PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

BASAGLAR®

Insulin glargine injection (rDNA origin)

Solution for injection, 100 U/mL

ATC code: A10AE04

Antidiabetic Agent

Long-Acting Recombinant Human Insulin Analogue

Eli Lilly Canada Inc.
Exchange Tower
130 King Street West, Suite 900
PO Box 73
Toronto, Ontario
M5X 1B1
1-888-545-5972
www.lilly.ca

Date of Initial Authorization:
September 1, 2015

Date of Revision:
August 26, 2022

Submission Control: 262218

RECENT MAJOR LABEL CHANGES

4 DOSAGE AND ADMINISTRATION, 4.4 Administration	03/2021
7 WARNINGS AND PRECAUTIONS	03/2021

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

Basaglar (insulin glargine injection) is a biosimilar biologic drug (biosimilar) to Lantus®.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Indications have been granted on the basis of similarity between Basaglar and the reference biologic drug Lantus.

Basaglar (insulin glargine (rDNA origin) injection) is a recombinant human insulin analogue indicated for once-daily subcutaneous administration in the treatment of patients over 17 years of age with type 1 or type 2 diabetes mellitus who require basal (long-acting) insulin for the control of hyperglycemia.

Basaglar is also indicated in the treatment of pediatric patients (>6 years old) with type 1 diabetes mellitus who require basal (long-acting) insulin for the control of hyperglycemia.

1.1 Pediatrics

Pediatrics (>6 years of age): Based on the reference product data submitted and reviewed by Health Canada, the safety and efficacy of Basaglar in pediatric patients has been established. Therefore, Health Canada has authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (>65 years of age): Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness. In elderly patients with diabetes, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemia reactions.

2 CONTRAINDICATIONS

Basaglar is contraindicated during episodes of hypoglycemia (see 5 OVERDOSAGE) and in patients who are hypersensitive to insulin glargine or to any ingredient in the formulation or component of the container. For a complete list of excipients, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Hypoglycemia is the most common adverse effect of insulin, including Basaglar (see 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hypoglycemia). As with all insulins, the timing of hypoglycemia may differ among various insulin formulations. Glucose monitoring is recommended for all patients with diabetes.
- Uncorrected hypoglycemic or hyperglycemic reactions can cause loss of consciousness, coma, or death.
- Any change of insulin should be made cautiously and only under medical supervision.
- Basaglar should not be used for intravenous, intramuscular or insulin pump administration. The prolonged duration of activity of insulin glargine is dependent on injection into subcutaneous tissue. Intravenous administration of the usual subcutaneous dose could result in severe hypoglycemia.
- **Basaglar must not be mixed with any other insulin or diluted with any other**

solution. If Basaglar is diluted or mixed, the solution may become cloudy, and the pharmacokinetic/pharmacodynamic profile (e.g., onset of action, time to peak effect) of Basaglar and/or the mixed insulin may be altered in an unpredictable manner (see 4 DOSAGE AND ADMINISTRATION).

- Basaglar shall not be used if it is not water-clear and colourless or if it has formed a deposit of solid particles on the wall of the cartridge (see 4 DOSAGE AND ADMINISTRATION).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Basaglar [insulin glargine injection (rDNA origin)] is a recombinant human insulin analogue. Its potency is stated in units and is approximately the same as human insulin. On average, it exhibits a glucose-lowering profile with no pronounced peak with a prolonged duration of action that permits once-daily basal dosing. Basaglar is administered subcutaneously once a day. It may be administered at any time during the day as long as it is administered 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 timing of administration, weight or lifestyle changes or other circumstances arise that increase susceptibility to hypoglycemia or hyperglycemia (see 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hypoglycemia and Hyperglycemia). The dose may also have to be adjusted during intercurrent illness (see 7 WARNINGS AND PRECAUTIONS, Intercurrent Conditions). Any change in insulin dose should be made under medical supervision.

The prolonged duration of activity of Basaglar is dependent on injection into subcutaneous space. Basaglar should not be administered intravenously, intramuscular administration or via an insulin pump. Intravenous administration of the usual subcutaneous dose could result in severe hypoglycemia (see 7 WARNINGS AND PRECAUTIONS).

In cases of insufficient glucose control or a tendency to hyper- or hypoglycemic 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 be reviewed before dose adjustment is considered.

Blood glucose monitoring is recommended for all patients with diabetes.

Basaglar must not be used for the treatment of diabetic ketoacidosis. Intravenous fast-acting insulin should be the preferred treatment.

4.2 Recommended Dose and Dosage Adjustment

Initiation of Basaglar therapy

In the clinical study ABEC (ELEMENT 2), insulin naïve patients with type 2 diabetes were started on Basaglar at a dose of 10 units once daily, and subsequently adjusted according to the patient's need (see 14 CLINICAL TRIALS).

Changeover to Basaglar

When changing from a treatment regimen with an intermediate or long-acting insulin to a regimen with Basaglar, the amount and timing of fast-acting insulin or the dose of any oral

antidiabetic drug may need to be adjusted secondary to the risk of hypoglycemia. In clinical studies when patients were transferred from once-daily NPH human insulin or ultralente human insulin to once-daily Lantus (the reference product), the initial dose was usually not changed.

However, in studies when patients were transferred from twice-daily NPH human insulin to Lantus (the reference product) once daily, the initial dose (U) was usually reduced by approximately 20% (compared to total daily IU of NPH human insulin) and then adjusted based on patient response.

If transferring patients from Lantus to Basaglar, the dose of Basaglar should be the same as Lantus and the time of day for administration should be determined by the physician.

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

A program of close metabolic monitoring under medical supervision is recommended during transfer and in the initial weeks thereafter. The amount and timing of fast-acting insulin may need to be adjusted. This is particularly true for patients with acquired antibodies to human insulin needing high-insulin doses and occurs with all insulin analogues. Such patients may experience a greater insulin response to Basaglar.

With improved metabolic control and resulting increase in insulin sensitivity, adjustment of the dose(s) of antidiabetic treatments may become necessary.

4.4 Administration

Basaglar is administered by subcutaneous injection. The injection area must not be rubbed.

As with all insulins, injection sites within an injection area (abdomen, thigh, buttock or deltoid) must be rotated from one injection to the next so that the same site is not used more than approximately once a month, in order to reduce the risk of lipodystrophy and localized cutaneous amyloidosis. Do not inject into areas of lipodystrophy or localized cutaneous amyloidosis (see 7 WARNINGS AND PRECAUTIONS and 8 ADVERSE REACTIONS). Patients should be rigorous with site rotation secondary to prolonged deposition. In clinical studies with the reference product (Lantus), there was no relevant difference in insulin glargine absorption after abdominal, thigh, or deltoid subcutaneous administration. As for all insulins, the rate of absorption, and consequently the onset and duration of action, may be affected by exercise and other variables.

Preparation and handling

Basaglar is a clear, colourless solution for injection, it is not a suspension.

Parenteral drug products should be inspected visually prior to administration. Basaglar must only be used if the solution is clear and colourless with no particles visible. To minimize local irritation at the injection site, it is recommended to allow the insulin to reach room temperature before injection.

Patient must be instructed to not re-use needles. INJECTION PENS, CARTRIDGES, AND NEEDLES MUST NOT BE SHARED. To prevent the possible transmission of disease, never share a Basaglar pen or cartridge between patients, even if the needle on the pen is changed.

Mixing and diluting

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

When the reference product (Lantus) and regular human insulin were mixed immediately before injection in dogs, a delayed onset of action and time to maximum effect for regular human insulin was observed. The total bioavailability of the mixture was also slightly decreased compared to separate injections of insulin glargine and regular human insulin. The relevance of these observations in dogs to humans is not known.

Basaglar must not be diluted. Diluting can change the time/action profile of Basaglar.

5 OVERDOSAGE

Symptoms

An excess of insulin relative to food intake, energy expenditure or both may lead to severe and sometimes prolonged and life-threatening hypoglycemia (see 7 WARNINGS AND PRECAUTIONS).

Symptoms of hypoglycemia may occur suddenly. They may include cold sweat, cool pale skin, fatigue, drowsiness, excessive hunger, vision changes, headache, nausea and palpitation. Nocturnal hypoglycemia is common in people taking insulin and symptoms can include restlessness, making unusual noises, attempting to get out of bed or accidentally rolling out of bed, sleepwalking, nightmares and sweating. Patients may wake with a headache in the morning if their blood sugar was low during the night.

Severe hypoglycemia may lead to unconsciousness and/or convulsions and may be fatal. In some cases, the first sign of hypoglycemia may be confusion or loss of consciousness (hypoglycemia unawareness). Severe hypoglycemia, resulting in seizures, is more likely to occur at nighttime (nocturnal hypoglycemia) than during the day.

Management

Mild episodes of hypoglycemia can usually be treated with oral carbohydrates. Adjustments in drug dosage, meal patterns, or exercise may be needed. It is therefore recommended that patients with diabetes carry sugar-containing products.

Severe hypoglycemic episodes, where the patient has become unconscious, can be treated by glucagon given intramuscularly, nasally, or subcutaneously by a trained person, or by glucose given intravenously by a health professional. Upon regaining consciousness, administration of oral carbohydrates is recommended for the patient in order to prevent a relapse.

After apparent clinical recovery from hypoglycemia, continued observation and additional carbohydrate intake may be necessary to avoid reoccurrence of hypoglycemia.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products, including biosimilars, health professionals should recognise the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 1: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients

Subcutaneous	Solution for injection 100 U/mL	glycerin, metacresol, zinc oxide and water for injection hydrochloric acid and sodium hydroxide for pH adjustment

Basaglar is a clear, colourless, aqueous solution for subcutaneous administration. Each milliliter of Basaglar contains insulin glargine 100 units. Basaglar has a pH of approximately 4.

Basaglar is available in cartridges or KwikPens (prefilled insulin delivery devices):

- Cartridge, 3 mL, 100 units/mL, 5 cartridges/box
- KwikPen, 3 mL prefilled pen, 100 units/mL, 5 pens/box
- KwikPen, 3 mL prefilled pen, 100 units/mL, 2 pens/box

Not all pack sizes and presentations may be marketed.

Reusable pens to be used with Basaglar cartridge

Basaglar cartridges are designed for use only with Lilly's insulin delivery devices. The cartridge containing Basaglar is not designed to allow any other insulin to be mixed in the cartridge or for the cartridge to be reused.

The Basaglar cartridge should only be used with the following pens:

- HumaPen® Savvio™ which delivers Basaglar in 1 unit dose increments.
- HumaPen Luxura® HD, which delivers Basaglar in 0.5 unit dose increments.
- HumaPen Luxura®, which delivers Basaglar in 1 unit increments.

This cartridge should not be used with any other reusable pen as the dosing accuracy has only been established with the listed pens.

Description

Basaglar [insulin glargine injection (rDNA origin)] is a recombinant human insulin analogue that is a long-acting, parenteral blood-glucose-lowering agent. Basaglar is produced by recombinant DNA technology utilizing a non-pathogenic laboratory strain of Escherichia coli (K12) as the production organism.

Insulin glargine differs from natural human insulin in that the amino acid asparagine at position 21 of the A-chain is replaced by glycine and two arginines are added to the C-terminus of the B-chain (see 13 PHARMACEUTICAL INFORMATION, Drug Substance).

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS .

General

As with all insulin preparations, the time course of Basaglar action may vary in different individuals or at different times in the same individual and the rate of absorption is dependent on blood supply, temperature, and physical activity.

Hypokalemia is among the potential clinical adverse effects associated with the use of all insulin therapies, particularly when given intravenously. However, Basaglar should not be given intravenously (see 4 DOSAGE AND ADMINISTRATION). If left untreated, hypokalemia may

cause respiratory paralysis, ventricular arrythmia, and death. This potential clinical adverse effect may be relevant in patients who are using potassium lowering drugs, taking medications sensitive to serum potassium concentrations, or losing potassium through other means (e.g., diarrhea).

Stress or concomitant illness, especially infectious and febrile conditions may change insulin requirements.

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

Patients with human insulin antibodies may be hypersensitive to other insulins, with a risk of hypoglycemia and/or cross-reactivity.

Thiazolidinediones (TZDs), alone or in combination with other antidiabetic agents (including insulin), can cause heart failure and edema. The combination of TZD with insulin is not indicated for the treatment of Type 2 diabetes mellitus. Please refer to the respective TZD product monograph 7 WARNINGS AND PRECAUTIONS information when the use of these drugs in combination with any insulin, including Basaglar, is contemplated.

To avoid transmission of disease, a cartridge or prefilled pen shall not be used by more than one person.

Accidental mix-ups between insulin glargine and other insulins, particularly fast-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 (see 8 ADVERSE REACTIONS).

Driving and Operating Machinery

The patient's ability to concentrate and react may be impaired as a result of hypoglycemia or hyperglycemia 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 hypoglycemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycemia or have frequent episodes of hypoglycemia. It should be considered whether it is advisable to drive or operate machinery in these circumstances.

Endocrine and Metabolism

Hypoglycemia

As with all insulin preparations, hypoglycemic reactions, especially during initiation of therapy, may be associated with the administration of Basaglar. Hypoglycemia is the most common adverse effect of insulins (see 8 ADVERSE REACTIONS). Hypoglycemia may occur if the insulin dose is too high in relation to the insulin requirement (see 5OVERDOSAGE). Early warning symptoms of hypoglycemia may be different, be less pronounced or absent under certain conditions, as for example, in patients whose glycemic control is markedly improved, in elderly patients, in patients where an autonomic neuropathy is present, in patients who hypoglycemia is developing gradually, in patients with a long history of diabetes, in patients with psychiatric illness, or in patients receiving concurrent treatment with certain other drugs such as beta-blockers. Hypoglycemia may occur with other substances including alcohol and psychiatric medications, street drugs, birth control pills, injections and patches (see 9DRUG INTERACTIONS, Drug-Drug Interactions). Such situations may result in severe hypoglycemia

(and possibly, loss of consciousness) prior to patients' awareness of hypoglycemia.

The time of occurrence of hypoglycemia depends on the action profile of the insulins used and may, therefore, change when the treatment regimen or timing of administration is changed.

As with all insulins, prolonged or severe hypoglycemic attacks, especially if recurrent, may lead to neurological damage, loss of consciousness, coma or death (see 8 ADVERSE REACTIONS). Severe hypoglycemia has been observed in clinical trials with insulin, including trials with insulin glargine.

As with all insulins, additional caution (including intensified blood glucose monitoring) should be exercised in patient populations who are at greater risk for clinically significant sequelae from hypoglycemic episodes.

In a clinical study with the reference product (Lantus), symptoms of hypoglycemia or counter regulatory hormone responses were similar after intravenous insulin glargine and regular human insulin both in healthy subjects and adult patients with type 1 diabetes.

Hypoglycemia reactions following treatment with insulin products such as Basaglar are mostly mild. Changes in insulin therapy or changes in lifestyle (i.e., diet, omission of a meal, exercise/physical activity) may require a change in dosage to avoid hypoglycemia. Glucose monitoring is recommended for all patients with diabetes.

Patients with diabetes should be instructed to carry a quick source of sugar (about 15 g of glucose) to prevent the progression of a hypoglycemic reaction, should one occur (see **Error! Reference source not found.**).

Hyperglycemia

The use of too low insulin dosages or discontinuation of treatment, especially in type 1 diabetes, may lead to hyperglycemia and diabetic ketoacidosis. Uncorrected hyperglycemic reactions can cause loss of consciousness, coma, or death.

Other

The presence of diseases such as Acromegaly, Cushing's Syndrome, Hyperthyroidism, and Pheochromocytoma can complicate the control of diabetes mellitus.

Hepatic/Biliary/Pancreatic/Renal

Although studies have not been performed in patients with diabetes and hepatic or renal impairment, Basaglar requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism (see 10 CLINICAL PHARMACOLOGY, Special Populations and Conditions). Careful glucose monitoring and dose adjustments of insulin or insulin analogues including Basaglar may be necessary in patients with hepatic or renal dysfunction.

Immune

Injection Site and Local Allergic Reactions

Injection site reactions with insulin therapy include redness, pain, itching at the injection site, hives, swelling, and inflammation. Continuous rotation of the injection site within a given area may help to reduce or prevent these reactions. Most minor reactions to insulins usually resolve in a few days to a few weeks. They may occur if the injection is not properly made (irritants in the skin cleansing agent or poor injection technique), or if the patient is allergic to the insulin or any excipients.

Reports of injection site pain were more frequent with the reference product (Lantus) than NPH human insulin (2.7% insulin glargine versus 0.7% human NPH). The reports of pain at the injection site were usually mild and did not result in discontinuation of therapy. Other possibly related treatment-emergent injection site reactions occurred at similar incidences with both insulin glargine and NPH human insulin.

Lipodystrophy and Cutaneous Amyloidosis

Subcutaneous (SC) administration of insulin products can result in lipoatrophy (depression in the skin) or lipohypertrophy (enlargement or thickening of tissue) or localized cutaneous amyloidosis (skin lumps) which may affect insulin absorption. Patients must be instructed to perform continuous rotation of the injection site to reduce the risk of developing lipodystrophy and localized cutaneous amyloidosis. Patients should be advised to consult their health professional if they notice any of these conditions and before changing the injection site. There is a potential risk of delayed insulin absorption and worsened glycemic 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 hypoglycemia. Blood glucose monitoring is recommended after the change in the injection site, and dose adjustment of antidiabetic medications may be considered (see 8 ADVERSE REACTIONS).

