Insulin Glargine

Basaglar® KwikPen

100 Units/mL Solution for Injection



1. Name of Medicinal Product

Insulin Glargine (Basaglar® KwikPen) 100 units/mL solution for injection in a pre-filled pen

2. Qualitative and Quantitative Composition

Each mL contains 100 units Insulin glargine* (equivalent to 3.64 mg).

Each pen contains 3 mL of solution for injection, equivalent to 300 units. *Insulin glargine is produced by recombinant DNA technology in Escherichia coli.

For the full list of excipients, see section 7.1.

3. Pharmaceutical Form

Solution for injection in prefilled pen. KwikPen.

Clear, colorless solution

4. Pharmacologic Category Antidiabetic

5. Clinical Particulars

5.1 Therapeutic Indications

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

5.2 Posology and Method of Administration

Insulin Glargine (Basaglar® KwikPen) contains insulin glargine, an insulin analogue, and has a prolonged duration of action.

Insulin glargine (Basaglar®) should be administered once daily at any time but at the same time each day

The Insulin Glargine (Basaglar®) dose regimen (dose and timing) should be individually adjusted. In patients with type 2 diabetes mellitus,

Insulin Glargine (Basaglar®) can also be given together with orally active antidiabetic medicinal products. The potency of this medicinal product is stated in units. These units are exclusive to insulin glargine and are not the same as IU or the

units used to express the potency of other insulin analogues (see section 6.1). Special populations

Elderly populations (≥ 65 years old) In the elderly, progressive deterioration of renal function may lead to a steady decrease in insulin requirements.

Renal impairment

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

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

Pediatric population Adolescents and children aged 2 years and older

Safety and efficacy of insulin glargine have been established in adolescents and children aged 2 years and older (see section 6.1). The dose regimen (dose and timing) should be individually adjusted. Currently available data are described in sections 5.8, 6.1 and 6.2. Children below 2 years of age

The safety and efficacy of insulin glargine have not been established in children below the age of 2 years. No data are available.

Switch from other insulins to Insulin Glargine (Basaglar®)

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

To reduce the risk of nocturnal and early morning hypoglycemia, patients who are changing their basal insulin regimen from a twice daily NPH insulin to a once daily regimen with Insulin Glargine (Basaglar®) should reduce their daily dose of basal insulin by 20-30 % during

Switch from insulin glargine 300 units/mL to Insulin Glargine (Basaglar®)

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

During the first weeks the reduction should, at least partially, be compensated by an increase in mealtime insulin, after this period the regimen should be adjusted individually. Close metabolic monitoring is recommended during the switch and in the initial weeks thereafter. With improved metabolic control and resulting increase in insulin sensitivity a further adjustment in dose regimen may become necessary. Dose adjustment may also be

required, for example, if the patient's weight or life-style changes, change of timing of insulin dose or other circumstances arise that increase susceptibility to hypoglycemia or hyperglycemia (see section 5.4). Patients with high insulin doses because of antibodies to human insulin may experience an improved insulin response with Insulin Glargine

(Basaglar®).

Method of administration

Insulin Glargine (Basaglar® KwikPen) is administered subcutaneously

 $Insulin\ Glargine\ (Basaglar^{@}\ KwikPen)\ should\ not\ be\ administered\ intravenously.\ The\ prolonged\ duration\ of\ action\ of\ insulin\ glargine\ is\ dependent$ on its injection into subcutaneous tissue. Intravenous administration of the usual subcutaneous dose could result in severe hypodycemia. There are no clinically relevant differences in serum insulin or glucose levels after abdominal, deltoid or thigh administration of insulin glargine.

Injection sites should always be rotated within a given region in order to reduce the risk of lipodystrophy and cutaneous amyloidosis (see

Insulin Glargine (Basaglar®) must not be mixed with any other insulin or diluted. Mixing or diluting can change its time/action profile and mixing can cause precipitation

For further details on handling, see section 7.6.

Before using Insulin Glargine (Basaglar® KwikPen), the instructions for use included in the package leaflet must be read carefully (see section 7.6). newborn/infant are anticipated since insulin glargine as a peptide is digested into amino acids in the human gastrointestinal tract.

