long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy. However, as for all insulin regimens, intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy.
In patients with proliferative retinopathy, particularly if not treated with photocoagulation, severe hypoglycaemic episodes may result in transient amaurosis (See Pharmacodynamics).

- **Lipodystrophy:** Lipodystrophy, as with any insulin therapy, may occur at the injection site and delay insulin absorption. In clinical studies, in regimens, which included insulin glargine, lipohypertrophy was observed in 1 to 2 % of patients, whereas lipoatrophy was uncommon. Continuous rotation of the injection site within a given area may help to reduce or prevent these reactions.

- **Injection site and allergic reactions:** In clinical studies, using regimens, which included insulin glargine, injection site reactions were observed in 3 to 4 % of patients. As with any insulin therapy, such reactions include redness, pain, itching, hives, swelling, and inflammation. Most minor reactions to insulins usually resolve in a few days to a few weeks.

Immediate-type allergic reactions are rare. Such reactions to insulin (including insulin glargine) or the excipients may, for example, be associated with generalised skin reactions, angiooedema, bronchospasm, and hypotension and shock, and may be life threatening.

- **Other reactions**

Insulin administration may cause insulin antibodies to form. In clinical studies, antibodies that cross-react with human insulin and insulin glargine were observed in both NPH and insulin glargine treatment groups with similar incidences. In rare cases, the presence of such insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyperglycaemia or hypoglycaemia.

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

Medication errors have been reported in which other insulins, particularly short-acting insulins, have been accidentally administered instead of insulin glargine.

- **Paediatric population**

The safety profile for patients ≤18 years of age is similar to the safety profile for patients > 18 years. No clinical study safety data are available in patients below 2 years of age.

Overdose

- **Symptoms**

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

- **Management**

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

More severe episodes culminating in coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose.

Sustained carbohydrate intake and observation may be necessary because hypoglycaemia may recur after apparent clinical recovery.

PHARMACODYNAMICS

MODE OF ACTION/PHARMACODYNAMIC CHARACTERISTICS

Insulin glargine is a human insulin analogue designed to have a low solubility at neutral pH. At pH 4 (as in the Lantus injection solution), it is completely soluble.

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 Pharmacokinetics).

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.

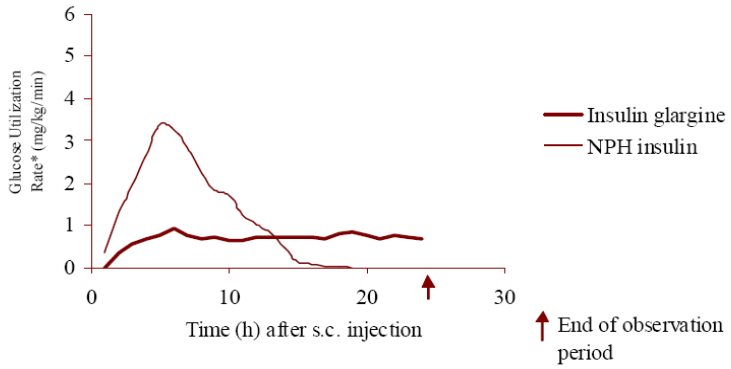
The total therapeutic insulin concentration (insulin glargine and its metabolites) found in type 1 diabetic patients was markedly lower than what would be required for a halfmaximal occupation of the IGF-1 receptor and the subsequent activation of the mitogenic-proliferative pathway initiated by the 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 use of insulin glargine and human insulin have been shown to be equipotent when given at the same doses.

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 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 majority of patients on insulin glargine were still showing a response at this point of time, indicating an even longer duration of action.

Figure 1. 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 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 but is, due to the lack of a peak, less variable with insulin glargine than with NPH insulin.

An euglycaemic clamp study in healthy volunteers showed less intra-individual (day to day) variability in the pharmacodynamic profile for insulin glargine compared to ultralente human insulin.

