PRODUCT MONOGRAPH

BASAGLAR™

insulin glargine (rDNA origin)
Solution for Injection, 100 units/mL

THERAPEUTIC CLASSIFICATION
Anti-diabetic Agent
ATC code: A10AE04

Long-acting Recombinant Human Insulin Analogue

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Subcutaneous	Solution for Injection, 100 units/mL	Glycerin, m-cresol, zinc oxide and water for injection. Hydrochloric acid and sodium hydroxide for pH adjustment.

DESCRIPTION

BASAGLAR™ [insulin glargine (rDNA origin)] injection 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 PHAMACEUTICAL INFORMATION, Drug Substance).

The similarity between the subsequent entry biologic (SEB) product BASAGLAR and the reference product Lantus® (insulin glargine) was established in accordance with the *Guidance for Sponsors: Information and Submission Requirements for Subsequent Entry Biologics (SEBs).*

INDICATIONS AND CLINICAL USE

Comparability between BASAGLAR and the reference product has been established based on comparative chemistry and manufacturing studies, comparative non-clinical studies and comparative pharmacokinetic/pharmacodynamic (PK/PD) and clinical trials. Comparative PK/PD and clinical trials were carried out in healthy volunteers and in adult patients with type 1

diabetes mellitus or type 2 diabetes mellitus. The indication for pediatric type 1 diabetes mellitus (age: >6 years old) has been granted on the basis of similarity, demonstrated between BASAGLAR and the reference product, in product quality, mechanism of action, disease pathophysiology, safety profile, dosage regimen and based on clinical experience with the reference products.

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.

CONTRAINDICATIONS

BASAGLAR is contraindicated 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 DOSAGE FORMS, COMPOSITION AND PACKAGING.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Hypoglycemia is the most common adverse effect of insulin, including BASAGLAR (see 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 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 DOSAGE AND ADMINISTRATION).

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 effect associated with the use of all insulin therapies, particularly when given intravenously. However, BASAGLAR should not be given intravenously (see DOSAGE AND ADMINISTRATION, Administration). If left untreated, hypokalemia may cause respiratory paralysis, ventricular arrhythmia, and death. This potential clinical adverse effect may be relevant in patients who are on potassium lowering drugs 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 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 syringe 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 ADVERSE REACTIONS).

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 ADVERSE REACTIONS). Hypoglycemia may occur if the insulin dose is too high in relation to the insulin requirement (see OVERDOSAGE). 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 whose 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 DRUG 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 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.

Hypoglycemic reactions following treatment with insulin products such as BASAGLAR are mostly mild and easily managed. Changes in insulin regimen or changes in life style (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.

Diabetic patients 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 PART III: CONSUMER INFORMATION).

The prolonged effect of subcutaneous BASAGLAR may delay recovery from hypoglycemia. For patients being switched from twice-daily neutral protamine hagedorn (NPH) insulin to once-daily BASAGLAR the recommended initial BASAGLAR dose is 80% of the total NPH dose that is being discontinued. This dose reduction will lower the likelihood of hypoglycemia.

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.

Immune

Injection Site and Local Allergic Reactions
Injection site reactions that have occurred 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 should be advised to consult their doctor if they notice any of these conditions. Continuous rotation of the injection site within a given area may help reduce or prevent these reactions.

Repeated insulin injections into areas of lipodystrophy or localized cutaneous amyloidosis have been reported to result in hyperglycemia, and a sudden change in the injection site (to an unaffected area) has been reported to result in hypoglycemia.

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 CONTRAINDICATIONS and 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.

Renal/Hepatic/Biliary/Pancreatic Impairment

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 ACTION AND 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.

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 ADVERSE REACTIONS, Eye disorders).

Changes in Insulin Regimen/Transferring Patients from Other Insulins

Changes in insulin regimen, strength, timing of administration, manufacturer, type (e.g., regular, NPH, or insulin analogues), species (animal, human), or method of manufacture (recombinant DNA versus animal-source insulin) may affect glycemic control and predispose to hypoglycemia or hyperglycemia. Make any changes to a patient's insulin regimen under close medical supervision with increased frequency of glucose monitoring. Changes in insulin dose or an adjustment in concomitant oral antidiabetic treatment may be needed.