Systemic allergic reactions

Immediate-type allergic reactions are rare. Such reactions to insulin (including insulin glargine) or the excipients may, for example, be associated with generalized skin reactions, angioedema, bronchospasm, hypotension, anaphylactic reaction or shock and may be life threatening (see 2 CONTRAINDICATIONS and 8 ADVERSE REACTIONS).

Antibody Production

Insulin administration may cause insulin antibodies to form. In clinical studies with the reference product (Lantus), antibodies that cross-react with human insulin and insulin glargine were observed in both NPH human insulin and insulin glargine treatment groups with similar percentages of increased and decreased titers. There was no correlation in either treatment group between increases or decreases in these antibody titers and changes in either A1c or total insulin requirements. In theory, the presence of such insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyperglycemia or hypoglycemia, but has not been found on review of Lantus clinical trials and available post-marketing data.

Intercurrent Conditions

Insulin requirements may be altered during intercurrent conditions such as infection or illness, emotional disturbances, or stress.

Ophthalmologic

Retinopathy

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

Long-term improved glycemic control decreases the risk of progression of diabetic retinopathy. However, as for all insulin regimens, intensification of insulin therapy with abrupt improvement in glycemic control may be associated with temporary worsening of diabetic retinopathy.

In patients with proliferative retinopathy, particularly if not treated with photocoagulation, severe hypoglycemic episodes may result in transient amaurosis (see 8 ADVERSE REACTIONS, Eye disorders).

Changes in Insulin Regimen/Transferring Patients from Other Insulins

Any change of insulin should be made cautiously and only under medical supervision. Changes in insulin regimen, strength, timing of administration, manufacturer, type (e.g., regular, NPH, or insulin analogs), species (animal, human), or method of manufacture (recombinant DNA versus animal-source insulin) may result in the need for a change in dosage. Concomitant oral antidiabetic treatment may need to be adjusted.

As with all insulins, when transferring to Basaglar, the early warning symptoms of hypoglycemia may be changed, be less pronounced, or absent. The prolonged effect of subcutaneous Basaglar may delay recovery from hypoglycemia (see 4 DOSAGE AND ADMINISTRATION).

7.1 Special Populations

7.1.1 Pregnant Women

Teratogenic effects

For insulin glargine no clinical data on exposed pregnancies from controlled clinical studies are available. Post Marketing data for the reference product (Lantus) on pregnant women (more than 1000 pregnancy outcomes) indicated no reports of specific adverse effects of insulin glargine on maternal and fetal/neonatal outcomes.

Animal data do not indicate toxicity for the reference product (Lantus) (see 16 NON-CLINICAL TOXICOLOGY, Reproduction Toxicity and Impairment of Fertility).

It is essential for patients with diabetes or a history of 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 hypoglycemia). Careful monitoring of glucose control is essential.

Patients with diabetes should be advised to inform their health professional if they are pregnant or are contemplating pregnancy.

7.1.2 Breast-feeding

It is unknown whether insulin glargine is excreted in significant amounts in human milk. Many drugs, including human insulin, are excreted in human milk. There are no adequate and well-controlled studies in nursing women. For this reason, caution should be exercised when Basaglar is administered to a nursing woman. Lactating women may require adjustments in insulin dose and diet.

7.1.3 Pediatrics

Pediatrics (>6 years of age): The use of Basaglar in pediatric patients (>6 years of age) with type 1 diabetes mellitus is supported by the similar product quality characteristics of Basaglar and Lantus and by the similar pathophysiology of pediatric type 1 diabetes mellitus compared to the studied population (adult type 1 diabetes mellitus). In addition, comparative non-clinical, human pharmacokinetic and clinical efficacy and safety studies have been conducted to demonstrate comparable clinical profiles between Basaglar and the reference product (Lantus).

7.1.4 Geriatrics

Geriatrics (>65 years of age): In controlled clinical studies comparing the reference product (Lantus) to NPH human insulin, 593 of 3890 patients with type 1 and type 2 diabetes were 65 years and older. The only difference in safety or effectiveness in this subpopulation compared to the entire study population was an expected higher incidence of cardiovascular events in both insulin glargine and NPH human insulin treated patients.

Of the total number of subjects in a clinical study of patients with type 2 diabetes who were treated with Basaglar or Lantus, each in combination with oral agents in a controlled clinical trial environment, 29.8% were 65 and over, while 5.6% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects in this 24-week study, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Nevertheless, caution should be exercised when Basaglar is administered to geriatric patients.

In elderly patients with diabetes, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemic reactions.

Hypoglycemia may be difficult to recognize in the elderly (see 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hypoglycemia). In the elderly, progressive deterioration of renal function may lead to steady decrease in insulin requirements. Careful glucose monitoring and dose adjustments of insulin or insulin analogues including Basaglar may be necessary (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic/Renal).

8 ADVERSE REACTIONS

The adverse drug reaction profiles reported in clinical studies that compared Basaglar to the reference biologic drug were comparable. The description of adverse reactions in this section is based on clinical experience with the reference biologic drug.

8.1 Adverse Reaction Overview

Type 1 and type 2 diabetes in adults:

The adverse events most commonly associated with the reference product Lantus [insulin glargine injection (rDNA origin)] include the following:

Eye disorders

Retinopathy was evaluated in the clinical studies by means of retinal adverse events reported and fundus photography. The numbers of retinal adverse events report for Lantus and human NPH treatment groups were similar for patients with type 1 and type 2 diabetes.

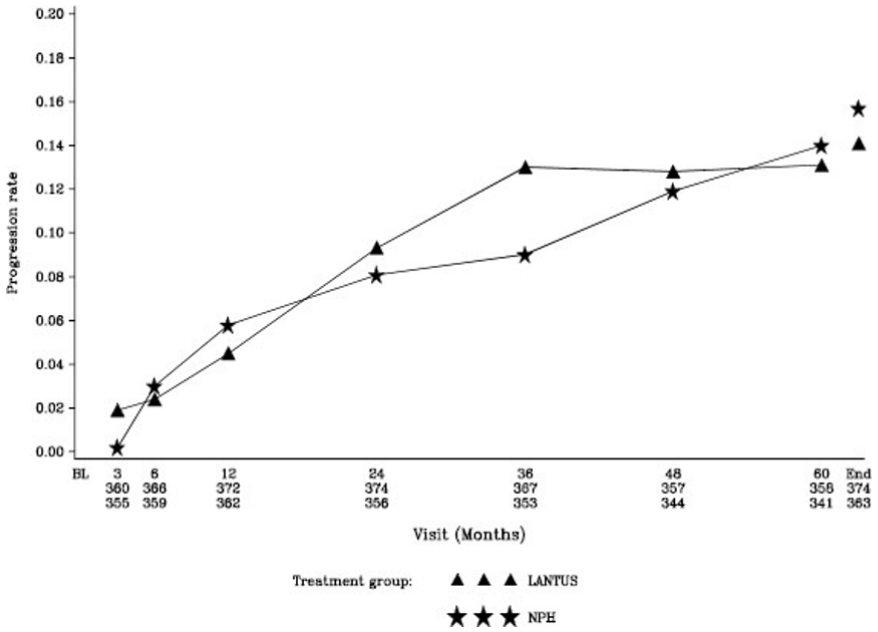
Effects of Lantus on diabetic retinopathy were evaluated in a large 5-year NPH-controlled study in patients with type 2 diabetes in which progression of retinopathy was investigated by fundus photography using a grading protocol derived from the Early Treatment Diabetic Retinopathy Study (ETDRS). The 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 the per-protocol (primary analysis) population and indicate non-inferiority of Lantus to NPH in the progression of diabetic retinopathy as assessed by this outcome. The per-protocol population, which comprised 72.0% of randomized patients, were patients treated with study drug for at least 4 years and had fundus photographs at baseline and after at least 4.5 years post-baseline. The results in the Intent to Treat (ITT) population are similar to the results in the per-protocol population.

Table 2: Number (%) of subjects with 3-step or greater progression in ETDRS at endpoint - per protocol population

	Insulin glargine (N=374)	NPH (N=363)
Subjects with 3-step or great progression (progression rate)	53/374 (14.2%)	57/363 (15.7%)
Difference in progression rate (SE) versus NPH	-1.98% (2.57%)	--
95% CI versus NPH	(-7.02% to 3.06%)	--

Note: % Calculated using number of PP subjects with non-missing data as denominator. ETDRS = early treatment diabetic retinopathy scale. Adjusted for baseline A1c stratum. Margin of noninferiority = 10%.

Figure 1: Plot of 3-step or greater progression rate over time - PP population



Two pre-specified secondary outcomes were the development of "clinically significant macular edema" (CSME) and "proliferative diabetic retinopathy" (PDR), both based on fundus photograph assessment. CSME developed in 15.6% of the Lantus group and 14.6% of the NPH group and PDR developed in 5.4% of the Lantus group and 3.9% of the NPH group. Cataracts were reported more commonly in the Lantus group, in particular cortical (but not nuclear) cataracts. There was a baseline imbalance in cataracts with a greater incidence in the Lantus treatment group. Diabetic retinopathy adverse events were reported in 4.9% of Lantus treated patients vs. 3.8% of NPH treated patients.

Benign prostatic hyperplasia (BPH) was reported as an Adverse Event by 2.7% of the Lantus group compared to 0.6% of the NPH group; urinary retention was reported by 1.2% vs. none, respectively. Neoplasms benign or malignant were seen in 11.1% of Lantus patients, vs. 12.3% of NPH patients.

Immune system disorders

- allergic reactions (see 7 WARNINGS AND PRECAUTIONS).

- injection site reaction

Investigations

- formation of antibodies (see 7 WARNINGS AND PRECAUTIONS).

Metabolism and nutrition disorders

Hypoglycemia: Hypoglycemia, a frequent adverse reaction to insulin therapy, may occur if the insulin dose is too high in relation to the insulin requirement.

As with all insulins, prolonged or severe hypoglycemic attacks, especially if recurrent, may lead to neurological damage, loss of consciousness, coma or death (see 7 WARNINGS AND PRECAUTIONS).

In the multinational ORIGIN trial conducted in 12,537 participants, the rates of severe hypoglycemia (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 hypoglycemia were 7.71 for insulin glargine and 2.44 for Standard Care group. Over the course of this study (median follow-up: 6.2 years), 42% of the patients in the insulin glargine group did not experience any hypoglycemia.

Skin and subcutaneous tissue disorders

- Lipodystrophy, pruritus, and rash (see 7 WARNINGS AND PRECAUTIONS).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Cardiovascular Safety

Study 4032 (ORIGIN Trial): randomized, 2x2 factorial design study: 12,537 participants. Participants were randomized to receive insulin glargine (n=6264), titrated to a Fasting Plasma Glucose (FPG) of 5.3 mmol/L or less, or Standard Care (n=6273). Overall, the incidence of major adverse cardiovascular outcomes was similar between groups. All-cause mortality was also similar between groups (see Table 3).

The objective of the trial was to demonstrate that insulin glargine use could significantly lower the risk of major cardiovascular outcomes compared to standard care. Two co-primary composite cardiovascular endpoints were used in ORIGIN. The first co-primary endpoint was the time to first occurrence of a major adverse cardiovascular event defined as the composite of CV death, nonfatal myocardial infarction and nonfatal stroke. The second co-primary endpoint was the time to the first occurrence of CV death or nonfatal myocardial infarction or nonfatal stroke or revascularization procedure or hospitalization for heart failure.

Anthropometric and disease characteristics were balanced at baseline. The mean age was 64 years and 8% of participants were 75 years of age or older. The majority of participants were male (65%). Fifty nine percent were Caucasian, 25% were Latin, 10% were Asian and 3% were Black. The median baseline BMI was 29 kg/m^2 and 88% had type 2 diabetes. For patients with type 2 diabetes, 59% were treated with a single oral antidiabetic drug, 23% had known diabetes

but were on no antidiabetic drug and 6% were newly diagnosed during the screening procedure. The mean A1c (SD) at baseline was 6.5% (1.0). Fifty nine percent of participants had had a prior cardiovascular event and 39% had documented coronary artery disease or other cardiovascular risk factors.

Vital status was available for 99.9% and 99.8% of participants randomized to Lantus and standard care respectively at end of trial. The median duration of follow-up was 6.2 years [range: 8 days to 7.9 years]. The mean A1c (SD) at the end of the trial was 6.5% (1.1) and 6.8% (1.2) in the Lantus and standard care group respectively. The median dose of Lantus at end of trial was 0.45 U/kg. Eighty-one percent of patients randomized to Lantus were using Lantus at end of the study.

Table 3: ORIGIN: Time to Onset of each Primary and Secondary Endpoint

	Lantus N=6264		**Standard care N=6273**		**Lantus vs Standard care**
	Participants with Events N (%) n	No./100 patient-yr	Participants with Events N (%) n	No./100 patient-yr	Hazard Ratio (95% CI)
Primary endpoints					
CV death, nonfatal myocardial infarction (MI), or nonfatal stroke	1041 (16.6)	(2.94)	1013 (16.1)	(2.85)	1.02 (0.94, 1.11)
CV death, nonfatal myocardial infarction (MI), or nonfatal stroke, or hospitalization for heart failure or revascularization procedure	1792 (28.6)	(5.52)	1727 (27.5)	(5.28)	1.04 (0.97, 1.11)
Secondary endpoints					
All-cause mortality	951 (15.2)	(2.57)	965 (15.4)	(2.60)	0.98 (0.90, 1.08)
Composite microvascular outcome*	1323 (21.1)	(3.87)	1363 (21.7)	(3.99)	0.97 (0.90, 1.08)
Components of coprimary endpoint					
CV death	580 (9.3)	(1.57)	576 (9.2)	(1.55)	1.00 (0.89, 1.13)
MI (fatal or non-fatal)	336 (5.4)	(0.93)	326 (5.2)	(0.90)	1.03 (0.88, 1.19)
Stroke (fatal or non-fatal)	331 (5.3)	(0.91)	319 (5.1)	(0.88)	1.03 (0.89, 1.21)
Revascularizations	908 (14.5)	(2.69)	860 (13.7)	(2.52)	1.06 (0.96, 1.16)

Hospitalization for heart failure	310 (4.9)	(0.85)	343 (5.56)	(0.95)	0.90 (0.77, 1.05)

* with components of: laser photocoagulation or vitrectomy or blindness for diabetic retinopathy; progression in albuminuria; or doubling of serum creatinine or development of the need for renal replacement therapy.

Lantus did not alter the relative risk for CV disease and CV mortality when compared to standard care. There were no differences between Lantus and Standard Care groups for the two co-primary outcomes; for any component endpoint comprising these outcomes; for all mortality; or for the composite microvascular outcome.

Malignancies

In the ORIGIN trial, the overall incidence of cancer (all types combined) or death from cancer was similar between treatment groups. The time to first event of any cancer or new cancer during the study was similar between the two treatment groups with respective hazard ratios of 0.99 (95% CI: 0.88, 1.11) and 0.96 (95% CI: 0.85, 1.09)

Body Weight

At the last on-treatment visit (median follow-up: 6.2 years), there was a mean increase in body weight from baseline of 1.4 kg in the Lantus group and a mean decrease of 0.8 kg in the Standard Care group.

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

Type 1 diabetes in children and adolescents

Table 4 lists adverse events that occurred in a pediatric controlled trial in at least 1% of patients treated with insulin glargine.

Table 4: Adverse Events by Body System ≥1% reported in Study 3003 (Percent Incidence)

Adverse event (diagnosis) Body Systems/Coded Term	Number (%) of subjects Insulin glargine n=174	Human NPH n=175
Body as a whole		
Infection	24 (13.8)	31 (17.7)
Accidental injury	5 (2.9)	4 (2.3)
Abdominal pain	2 (1.1)	2 (1.1)
Allergic reaction	2 (1.1)	(-)
Flu syndrome	(-)	3 (1.7)
Pain in extremity	2 (1.1)	(-)
Digestive system		
Gastroenteritis	8 (4.6)	10 (5.7)
Diarrhea	2 (1.1)	2 (1.1)
Sore throat	2 (1.1)	(-)
Endocrine system		
Diabetes mellitus	1 (0.6)	4 (2.3)
Injection site reactions		
Injection site mass	8 (4.6)	6 (3.4)
Injection site reaction	5 (2.9)	6 (3.4)
Injection site hemorrhage	2 (1.1)	2 (1.1)

Metabolic and nutritional disorders		
Hypoglycemic reaction*	3 (1.7)	7 (4.0)
Hyperglycemia	1 (0.6)	3 (1.7)
Ketosis	1 (0.6)	5 (2.9)
Lipodystrophy	3 (1.7)	2 (1.1)
Musculo-skeletal system		
Bone fracture (not spontaneous)	3 (1.7)	3 (1.7)
Bone disorder	2 (1.1)	(-)
Nervous system		
Headache	6 (3.4)	5 (2.9)
Respiratory system		
Upper respiratory infection	24 (13.8)	28 (16.0)
Pharyngitis	13 (7.5)	15 (8.6)
Rhinitis	9 (5.2)	9 (5.1)
Bronchitis	6 (3.4)	7 (4.0)
Sinusitis	5 (2.9)	5 (2.9)
Asthma	1 (0.6)	2 (1.1)
Cough increased	3 (1.7)	(-)
Skin and appendages		
Fungal dermatitis	1 (0.6)	2 (1.1)
Skin benign neoplasm	1 (0.6)	2 (1.1)
Eczema	2 (1.1)	1 (0.6)
Herpes zoster	2 (1.1)	1 (0.6)
Urticaria	2 (1.1)	(-)

* Non-serious hypoglycemia episodes are reported separately.