5.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 7.1

5.4 Special Warnings and Special Precautions for Use

Insulin Glargine (Basaglar®) is not the insulin of choice for the treatment of diabetic ketoacidosis. Instead, regular insulin administered

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

Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (regular, NPH, lente, long-acting, etc.), origin (animal, human, human insulin analogue) and/or method of manufacture

may result in the need for a change in dose. <u>Hypoglycemia</u>

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

can be expected. Particular caution should be exercised, and intensified blood glucose monitoring is advisable in patients in whom hypoglycemic episodes night be of particular clinical relevance, such as in patients with significant stenoses of the coronary arteries or of the blood vessels supplying the brain (risk of cardiac or cerebral complications of hypoglycemia) as well as in patients with proliferative retinopathy, particularly if not treated with photocoagulation (risk of transient amaurosis following hypoglycemia)

Patients should be aware of circumstances where warning symptoms of hypoglycemia are diminished. The warning symptoms of hypoglycemia may be changed, be less pronounced or be absent in certain risk groups. These include patients:

- in whom glycemic control is markedly improved, in whom hypoglycemia develops gradually,
- who are elderly,
- after transfer from animal insulin to human insulin
- in whom an autonomic neuropathy is present,
- with a long history of diabetes,
- suffering from a psychiatric illness receiving concurrent treatment with certain other medicinal products (see section 5.5).

Such situations may result in severe hypoglycemia (and possibly loss of consciousness) prior to the patient's awareness of hypoglycemia. The prolonged effect of subcutaneous insulin glargine may delay recovery from hypoglycemia.

If normal or decreased values for glycated hemoglobin are noted, the possibility of recurrent, unrecognized (especially nocturnal) episodes of hypoglycemia must be considered

Adherence of the patient to the dose and dietary regimen, correct insulin administration and awareness of hypoglycemia symptoms are essential to reduce the risk of hypoglycemia. Factors increasing the susceptibility to hypoglycemia require particularly close monitoring

- change in the injection area, improved insulin sensitivity (e.g., by removal of stress factors).
- unaccustomed, increased or prolonged physical activity,
- intercurrent illness (e.g. vomiting, diarrhea),
- inadequate food intake.
- missed meals, alcohol consumption
- certain uncompensated endocrine disorders, (e.g. in hypothyroidism and in anterior pituitary or adrenocortical insufficiency) concomitant treatment with certain other medicinal products.

Injection technique tients must be instructed to perform continuous rotation of the injection site to reduce the risk of developing lipodystrophy and cutaneous

amyloidosis. There is a potential risk of delayed insulin absorption and worsened divcemic control following insulin injections at sites with these reactions. A sudden change in the injection site to an unaffected area has been reported to result in hypoglycemia. Blood glucose monitoring is recommended after the change in the injection site, and dose adjustment of antidiabetic medications may be considered.

Intercurrent illness requires intensified metabolic monitoring. In many cases urine tests for ketones are indicated, and often it is necessary to adjust the insulin dose. The insulin requirement is often increased. Patients with type 1 diabetes must continue to consume at least a small amount of carbohydrates on a regular basis, even if they are able to eat only little or no food, or are vomiting etc. and they must never omit insulin entirely.

Insulin administration may cause insulin antibodies to form. In rare cases, the presence of such insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyper- or hypoglycemia (see section 5.8).

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

Combination of Insulin Glargine (Basaglar®) with pioglitazone

ases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors development of cardiac heart failure. This should be kept in mind if treatment with the combination of pioglitazone and Insulin Glargine (Basadlar®) is considered. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and edema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e., essentially "sodium-free".

5.5 Interaction with other medicinal products and other forms of interaction

A number of substances affect glucose metabolism and may require dose adjustment of insulin glargine. Substances that may enhance the blood-dlucose-lowering effect and increase susceptibility to hypoglycemia include oral antidiabetic medicinal products, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, pentoxifylline, propoxyphene, salicylates, somatostatin analogues and sulphonamide antibiotics.

ubstances that may reduce the blood-glucose-lowering effect include corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid estrogens, progestogens, phenothiazine derivatives, somatropin, sympathomimetic medicinal products (e.g. epinephrine [adrenaline], albutamon, terbutaline), thyroid hormones, atypical antipsychotic medicinal products (e.g. clozapine and olanzapine) and protease inhibitors. Beta-blockers, clonidine, lithium salts or alcohol may either potentiate or weaken the blood-glucose lowering effect of insulin. Pentamidine

may cause 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 adrenergic counter-regulation may be reduced or absent.