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 DOSAGE AND ADMINISTRATION).

Special Populations

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) indicate no reports of specific adverse effects of insulin glargine on maternal and fetal/neonatal outcomes.

Animal data do not indicate reproductive toxicity for the reference product (Lantus®) (see Part II: 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 doctor if they are pregnant or are contemplating pregnancy.

Nursing Women

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.

Pediatrics (>6 years of age)

BASAGLAR can be used in children over 6 years of age with type 1 diabetes mellitus, based on the established safety and effectiveness of the reference product (Lantus®) in children over 6

years of age with type 1 diabetes mellitus (see ACTIONS AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, and INDICATIONS AND CLINICAL USE).

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 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 WARNINGS AND PRECAUTIONS, Renal/ Hepatic/ Biliary/ Pancreatic Impairment).

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

Re-usable pens to be used with BASAGLAR cartridge
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.

Occupational Hazards

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.

ADVERSE REACTIONS

Adverse Drug Reaction Overview- BASAGLAR studies

Type 1 and type 2 diabetes in adults
Two phase 3 safety and efficacy clinical trials were conducted comparing BASAGLAR and Lantus® (insulin glargine), Study ABEB in patients with type 1 diabetes mellitus and Study ABEC in patients with type 2 diabetes mellitus. A total of 1291 patients received at least 1 dose of randomly assigned study drug, with a total of 644 patients receiving BASAGLAR, and 647 patients receiving Lantus® across the 2 studies.

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.

In these clinical trials, BASAGLAR and Lantus® were similar in terms of incidences of severe and total hypoglycemia, overall incidence of serious adverse events (SAEs), discontinuations due to adverse events (AEs), treatment-emergent adverse events (TEAEs) (including those possibly related to study drug, procedure, or disease), injection site AEs, or TEAEs captured by the special topic assessment of allergic events.

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.

Adverse Drug Reaction Overview: Studies with the reference product (Lantus®)

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 reported for Lantus® and human NPH treatment groups were similar for patients with type 1 and type 2 diabetes.

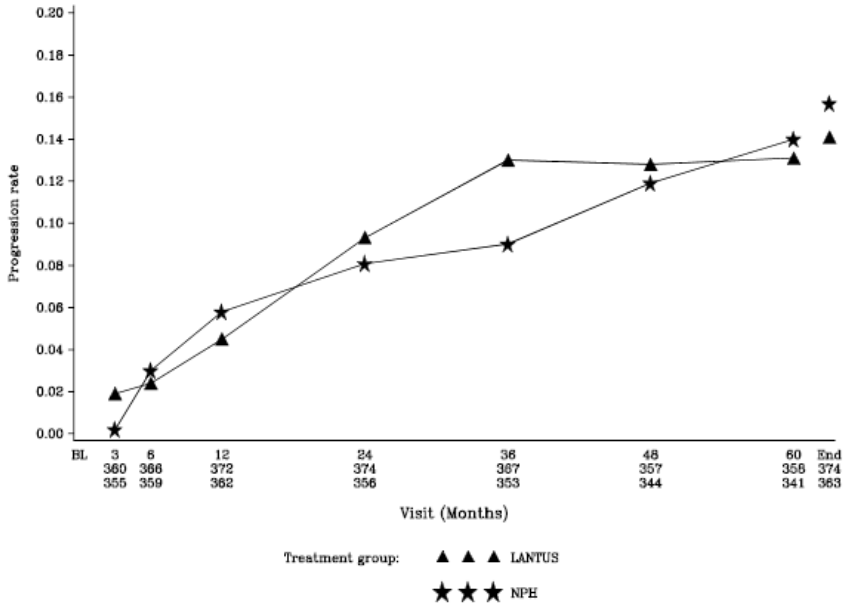
Effects of Lantus® on diabetic retinopathy were evaluated in a large 5-year NPH-controlled study in patients with type 2 diabetes in which progression of retinopathy was investigated by fundus photography using a grading protocol derived from the Early Treatment Diabetic Retinopathy Study (ETDRS). The 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 1: 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 greater 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 reaction (see WARNINGS AND PRECAUTIONS).
- injection site reaction

Investigations
- antibodies formation (see 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 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 WARNINGS AND PRECAUTIONS).