Study 3003: The most commonly reported event was lipodystrophy, a known consequence of insulin injections. The intensity was mostly mild. Injection site events were assessed as possibly related in 9 (5.2%) insulin glargine subjects and 5 (2.9%) human NPH subjects however none of these subjects discontinued due to these events.

Study 3013: extension of Study 3003, uncontrolled long-term follow-up study of 143 patients who were well-controlled on insulin glargine from 3003, for 201-1159 days. The most common adverse events were upper respiratory infections, infection, and rhinitis. Note that when comparing safety findings between studies, the difference in length of exposure needs to be kept in mind.

Study 4005: controlled, randomized, double-cross-over: 26 subjects (age range: 12-20), regimen of insulin glargine + lispro vs. human NPH + human regular. Adverse events were equally distributed between the two treatment regimens. The most common adverse events were upper respiratory tract infection and gastroenteritis.

Patients in the pediatric clinical trials of insulin glargine were treated with a human NPH-based regimen pre-study, and patients assigned to receive human NPH during the study began study treatment on the same human NPH regimen they had taken pre-study. This may have been a factor in the increased incidence of hypoglycemia seen in insulin glargine-treated patients during (but not following) initial titration in these trials, as an increase in hypoglycemia may be expected when switching from one insulin to another and titrating the dose of the new insulin.

8.5 Post-Market Adverse Reactions

Other:

Medication errors have been reported from post-marketing experience with the reference product Lantus (insulin glargine) in which other insulins, particularly fast-acting insulins, have been accidentally administered instead of insulin glargine.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

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

9.3 Drug-Behavioural Interactions

Patients should be offered continued education and advice on insulin therapies, life-style management, self-monitoring, complications of insulin therapy, timing of dosage, instruction for use of injection devices and storage of insulin.

The need for regular blood glucose self-monitoring should be considered when using Basaglar to obtain optimal glycemic control.

Alcohol may intensify or reduce the hypoglycemic effect of insulin.

9.4 Drug-Drug Interactions

Substances that may increase the blood-glucose-lowering effect and susceptibility to hypoglycemia, for example: oral antidiabetic products, ACE inhibitors, disopyramide, fibrates, fluoxetine, MAO inhibitors, pentoxifylline, propoxyphene, salicylates, somatostatin analog (e.g., octreotide), sulfonamide antibiotics.

Substances that may reduce the blood-glucose-lowering effect, for example: corticosteroids, danazol, diazoxide, diuretics, sympathomimetic agents (e.g., epinephrine, salbutamol, terbutaline), glucagon, isoniazid, phenothiazine derivatives, 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 hypoglycemia, which may sometimes be followed by hyperglycemia. In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine, and reserpine, the signs of hypoglycemia may be reduced or absent.

Other:

To avoid the risk of developing new or worsening heart failure, the use of TZDs in combination therapy with insulin is not indicated (see 7 WARNINGS AND PRECAUTIONS).

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

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

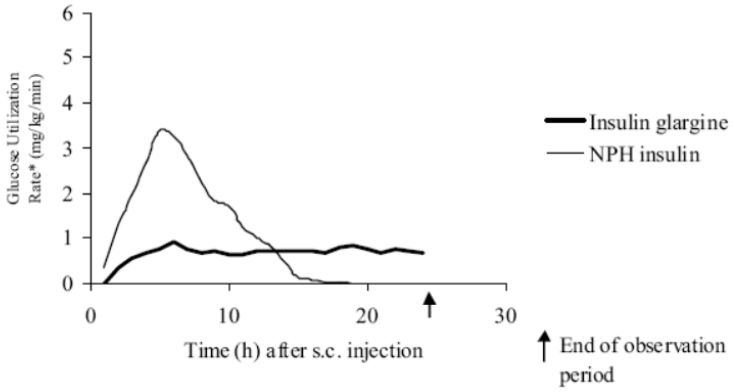
10.2 Pharmacodynamics

Insulin glargine is a human insulin analogue designed to have low solubility at neutral pH. At pH 4, as in the Basaglar injection solution, it is completely soluble. 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 slowly released, resulting in a relatively constant concentration/time profile over 24 hours with no pronounced peak. This allows once-daily dosing to meet a patient's basal insulin needs.

Insulin glargine and human insulin have been shown to be equipotent in glucose-lowering effect on a molar basis (when administered intravenously at the same doses). In euglycemic clamp studies with the reference product (Lantus) in healthy subjects or in patients with type 1 diabetes, the onset of action of subcutaneous insulin glargine was slower than NPH human insulin. The effect profile of insulin glargine was relatively constant with no pronounced peak, and the duration of its effect was prolonged compared to NPH human insulin.

Figure 2 shows results from a study with the reference product (Lantus) in patients with type 1 diabetes conducted for a maximum of 24 hours after the injection. The median time between injection and the end of pharmacological effect was 14.5 hours (range: 9.5 to 19.3 hours) for NPH human insulin, and 24 hours (range: 10.8 to >24.0 hours) (24 hours was the end of the observation period) to insulin glargine.

Figure 2: Activity Profile in Patients with Type 1 Diabetes



* Determined as amount of glucose infused to maintain constant plasma glucose levels (hourly mean values). Indicative of insulin activity. Between-patient variability (CV, coefficient of variation), insulin glargine, 84% and human NPH, 78%

10.3 Pharmacokinetics

Absorption

After subcutaneous injection of Lantus (the reference product) in healthy subjects and patients

with diabetes, the insulin serum concentrations indicated a slower, more prolonged absorption and relatively constant concentration/time profile over 24 hours with no pronounced peak in comparison to NPH human insulin. Serum insulin concentrations were thus consistent with the time profile of the pharmacodynamic activity of insulin glargine.

After subcutaneous injection of 0.3 units/kg insulin glargine in patients with type 1 diabetes, a relatively constant concentration-time profile has been demonstrated. The duration of action after abdominal, thigh, or deltoid subcutaneous administration was similar.

Metabolism:

After subcutaneous injection of the reference product (Lantus) in healthy subjects and patients with diabetes, insulin glargine is rapidly metabolized at the carboxyl terminus of the Beta chain with formation of two active metabolites M1 (21A-Gly-insulin) and M2 (21A-Gly-des-30B-Thr-insulin). In plasma, the principal circulating compound is the metabolite M1. The exposure to M1 increases with the administered dose of insulin glargine. The pharmacokinetic and pharmacodynamic findings indicate that the effect of the subcutaneous injection with insulin glargine is principally based on exposure to M1. Insulin glargine and the metabolite M2 were not detectable in the vast majority of subjects and, when they were detectable their concentration was independent of the administered dose of the insulin glargine.

Duration of Effect

The longer duration of action (up to 24 hours) of insulin glargine is directly related to its slower rate of absorption and supports once-daily subcutaneous administration. The time course of action of insulins including Basaglar may vary between individuals and/or within the same individual. The doses and timing of antidiabetic medications must be determined and adjusted individually to achieve the desired blood glucose levels.

Special Populations and Conditions

- **Age, race, and gender:** Information of the effect of age, race, and gender on the pharmacokinetics of insulin glargine is unavailable. However, in controlled clinical trials for the reference product (Lantus) in adults (n=3890, Studies 3001, 3002, 3004, 3005, and 3006), and a controlled clinical trial in pediatric patients (n=349, Study 3003) subgroup analyses based on age, race (white, black, Asian/oriental, multiracial and Hispanic) and gender did not show differences in safety and efficacy between insulin glargine and NPH human insulin.
- **Pregnancy and Breast-feeding:** The effect of pregnancy on the pharmacokinetics and pharmacodynamics of insulin glargine has not been studied (see 7WARNINGS AND PRECAUTIONS, Special Populations).
- **Hepatic Insufficiency:** No studies were performed in patients with hepatic insufficiency. However, some studies with human insulin have shown increased circulating levels of insulin in patients with liver failure. Careful glucose monitoring and dose adjustments of insulin or insulin analogues including Basaglar may be necessary in patients with hepatic dysfunction (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic/Renal).
- **Renal Insufficiency:** No studies were performed in patients with renal insufficiency. However, some studies with human insulin have shown increased circulating levels of insulin in patients with renal failure. Careful glucose monitoring and dose adjustments of insulin or insulin analogues including Basaglar may be necessary in patients with renal

dysfunction (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic/Renal).

- **Obesity:** In controlled clinical trials for the reference product (Lantus), which included patients with Body Mass Index (BMI) up to and including 49.6 kg/m^2, subgroup analyses based on BMI did not suggest any differences in safety and efficacy between insulin glargine and NPH human insulin.
- **Smoking:** Information on the effect of smoking on the pharmacokinetics and pharmacodynamics of Basaglar has not been studied.

11 STORAGE, STABILITY AND DISPOSAL

Unopened (not-in-use) Basaglar Cartridges and Basaglar KwikPens

Unopened Basaglar cartridges and Basaglar KwikPens should be stored in a refrigerator, between 2°C and 8°C. Do not freeze. Do not use Basaglar if it has been frozen. Unopened Basaglar cartridges or Basaglar KwikPens may be used until the expiration date printed on the label. Do not use past the expiration date. If Basaglar freezes, discard it.

Opened (in-use) Basaglar Cartridges and Basaglar KwikPens

Open (in-use) Basaglar cartridges and Basaglar KwikPens should be stored at room temperature, below 30°C and away from direct heat and light. In-use Basaglar cartridges or Basaglar KwikPens must be used within 28 days, and should be discarded after 28 days even if they still contain Basaglar. Do not use past the expiration date. If Basaglar freezes, discard it.

As with all medications and devices, keep out of reach and sight of children.

12 SPECIAL HANDLING INSTRUCTIONS

Information to be provided to the patient

Inspect the cartridge or KwikPen of Basaglar before use. Basaglar must only be used if the solution is clear and colourless with no particles visible. (see 4 DOSAGE AND ADMINISTRATION, Administration). Basaglar is a clear solution, not a suspension. Basaglar can be confused with other insulin types, since it visually resembles fast-acting insulins. The insulin label must always be checked before each injection to avoid medication errors between Basaglar and other insulins. Do not shake the cartridge or KwikPen before use. Patients must be advised that Basaglar must not be mixed with any other insulin or diluted with any other solution. Mixing or diluting can change the time/action profile of Basaglar and mixing can cause precipitation (see 7 WARNINGS AND PRECAUTIONS).

Patients should be instructed on self-management procedures including glucose monitoring, proper injection technique, and hypoglycemia and hyperglycemia management. Patients must be instructed on handling of special situations such as intercurrent conditions (illness, stress, or emotional disturbances), 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 hypoglycemia. Patients and their relatives must know what steps to take if hyperglycemia or hypoglycemia occurs or is suspected, and they must know when to inform a physician.

Patients with diabetes should be advised to inform their health professional if they are pregnant or are contemplating pregnancy.

To prevent the possible transmission of disease, each pen must be used by one patients only.

Empty Basaglar cartridges and Basaglar KwikPens must never be reused and must be properly discarded.

Refer patients to the **Error! Reference source not found.** for Basaglar for additional information. Also refer patients to the Instructions for Use for Basaglar KwikPen, and Lilly's reusable pens for additional information on use of the pens.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

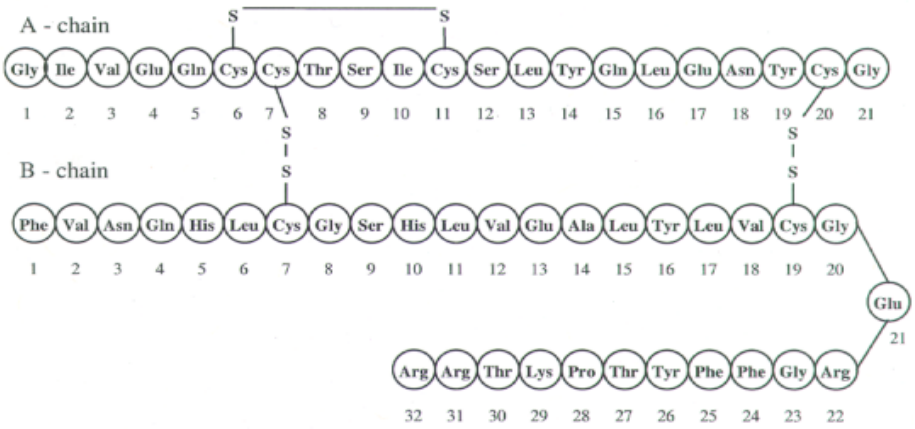
Drug Substance

Proper name: insulin glargine (rDNA origin)

Chemical name: 21^{A}-Gly-30^{B}a-L-Arg-30^{B}b-L-Arg-human insulin

Molecular formula and molecular mass: $C_{267}H_{404}N_{72}O_{78}S_6$ and 6063 Daltons

Structural formula:



Physicochemical properties, solubility:

- Very soluble (greater than 1000 mg/mL) in pH 1.2 buffer
- Practically insoluble (less than 0.1 mg/mL) in pH 7.4 to 9.0 buffer, as well as water, ethanol and acetonitrile

Physical Form: white to almost white solid

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Clinical studies conducted to support similarity between Basaglar (insulin glargine injection) and the reference biologic drug included:

- ABEO, a randomized, crossover study conducted in healthy adult subjects to evaluate the PK and PD similarity of Basaglar and Lantus.
- ABEB, a randomized 52-week study performed in adult patients with type 1 diabetes comparing the safety and efficacy of Basaglar to Lantus.
- ABEC, a randomized 24-week study performed in adult patients with type 2 diabetes comparing the safety and efficacy of Basaglar to Lantus.

An overview of the study designs and demographic characteristics of patients enrolled in each clinical study are presented in Table 5.

Table 5: Summary of patient demographics for clinical trials in specific indication

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n = number)	Mean age (Range)	Gender (M/F)
ABEO	Phase 1, randomized, double-blind, 2-treatment, 4-period, replicate crossover to evaluate the PK and PD similarity of Basaglar and Lantus	On 4 separate occasions, a single 0.5-U/kg dose of Basaglar or Lantus was administered by subcutaneous injection per the following sequences: • Basaglar – Lantus - Basaglar - Lantus or • Lantus - Basaglar - Lantus - Basaglar Minimum 7-day washout between doses	91 healthy subjects	32.7 years (22 - 62 years)	85 M 6 F
ABEB (T1DM) (ELEMENT 1)	Phase 3, prospective, randomized, 2-arm, active control, open label, parallel, 24-week treatment with a 28-week active-control, open-label extension, and 4-week post-treatment follow up to compare Basaglar and Lantus, when each is used with mealtime insulin lispro in patients with T1DM	Basaglar was initiated at the same dose as the patient's prestudy once-daily basal insulin. Insulin lispro was administered with meals at the same dose as the patient's prestudy mealtime insulin dose while avoiding hypoglycemia. Investigators recommended basal and bolus insulin dose adjustments to achieve glycemic targets.	535 patients received study drug Basaglar: 268 patients Lantus: 267 patients	41.2 years (18.3 – 81.4 years)	310 M 225 F
ABEC (T2DM) (ELEMENT 2)	Phase 3, prospective, randomized, 2-arm, active-control, double-blind, parallel, 24-week treatment study with a 4-week post-treatment follow-up to compare Basaglar and Lantus, each used in combination with at least 2 oral antihyperglycemic medications in adult patients with T2DM. Patients were either insulin-naïve or already administering QD Lantus.	If the patient was insulin- naïve, the starting dose for Basaglar was 10 units QD. If the patient was already taking Lantus, Basaglar was initiated at the same dose as the patient's prestudy Lantus dose. All patients were to then follow a patient-driven dosing algorithm under investigator supervision throughout the study.	756 patients received study drug Basaglar: 376 patients Lantus: 380patients	58.8 years (23.4 - 84.3 years)	378 M 378 F

QD = once daily; T1DM=type 1 diabetes mellitus; T2DM=type 2 diabetes mellitus

Comparative Pharmacokinetic/Pharmacodynamic (PK/PD) Studies

Pivotal PK/PD Study

Study ABEO is a Phase 1, randomized, double-blind, 2-treatment, 4-period, replicate crossover study conducted in 91 healthy subjects (85 males, 6 females, 22 to 62 years of age) to evaluate the PK and PD similarity of Basaglar and Lantus . On 4 separate occasions, fasted subjects received a single SC 0.5-U/kg dose of Basaglar or Lantus according to the following sequences: Basaglar - Lantus- Basaglar -Lantus or Lantus- Basaglar -Lantus-Basaglar. A minimum 7-day washout separated doses. Serial blood samples were collected predose and at time points up to 24 hours postdose to assess PK, and a euglycemic glucose clamp procedure lasting up to 24 hours was conducted to assess PD. The primary PK parameters were $AUC_{(0-24)}$ and C_{max}, and the primary PD parameters were G_{tot} and R_{max}.