5.6 Fertility, pregnancy and lactation

For insulin glargine no clinical data on exposed pregnancies from controlled clinical studies are available. A large amount of data on pregnant women (more than 1,000 pregnancy outcomes) indicate no specific adverse effects of insulin glargine on pregnancy and no specific malformative nor feto/neonatal toxicity of insulin glargine.

Careful monitoring of glucose control is essential.

The use of Insulin Glargine (Basaglar®) may be considered during pregnancy, if clinically needed. It is essential for patients with pre-existing or gestational diabetes to maintain good metabolic control throughout pregnancy to prevent adverse outcomes associated with hyperglycemia. Insulin requirements may decrease during the first trimester and generally increase during the second and third trimesters. Immediately after delivery, insulin requirements decline rapidly (increased risk of hypoglycemia).

It is unknown whether insulin glargine is excreted in human milk. No metabolic effects of ingested insulin glargine on the breastfed In vitro studies indicate that the affinity of insulin glargine and its metabolites M1 (21A-Gly-insulin) and M2 (

Breastfeeding women may require adjustments in insulin dose and diet.

Fertility

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

5.7 Effect on ability to drive and use machines

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 using machines) 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 machines in these circumstances.

Summary of safety profile

Hypoglycemia (very common), in general the most frequent adverse reaction of insulin therapy, may occur if the insulin dose is too high in relation to the insulin requirement (see section 5.4).

The following related adverse reactions from clinical trials are listed below as MedDRA preferred term by system organ class and in order of decreasing incidence (very common: ≥1/10; common: ≥1/100 to <1/10; uncommon: ≥1/1,000 to <1/100; rare: ≥1/10,000 to <1/1,000; Figure 1: Activity profile in patients with type 1 diabetes very rare: <1/10,000) and not known (cannot be estimated from the available data).

MedDRA system organ classes	Very common	Common	Uncommon	Rare	Very rare	Not known
Immune system disorders						
Allergic reactions				Х		
Metabolism and nutrition disorders	;					
Hypoglycemia	X					
Nervous system disorders						
Dysgeusia					X	
Eyes disorders						
Visual impairment				Х		
Retinopathy				Х		
Skin and subcutaneous tissue disc	orders					
Lipohypertrophy		Х				
Lipoatrophy			Х			
Cutaneous amyloidosis						X
Musculoskeletal and connective tis	sue disorders					
Myalgia					X	
General disorders and administrati	on site conditions					
Injection site reactions		Х				
Edema		İ		Х		

Description of selected adverse reactions

Metabolism and nutrition disorders Severe hypoglycemic attacks, especially if recurrent, may lead to neurological damage. Prolonged or severe hypoglycemic episodes may be life-threatening. In many patients, the signs and symptoms of neuroglycopenia are preceded by signs of adrenergic counter-regulation

Generally, the greater and more rapid the decline in blood glucose, the more marked is the phenomenon of counter-regulation and its symptoms Immune system disorders Immediate-type allergic reactions to insulin are rare. Such reactions to insulin (including insulin glargine) or the excipients may, for example,

be associated with generalized skin reactions, angio-edema, bronchospasm, hypotension and shock, and may be life-threatening. A marked change in glycemic control may cause temporary visual impairment, due to temporary alteration in the turgidity and refractive

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

Skin and subcutaneous tissue disorders Lipodystrophy and cutaneous amyloidosis may occur at the injection site and delay local insulin absorption. Continuous rotation of the

injection site within the given injection area may help to reduce or prevent these reactions (see section 4.4). General disorders and administration site conditions Injection site reactions include redness, pain, itching, hives, swelling, or inflammation. Most minor reactions to insulins at the injection site

usually resolve in a few days to a few weeks. Rarely, insulin may cause sodium retention and edema particularly if previously poor metabolic control is improved by intensified insulin therapy

In general, the safety profile for children and adolescents (≤ 18 years of age) is similar to the safety profile for adults. The adverse reaction reports received from post marketing surveillance included relatively more frequent injection site reactions (injection site pain, injection site reaction) and skin reactions (rash, urticaria) in children and adolescents (≤ 18 years of age) than in adults. Clinical study safety data

Reporting of suspected adverse reactions

are not available for children under 2 years

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions (see section 12) 5.9 Overdose

nsulin overdose may lead to severe and sometimes long-term and life-threatening hypoglycemia.

Mild episodes of hypoglycemia can usually be treated with oral carbohydrates. Adjustments in dose of the medicinal product, meal patterns

More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/ subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycemia may recur after apparent clinical recovery.