Comparative Clinical Trial Adverse Drug Reactions - BASAGLAR

Because clinical trials are conducted under very specific conditions the adverse drug reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Study ABEB- Type 1 diabetes in adults
Study ABEB compared the efficacy and safety of once-daily BASAGLAR and Lantus®, when used subcutaneously in combination with pre-meal insulin lispro for a total of 52 weeks in adult patients with type 1 diabetes mellitus (T1DM).

A total of 535 patients were randomized and received at least 1 dose of study drug (BASAGLAR: 268 patients; Lantus®: 267 patients), of these patients, 167 patients (62.3%) in the BASAGLAR group and 166 patients (62.2%) in the Lantus® group reported TEAEs. Overall, the most frequently reported TEAEs were nasopharyngitis (BASAGLAR 43 patients [16.0%]; Lantus® 45 patients [16.9%]), upper respiratory tract infection (BASAGLAR 22 patients [8.2%]; Lantus® 21 patients [7.9%]), hypoglycemia (BASAGLAR 13 patients [4.9%]; Lantus® 12 patients [4.5%]), and diarrhea (BASAGLAR 12 patients [4.5%]; Lantus® 10 patients [3.7%]).

The most frequently reported TEAEs possibly related to study drug were hypoglycemia (BASAGLAR 10 patients [3.7%]; Lantus® 9 patients [3.4%]) and injection site reaction (BASAGLAR 2 patients [0.7%]; Lantus® 1 patient [0.4%]). The incidence of TEAEs possibly related to study drug were similar between treatment groups.

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 2 shows the treatment emergent adverse events occurring in ≥1% of patients in either the BASAGLAR or Lantus® treatment group.

Table 2: 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)

Adverse Event	BASAGLAR (N=268)	Lantus® (N=267)
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

Study ABEC compared the efficacy and safety of once-daily BASAGLAR and Lantus®, when used subcutaneously in combination with oral antihyperglycemic medications (OAMs) for 24 weeks in adult patients with type 2 diabetes mellitus (T2DM). Both United States (US) and European (EU) approved Lantus® were used as the reference product.

A total of 756 patients were randomized and received at least 1 dose of study drug (BASAGLAR 376 patients; Lantus® 380 patients).

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%)].

An additional four potentially cardiac-related events were observed [cerebrovascular event 1 patient BASAGLAR (0.27%), pulmonary embolism 1 patient BASAGLAR (0.27%), amaurosis 1 patient Lantus® (0.26%), cerebral ischemia 1 patient Lantus® (0.26%)].

Table 3 shows the treatment emergent adverse events occurring in ≥1% of patients in either the BASAGLAR or Lantus® treatment group. The following TEAE were reported at a higher incidence in the BASAGLAR arm compared to the Lantus® arm: upper respiratory tract infection, urinary tract infection, gastroenteritis viral, sinusitis, abnormal weight gain, abnormal loss of weight, muscle spasms, headache, dizziness, sinus headache, oropharyngeal pain, sinus congestion, and hypertension.

Table 3: 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)

Adverse Event	BASAGLAR (N=376)	Lantus® (N=380)
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)

Type 1 diabetes in children and adolescents- Studies with the reference product (Lantus®)

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)	Number (%) of subjects	
Body System/Coded Term	**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.

Cardiovascular Safety – studies with reference product Lantus®
Study 4032 (ORIGIN Trial): randomized, 2x2 factorial design study: 12,537 participants. Participants were randomized to receive Lantus® (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 5).

The objective of the trial was to demonstrate that Lantus® 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/m2 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 5: 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, 1.05)
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 – reference product Lantus®

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 – reference product Lantus®
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.

Post-Market Adverse Drug 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.

DRUG INTERACTIONS

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

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 analogue (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 WARNINGS AND PRECAUTIONS).