Comparative Clinical Efficacy and Safety Studies- Adults

The safety and efficacy of once-daily Basaglar was compared to that of once-daily Lantus in an open-label, randomized, active-controlled, parallel study of 535 adults with type 1 diabetes (Study ABEB, also known as ELEMENT 1). The stratification factors at randomization were country, A1c level (<8.5 vs. ≥8.5%), and time of basal insulin injection (daytime, evening/bedtime). As shown in Table 7 below, similar efficacy outcomes were observed in this non-inferiority study designed for 52-week treatment duration, with a primary efficacy endpoint evaluation at 24 weeks.

The safety and efficacy of once-daily Basaglar was also compared to that of once-daily Lantus in a double-blind, randomized, active-controlled parallel study of 756 adults with type 2 diabetes (Study ABEC, also known as ELEMENT 2). The stratification factors at randomization were country, A1c levels (<8.5% vs ≥8.5%), sulfonylurea use (yes/no) and time of basal insulin injection (daytime, evening/bedtime). Similar efficacy outcomes were observed in this non-inferiority study (Table 8).

Demographic and baseline characteristics were generally balanced between treatment groups in each of these studies. The populations were predominantly white (in Study ABEB, Basaglar 73.8% and Lantus 75.3%; in Study ABEC, Basaglar 80.3% and Lantus 76.6%). Patients had a mean age of 41.2 years in Study ABEB (Basaglar 41.0 years, Lantus 41.4 years) and 58.8 years in Study ABEC (Basaglar 59.0 years, Lantus 58.7 years). In Study ABEB, 14 patients (5.2%) in the Basaglar arm and 11 patients (4.1%) in the Lantus arm were ≥65 years old. In Study ABEC, 112 patients (29.8%) in the Basaglar arm and 102 patients (26.8%) in the Lantus arm were ≥65 years old. Few patients were ≥75 years old [Study ABEB: Basaglar 2 (0.7%) and Lantus 0; Study ABEC: Basaglar 21 (5.6%) and Lantus 13 (3.4%)]. The mean duration of diabetes was 16.4 years in Study ABEB (Basaglar 16.2 years; Lantus16.6 years) and 11.5 years in Study ABEC (Basaglar 11.7 years, Lantus 11.2 years).

Overall, the mean A1c at baseline in Study ABEB was 7.77% (Basaglar: 7.75%; Lantus: 7.79%), and for ABEC was 8.33% (Basaglar: 8.34%; Lantus: 8.31%).

14.2 Study Results

See 14.3 Comparative Bioavailability Studies

14.3 Comparative Bioavailability Studies

14.3.1 Comparative PK/PD Study: Pivotal PK/PD Study

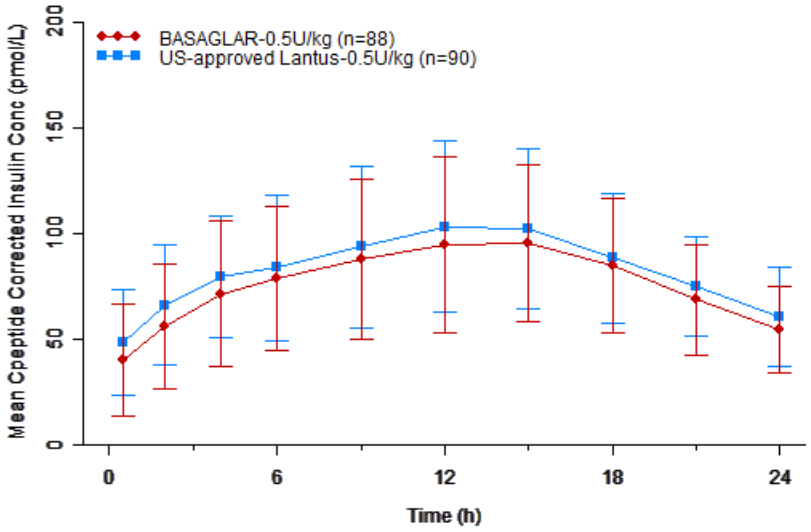
The pharmacokinetic and pharmacodynamic parameters for study ABEO are summarized in Table 6. Figure 3 shows the PK profiles for Basaglar and Lantus. Basaglar was determined to have similar PK and PD properties compared to Lantus.

Table 6: Comparative PK and PD data for Basaglar vs. Lantus in Healthy Subjects (Study ABEO)

Parameter	Basaglar Geometric Mean (%CV)	Lantus Geometric Mean (%CV)	Ratio of Least Squares Geometric Means	99% Confidence Interval (for PK) 95% Confidence Interval (for PD)
Pharmacokinetic Properties				
AUC_{0-24h} (pmol•h/L)	1720 (42)	1900 (35)	0.90	(0.86, 0.94)
C_{max} (pmol/L)	103 (41)	111 (34)	0.92	(0.87, 0.96)
t_{max} (h)[a]	12.0 (2.00-21.0)	12.0 (2.00-24.0)	Not applicable	Not applicable
Pharmacodynamic Properties				
G_{tot} (mg/kg)[b]	1670 (60)	1820 (74)	0.91	(0.84, 1.00)
R_{max} (mg/kg/min)[b]	2.12 (54)	2.27 (58)	0.93	(0.87, 0.99)

Abbreviations: CV= coefficient of variation, t1/2 = terminal elimination half-life, tmax = time to achieve the maximum plasma concentration, C_{max} = maximum plasma concentration, AUC_{0-24} = area under the plasma-concentration-versus-time curve from Time 0 to 24 hours; G_{tot}=total glucose infusion over the clamp duration; R_{max}=maximum glucose infusion rate.[a] Median (range)[b] G_{tot} and R_{max} parameter estimates are based on LOESS (locally weighted regression in smoothing scatterplots) smoothed GIR (glucose infusion rate) profiles.

Figure 3: Mean (±standard deviation) C-peptide corrected serum insulin concentration versus time profile following subcutaneous administration of a single dose of Basaglar (0.5 U/kg) and Lantus (0.5 U/kg).



14.3.2 Comparative Safety and Efficacy

Data from the two Phase 3 clinical studies provide evidence of comparable efficacy by meeting the primary test of the noninferiority of Basaglar to Lantus, as well as by demonstrating that the change in A1c after 24 weeks in patients with type 1 diabetes mellitus (ABEB) and type 2 diabetes mellitus (ABEC) is entirely contained within the pre-specified margins of ±0.4%.

14.3.2.1 Efficacy Results

The primary outcome in both studies was change in A1c from baseline to 24-week endpoint. Both studies confirmed that Basaglar once daily is non-inferior to Lantus® once daily, using non-inferiority margins (NIM) of both 0.4% and 0.3% (full analysis set, FAS) (Table 7 and Table 8). In addition, based on protocol specified testing, Basaglar and Lantus were considered to have comparable efficacy in both studies, in terms of change in A1c from baseline to week 24, at the 0.4% margin.

Table 7: Summary of Efficacy Results for Basaglar vs. Lantus in T1DM – Study ABEB

	Study ABEB (T1DM) 24-week endpoint N=535		Study ABEB (T1DM) 52-week endpoint N=534	
	Basaglar n=268	Lantus n=267	Basaglar n=267	Lantus n=267
A1c (%)[c]				
Number of patients at endpoint[a]	256	258	248	246
Mean baseline	7.76	7.79	7.76	7.79
LS Mean change from baseline[b]	-0.38	-0.48	-0.29	-0.30
LS Mean treatment difference (Basaglar - Lantus)*	0.103		0.016	
95% CI from treatment difference	(-0.009, 0.215)		(-1.107, 0.140)	

Basal Insulin Dose (U/day)				
Number of patients[a]	268	266	268	266
Mean baseline	25.1	23.3	25.1	23.3
LS Mean change from baseline[b]	2.0	2.0	2.7	2.4
Total Insulin Dose (U/day)				
Number of patients[a]	264	266	264	266
Mean baseline	55.5	52.8	55.5	52.8
LS Mean change from baseline[b]	0.7	0.6	2.9	2.9

[a] Only patients with nonmissing baseline value and at least one nonmissing postbaseline value of the response variable were included in analysis.
[b] Change from baseline to endpoint values are LS means, reflecting adjustment for the design factors of the study. Baseline values are unadjusted means.
[c] Mixed effects model for repeated measures (MMRM) methodology utilized.
Abbreviations: CI=confidence interval; A1c=hemoglobin A1c; LS=least squares; N=total number of patients; n=number of patients in defined subgroup; NA=not applicable; T1DM=type 1 diabetes mellitus
* Non-inferiority testing approach: Basaglar was non-inferior to Lantus in the primary treatment comparison at both 0.4% and 0.3% non-inferiority margins (NIMs) based on the full analysis set (FAS) population. The non-inferiority test was only pre-specified for the 24-week A1c endpoint.

Table 8: Summary of Efficacy Results for Basaglar vs. Lantus in T2DM – Study ABEC

	Study ABEC (T2DM) 24-week endpoint N=756	
	Basaglar n=376	**Lantus n=380**
A1c (%)[c]		
Number of patients at endpoint[a]	331	329
Mean baseline	8.35	8.31
LS Mean change from baseline[b]	-1.26	-1.31
LS Mean treatment difference (Basaglar - Lantus)*	0.051	
95% CI from treatment difference	(-0.095, 0.196)	
Basal Insulin Dose (U/day)		
Number of patients[a]	374	379
Mean baseline	15.4	12.0
LS Mean change from baseline[b]	32.3	32.6
Total Insulin Dose (U/day)		
Number of patients[a]	N/A	N/A
Mean baseline	N/A	N/A
LS Mean change from baseline[b]	N/A	N/A

[a] Only patients with nonmissing baseline value and at least one nonmissing postbaseline value of the response variable were included in analysis.
[b] Change from baseline to endpoint values are LS means, reflecting adjustment for the design factors of the study. Baseline values are unadjusted means.
[c] Mixed effects model for repeated measures (MMRM) methodology utilized.
Abbreviations: CI=confidence interval; A1c=hemoglobin A1c; LS=least squares; N=total number of patients; n=number of patients in defined subgroup; NA=not applicable; T1DM=type 1 diabetes mellitus
* Non-inferiority testing approach: Basaglar was non-inferior to Lantus in the primary treatment comparison at both 0.4% and 0.3% non-inferiority margins (NIMs) based on the full analysis set (FAS) population. The non-inferiority test was only pre-specified for the 24-week A1c endpoint.

Subgroup analyses based on age, race, gender, and BMI did not suggest a difference in safety and efficacy for patients treated with Basaglar compared to those treated with Lantus.

Body Weight

In Study ABEB the mean change from baseline for the body weight was 0.36 kg for Basaglar and 0.12 kg for Lantus at 24 weeks; at 52 weeks the changes were 0.71 kg and 0.36 kg respectively. In Study ABEC the mean change from baseline for the body weight was 1.78 kg for Basaglar and 2.02 kg for Lantus at 24 weeks.

Basal Insulin Dose

In Study ABEB, the change in basal insulin dose from baseline to any visit or endpoints (LOCF) was similar between Basaglar and Lantus. The actual basal insulin dose at endpoints (LOCF), and the actual measurements adjusted for weight (U/kg/day) were also similar between Basaglar and Lantus. Likewise, the actual measurements not adjusted for weight (as measured in U/day) at Week 36, Week 44 and Week 52 were also similar between treatment arms.

In Study ABEC, the actual daily basal insulin dose at endpoint (LOCF) and the change from baseline in basal insulin dose (in U/day or U/kg/day) at any visit or endpoint (LOCF) were similar between Basaglar and Lantus.

Total Insulin Dose

In Study ABEB, the increases in mean total insulin dose from baseline to endpoint were similar in both treatment groups

14.3.2.2 Safety Results

Overview

The safety profile of Basaglar was consistent with that previously reported for the reference product in patients with type 1 diabetes mellitus or type 2 diabetes mellitus.

The types, frequency, and severity of adverse events were comparable between the Basaglar and the reference biologic drug.

The most frequently reported TEAEs included nasopharyngitis (Basaglar: 9.9%; Lantus:10.4%), upper respiratory tract infection (Basaglar: 6.4%; Lantus: 5.6%), and diarrhea (Basaglar: 3.3%; Lantus: 3.7%).

In study ABEB, 20 patients (7.5%) in the Basaglar group and 11 patients (4.1%) in the Lantus group reported treatment-emergent allergic events. Most events were mild or moderate in severity, none were reported as serious and none led to discontinuation.

In Study ABEC, the incidence of treatment-emergent allergic events was similar among treatment groups: 21 patients (5.6%) in the Basaglar group and 27 patients (7.1%) in the Lantus group reported treatment-emergent allergic events. Most events were mild or moderate in severity, and none led to discontinuation. One event of severe asthma in the Basaglar treatment group was reported as serious, but unrelated to study drug, procedure, or disease.

In clinical studies comparing Basaglar to Lantus in adult patients with type 1 or type 2 diabetes mellitus, the incidence of injection site or local allergic reactions was similar between the two treatment arms.

Injection site adverse events (AEs) were evaluated for pain, pruritus, and rash associated with the injection, as well as the characteristics of the injection site (abscess, nodule, lipoatrophy, lipohypertrophy, or induration). The number of patients experiencing injection site AEs in studies

ABEB and ABEC combined were 20 (3.1%) for Basaglar and 14 (2.2%) for Lantus. Most patients in both treatment groups with injection site AEs reported having mild or moderate pain associated with the injection. A total of 3 patients (Basaglar: 1 patient; Lantus: 2 patients) discontinued from the phase 3 studies due to injection site AEs.

Study ABEB- Type 1 diabetes in adults

A total of 167 patients (62.3%) in the Basaglar group and 166 patients (62.2%) in the Lantus group reported TEAEs.

Overall during the 52-week study, 515 patients (96.3%) reported 40,393 events of total hypoglycemia, (Basaglar 256 patients [95.5%], 19,541 events; Lantus 259 patients [97.0%], 20,852 events). This included events meeting the criteria for severe hypoglycemia, documented symptomatic hypoglycemia with blood glucose (BG) ≤3.9 mmol/L (70 mg/dL), asymptomatic hypoglycemia with BG ≤3.9 mmol/L (70 mg/dL), probable symptomatic hypoglycemia, or unspecified hypoglycemia with BG ≤3.9 mmol/L (70 mg/dL).Overall during the 52-week study, a total of 21 patients (3.9%) reported 29 events of severe hypoglycemia (Basaglar 10 patients [3.7%], 13 events; Lantus 11 patients [4.1%], 16 events). Severe hypoglycemia was defined as symptoms requiring assistance of another person, and included severe hypoglycemia events with BG ≤3.9 mmol/L (70 mg/dL), BG <3.0 mmol/L (54 mg/dL), BG missing, or BG not aligned with severe symptoms.

Overall, 3 patients (1.1%) on BASAGLAR reported cardiac events [sinus tachycardia 2 patients (0.7%), cardiac failure 1 patient (0.4%)], and 6 patients (2.2%) on Lantus® reported cardiac events [palpitation 2 patients (0.7%), sinus tachycardia 1 patient (0.4%), bradycardia 1 patient (0.4%), hypertrophic cardiomyopathy 1 patient (0.4%), tachycardia 1 patient (0.4%)].

Overall, 12 patients (4.5%) on BASAGLAR reported vascular events [hypertension 9 patients (3.4%), peripheral arterial occlusive disease 2 patients (0.7%), hot flush 1 patient (0.4%)], and 6 patients (2.2%) on Lantus® reported vascular events [hypertension 5 patients (1.9%), microangiopathy 1 patient (0.4%)].

Table 9 shows the treatment emergent adverse events occurring in ≥1% of patients in either the Basaglar or Lantus treatment group.