6. Pharmacological Properties 6.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Drugs used in diabetes, insulins and analogues for injection, long-acting. ATC Code: A10AE04. Insulin Glargine (Basaglar®) is a biosimilar medicinal product. Detailed information is available on the website of the European Medicines

Insulin glargine is a human insulin analogue designed to have a low solubility at neutral pH. It is completely soluble at the acidic pH of the Insulin glargine (Basaglar®) injection solution (pH 4). After injection into the subcutaneous tissue, the acidic solution is neutralized leading to formation of micro-precipitates from which small amounts of insulin glargine are continuously released, providing a smooth, peakless,

predictable concentration/time profile with a prolonged duration of action Insulin glargine is metabolised into 2 active metabolites M1 and M2 (see section 6.2).

one of human insulin.

IGF-1 receptor binding: The affinity of insulin glargine for the human IGF-1 receptor is approximately 5 to 8-fold greater than that of human insulin (but approximately 70 to 80-fold lower than the one of IGF-1), whereas M1 and M2 bind the IGF-1 receptor with slightly lower affinity compared to human insulin

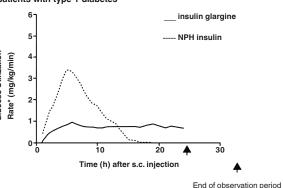
The total therapeutic insulin concentration (insulin glargine and its metabolites) found in type 1 diabetic patients was markedly lower than what would be required for a half maximal occupation of the IGF-1 receptor and the subsequent activation of the mitogenic-proliferative hway initiated by the IGF-1 receptor. Physiological concentrations of endogenous IGF-1 may activate the mitogenic-proliferative pathway however, the therapeutic concentrations found in insulin therapy, including in insulin glargine therapy, are considerably lower than the pharmacological concentrations required to activate the IGF-1 pathway

Pharmacodynamic effects

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

In clinical pharmacology studies, intravenous insulin glargine and human insulin have been shown to be equipotent when given at the same doses. As with all insulins, the time course of action of insulin glargine may be affected by physical activity and other variables. In euglycemic clamp studies in healthy subjects or in patients with type 1 diabetes, the onset of action of subcutaneous insulin glargine

was slower than with human NPH insulin, its effect profile was smooth and peakless, and the duration of its effect was prolonged. The following graph shows the results from a study in patients:



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

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

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

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

Effects of insulin glargine (once daily) on diabetic retinopathy were evaluated in an open-label 5-year NPH-controlled study (NPH given bid) in 1024 type 2 diabetic patients in which progression of retinopathy by 3 or more steps on the Early Treatment Diabetic Retinopathy dy (ETDRS) scale was investigated by fundus photography. No significant difference was seen in the progression of diabetic retinopathy

The ORIGIN (Outcome Reduction with Initial Glargine INtervention) study was a multicenter, randomized, 2x2 factorial design study conducted in 12,537 participants at high cardiovascular (CV) risk with impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) l% of participants) or type 2 diabetes mellitus treated with ≤1 antidiabetic oral agent (88% of participants). Participants were randomized (1:1) to receive insulin glargine (n=6264), titrated to reach FPG ≤95 mg/dL (5.3 mM), or standard care (n=6273).

The first co-primary efficacy outcome was the time to the first occurrence of CV death, non-fatal myocardial infarction (MI), or nonfatal stroke, and the second co-primary efficacy outcome was the time to the first occurrence of any of the first co-primary events, or revascularization procedure (coronary, carotid, or peripheral), or hospitalization for heart failure.

Secondary endpoints included all-cause mortality and a composite microvascular outcome

when insulin glargine was compared to NPH insulin.

Insulin glargine did not after the relative risk for CV disease and CV mortality when compared to standard of care. There were no differences between insulin glargine and standard care for the two co-primary outcomes; for any component endpoint comprising these outcomes; for all-cause mortality; or for the composite microvascular outcome.

Mean dose of insulin glargine by study end was 0.42 U/kg. At baseline, participants had a median HbA1c value of 6.4% and median on-treatment HbA1c values ranged from 5.9 to 6.4% in the insulin glargine group, and 6.2% to 6.6% in the standard care group throughout the duration of follow-up. The rates of severe 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 6-year study, 42% of the insulin glargine group did not experience any hypoglycemia. At the last on-treatment visit, there was a mean increase in body weight from baseline of 1.4 kg in the insulin glargine group and a mean decrease of 0.8 kg in the standard care group.