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

BASAGLAR [insulin glargine (rDNA)] injection 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 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hypoglycemia and Hyperglycemia). The dose may also have to be adjusted during intercurrent illness (see 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, intramuscularly or via an insulin pump. Intravenous administration of the usual subcutaneous dose could result in severe hypoglycemia (see 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.

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 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 analogue 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 analogue 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.

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 alternated 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. 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.

To prevent the possible transmission of disease, never share a BASAGLAR pen or cartridge between patients, even if the needle on the delivery device 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.

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 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 (for adult: 1 mg; for children weighing less than 20 kg: 0.5 mg) given intramuscularly or subcutaneously by a trained person, or by glucose given intravenously by a medical 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.

ACTION AND CLINICAL PHARMACOLOGY

Pharmacodynamics

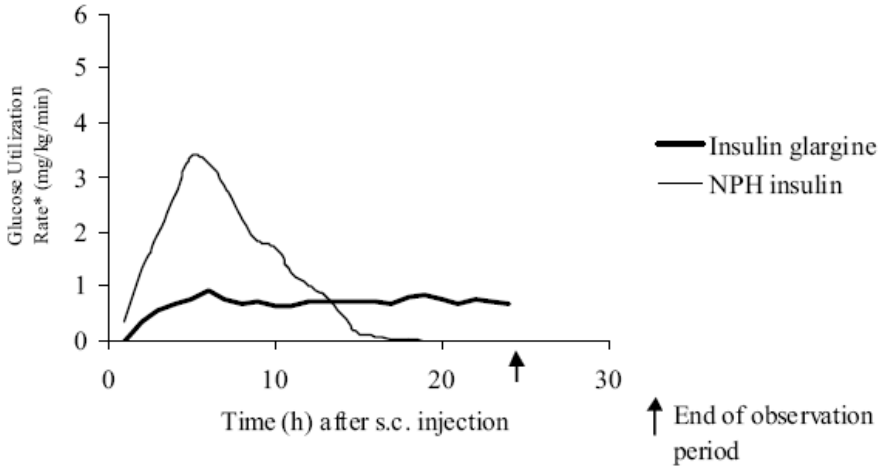
Insulin glargine is a human insulin analogue designed to have low solubility at neutral pH. At pH 4, as in the BASAGLAR injection solution, it is completely soluble. After injection into the subcutaneous tissue, the acidic solution is neutralized, leading to formation of micro-precipitates from which 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.

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.

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) for insulin glargine.

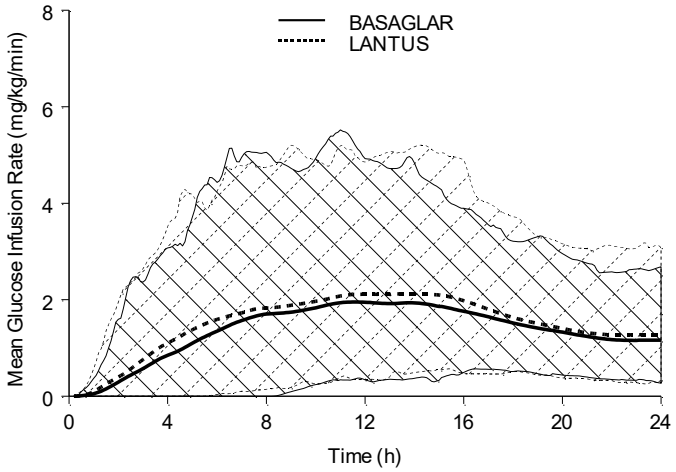
Figure 2 - Activity Profile in Patients with Type 1 Diabetes



*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%

BASAGLAR demonstrated similar pharmacodynamic profile and similar mean pharmacodynamic responses (R_{max} and G_{tot}) compared to that of Lantus® when administered as a single dose of 0.5 U/kg subcutaneously to healthy subjects (see Figure 3 and CLINICAL TRIALS – Comparative Pharmacokinetic/Pharmacodynamic Studies).