Table 9: Treatment Emergent Adverse Events reported in ≥1% of Basaglar-treated or Lantus-treated patients with T1DM (study ABEB)

Adverse Event	**Basaglar (N=268)**	**Lantus (N=267)**
System Organ Class Preferred Term	n (%)	n (%)
Gastrointestinal disorders		
Diarrhea	12 (4.5)	10 (3.7)
Abdominal pain upper	3 (1.1)	5 (1.9)
Vomiting	6 (2.2)	2 (0.7)
Gastritis	3 (1.1)	4 (1.5)
Gastrooesophageal reflux disease	4 (1.5)	3 (1.1)
Toothache	4 (1.5)	1 (0.4)
Nausea	1 (0.4)	3 (1.1)
General disorders and administration site conditions		
Influenza like illness	3 (1.1)	5 (1.9)

Fatigue	4 (1.5)	3 (1.1)
Injection site reaction	3 (1.1)	2 (0.7)
Pyrexia	4 (1.5)	0 (0.0)
Infections and infestations		
Nasopharyngitis	43 16.0)	45 16.9)
Upper respiratory tract infection	22 (8.2)	21 (7.9)
Gastroenteritis	8 (3.0)	8 (3.0)
Sinusitis	7 (2.6)	8 (3.0)
Influenza	5 (1.9)	9 (3.4)
Bronchitis	4 (1.5)	8 (3.0)
Urinary tract infection	4 (1.5)	5 (1.9)
Gastroenteritis viral	5 (1.9)	3 (1.1)
Pharyngitis	3 (1.1)	4 (1.5)
Tooth abscess	1 (0.4)	4 (1.5)
Viral upper respiratory tract infection	3 (1.1)	2 (0.7)
Cystitis	0 (0.0)	3 (1.1)
Immune system disorders		
Seasonal allergy	3 (1.1)	2 (0.7)
Injury, poisoning and procedural complications		
Ligament sprain	3 (1.1)	0 (0.0)
Metabolism and nutrition disorders		
Hypoglycemia	13 (4.9)	12 (4.5)
Musculoskeletal and connective tissue disorders		
Back pain	10 (3.7)	9 (3.4)
Arthralgia	3 (1.1)	5 (1.9)
Musculoskeletal pain	2 (0.7)	5 (1.9)
Neck pain	2 (0.7)	3 (1.1)
Pain in extremity	3 (1.1)	2 (0.7)
Nervous system disorders		
Headache	7 (2.6)	7 (2.6)
Dizziness	6 (2.2)	0 (0.0)
Psychiatric disorders		
Depression	3 (1.1)	2 (0.7)
Respiratory, thoracic and mediastinal disorders		
Cough	6 (2.2)	8 (3.0)
Sinus congestion	6 (2.2)	5 (1.9)
Oropharyngeal pain	5 (1.9)	4 (1.5)
Nasal congestion	3 (1.1)	3 (1.1)
Upper respiratory tract inflammation	4 (1.5)	2 (0.7)
Skin and subcutaneous tissue disorders		
Acne	2 (0.7)	3 (1.1)
Dermatitis contact	1 (0.4)	4 (1.5)
Vascular disorders		
Hypertension	9 (3.4)	5 (1.9)

Study ABEC – Type 2 diabetes in adults

A total of 196 patients (52.1%) in the Basaglar group and 184 patients (48.4%) in the Lantus group reported TEAEs. Overall, the most frequently reported TEAEs (≥3%) in either treatment group were nasopharyngitis (5.6% in the Basaglar arm and 5.8% in the Lantus arm), upper respiratory tract infection (5.1% in the Basaglar arm and 3.9% in the Lantus arm), and diarrhea (2.4% in the Basaglar arm and 3.7% in the Lantus arm).

Overall, 588 patients (78.5%) reported 7409 events of total hypoglycemia including events with BG ≤70 mg/dL (Basaglar 296 patients [79.4%], 3564 events; Lantus 292 patients [77.7%], 3845 events). Overall, a total of 4 patients (0.5%) reported 9 events of severe hypoglycemia (Basaglar 2 patients [0.5%], 7 events; Lantus 2 patients [0.5%], 2 events).

Overall, **10 patients (2.7%) on BASAGLAR reported 11 cardiac events** [palpitations 3 patients (0.8%), tachycardia 2 patients (0.5%), coronary artery disease 1 patient (0.3%), cardiac failure congestive 1 patient (0.3%), diastolic dysfunction 1 patient (0.3%), left ventricular hypertrophy 1 patient (0.3%), mitral valve incompetence 1 patient (0.3%), ventricular extrasystoles 1 patient (0.3%)], **and 8 patients (2.1%) on Lantus® reported 11 cardiac events** [coronary artery disease 3 patients (0.8%), cardiac failure congestive 2 patients (0.5%), angina pectoris 1 patient (0.3%), arrhythmia 1 patient (0.3%), atrial fibrillation 1 patient (0.3%), bradycardia 1 patient (0.3%), hypertensive heart disease 1 patient (0.3%), myocardial infarction 1 patient (0.3%)].

Overall, **21 patients (5.6%) on BASAGLAR reported 21 vascular events** [hypertension 8 patients (2.1%), hypertensive crisis 3 patients (0.8%), essential hypertension 1 patient (0.3%), hypotension 1 patient (0.3%), aortic arteriosclerosis 1 patient (0.3%), deep vein thrombosis 1 patient (0.3%), femoral artery occlusion 1 patient (0.3%), hematoma 1 patient (0.3%), hypertensive angiopathy 1 patient (0.3%), peripheral arterial occlusive disease 1 patient (0.3%), varicose vein 1 patient (0.3%), venous insufficiency 1 patient (0.3%)], and **9 patients (2.4%) on Lantus® reported 9 vascular events** [hypertension 3 patients (0.8%), essential hypertension 1 patient (0.3%), hypotension 1 patient (0.3%), diabetic vascular disorder 1 patient (0.3%), hot flush 1 patient (0.3%), pallor 1 patient (0.3%), subclavian artery occlusion 1 patient (0.3%)].

Table 10 shows the treatment emergent adverse events occurring in ≥1% of patients in either the Basaglar or Lantus treatment group.

Table 10: Treatment Emergent Adverse Events reported in ≥1% of Basaglar-treated or Lantus-treated patients with T2DM (Study ABEC)

Adverse Event	**Basaglar (N=376)**	**Lantus (N=380)**
System Organ Class Preferred Term	**n (%)**	**n (%)**
Gastrointestinal disorders		
Diarrhea	9 (2.4)	14 (3.7)
Nausea	8 (2.1)	8 (2.1)
Vomiting	5 (1.3)	6 (1.6)
Constipation	4 (1.1)	5 (1.3)
Abdominal pain upper	1 (0.3)	4 (1.1)
Gastrooesophageal reflux disease	1 (0.3)	4 (1.1)
General disorders and administration site conditions		
Oedema peripheral	5 (1.3)	6 (1.6)
Infections and infestations		

Nasopharyngitis	21 (5.6)	22 (5.8)
Upper respiratory tract infection	19 (5.1)	15 (3.9)
Influenza	7 (1.9)	11 (2.9)
Urinary tract infection	7 (1.9)	7 (1.8)
Bronchitis	6 (1.6)	7 (1.8)
Gastroenteritis viral	7 (1.9)	6 (1.6)
Sinusitis	8 (2.1)	3 (0.8)
Gastroenteritis	2 (0.5)	4 (1.1)
Investigations		
Weight increased	5 (1.3)	7 (1.8)
Metabolism and nutrition disorders		
Abnormal weight gain	10 (2.7)	3 (0.8)
Abnormal loss of weight	4 (1.1)	3 (0.8)
Musculoskeletal and connective tissue disorders		
Back pain	9 (2.4)	10 (2.6)
Arthralgia	7 (1.9)	8 (2.1)
Pain in extremity	4 (1.1)	5 (1.3)
Muscle spasms	4 (1.1)	1 (0.3)
Myalgia	1 (0.3)	4 (1.1)
Nervous system disorders		
Headache	8 (2.1)	6 (1.6)
Dizziness	6 (1.6)	5 (1.3)
Hypoaesthesia	4 (1.1)	4 (1.1)
Sinus headache	5 (1.3)	2 (0.5)
Paraesthesia	0 (0.0)	4 (1.1)
Psychiatric disorders		
Depression	1 (0.3)	4 (1.1)
Respiratory, thoracic and mediastinal disorders		
Cough	8 (2.1)	8 (2.1)
Oropharyngeal pain	6 (1.6)	4 (1.1)
Sinus congestion	5 (1.3)	4 (1.1)
Asthma	2 (0.5)	5 (1.3)
Dyspnoea	3 (0.8)	4 (1.1)
Skin and subcutaneous tissue disorders		
Pruritus	4 (1.1)	4 (1.1)
Vascular disorders		
Hypertension	8 (2.1)	3 (0.8)

14.4 Immunogenicity

In a 52-week study (ABEB) in patients with type 1 diabetes, 107 of 265 (40.4%) patients randomized to Basaglar had detectable antibodies to insulin at least once during the treatment period, compared to 105 of 267 (39.3%) randomized to Lantus (Table 11).

In a 24-week study (ABEC) in patients with type 2 diabetes, 56 of 365 (15.3%) patients randomized to Basaglar had detectable antibodies to insulin at least once during the treatment period, compared to 40 of 365 (11.0%) randomized to Lantus. Among patients on prior Lantus,

29 of 151 (19.2%) patients randomized to Basaglar had detectable antibodies to insulin at least once during the treatment period, compared to 11 of 139 (7.95%) Lantus patients. Among insulin-naïve patients, 27 of 214 (12.6%) patients randomized to Basaglar had detectable antibodies to insulin at least once during the treatment period, compared to 29 of 226 (12.8%) Lantus patients (Table 11). The mean antibody level (% binding) among patients with type 1 diabetes at 52 weeks was 2.04% in the Basaglar arm versus 1.98% in the Lantus arm; and in patients with type 2 diabetes treated for 24 weeks it was 3.72% in the Basaglar arm versus 2.38% in the Lantus arm.

The level of antibody production did not appear to be correlated to hemoglobin A1c (A1c), insulin dose, or incidence and rate of hypoglycemia. The long-term effect of Basaglar immunogenicity is unknown.

Table 11: Proportion of Patients with Detected Antibodies by Study Treatment and Baseline Antibody Status - Studies ABEB and ABEC

Study	Population	Visit	Basaglar		Lantus	
			Number of Patients (a)	Number (%) of Patients with Detected Antibodies	Number of Patients (a)	Number (%) of Patients with Detected Antibodies
ABEB	FAS	Baseline	265	45 (17.0)	267	55 (20.6)
		Week 24 Overall	265	80 (30.2)	267	90 (33.7)
		Week 52 Overall	265	107 (40.4)	267	105 (39.3)
		Week 52 (LOCF)	265	73 (27.5)	267	59 (22.1)
ABEC	FAS	Baseline	365	20 (5.5)	365	13 (3.6)
		Week 24 Overall	365	56 (15.3)	365	40 (11.0)
		Week 24 (LOCF)	365	30 (8.2)	365	22 (6.0)
ABEC	Prior Lantus Patients	Baseline	151	10 (6.6)	138	6 (4.4)
		Week 24 Overall	151	29 (19.2)	139	11 (7.9)
		Week 24 (LOCF)	151	13 (8.6)	139	5 (3.6)
ABEC	Insulin-naïve Patients	Baseline	214	10 (4.7)	226	7 (3.1)
		Week 24 Overall	214	27 (12.6)	226	29 (12.8)
		Week 24 (LOCF)	214	17 (7.9)	226	17 (7.5)

(a) Only patients with detected or non-detected insulin antibody levels at baseline and post-baseline were included in analysis.

Abbreviations: LOCF=last observation carried forward; FAS=full analysis set.

14.5 Clinical Trials - Reference Biologic Drug

Trial Design and Study Demographics

The safety and efficacy of once-daily insulin glargine at bedtime was compared to that of once-daily and twice-daily NPH human insulin in open-label, randomized, active-control, parallel studies of 2327 adult patients and 518 pediatric patients with type 1 diabetes mellitus and 1563 adult patients with type 2 diabetes mellitus.

In general, insulin glargine maintained the level of glycemic control as measured by glycohemoglobin and fasting glucose.

Type 1 diabetes in adults (see Table 13). In two large, randomized, controlled Phase III studies (Studies 3001 and 3004), patients with type 1 diabetes (n=1119) were randomized to basal bolus treatment with Lantus (insulin glargine) once daily or with NPH human insulin once or twice daily and treated for 28 weeks. Regular human insulin was administered before each meal. Lantus was administered at bedtime. NPH human insulin was administered once daily at bedtime or in the morning and at bedtime when used twice daily. In these studies, Lantus and human NPH had a similar effect on glycohemoglobin with a similar overall rate of hypoglycemia.

In another large, randomized, controlled Phase III study, patients with type 1 diabetes (Study 3005, n=619) were treated for 16 weeks with a basal bolus insulin regimen where insulin lispro was used before each meal. Lantus was administered once daily at bedtime and NPH human insulin was administered once or twice daily. In this study. Lantus and NPH human insulin had a similar effect on glycohemoglobin with a similar overall rate of hypoglycemia.

Type 2 diabetes in adults (see Table 13). In one large, randomized, controlled Phase III study (Study 3002, n=570), Lantus was evaluated for 52 weeks as part of a regimen of combination therapy with insulin and oral antidiabetic agents (93.9% sulfonylureas, 51.1% biguanides, 12.3% acarbose, or 2.8% other, percentages add up to greater than 100% due to combination therapy). Lantus administered once daily at bedtime was as effective as NPH human insulin administered once daily at bedtime in reducing glycohemoglobin and fasting glucose. There was a low rate of hypoglycemia that was similar in Lantus and NPH human insulin treated patients.

In another large, randomized, controlled Phase III study in patients with type 2 diabetes not using oral antidiabetic agents (Study 3006, n=518), a basal-bolus regimen of Lantus once daily at bedtime or NPH human insulin administered once or twice daily was evaluated for 28 weeks. Regular human insulin was used before meals as needed.

Lantus had similar effectiveness as either once- or twice-daily NPH human insulin in reducing glycohemoglobin and fasting glucose with a similar incidence of hypoglycemia.

Type 2 Diabetes - Adults (see Table 12). In a randomized, open-label, parallel, 24-week clinical study in adult patients with type 2 diabetes (Study 4002, n=756) with an A1c>7.5% (mean 8.6%) on one or two oral antidiabetes agents (88.5% sulfonylureas, 82.8% biguanides, or 9.0% TZDs, percentages add up to greater than 100% due to combination therapy), Lantus or NPH human insulin, once daily at bedtime, was added to their prior regimen. In order to reach the target fasting plasma glucose ≤5.5 mmol/L, the dose of Lantus and NPH human insulin was adjusted according to the structured dose-titration regimen as described in Table 12.

Table 12: Dose titration schedule

Period	Dose or dose adjustment
Start of treatment	10 U/day
Then adjustment every 7 days based on FPG (Fasting Plasma Glucose) as follows:	

Mean FPG ≥10 mmol/L for the last 2 consecutive days and no episodes of severe hypoglycemia or no PG <4.0 mmol/L	Increase daily dose by 8 U
Mean FPG ≥7.8 mmol/L and <10 mmol/L for the last 2 consecutive days and no episodes of severe hypoglycemia or no PG <4.0 mmol/L	Increase daily dose by 6 U
Mean FPG ≥6.7 mmol/L and <7.8 mmol/L for the last 2 consecutive days and no episodes of severe hypoglycemia or no PG <4.0 mmol/L	Increase daily dose by 4 U
Mean FPG ≥5.5 mmol/L and <6.7 mmol/L for the last 2 consecutive days and no episodes of severe hypoglycemia or no PG <4.0 mmol/L	Increase daily dose by 2 U
Then maintain target FPG ≤5.5 mmol/L	

PG = Plasma Glucose

Using this dose-titration schedule; A1c was reduced to a mean of 6.96% for Lantus and 6.97% for NPH human insulin. More than half of the subjects in each group achieved an A1c value of ≤7.0% Lantus, 58.0%; NPH human insulin, 57.3%; mean dose at study endpoint was 47.2 U for Lantus and 41.8 U for NPH human insulin). In the Lantus-treated group, 33.2% of the patients reached the primary efficacy endpoint (A1c of ≤7.0% in the absence of plasma glucose-confirmed nocturnal hypoglycemia ≤4.0 mmol/L, compared to 26.7% in the NPH human insulin-treated group (p=0.0486).

In this study, fewer patients with type 2 diabetes treated with Lantus experienced nocturnal hypoglycemia compared with patients treated with NPH human insulin. Other clinical trials in type 2 diabetes showed similar results with less nocturnal hypoglycemia with patients treated with Lantus compared to patients treated with NPH human insulin.

Results

Type 1 and type 2 diabetes in adults. Table 13 compares regimens of Lantus once daily to NPH human insulin either once or twice daily in subgroups of patients from Phase III studies based upon prior basal insulin regimens.

Summary of main therapeutic outcomes of the clinical studies

Table 13: Adult Patients

Type 1 diabetes mellitus					
Diabetes population	Treatment	n[a]	n[b]	Endstudy mean (mean change from baseline)	
				Glycated hemoglobin (%)[c]	Fasting blood glucose (mmol/L)[c]
Previous use of once-daily basal injection regimen					
with regular human insulin	Lantus	222	206	7.98 (0.01)	8.51 (0.93)
	NPH human insulin	218	205	7.95 (-0.05)	8.16 (-1.21)
with insulin lispro	Lantus	73	71	7.11 (-0.25)	8.01 (-1.26)
	NPH human insulin	69	64	7.46 (-0.23)	8.65 (-1.17)
Previous use of more than once-daily basal injection regimen					
with regular human insulin	Lantus	334	303	7.77 (0.06)	7.83 (-1.31)[d]
	NPH human insulin (x2)	345	315	7.69 (-0.05)	8.78 (-0.72)

with insulin lispro	Lantus NPH human insulin (x2)	237 240	224 229	7.66 (-0.03) 7.64 (-0.05)	8.0 (-1.42)[d] 8.57 (-0.81)
Type 2 diabetes mellitus					
Diabetes population	Treatment	n[a]	n[b]	Endstudy mean (mean change from baseline)	
				Glycated hemoglobin (%)[c]	Fasting blood glucose (mmol/L)[c]
Insulin in combination with oral antidiabetic agents					
No previous insulin use	Lantus NPH human insulin	222 204	218 194	8.07 (-1.00) 7.92 (-1.00)	7.22 (-3.14) 7.29 (-3.19)
Previous insulin use	Lantus NPH human insulin	67 77	61 68	8.71 (-0.14) 8.75 (-0.05)	7.43 (-0.82) 7.72 (-0.79)
Insulin without oral antidiabetic agent					
Previous use of once-daily basal insulin	Lantus NPH human insulin (x2)	52 48	47 46	8.07 (-0.34) 7.92 (-0.45)	8.49 (-0.95) 7.94 (-1.13)
Previous use of more than once-daily basal insulin	Lantus NPH human insulin (x2)	207 211	184 192	8.15 (-0.44) 7.96 (-0.61)	7.71 (-1.34) 8.05 (-1.19)

[a] Number of patients randomized and treated.
[b] Number of patients randomized, treated, and completed study (without early endpoint).
[c] Intention to treat population.
[d] $p<0.05$; Lantus compared with NPH human insulin.