Pediatric population In a randomized, controlled clinical study, pediatric patients (age range 6 to 15 years) with type 1 diabetes (n=349) were treated for 28 weeks with a basal-bolus insulin regimen where regular human insulin was used before each meal. Insulin glargine was administered once daily at bedtime and NPH human insulin was administered once or twice daily. Similar effects on glycohaemoglobin and the incidence o symptomatic hypoglycemia were observed in both treatment groups, however fasting plasma glucose decreased more from baseline in

the insulin glargine group than in the NPH group. There was less severe hypoglycemia in the insulin glargine group as well. One hundred forty-three of the patients treated with insulin glargine in this study continued treatment with insulin glargine in an uncontrolled extension study with mean duration of follow-up of 2 years. No new safety signals were seen during this extended treatment with insulin glargine.

A crossover study comparing insulin glargine plus lispro insulin to NPH plus regular human insulin (each treatment administered for 16 weeks in random order) in 26 adolescent type 1 diabetic patients aged 12 to 18 years was also performed. As in the pediatric study described above, fasting plasma glucose reduction from baseline was greater in the insulin glargine group than in the NPH group.

HbA1c changes from baseline were similar between treatment groups; however blood glucose values recorded overnight were significantly higher in the insulin glargine/ lispro group than the NPH/regular group, with a mean nadir of 5.4 mM vs. 4.1 mM. Correspondingly, the incidences of nocturnal hypoglycemia were 32 % in the insulin glargine / lispro group vs. 52 % in the NPH / regular group A 24-week parallel group study was conducted in 125 children with type 1 diabetes mellitus aged 2 to 6 years, comparing insulin glargine given once daily in the morning to NPH insulin given once or twice daily as basal insulin. Both groups received bolus insulin before meals

increase of hypoglycemic events with insulin glargine [insulin glargine: NPH rate ratio (95% CI) = 1.18 (0.97-1.44)]. Glycohaemoglobin and glucose variabilities were comparable in both treatment groups. No new safety signals were observed in this trial.

In healthy subjects and diabetic patients, insulin serum concentrations indicated a slower and much more prolonged absorption and showed a lack of a peak after subcutaneous injection of insulin glargine in comparison to human NPH insulin. Concentrations were thus onsistent with the time profile of the pharmacodynamics activity of insulin glargine. Figure 1 shows the activity profiles over time of insulin glargine and NPH insulin

Insulin glargine injected once daily will reach steady state levels in 2-4 days after the first dose. Biotransformation

is the metabolite M1. The exposure to M1 increases with the administered dose of insulin glargine.

The pharmacokinetic and pharmacodynamics 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 ectable their concentration was independent of the administered dose of insulin glargine

When given intravenously the elimination half-life of insulin glargine and human insulin were comparable.

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

Pediatric population Pharmacokinetics in children aged 2 to less than 6 years with type 1 diabetes mellitus was assessed in one clinical study (see section 6.1). Plasma trough levels of insulin glargine and its main M1 and M2 metabolites were measured in children treated with insulin glargine, revealing plasma concentration patterns similar to adults, and providing no evidence for accumulation of insulin glargine or its metabolites

with chronic dosing. 6.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity,

genotoxicity, carcinogenic potential, toxicity to reproduction. 7. Pharmaceutical Particulars

7.1 List of Excipients Metacresol (2.7 mg/mL) as preservative

Hydrochloric acid (for pH adjustment)

Sodium hydroxide (for pH adjustment) Water for injection

7.2 Major Incompatibilities

This medicinal product must not be mixed with other medicinal products. 7.3 Shelf Life

Shelf life after first use

The medicinal product may be stored for a maximum of 28 days up to 30°C and away from direct heat or direct light. Pens in use must not be stored in the refrigerator The pen cap must be put back on the pen after each injection in order to protect from light.

7.4 Special Precautions for Storage

o not store Insulin Glargine (Basaglar® KwikPen) next to the freezer compartment or a freezer pack. Keep the pre-filled pen in the outer carton in order to protect from light.

Store at room temperature up to 30°C during use.

Store in a refrigerator at 2°C to 8°C until use.

Do not freeze. Do not use if it has been frozer

7.5 Nature and contents of container

3 mL solution in a cartridge (type1 clear glass) with a plunger (chlorobutyl rubber) and a disc seal (laminate of polyisoprene and chlorobutylrubber) with aluminum seal.