Figure 3 - Activity Profile in Healthy Subjects



Mean glucose infusion rate (mg/kg/min) over time with 95% CI

Pharmacokinetics

Absorption and Bioavailability

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 a 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.

The relative bioavailability of BASAGLAR to Lantus® was close to 1, with the 90% confidence interval of the least square mean ratio of AUC (0-24) of BASAGLAR to Lantus® being contained within the window of 0.8 to 1.25 in healthy subjects following a single dose administration of 0.5 units/kg subcutaneously (see CLINICAL TRIALS- Comparative Pharmacokinetic/Pharmacodynamic Studies).

Metabolism
After subcutaneous injection of the reference product (Lantus®) in healthy subjects and diabetic patients, insulin glargine is rapidly metabolized at the carboxyl terminus of the Beta chain with formation of two active metabolites M1 (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.

Special Populations and Conditions

Age, race, and gender
Information on 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.

In controlled clinical studies with BASAGLAR in adults (n=1291), subgroup analyses based on age, race and gender did not suggest a difference in safety and efficacy for patients treated with BASAGLAR compared to those treated with Lantus®.

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 WARNINGS AND PRECAUTIONS, Renal/ Hepatic/ Biliary/ Pancreatic Impairment).

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 WARNINGS AND PRECAUTIONS, Renal/ Hepatic/ Biliary/ Pancreatic Impairment).

Pregnancy
The effect of pregnancy on the pharmacokinetics and pharmacodynamics of insulin glargine has not been studied (see WARNINGS AND PRECAUTIONS, Special Populations).

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.

In controlled clinical trials, subgroup analysis based on BMI did not show differences in safety and efficacy between BASAGLAR and Lantus®.

Smoking
Information on the effect of smoking on the pharmacokinetics and pharmacodynamics of BASAGLAR has not been studied.

Duration of Effect

The duration of action of BASAGLAR is up to 24 hours. The longer duration of action 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.

BASAGLAR demonstrated similar duration of action and pharmacodynamics responses (R_{max} and G_{tot}) compared to Lantus® when administered as a single 0.3 U/kg subcutaneous (SC) dose in a randomized, investigator- and subject-blind, 2-period crossover, 42-hour euglycemic clamp study in 20 patients with type 1 diabetes.

STORAGE AND STABILITY

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

Unopened BASAGLAR cartridges and BASAGLAR KwikPens should be stored in a refrigerator, between 2°C - 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

Opened (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.

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 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 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 doctor if they are pregnant or are contemplating pregnancy.

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

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

Refer patients to the Consumer Information leaflet 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.

DOSAGE FORMS, COMPOSITION AND PACKAGING

BASAGLAR is a clear, colourless, aqueous solution for subcutaneous administration.

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, 1 pen/box

Not all pack sizes and presentations may be marketed.

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.

Each milliliter of BASAGLAR contains insulin glargine 100 units. Each milliliter also contains excipients: glycerin, m-cresol, zinc oxide and water for injection. BASAGLAR has a pH of approximately 4. The pH is adjusted by addition of aqueous solutions of hydrochloric acid and sodium hydroxide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

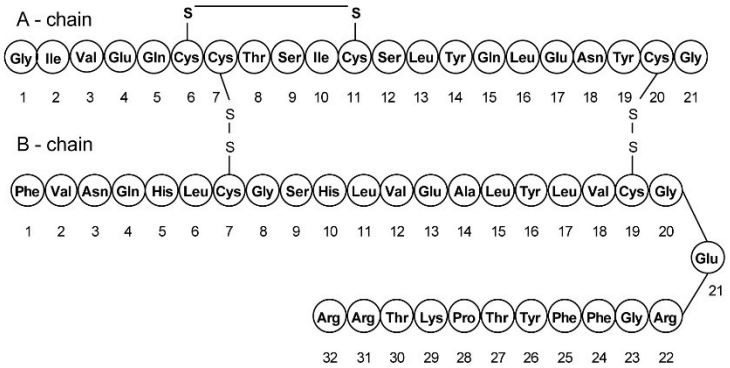
Proper name: insulin glargine (rDNA origin)

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

Molecular formula: $C_{267}H_{404}N_{72}O_{78}S_6$

Molecular weight: 6063 daltons

Structural formula:



Description: white or almost white solid

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

CLINICAL TRIALS

BASAGLAR™ [insulin glargine (rDNA origin)] injection is a subsequent entry biologic.