Type 1 diabetes in children and adolescents (see Table 14)

Study 3003: pivotal study: randomized, open-label, parallel study of 349 children with Type 1 diabetes aged 6 to 15 years: treated for 28 weeks with Lantus once daily versus the most commonly used insulin in children, human NPH once or twice daily. Lantus had a significant reduction in FBG and similar A1c and 24-hour BG profile when compared to human NPH once or twice daily. The results of this study show that the overall level of glycemic control as measured by A1c and incidence of hypoglycemia achieved after initial titration following switching to Lantus from pre-study human NPH is similar to that achieved by once or twice daily NPH human insulin.

Table 14: Pediatric Patients (Study 3003)

Type 1 Diabetes Mellitus

Treatment duration	28 weeks	
Treatment in combination with	Regular insulin	
	Lantus	Human NPH
Number of subjects treated	174	175
GHb		
Endstudy mean	8.91	9.18
Adjusted mean change from baseline	+0.28	+0.27
Basal insulin dose		
Endstudy mean	18.2	21.1
Mean change from baseline	-1.3	+2.4

Total insulin dose		
Endstudy mean	45.0	46.0
Mean change from baseline	+1.9	+3.4
Fasting blood glucose (mmol/L)		
Endstudy mean	9.48	10.15
Adjusted mean change from baseline	-1.29	-0.68

Study 3013: pivotal study: extension of Study 3003: open-labelled, uncontrolled long-term follow-up study of 143 patients who were well-controlled on Lantus from 3003, for 201-1159 days, 26 subjects did not continue for administrative and unknown reasons. The level of glycemic control established in Study 3003 was maintained in this study, despite an increase of 0.35% in A1c from baseline in Study 3003. This increase can be attributed to many factors; the deterioration of control with time; puberty, which often has a detrimental impact on glycemic control and is associated with increased insulin resistance and increased insulin requirements; although less common in a post-pubescent population, lack of aggressive titration could be another factor, since pediatricians and parents are often afraid of the deleterious effects of hypoglycemia on children.

Study 4005: open-label, controlled, randomized, double-cross-over: 26 subjects (age range 12-20), Tanner B2G2 (puberty stages) or greater were on 16 weeks of each regimen of Lantus + lispro vs. human NPH + human regular. This non-pivotal trial lacked the necessary power to demonstrate significance for the primary outcome.

The higher episodes of all symptomatic hypoglycemia with Lantus (308 vs. 237) were only observed in the second period and were associated with a lower A1c for Lantus (8.6% vs. 9.9%).

The combination of Lantus and lispro was chosen to best approximate a normal physiologic insulin response during the day. Lantus' peakless 24-hour duration better resembles true basal pancreatic insulin secretion than NPH human insulin, and lispro insulin has a more rapid appearance and disappearance from the plasma than regular human insulin, resulting in lower prandial glucose excursions and a lower incidence of postprandial hypoglycemia, compared to regular human insulin.

Compared to human NPH, Lantus has a similar 24-hour BG profile and A1c in Study 3003. IN the uncontrolled extension study, Study 3013, the level of glycemic control established in Study 3003 was maintained, despite an increase of 0.35% in A1c from baseline in Study 3003.

During initiation of treatment (and consequent dose titration) with any insulin, the risk of hypoglycemia is higher than after the dose has stabilized following titration. In pediatric clinical trials comparing Lantus to NPH human insulin, all patients were on human NPH-based regimens prior to the study, which were not changed for patients entering treatment in the human NPH arm. Patients beginning treatment with Lantus, however, all required dose titration on the new insulin, which may have been in large measure responsible for the increase in hypoglycemia seen in Lantus-treated patients during titration. In addition, in some studies (Study 4005) A1c and glucose levels were lower in the Lantus group than in the human NPH group during the titration phase, which would also tend to foster more episodes of hypoglycemia. Post-initiation in Study 3003, Lantus treatment was associated with a significantly greater reduction in mean FBG and no significant difference in A1c, 24-hr BG profile, and hypoglycemia incidence compared to NPH human insulin given once or twice daily. Post-initiation in crossover Study 4005, Lantus treatment was associated with no significant difference in FBG, 24-hr BG profile or hypoglycemia incidence compared to NPH human insulin. During the first treatment phase of Study 4005, A1c decreased in both treatment groups. In the second treatment phase, improvement in A1c was maintained in

patients on Lantus + lispro, while A1c increased in subjects who switched to human NPH + human regular.

Lantus Flexible Daily Administration

The safety and efficacy of Lantus administered pre-breakfast, pre-dinner or at bedtime were evaluated in a large, randomized, controlled clinical study (Study 4007). In this study in patients with type 1 diabetes (n=378), who were also treated with insulin lispro at meals, Lantus administered at different times of the day resulted in equivalent glycemic control to that at bedtime (see Table 15).

The safety and efficacy of Lantus administered pre-breakfast or at bedtime were also evaluated in a large, randomized, active-controlled clinical study (Study 4001, n=697) in patients with type 2 diabetes no longer adequately controlled on oral agent therapy. All patients in this study also received AMARYL® (glimepiride) 3 mg daily. Lantus given before breakfast was as effective in lowering glycated hemoglobin A1c as Lantus given at bedtime or NPH human insulin given at bedtime (see Table 15).

Table 15: Flexible Lantus Daily Administration in Type 1 and Type 2 Diabetes Mellitus

Diabetes population Treatment duration Treatment in combination with:	Type 1 diabetes mellitus 24 weeks Insulin lispro			Type 2 diabetes mellitus 24 weeks AMARYL® (glimepiride)		
	Lantus			Lantus		NPH
	Breakfast	Dinner	Bedtime	Breakfast	Bedtime	Bedtime
n[a]	112	124	128	234	226	227
n[b]	104	123	125	226	211	205
Glycated Hemoglobin A1c[c]						
Baseline mean	7.56	7.53	7.61	9.13	9.07	9.09
Endstudy mean	7.39	7.42	7.57	7.87	8.12	8.27
Mean change from baseline	-0.17	-0.11	-0.04	-1.26	-0.95	-0.83
Basal insulin dose (U)[c]						
Endstudy mean	27.3	24.6	22.8	40.4	38.5	36.8
Mean change from baseline	5	1.8	1.5			
Total insulin dose (U)[c]				NA	NA	NA
Endstudy mean	53.3	54.7	51.5			
Mean change from baseline	1.6	3	2.3			

[a] Number of patients randomized and treated.
[b] Number of patients randomized, treated, and completed study (without early endpoint).
[c] Intention to treat population.

All data collected during study treatment are included in the calculations whenever possible, unless specified for a particular purpose (such as per-protocol which may exclude patients with very early withdrawal), regardless if patients withdrew or not during the study.

Lantus Comparative Bioavailability Study

In a randomized, controlled, double-blink, four-way crossover trial in healthy male volunteers (n=24), Lantus with Polysorbate 20 (Test) was found to be bioequivalent to Lantus.

Table 16: Pharmacokinetic parameters from measured insulin serum concentration data

Lantus (Formulation: 100 U/mL; dosing: 0.4 U/kg body weight) From measured insulin serum concentration Geometric Mean Arithmetic Mean (CV %)				
PK Parameter	**Test Lantus with Polysorbate 20**	**Reference Lantus** (sanofi-aventis) Deutschland GmbH, Germany)	**% Ratio of Geometric Means**	**Confidence Interval (90%)**
$AUC_{(0-24)}$ (µU.h/mL)	343 359 (34%)	355 367 (26%)	96.6	(91.0; 102.6)
$AUC_{(0-Inf)}$ (µU.h/mL)	672 716 (37)	694 757 (46)	96.9	(87.1; 107.7)
C_{MAX} (µU/mL)	20 21 (34%)	22 23 (28%)	89.6	(83.5; 96.1)
T_{MAX} [1] (h)	14.4 (1.0-30.0)	12.5 (0.5-30.0)		
$T_{½}$ [2] (h)	14.3 (59%)	16.0 (96%)		

[1] Median (range) only.
[2] Arithmetic mean (CV%) only.

Table 17: Pharmacodynamic parameters from standardized glucose infusion rate data

Lantus (Formulation: 100 U/mL; dosing: 0.4 U/kg body weight) From standardized glucose infusion rate measured data (GIR) Arithmetic Mean (CV %) Geometric Mean				
PD Parameter	**Test Lantus with Polysorbate 20**	**Reference Lantus** (sanofi-aventis) Deutschland GmbH, Germany)	**% Ratio of Means**	**% Confidence Interval (90%)**
$AUC_{(0-24)}$ (mg/kg)	2373 (41%) 2195	2367 (40%) 2197	100.1	(88.1; 113.8)
$AUC_{(0-end)}$ (mg/kg)	2796 (39%) 2605	2743 (37%) 2576	101.9	(90.6; 114.7)
GIR_{MAX} [1] (mg/(min.kg))	3.1 (35%)	3.2 (42%)	95.6	(83.3; 109.7)
Time to GIR_{MAX} [2](h)	12.8 (3.2-29.0)	12.5 (5.2-30.0)		

[1] Based on smoothed GIR profiles. Expressed as the arithmetic mean (CV%) only.
[2] Based on smoother GIR profiles. Expressed as median (range) only.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

Acute toxicity: The acute toxicity of i.v. and s.c. administration of insulin glargine was tested in mice and rats. The LD50 in each species was in the range of greater than or equal to 1000 U/kg.

Chronic toxicity: In repeated subcutaneous dose toxicity studies of insulin glargine in mice, rats, and dogs only expected pharmacodynamic results were observed.

Carcinogenicity: The carcinogenic potential of insulin glargine was evaluated in mice and rats at three different dose levels. These two-year carcinogenicity studies were performed in mice and rats. The results do not suggest a cancer risk to humans.

In mice and rats, standard two-year carcinogenicity studies with insulin glargine were performed at doses up to 0.455 mg/kg, which is for the rat approximately 10 times and for the mouse approximately 5 times the recommended human subcutaneous starting dose of 10 U (0.008 mg/kg/day), based on mg/m^2. The findings in female mice were not conclusive due to excessive mortality in all dose groups during the study. No clear explanation was found for the excessive mortalities. A similar effect was seen in the female mice control groups: the saline controls mortality (34%) was comparable to the mortality of high dosed female mice (28%) whereas in the vehicle controls mortality reached 42% which is in the same range as the mortality of low dosed female mice (46%). In contrast, the mortality was the same in the male mice saline and vehicle control groups (both 16%). Therefore, these findings are considered as an accidental one due to biological variability. Histiocytomas were found at injection sites in male rats (statistically significant) and male mice (not statistically significant) in acid vehicle containing groups. These tumors were not found in female animals, in saline control, or insulin comparator groups using a different vehicle. The relevance of these findings to humans is unknown.

Mutagenesis: Insulin glargine was not mutagenic in tests for detection of gene mutations in bacteria and mammalian cells (Ames- and HGPRT-test) and in tests for detection of chromosomal aberrations (cytogenetics in vitro in V79 cells and in vivo in Chinese hamsters).

Reproductive Toxicity and Impairment of Fertility: In an embryotoxicity study in rats, hypoglycemia, but no maternal toxicity, occurred. Insulin glargine was not embryotoxic and not teratogenic. In an embryotoxicity study in rabbits, maternal (hypoglycemic shock, intrauterine deaths) and embryo-fetal hypoglycemia-induced toxicity, including single anomalies in the middle- and high-dose groups, were observed. Similar effects were observed with NPH human insulin.

In a combined fertility and prenatal and postnatal study in male and female rats at subcutaneous doses up to 0.36 mg/kg/day, which is approximately 7 times the recommended human subcutaneous starting dose of 10 U (0.008 mg/kg/day), based on mg/m2, maternal toxicity due to dose-dependent hypoglycemia, including some deaths, was observed. Consequently, a reduction of the rearing rate occurred in the high-dose group only. Similar effects were observed with NPH human insulin.

Studies in rats with doses up to 40 times the average daily basal human dose (0.5 U/kg) and a study in rabbits at two times the human dose (0.5 U/kg) do not indicate direct harmful effects on the pregnancy during the different stages of pregnancy. The effects of insulin glargine did not generally differ from those observed with regular human insulin; however, in rabbits, five foetuses from 2 litters of the high dose group exhibited dilation of the cerebral ventricles.

Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clinically needed.

Nonclinical Pharmacology and Toxicology

Insulin glargine is metabolized 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 lower than the one of human insulin (0.68, 0.48 and 0.74, respectively).

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 lower affinity compared to human insulin (0.4-0.5 and 0.7-0.8), respectively.

16.1 Comparative Non-Clinical Pharmacology and Toxicology

Since Basaglar is a biosimilar, where the pharmacodynamics, pharmacokinetic, and animal toxicology properties of insulin glargine have already been described for the reference biologic drug Lantus, this section summarizes the comparative studies that were conducted to compare the pharmacology and toxicology of Basaglar to Lantus.

16.1.1 Comparative Non-Clinical Pharmacodynamics

In vitro Studies

Insulin receptor (IR) binding: Based on comparative in vitro studies (DBT149 and DBT93), Basaglar is similar to Lantus with respect to IR binding affinity (isoforms A and B).

In comparative studies (DBT149 and DBT93) using a panel of eight different in vitro assays, Basaglar and Lantus insulin glargine were similar in their in vitro pharmacological properties as determined by human insulin receptor (hIR) and human insulin-like growth factor - 1 receptor (hIGF-1R) binding affinity, hIR receptor activation, de novo lipogenesis or intrinsic metabolic activity in adipocytes, and mitogenic potential.

16.1.2 Comparative Toxicology

The toxicity profile of Basaglar was characterized alongside Lantus in separate 1-month subchronic toxicity studies in non-diabetic rats (Table 18), including glucodynamic and toxicokinetic assessments. The repeat-dose toxicity of Basaglar was evaluated in rats administered once daily subcutaneous doses of 0, 0.3, 1.0, and 3.0/2.0 mg/kg for 4 weeks (Study 8229488). In a second repeat-dose toxicity study (Study 8259267), Basaglar doses of 0, 0.3, 1.0, and 2.0 mg/kg were given for 4 weeks. Lantus was the reference compound in both of these studies and was given to additional animals at identical doses as Basaglar.

For Basaglar and Lantus, these studies demonstrated a similar spectrum of effects that are typically associated with sustained hyperinsulinemia and/or hypoglycemia, including clinical signs, polyphagia, neuropathy, and pancreatic islet cell atrophy (Table 18). Microscopic finding in the skin/subcutis was also observed. The dose-limiting toxicity (DLT) in rats for Basaglar and Lantus was severe hypoglycemia resulting in clinical signs of toxicity and sometimes mortality or moribundity. The maximum-tolerated dose (MTD) for Basaglar and Lantus was 0.3 mg/kg. All findings were considered to be typical of insulin analogues in animals and were easily monitored in human subjects via routine serum glucose testing. While the margins of safety were moderate

in animals (15.9-fold), these modest margins are not unusual in the development of insulin analogues. In conclusion, the toxicity profiles of Basaglar and Lantus were similar (Table 18).

Table 18: Comparison of Important Attributes from 1-Month Subchronic Toxicity Studies of Basaglar

Study	8259267	8229488
Materials	Basaglar and Lantus (EU-approved)	Basaglar and Lantus (US-approved)
Doses	0, 0.3, 1.0, 2.0 mg/kg	0, 0.3, 1.0, 3.0/2.0 mg/kg
PK/PD	Days 1 and 29	Days 1, 15, and 29/32
Results	• MTD exceeded for Basaglar and Lantus at ≥1.0 mg/kg due to multiple hypoglycemia deaths and clinical signs • Hypoglycemia occurred in all Basaglar and Lantus groups: o Dose-dependent duration o Compensatory ↑FC/BWG at 2.0 mg/kg • Sciatic nerve degeneration for Basaglar and Lantus at 2.0 mg/kg • Pancreatic islet cell atrophy for Basaglar and Lantus at ≥1.0 mg/kg • ↑Fat in skin subcutis for Basaglar and Lantus at ≥1.0 mg/kg	• MTD exceeded for Basaglar and Lantus at ≥1.0 mg/kg due to multiple hypoglycemia deaths and clinical signs • Hypoglycemia occurred in all Basaglar and Lantus groups: o Dose-dependent duration o Compensatory ↑FC/BWG at 3.0/2.0 mg/kg • Sciatic nerve degeneration for Basaglar and Lantus at 3.0/2.0 mg/kg • Pancreatic islet cell atrophy for Basaglar and Lantus at ≥1.0 mg/kg • ↑Fat in skin/subcutis for Basaglar and Lantus at ≥0.3 mg/kg
MTD	0.3 mg/kg for Basaglar and Lantus	0.3 mg/kg for Basaglar and Lantus

Abbreviations: BWG= body weight gain; FC= food consumption; MTD= maximum-tolerated dose; PD= pharmacodynamics; PK= pharmacokinetics.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Non-clinical data (for the reference product Lantus) reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, or toxicity to reproduction.