CLINICAL EFFICACY/CLINICAL STUDIES
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 open-label, randomised, active-control, parallel studies of 2327 patients with type 1 diabetes mellitus and 1563 patients with type 2 diabetes mellitus. In general, insulin glargine maintained or improved the level of glycaemic control as measured by glycohemoglobin and fasting glucose. In addition, fewer patients using insulin glargine reported a hypoglycaemic episode compared to patients using NPH human insulin.
• ORIGIN Trial (Study 4032)
The ORIGIN (Outcome Reduction with Initial Glargine Intervention) trial was a, international, multicenter, randomized, 2x2 factorial design study conducted in 12,537 participants with impaired fasting glucose (IFG), impaired glucose tolerance (IGT) or early type 2 diabetes mellitus and evidence of CV disease. Participants were randomized to receive Lantus (n=6264), titrated to a FPG of 95 mg/dL (5.3mM) or less, or Standard Care (n=6273). Participation in ORIGIN for a median of approximately 6.2 years showed that treatment with Lantus did not alter the risk for cardiovascular outcomes, all-cause mortality or cancer, when compared to standard glucose lowering therapy. In addition, metabolic control was maintained at a lower level of glycemia, with a decrease in the percentage of participants developing diabetes, at a cost of a modest increase in hypoglycemia and weight gain.

PHARMACOKINETICS

ABSORPTION
None

DISTRIBUTION
After subcutaneous injection of insulin glargine in healthy subjects and diabetic patients, the insulin serum concentrations indicated a slower and much more prolonged absorption and a lack of a peak in comparison to human NPH insulin. Concentrations were, thus, consistent with the time profile of the pharmacodynamic activity of insulin glargine.

After subcutaneous injection of 0.3 IU/kg insulin glargine in diabetic patients, a flat concentration-time profile has been demonstrated; this is also reflected in the wide range of tmax values (between 1.5 and 22.5 hours) compared to NPH (2.5 to 10.0 hours).

When given intravenously, the concentration profiles and the apparent elimination half-life of insulin glargine and human insulin were comparable. There were no relevant differences in serum insulin levels after abdominal, deltoid or thigh administration of insulin glargine.

Insulin glargine has less intra- and inter-individual variability in pharmacokinetic profile compared to human ultralente insulin.

METABOLISM
After subcutaneous injection of Lantus in healthy subjects and diabetic patients, insulin glargine is rapidly metabolized at the carboxyl terminus of the Beta chain with formation of two active metabolites M1 (21AGly-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.

ELIMINATION
None

SPECIAL POPULATIONS
Age and Gender: Information on the effect of age and gender on the pharmacokinetics of insulin glargine is unavailable. However, in large clinical trials, subgroup analysis based on age and gender did not indicate any difference in safety and efficacy in insulin glargine treated patients over the entire study population. The same holds true for NPH treated patients.

Smoking: In clinical trials a subgroup analysis showed no differences in safety and efficacy of insulin glargine between the group of smokers and the total study population. The same is true for NPH insulin.

Obesity: In clinical trials subgroup analysis based on BMI showed no differences in safety and efficacy of insulin glargine in this group of patients compared to the total study population. The same is true for NPH insulin.

Children: Pharmacokinetics in children aged 2 to less than 6 years of age with type 1 diabetes mellitus was assessed in one clinical study (see Pharmacodynamics). Plasma "trough" levels of insulin glargine and its main metabolites M1 and M2 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.

Storage Conditions
Unopened/not in use vials, cartridge:
Lantus® must be stored between +2°C (36°F) and +8 °C (46°F) (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.

Opened/in use:
Do not allow the insulin to freeze, discard if frozen.

Opened 10 ml vials, cartridges, whether or not refrigerated, must be discarded after 28 days (4 weeks) from the first use. If refrigeration is not possible, the open 10 ml vial, cartridge of Lantus® can be kept unrefrigerated for up to 28 days (4 weeks) away from direct heat and light, as long as the temperature is not greater than 30°C (86°F).

Unrefrigerated 10 ml vials, 3 ml cartridges, whether in use or not, must be discarded after the 28-day (4 week) period.

If a cartridge is placed in a pen, it must <u>not</u> be put in the refrigerator.

These storage conditions are summarized in the following table:

	Not in use (unopened) Refrigerated	Not in use (unopened) Room Temperature	In use (opened) See Temperature below
10ml vial	Until expiration date	28 days	28 days. Refrigerated or room temperature
3ml cartridge	Until expiration date	28 days	28 days. Refrigerated or room temperature
3ml cartridge inserted into pen (Solostar®)	Until expiration date	28 days	28 days. Room temperature only (Do not refrigerate)

Preparation and Handling
Inspect Lantus® before use. Lantus® must only be used if the solution is clear, colourless, with no solid particles visible, and if it is of water-like consistency.

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

Imported and packed by:
Sanofi Healthcare India Private Limited
Insulin Plant, Sy. No. 354, Muppireddipalli Village -502236.

Marketed by:
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