The clinical development program to demonstrate clinical similarity between BASAGLAR and Lantus® is based on comparative pharmacokinetic/pharmacodynamics (PK/PD) studies in healthy subjects; comparative bioavailability and PD response studies in healthy subjects; a comparative duration of action study in patients with type 1 diabetes mellitus; and comparative safety and efficacy studies in patients with type 1 and 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 (Test) and Lantus® (Reference). 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 $R_{max.}$

The pharmacokinetic and pharmacodynamic parameters for study ABEO are summarized in Table 6. Figure 4 shows the PK profiles for BASAGLAR and Lantus®. BASAGLAR was determined to have similar PK and PD properties compared to Lantus®.

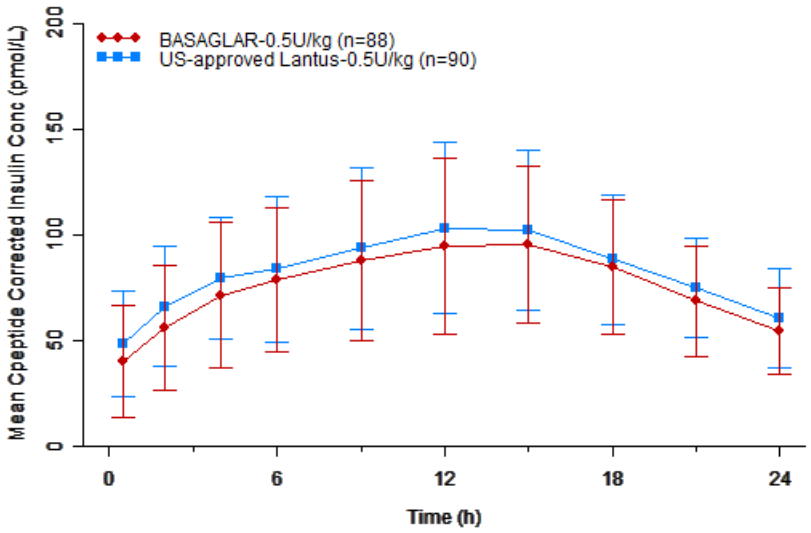
Table 6: Comparative PK and PD data for BASAGLAR vs. Lantus® in Healthy Subjects (Study ABEO)

Parameter	BASAGLAR Geometric Mean (%CV)	LANTUS® Geometric Mean (%CV)	Ratio of Least Squares Geometric Means	90% 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)		
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, $t_{1/2}$ = terminal elimination half-life, t_{max} = 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; LOESS=locally weighted regression in smoothing scatterplots; GIR=glucose infusion rate.
[a] Median (range)
[b] G_{tot} and R_{max} parameter estimates are based on LOESS smoothed GIR profiles.

Figure 4: 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).



Antibody Production – BASAGLAR

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 7).

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 7). 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 7: 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)	139	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.
(b) Fisher's exact test
Abbreviations: LOCF=last observation carried forward

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 9 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 10).

Demographic and baseline characteristics were generally balanced between treatment groups in each of the 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; Lantus®16.6 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%).

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%.

Table 8 provides a summary of the study design for both Studies ABEB and ABEC.

Table 8: Summary of patient demographics for clinical trials in specific indication

Study #	Trial design and duration	Dosage and route of administration	Study subjects (n=number) Full analysis set (FAS)	Mean age (Range)	Gender % (number)
ABEB (T1DM) ELEMENT 1	Phase 3, prospective, randomized, multinational, multicenter, 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 in combination with mealtime insulin lispro in adult 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 (full analysis set) BASAGLAR: 268 patients: Lantus®: 267 patients	41.2 years Range: 18.3-81.4 years	Females: 225 (42%) Males: 310 (58%)