17 SUPPORTING PRODUCT MONOGRAPHS

1. LANTUS solution for injection 100 U/mL, submission control no. 254078, Product Monograph, sanofi-aventis Canada Inc. (December 01, 2021)

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

BASAGLAR® Cartridge

BASAGLAR® KwikPen® **(Pre-filled disposable pen)**

Insulin glargine injection (rDNA origin), 100 Units/mL

Read this carefully before you start taking **Basaglar** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Basaglar**.

Basaglar is a biosimilar biologic drug (biosimilar) to the reference biologic drug Lantus®. A biosimilar is authorized based on its similarity to a reference biologic drug that was already authorized for sale.

Serious Warnings and Precautions

- Hypoglycemia (low blood sugar) is the most common adverse effect of insulin, including Basaglar.
- Glucose monitoring is recommended for all patients with diabetes.
- Uncorrected hypoglycemic or hyperglycemic reactions can cause loss of consciousness, coma, or death.
- Any change of insulin regimen should be made cautiously and only under medical supervision.
- Basaglar should not be used for intravenous, intramuscular or insulin pump administration.
- **Basaglar must not be mixed with any other insulin or diluted with any other solution because it might not work as intended.**
- Basaglar shall not be used if it is not water-clear and colourless or if it has formed a deposit of solid particles on the wall of the cartridge.

What is Basaglar used for?

Basaglar [insulin glargine injection (rDNA origin)] is a recombinant human insulin analogue that is a long-acting blood-glucose-lowering agent administered subcutaneously (under the skin) once a day. Basaglar is indicated in the treatment of patients over 17 years of age with type 1 or type 2 diabetes mellitus who require basal (long-acting) insulin for the control of hyperglycemia (high blood sugar). Basaglar is also indicated in the treatment of pediatric patients (>6 years old) with type 1 diabetes mellitus who require basal (long-acting) insulin for the control of hyperglycemia.

How does Basaglar work?

Insulin is a hormone produced by the pancreas, a large gland that lies near the stomach. This hormone is necessary for your body to use food, especially sugar, correctly. Diabetes occurs either when the pancreas does not make enough insulin to meet your body's needs or when your body cannot properly use the insulin you normally produce.

When your body does not make enough insulin, you need an external source of insulin. That is why you must take insulin injections. Basaglar is similar to the insulin made by your body.

Insulin injections, such as Basaglar, play a key role in keeping your diabetes under control. In addition to proper insulin therapy, it is important to maintain a healthy lifestyle – this includes eating a balanced diet, participating in regular exercise or other physical activities, carefully monitoring your glucose levels and following your healthcare professional's recommendations. These simple actions will compliment your insulin therapy and will ultimately help you gain greater control of your diabetes.

You have been instructed to test your blood and/or your urine regularly for glucose; it is especially important to test even more often when changing insulins or changing your dosing schedule. If your blood tests consistently show above- or below-normal glucose levels, or your urine tests consistently show the presence of glucose, your diabetes is not properly controlled and you must let your healthcare professional know.

Insulin injections play an important role in keeping your diabetes under control. But the way you live – your diet, careful monitoring of your glucose levels, exercise, or planned physical activity and following your healthcare professional's recommendations– all work with your insulin to help you control your diabetes.

Always keep an extra supply of Basaglar on hand. Always wear medical alert identification and carry information about your diabetes so that appropriate treatment can be given if complications occur while you are away from home.

What are the ingredients in Basaglar?

Medicinal ingredients: insulin glargine (rDNA origin)]

Non-medicinal ingredients: glycerin, metacresol, zinc oxide, and water for injection. Hydrochloric acid and sodium hydroxide are added for pH adjustment.

Basaglar comes in the following dosage forms:

Solution for injection (100 U/mL):

- 3 mL cartridges in packages of 5 (for use only with Lilly's reusable insulin pens)
- KwikPen, 3 mL prefilled pen, in packages of 5

Do not use Basaglar:

- if you are allergic to this drug or to any ingredient in the formulations or component of the container,
- if you have diabetic ketoacidosis,
- for intravenous or intramuscular injections.
- if your blood sugar is too low (hypoglycemia). After treating your low blood sugar, follow your health care provider's instructions on the use of Basaglar.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Basaglar. Talk about any health conditions or problems you may have, including if you:

- are planning to have a baby, are pregnant, or are nursing a baby;
- are taking any medication;
- develop skin changes at the injection site.

The injection site should be rotated to prevent skin changes such as lumps under the skin. The insulin may not work very well if you inject into a lumpy area (see "How to take Basaglar"). Contact your healthcare professional if you are currently injecting into a lumpy area before you start injecting in a different area. A sudden change of site may result in hypoglycemia. Your

healthcare professional may tell you to check your blood sugar more closely, and to adjust your insulin or your other antidiabetic medications dose.

Accidental mix-ups between insulin glargine and other insulins, particularly fast-acting insulins, have been reported. To avoid medication errors between insulin glargine and other insulins, always check your insulin labels before every injection.

Hypokalemia (low potassium) is a possible side effect with all insulins. You might be more at risk if you are using potassium lowering drugs or losing potassium through other means (e.g., diarrhea). Symptoms of hypokalemia include: fatigue, muscle weakness or spasms, constipation, tingling or numbness, feeling of skipped heart beats or palpitations.

If you have diabetic retinopathy (condition affecting the retina of the eye) and you have a marked change in blood glucose levels, the retinopathy may temporarily get worse. Ask your doctor about this.

Other warnings you should know about:

The use of thiazolidinediones (such as rosiglitazone and pioglitazone), alone or in combination with other antidiabetic agents (including insulin), has been associated with heart failure and swelling of the lower extremities. Contact your physician immediately if you develop symptoms of shortness of breath, fatigue, exercise intolerance, or swelling of the lower extremities while you are on these medications.

Concomitant oral antidiabetic treatment may need to be adjusted.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Basaglar:

Other medicines, including non-prescription medicines, and dietary supplements (such as vitamins) can change the way insulin works. Your dose of insulin or other medications may need to be changed in consultation with your healthcare professional. Please see "Usual Dose, Medication" section below for potential medication interactions with insulin.

How to take Basaglar:

Your doctor has recommended the type of insulin that he/she believes is best for you. DO NOT USE ANY OTHER INSULIN EXCEPT ON THE ADVICE AND DIRECTION OF YOUR DOCTOR.

Basaglar is a clear solution and looks like some fast-acting insulins. Always check for the name of the insulin on your carton and the label when you pick it up from the pharmacy to make sure it is the same as what your doctor has recommended.

CAREFULLY FOLLOW YOUR HEALTHCARE PROFESSIONAL'S DIRECTION ON HOW TO USE BASAGLAR CARTRIDGES AND KWIKPENS TO:

- **HELP AVOID CONTAMINATION AND POSSIBLE INFECTION**
- **OBTAIN AN ACCURATE DOSE.**

Do not reuse needles. DO NOT SHARE INJECTION PENS, CARTRIDGES, OR NEEDLES WITH ANYONE ELSE. **Do not** share an injection pen or Basaglar cartridge with anyone, including family members, even if the needle on the injection pen is changed. **You may give another person a serious infection, or get a serious infection from them.**

Injection sites within an injection area (abdomen, thigh, buttock, or upper arm) must be rotated from one injection to the next so that the same site is not used more than approximately once a month. Do not inject into pits (depressions), thickened skin or lumps.

How to use a Basaglar cartridge

It is important to use the Basaglar cartridge only with Lilly reusable insulin pens.

Using the cartridge in any other injection pen not suitable for the Basaglar cartridge could lead to a mistake in dosing and cause medical problems for you, such as a blood glucose level that is too low or too high.

- HumaPen® Savvio™ and HumaPen Luxura® deliver Basaglar in 1 unit dose increments.
- HumaPen Luxura® HD delivers Basaglar in 0.5 unit dose increments.

Follow the Instructions for Use that comes with the reusable pen injector.

Although rare, technical problems with the cartridge can occur which may prevent correct dosing. They include: broken, cracked or damaged cartridges, air bubbles or foam, and blocked needles. If technical problems occur or are suspected, contact your healthcare professional or the Lilly Customer Response Centre (1-888-545-5972).

How to use the Basaglar KwikPen

Please refer to the Instruction for Use provided with your Basaglar KwikPen.

Hypoglycemia or hyperglycemia can result from injecting insulin in the wrong site or incorrectly. Hypoglycemia can result from injection directly into a blood vessel and if not recognized or treated may be followed by hyperglycemia since there was not Basaglar deposition for long-term absorption.

Usual dose:

The dosage of Basaglar should be individualized and determined based on your healthcare professional's advice in accordance with your needs. You may take Basaglar at any time during the day, but you must take it at the same time every day.

Many factors may affect your usual Basaglar dose, which may include changes in your diet, activity, or work schedule. Follow your healthcare professional's instructions carefully. Consult your healthcare professional if you notice your insulin requirements changing markedly. Other factors that may affect your dose of insulin or your need to do additional blood/urine testing are described below:

Illness

Illness, especially with nausea and vomiting, diarrhea and/or fever, may cause your insulin requirements to change. Even if you are not eating, you will still require insulin. You and your doctor should establish a sick day plan for you to use in case of illness. When you are sick, test your blood/urine frequently and call your doctor as instructed.

Pregnancy

If you are planning to have a baby, are pregnant, or are nursing a baby, consult your doctor. Good control of diabetes is especially important for you and your unborn baby. Pregnancy may make managing your diabetes more difficult.

Medication

Always discuss any medications you are taking, prescription or "over-the-counter (OTC)", with your healthcare professional. To prevent drug interactions, provide the names of everything you

are taking even before they ask if there have been any changes. Insulin requirements may be increased in the presence of drugs with hyperglycemic activity, such as contraceptives (for example, birth control pills, injections and patches), and hormone replacement therapies, corticosteroids, thyroid replacement therapy, and medications such as decongestants and diet pills. Insulin requirements may be reduced in the presence of drugs with hypoglycemic activity, such as oral antidiabetic agents, salicylates (for example, aspirin), sulfa antibiotics, blood pressure medications including angiotensin-converting-enzyme (ACE) inhibitors, and certain psychiatric medications including monoamine oxidase (MAO) inhibitors or anti-depressants and anti-anxiety medications.

Substances such as beta-blockers (medicines used for conditions including blood pressure, heart arrhythmias, palpitations and headache) and alcohol may enhance or weaken the blood-glucose-lowering effect of insulins, and signs of hypoglycemia may be reduced or absent, as well.

Exercise

If your exercise routine changes, discuss with your healthcare professional the possible need to adjust your insulin regimen. Exercise may lower your body's need for insulin during, and for some time after, the activity. As for all insulins, the rate of absorption, and consequently the onset and duration of action, may be affected by exercise and other variables.

Travel

Consult your healthcare professional concerning possible adjustments in your insulin schedule if you will be traveling across time zones. You may want to take along extra insulin and supplies whenever you travel.

Overdose:

If you **have injected too much Basaglar,** your blood sugar may become too low (hypoglycemia). Check your blood sugar frequently. In general, to prevent hypoglycemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycemia, see "Common Problems of Diabetes" below.

Hypoglycemia may occur as a result of an excess of insulin relative to food intake, energy expenditure or both.

If you think you, or a person you are caring for, have taken too much Basaglar, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you **have missed a dose of Basaglar** or if you **have not injected enough insulin**, your blood sugar level may become too high (hyperglycemia). Check your blood sugar frequently. For information on the treatment of hyperglycemia, see "Common Problems of Diabetes" below.

Do not take a double dose to make up for a forgotten dose.

What are possible side effects from using Basaglar?

These are not all the possible side effects you may have when taking Basaglar. If you experience any side effects not listed here, tell your healthcare professional.

Common Problems of Diabetes:

Hypoglycemia (Insulin Reaction)

Hypoglycemia (low blood sugar) is one of the most frequent adverse events experienced by insulin users. It can be brought on by situations such as:

- intercurrent conditions (illness, stress, or emotional disturbances),
- accidental injection of too much insulin,
- malfunction and/or misuse of injection devices,
- not eating enough, or skipped meals,
- an increase in exercise,
- a new insulin type or schedule,
- some new medications, including prescriptions, over-the-counter medication, herbs, vitamins, and street drugs.

Symptoms of mild to moderate hypoglycemia may occur suddenly and can include:

- abnormal behavior (anxiety, irritability, restlessness, trouble concentrating, personality changes, mood changes, confusion or nervousness),
- fatigue,
- tingling in your hands, feet, lips, or tongue,
- tremor (shaking),
- unsteady gait (walking),
- dizziness, light-headedness, or drowsiness,
- headache,
- blurred vision,
- slurred speech,
- palpitations (rapid heartbeat),
- cold sweat,
- pale skin,
- nightmares or trouble sleeping,
- nausea,
- hunger.

Mild to moderate hypoglycemia may be treated by consuming foods or drinks that contain sugar. Patients should always carry an adequate amount (about 15 grams of glucose) of a quick source of sugar, such as candy, juice or glucose tablets, prominently labelled for rescuers. Contact your healthcare professional about appropriate proportions of carbohydrates.

Signs of severe hypoglycemia can include:

- disorientation,
- convulsions,
- loss of consciousness
- seizures.

Severe hypoglycemia may require the assistance of another person. Patients who are unable to take sugar orally or who are unconscious may require a glucagon rescue product (nasal or injection) or should be treated with intravenous administration of glucose by medical personnel. Without immediate medical help, serious reactions or even death could occur.

The early warning symptoms of hypoglycemia may be changed, be less pronounced, or be absent, as for example, in patients whose sugar levels are markedly improved, in elderly

patients, in patients with diabetic nerve disease, in patients with a long history of diabetes, or in patients receiving treatment with certain other drugs. Such situations may result in severe hypoglycemia (and possibly, loss of consciousness) before a patient has symptoms.

Some people may not recognize when their blood sugar drops too low. Often the first sign of this is confusion or loss of consciousness. Educational and behavioural programs, including blood glucose awareness training, may help improve your ability to detect hypoglycemia and reduce the frequency of severe hypoglycemia.

Without recognition of early warnings symptoms, you may not be able to take steps to avoid more serious hypoglycemia. Be alert for all of the various types of symptoms that may indicate hypoglycemia. Patients who experience hypoglycemia without early warning symptoms should monitor their blood glucose frequently, especially prior to activities such as driving a car or using mechanical equipment. If the blood glucose is below your normal fasting glucose, you should consider eating or drinking sugar-containing foods to treat your hypoglycemia.

Other people may develop hypoglycemia during the night – this is called nocturnal hypoglycemia. It is fairly common and lasts over 4 hours. Because the person is usually asleep when it occurs, nocturnal hypoglycemia can go undetected, resulting in increased risk of severe hypoglycemia compared to the daytime. To help reduce your risk of asymptomatic nocturnal hypoglycemia, your doctor may ask you to periodically monitor your overnight blood glucose levels.

If you have frequent episodes of hypoglycemia, experience difficulty in recognizing the symptoms, or if your diabetes is getting worse, you should consult your healthcare professional to discuss possible changes in therapy, meal plans, and/or exercise programs to help you avoid hypoglycemia.

Hyperglycemia

Hyperglycemia (high blood sugar) may develop if your body has too little insulin.

Hyperglycemia can be brought about by:

- intercurrent conditions (illness, stress, or emotional disturbances),
- not taking your insulin or taking less than recommended by your healthcare professional,
- malfunction and/or misuse of injection devices,
- eating significantly more than your meal plan suggests,
- a new insulin type or schedule,
- some new medications, including prescriptions, over-the-counter medication, herbs, vitamins and street drugs.

Symptoms of hyperglycemia include:

- confusion or drowsiness,
- increased thirst,
- decreased appetite, nausea, or vomiting,
- palpitations (rapid heartbeat)
- increased urination and dehydration (too little fluid in your body),
- blurred vision,
- flushed dry skin,
- acetone odour of breath.

Hyperglycemia can be mild or severe. It can **progress to high glucose levels, diabetic ketoacidosis (DKA), and result in unconsciousness and death.**

Diabetic ketoacidosis

The first symptoms of diabetic ketoacidosis (DKA) usually come on over a period of hours or days. With DKA, urine tests show large amounts of glucose and acetone.

Symptoms of DKA include:
First symptoms:

- drowsiness,
- flushed face,
- thirst,
- loss of appetite,
- fruity smelling breath
- rapid, deep breathing,
- abdominal (stomach area) pain.

Severe symptoms:

- heavy breathing,
- palpitations (rapid heartbeat).

Prolonged hyperglycemia or DKA can lead to:

- nausea,
- vomiting,
- dehydration,
- loss of consciousness,
- death.