Study #	Trial design and duration	Dosage and route of administration	Study subjects (n=number) Full analysis set (FAS)	Mean age (Range)	Gender % (number)
ABEC (T2DM) ELEMENT 2	Phase 3, prospective, randomized, multinational, multicenter, 2-arm, active-control, double-blind, parallel, 24-week treatment study with a 4-week post-treatment follow-up to compare BASAGLAR and Lantus® when each is used in combination with at least 2 oral antihyperglycemic medications in adult patients with T2DM. Patients were either insulin-naïve or already administering once-daily (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 (full analysis set) BASAGLAR: 376 patients: Lantus®: 380 patients	58.8 years Range: 23.4- 84.3 years	Females: 378 (50%) Males: 378 (50%)

T1DM=type 1 diabetes mellitus; T2DM=type 2 diabetes mellitus

Study 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). 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 9: 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)		(-0.107, 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 10: 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; T2DM = type 2 diabetes mellitus.
*Non-inferiority testing approach: BASAGLAR was non-inferior to Lantus® in the primary treatment comparison at both 0.4% and 0.3% NIMs based on FAS population. The non-inferiority test was only prespecified for the 24 week A1c endpoint.

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.

Pediatric Type 1 Diabetes Mellitus

There are no clinical trials conducted with BASAGLAR in pediatric patients (>6 years of age) with type 1 diabetes mellitus. The use of BASAGLAR in pediatric (>6 years of age) 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®).

DETAILED PHARMACOLOGY

Since BASAGLAR is a Subsequent Entry Biologic, where the pharmacodynamics and pharmacokinetic 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 of BASAGLAR to Lantus®.

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.

TOXICOLOGY

Since BASAGLAR is a Subsequent Entry Biologic, where the 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 toxicology of BASAGLAR to Lantus®.

Comparative Toxicity - BASAGLAR vs Lantus®

The toxicity profile of BASAGLAR was characterized alongside Lantus® in separate 1-month subchronic toxicity studies in non-diabetic rats (Table 11), 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 11). 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 11).

Table 11: 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.

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PART III: CONSUMER INFORMATION

BASAGLAR™ CARTRIDGES
insulin glargine (rDNA origin)
Solution for Injection, 100 units/mL

BASAGLAR™ KWIKPEN®
insulin glargine (rDNA origin)
Solution for Injection, 100 units/mL

This leaflet is part III of a three-part "Product Monograph" published when BASAGLAR was approved for sale in Canada and is designed specifically for Consumers. BASAGLAR™ is a subsequent entry biologic (SEB), which is a protein drug product that is authorized based on its likeness to a protein drug product already authorized for sale in Canada. This leaflet is a summary and will not tell you everything about BASAGLAR. Contact your healthcare professional if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
BASAGLAR [insulin glargine (rDNA origin)] injection 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.

What it does:
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 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.

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 away from home.

When it should not be used:
BASAGLAR should not be used:
- if you are allergic to this drug or to any ingredient in the formulation or component of the container
- if you have diabetic ketoacidosis
- for intravenous or intramuscular injections

What the medicinal ingredient is:
The active ingredient in BASAGLAR is insulin glargine (rDNA origin).

What the non-medicinal ingredients are:
The nonmedicinal ingredients in the 3 mL cartridges and KwikPen are glycerin, m-cresol, zinc oxide, and water for injection. Hydrochloric acid and sodium hydroxide are added for pH adjustment.

What dosage forms it comes in:
BASAGLAR is a solution for injection (100 units/mL) available in:
- 3 mL cartridges in packages of 5 (for use only with Lilly's re-usable insulin pens)
- KwikPen, 3 mL prefilled pen, in packages of 5

WARNINGS AND PRECAUTIONS

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 or intramuscular 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.

Concomitant oral antidiabetic treatment may need to be adjusted.

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 healthcare professional immediately if you develop symptoms of shortness of breath, fatigue, exercise intolerance, or swelling of the lower extremities while you are taking these medications.

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 label before each 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 may 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.

BEFORE you use BASAGLAR talk to your healthcare professional if:

- you are planning to have a baby, are pregnant, or are nursing a baby
- you are taking any medication

INTERACTIONS WITH THIS MEDICATION

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 "Proper use of this medication" section below for potential medication interactions with insulin.

INSTRUCTIONS FOR USE

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 the carton and the cartridge label when you pick it up from the pharmacy to make sure it is the same as the one your doctor has recommended.

It is important to use the BASAGLAR cartridge only with Lilly re-usable 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.

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).

CAREFULLY FOLLOW YOUR HEALTHCARE PROFESSIONAL'S DIRECTIONS ON HOW TO USE BASAGLAR CARTRIDGES AND KWIKPENS TO HELP AVOID CONTAMINATION AND POSSIBLE INFECTION, AND TO OBTAIN AN ACCURATE DOSE.

DO NOT SHARE INJECTION PENS, CARTRIDGES, OR NEEDLES WITH ANYONE ELSE. To prevent the possible transmission of disease, never share a BASAGLAR cartridge or pen between patients, even if the needle on the delivery device is changed.

Preparing the BASAGLAR Cartridge for insertion into a re-usable insulin pen

1. To avoid medication errors, check the insulin cartridge label before each insertion.
2. Inspect the insulin cartridge. BASAGLAR should be a clear and colourless solution with no visible particles. Do not use it if you notice anything unusual in the appearance of the solution.

3. Make sure the insulin is at room temperature to minimize local irritation at the injection site.
4. Wash your hands.
5. Carefully follow the injection pen directions for loading the cartridge into the injection pen.

Preparing the KwikPen
Please refer to the Instructions for Use provided with your BASAGLAR KwikPen.

Injecting Each Dose
1. Wash your hands.
2. Inspect the insulin. BASAGLAR should be a clear and colourless solution with no visible particles. Do not use it if you notice anything unusual in the appearance of solution.
3. Do not shake or rotate the cartridge or KwikPen before use.
4. Remove the protective cap.
5. Follow the injection pen directions for attaching and changing the needle.
6. Check the cartridge inserted into the injection pen for air bubbles. If bubbles are present, remove them as instructed in the injection pen directions.
7. **Follow the injection pen directions for performing the Safety Test or Priming.**
8. Set the injection pen to the correct BASAGLAR dose as instructed in the injection pen directions.
9. There is no relevant difference in absorption of BASAGLAR between abdominal, thigh, or upper arm subcutaneous injection areas. However, 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.
10. Prepare the injection site as directed by your healthcare professional
11. Insert the needle attached to the injection pen as instructed by your doctor or diabetes educator.
12. To inject BASAGLAR, follow the directions for the injection pen.
13. Slowly count to 5 before removing the needle from the injection site and gently apply pressure for several seconds. DO NOT RUB THE AREA.
14. Remove the needle from the injection pen immediately after each injection as instructed in the directions for the injection pen. Dispose of the needle in a sharps container or a hard plastic container with a secure lid or as directed by your healthcare professional. Do not reuse the needle.

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 no BASAGLAR deposition for long-term absorption.

PROPER USE OF THIS MEDICATION

Dosage:

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 (used for conditions including high blood pressure, heart arrhythmias, heart 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.

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.

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 "Side Effects and What To Do About Them" below.

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

Overdose:
If you **have injected too much BASAGLAR**, your blood sugar level 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 "Side Effects and What To Do About Them" below.

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

In case of drug overdose, contact a healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

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 an injection of glucagon 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 our ability to detect hypoglycemia and reduce the frequency of severe hypoglycemia.

Without recognition of early warning 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 (DKA)
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 prompt 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 having an injection site reaction if you change the injection site each time. If you have local injection site reactions, contact your healthcare professional.

This is not a complete list of side effects. For any unexpected effects while taking BASAGLAR, contact your healthcare professional.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

HOW TO STORE IT

Unopened Cartridge or KwikPen:
Unopened BASAGLAR cartridges or KwikPens should be stored in a refrigerator, between 2°C - 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.

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 have removed the needle.

MORE INFORMATION

For more information, please contact your healthcare professional or pharmacist first, or Eli Lilly Canada Inc at:

1-888-545-5972 or visit the website at www.lilly.ca

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.

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