Severe or continuing hyperglycemia or DKA requires evaluation and treatment by your healthcare professional. Basaglar should not be used to treat DKA, and the persons treating you should be advised you are taking a long-acting insulin and about your regimen.

Allergic reactions

In rare cases, a patient may be allergic to an insulin product. Severe insulin allergies may be life-threatening. If you think you are having an allergic reaction, seek medical help immediately.

Signs of insulin allergy include:

- a rash all over your body,
- shortness of breath,
- wheezing (trouble breathing),
- palpitations (rapid heartbeat),
- sweating,
- low blood pressure.

Possible reactions on the skin at the injection site

Injecting insulin can cause the following reactions on the skin at the injection site:

- a little depression in the skin (lipoatrophy),
- skin thickening (lipohypertrophy),
- skin lumps (localized cutaneous amyloidosis),
- redness, swelling, or itching at injection site.

In some instances, these reactions may be related to factors other than insulin, such as irritants in the skin cleansing agent or poor injection technique. You can reduce the chance of getting an

injection site reaction if you change the injection site each time. If you have local injection site reactions, contact your healthcare professional as a sudden change of site may result in hypoglycemia.

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Unopened Cartridge or KwikPen:

Unopened Basaglar cartridges or KwikPen should be stored in a refrigerator, between 2°C and 8°C. Keep Basaglar away from direct heat and light. Basaglar should not be stored in the freezer and should not be allowed to freeze. If Basaglar freezes, discard it.

Opened (In Use) Cartridge or KwikPen:

The opened Basaglar cartridge or KwikPen in use should be stored at room temperature (below 30°C) for up to 28 days away from direct heat and light. If there is any remaining insulin after 28 days, discard it. The opened cartridge in use must never be removed from and reinserted into the injection pen. If Basaglar freezes discard it.

Do not use a Basaglar cartridge or KwikPen after the expiration date stamped on the label or if it is cloudy or contains visible particles.

Keep out of reach and sight of children.

Disposal:

Dispose of used needles in a sharps container or a hard plastic container with a secure lid. Do not throw needles directly into your household trash. Do not recycle the filled sharps container. Ask your healthcare professional about options available to dispose of the sharps container properly.

You can also check the Canadian Diabetes Association website at www.diabetes.ca for information on sharps disposal.

The directions regarding needle handling are not intended to replace local, healthcare professional or institutional policies.

Dispose of the used KwikPen as instructed by your healthcare professional after you remove the needle.

If you want more information about Basaglar:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.lilly.ca, or by calling 1-888-545-5972.

The information in this document is current as of the last revision date shown below. For the most current information please visit our website or contact us directly.

You may need to read this package insert again. Please do not throw it away until you have finished your medicine.

Basaglar and KwikPen are trademarks owned by or licensed to Eli Lilly and Company, its subsidiaries, or affiliates.

Lantus is a trademark owned by sanofi-aventis Canada Inc.

This leaflet was prepared by Eli Lilly Canada Inc.

Last Revised August 26, 2022

BAS-0004-PMI-20220826

Instructions for Use

BASAGLAR® KwikPen®
Insulin glargine (rDNA origin)
100 units/mL, 3 mL pen

www.lilly.ca Lilly (logo)

PLEASE READ THESE INSTRUCTIONS BEFORE USE

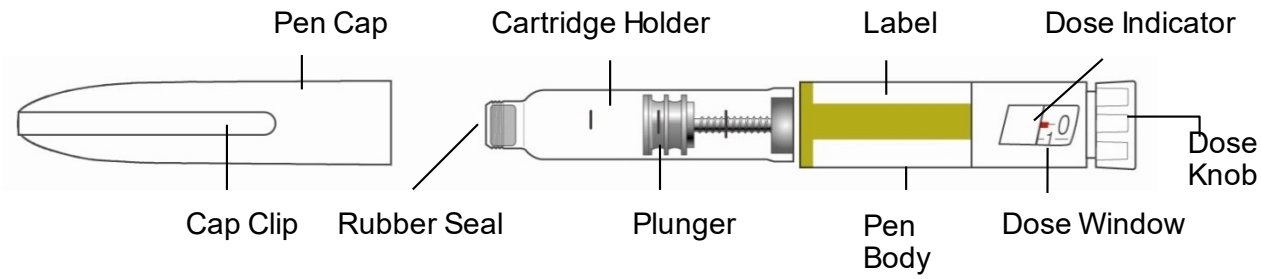
Read the entire Instructions for Use before you start taking BASAGLAR® and each time you get another BASAGLAR® KwikPen®. There may be new information. This information does not take the place of talking to your healthcare professional about your medical condition or your treatment.

BASAGLAR KwikPen ("Pen") is a disposable prefilled pen containing 300 units of BASAGLAR. You can give yourself multiple doses using one Pen. The Pen dials 1 unit at a time. You can give from 1 to 80 units in a single injection. **If your dose is more than 80 units, you will need to give yourself more than one injection.** The plunger only moves a little with each injection, and you may not notice that it moves. The plunger will only reach the end of the cartridge when you have used all 300 units in the Pen.

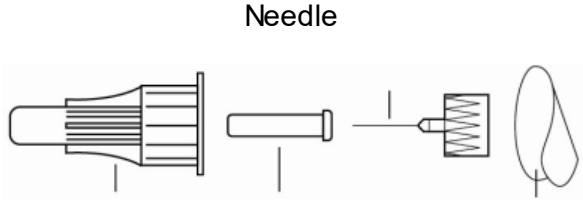
The Pen is for single patient use only. Do not share your Pen with other people, even if the needle has been changed. Do not reuse or share needles with other people. You may give an infection to them or get an infection from them.

This Pen is not recommended for use by the blind or visually impaired without the help of someone trained to use the Pen.

KwikPen Parts



Pen Needle Parts (Needles Not Included)



Dose Knob with green ring

How to recognize your Basaglar KwikPen

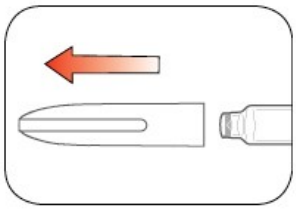
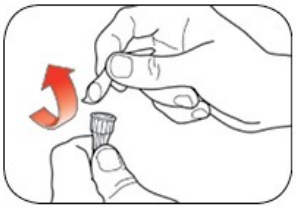
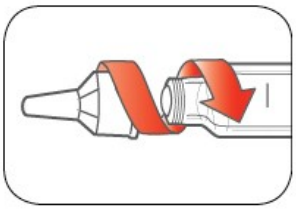
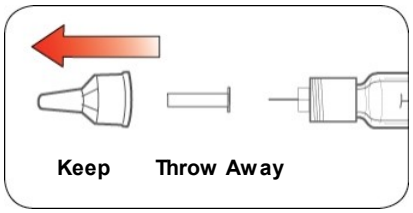
- Pen color: Light grey
- Dose Knob: Light grey with green ring on the end
- Labels: Light grey with green colour bars

Supplies needed to give your injection

- BASAGLAR KwikPen
- KwikPen compatible Needle (BD Pen Needles recommended)
- Alcohol swab

Preparing your Pen

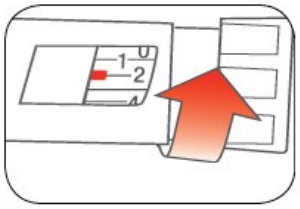
- Wash your hands with soap and water.
- Check the Pen to make sure you are taking the right type of insulin. This is especially important if you use more than 1 type of insulin.
- **Do not** use your Pen past the expiration date printed on the Label or for more than 28 days after you first start using the Pen.
- Always use a **new Needle** for each injection to help prevent infections and blocked Needles.

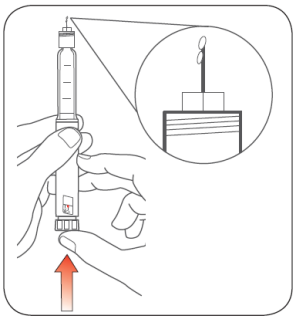
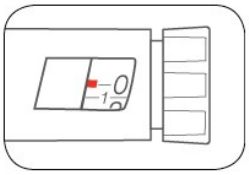
Step 1: • Pull the Pen Cap straight off. - **Do not** remove the Pen Label. • Wipe the Rubber Seal with an alcohol swab. BASAGLAR should look clear and colourless. **Do not** use if it is cloudy, coloured, or has particles or clumps in it.	
Step 2: • Select a new Needle. • Pull off the Paper Tab from the Outer Needle Shield.	
Step 3: • Push the capped Needle straight onto the Pen and twist the Needle on until it is tight.	
Step 4: • Pull off the Outer Needle Shield. **Do not** throw it away. • Pull off the Inner Needle Shield and throw it away.	

Priming your Pen

Prime before each injection.

- Priming your Pen means removing the air from the Needle and Cartridge that may collect during normal use and ensures that the Pen is working correctly.
- If you **do not** prime before each injection, you may get too much or too little insulin.

Step 5: • To prime your Pen, turn the Dose Knob to **select 2 units**.	

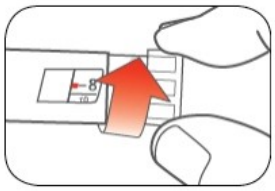
Step 6: • Hold your Pen with the Needle pointing up. Tap the Cartridge Holder gently to collect air bubbles at the top.	
Step 7: • Continue holding your Pen with Needle pointing up. Push the Dose Knob in until it stops, and "**0**" is seen in the Dose Window. Hold the Dose Knob in and **count to 5 slowly**. You should see insulin at the tip of the Needle. - If you **do not** see insulin, repeat the priming steps, but not more than 4 times. - If you **still do not** see insulin, change the Needle and repeat the priming steps. Small air bubbles are normal and will not affect your dose.	 

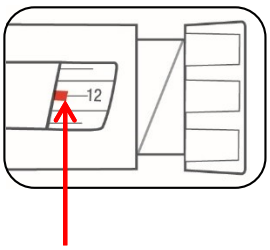
Selecting your dose

- You can give from 1 to 80 units in a single injection.
- If your dose is more than 80 units, you will need to give more than one injection.
  - If you need help deciding how to divide up your dose, ask your healthcare professional.
  - You should use a new Needle for each injection and repeat the priming step.

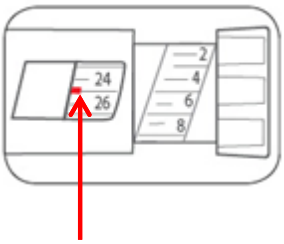
Step 8:

- Turn the Dose Knob to select the number of units you need to inject. The Dose Indicator should line up with your dose.
  - The Pen dials 1 unit at a time.
  - The Dose Knob clicks as you turn it.
  - **DO NOT** dial your dose by counting the clicks because you may dial the wrong dose.
  - The dose can be corrected by turning the Dose Knob in either direction until the correct dose lines up with the Dose Indicator.
  - The **even** numbers are printed on the dial.
  - The **odd** numbers, after the number 1, are shown as full lines.
- **Always check the number in the Dose Window to make sure you have dialed the correct dose.**





(Example: 12 units shown in the Dose Window)

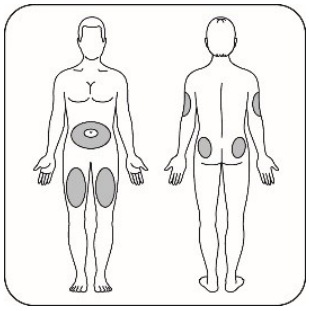
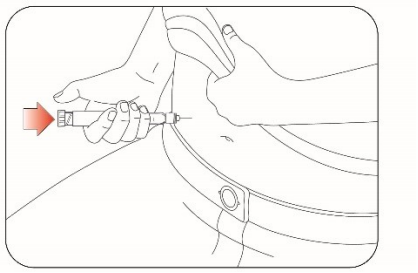


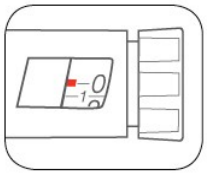
(Example: 25 units shown in the Dose Window)

- The Pen will not let you dial more than the number of units left in the Pen.
- If you need to inject more than the number of units left in the Pen, you may either:
  - inject the amount left in your Pen and then use a new Pen to give the rest of your dose, **or**
  - get a new Pen and inject the full dose.
- It is normal to see a small amount of insulin left in the Pen that you can not inject.

Giving your injection

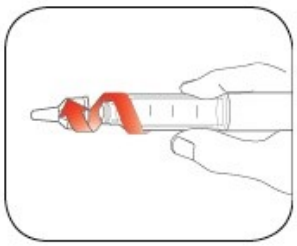
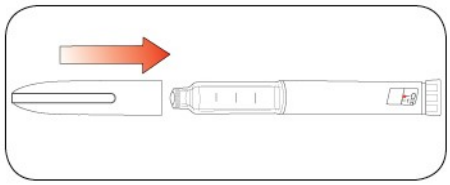
- Inject your insulin as your healthcare professional has shown you.
- Change (rotate) your injection site for each injection.
- **Do not** try to change your dose while injecting.

Step 9: Choose your injection site. • BASAGLAR is injected under the skin (subcutaneously) of your stomach area, buttocks, upper legs or upper arms. • **Follow the instructions for sanitary injection technique recommended by your healthcare professional.**	
Step 10: • Insert the Needle into your skin. • Push the Dose Knob all the way in. • Continue to hold the Dose Knob in and **slowly count to 5** before removing the Needle.  **Do not** try to inject your insulin by turning the Dose Knob. You will **NOT** receive your insulin by turning the Dose Knob.	

Step 11: • Pull the Needle out of your skin. - A drop of insulin at the Needle tip is normal. It will not affect your dose. • Check the number in the Dose Window - If you see “0” in the Dose Window, you have received the full amount you dialed. - If you do not see “0” in the Dose Window, do not redial. Insert the needle into your skin and finish your injection. - If you **still** do not think you received the full amount you dialed for your injection, **do not start over or repeat that injection.** Monitor your blood glucose as instructed by your healthcare professional. - If you normally need to give 2 injections for your full dose, be sure to give your second injection. The plunger only moves a little with each injection, and you may not notice that it moves. If you see blood after you take the Needle out of your skin, press the injection site lightly with a piece of gauze or an alcohol swab. **Do not** rub the area.	

After your injection

Step 12: • Carefully replace the Outer Needle Shield.	

Step 13: • Unscrew the capped Needle and dispose of it as described below (see **Disposing of Pens and Needles** section). • Do not store the Pen with the Needle attached to prevent leaking, blocking the Needle, and air from entering the Pen.	
Step 14: • Replace the Pen Cap by lining up the Cap Clip with the Dose Indicator and pushing straight on.	

Disposing of Pens and Needles

- Dispose of used Needles in a sharps container or a hard plastic container with a secure lid. **Do not** throw Needles directly into your household trash.
- Dispose of the used Pen as instructed by your healthcare professional after you have removed the Needle.
- Do not recycle the filled sharps container.
- Ask your healthcare professional about options available to dispose of the sharps container properly. You can also check the Canadian Diabetes Association website at www.diabetes.ca for information on sharps disposal.
- The directions regarding Needle handling are not intended to replace local, healthcare professional or institutional policies.

Storing your Pen

Unused Pens

- Store unused Pens in the refrigerator at 2°C to 8°C.
- **Do not** freeze BASAGLAR. **Do not** use if it has been frozen.
- Unused Pens may be used until the expiration date printed on the Label, if the Pen has been kept in the refrigerator.

In-use Pen

- Store the Pen you are currently using at room temperature (up to 30°C) and away from heat and light.
- Throw away the Pen you are using after 28 days, even if it still has insulin left in it.

Refer to the Consumer Information Leaflet for complete insulin storage instructions.

General information about the safe and effective use of your Pen

- **Keep your Pen and Needles out of the sight and reach of children.**
- **Do not** use your Pen if any part looks broken or damaged.
- Always carry an extra Pen in case yours is lost or damaged.

Troubleshooting

- If you cannot remove the Pen Cap, gently twist the cap back and forth, and then pull the cap straight off.
- If the Dose Knob is hard to push:
  - Pushing the Dose Knob more slowly will make it easier to inject.
  - Your Needle may be blocked. Put on a new Needle and prime the Pen.
  - You may have dust, food, or liquid inside the Pen. Throw the Pen away and get a new Pen.

If you have any questions or problems with your BASAGLAR KwikPen, contact your healthcare professional for assistance or call Lilly at 1-888-545-5972.

For more information on BASAGLAR KwikPen and insulin, please visit our website at www.lilly.ca.

BASAGLAR and KWIKPEN are trademarks owned or licensed by Eli Lilly and Company, its subsidiaries or affiliates.

Manufactured by:

Eli Lilly and Company
Pen Assembly Facility
Indianapolis, Indiana 46285
USA

Distributed by:

Eli Lilly Canada Inc.
PO Box 73
Toronto, Ontario
M5X 1B1

BASAGLAR **KwikPen** meets the current dose accuracy and functional requirements of ISO 11608-1.

The information in this document is current as of the revision date shown below. For the most current information please visit our website at www.lilly.ca or contact us directly at 1-888-545-5972.

Document Revision Date: August 26, 2022

BASKP-0003-CA-IFU-August 26, 2022

Lilly (*red script)*