The cartridge is sealed in a disposable pen injector. Box of 1's and 5's.

7.6 Special precautions for disposal and other handling Insulin Glargine (Basaglar®) must not be mixed with any other insulin or medicinal product or diluted. Mixing or diluting can change its

time/action profile and mixing can cause precipitation. Insulin Glargine (Basaglar® KwikPen) Inspect the cartridge before use. It must only be used if the solution is clear, colorless, with no solid particles visible, and if it is of water-like

onsistency. Since Insulin Glargine (Basaglar®) is a solution, it does not require re-suspension before use Insulin Glargine (Basaglar®) must not be mixed with any other insulin or diluted. Mixing or diluting can change its time/action profile and

mixing can cause precipitation. Empty pens must never be reused and must be properly discarded.

To prevent the possible transmission of disease, each pen must be used by one patient only. Insulin label must always be checked before each injection to avoid medication errors between Insulin Glargine (Basaglar®) and other

The patient should be advised to read the instructions for use included in the package leaflet carefully before using Insulin Glargine

8. Availability

(Basaglar® KwikPen)

9. Manufactured by

Eli Lilly Italia S.p.A. V. Gramsci, 731-733-50019 Sesto Fiorentino (Firenze), Italy

Lilly France (Fegersheim) Zone Industrielle, 2 rue du Colonel Lilly, Fegersheim, 67640, France

10. Imported and Distributed by

Zuellig Pharma Corporat Km. 14 West Service Rd., South Superhighway corner Edison Ave., Sun Valley, Parañaque City, Philippines

Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

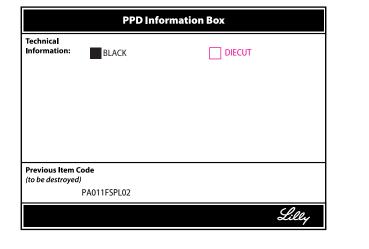
12. ADR Reporting Statement

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph The primary aim of demonstrating non-inferiority of insulin glargine to NPH in all hypoglycemia was not met and there was a trend to an Seek medical attention immediately at the first sign of any adverse drug reaction.

> 13. Registration number 14. Date of First Authorization

19 August 2016 15. Date of Revision of Package Insert

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Instructions for Use Insulin Glargine

Basaglar® KwikPen

100 units/mL Solution for Injection



PLEASE READ THESE INSTRUCTIONS BEFORE USE

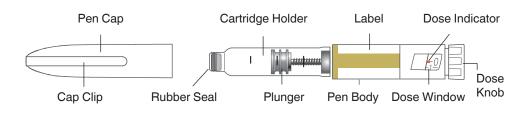
Read the Instructions for Use before you start taking Insulin Glargine (Basaglar® KwikPen) and each time you get another Insulin Glargine (Basaglar® KwikPen). There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or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

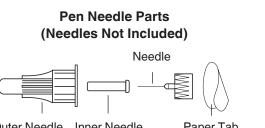
Insulin Glargine (Basaglar® KwikPen) "Pen" is a disposable prefilled pen containing 300 units of Insulin Glargine (Basaglar® KwikPen) You can give yourself multiple doses using one Pen. The Pen dials 1 unit at a time. You can give from 1 to 80 units in a single injection. If your dose is more than 80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

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

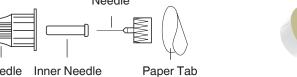
This Pen is not recommended for use by the blind or visually impaired without the help of someone trained to use the Pen.

KwikPen Parts





Dose Knob with green ring



Outer Needle Inner Needle Shield

How to recognize your Insulin Glargine (Basaglar® KwikPen):

 Pen color: Light grey

 Dose Knob: Light grey with green ring on the end Labels:

Light grey with green color bars

Supplies needed to give your injection:

- Insulin Glargine (Basaglar® KwikPen)
- KwikPen compatible Needle (BD Pen Needles recommended)
- Alcohol swab

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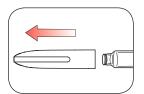
Preparing your Pen

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

Step 1:

 Pull the Pen Cap straight off. Do not remove the Pen Label.

 Wipe the Rubber Seal with an alcohol swab. Insulin Glargine (Basaglar®) should look clear and colorless. **Do not** use if it is cloudy, colored, or has particles or clumps in it.



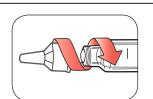
Step 2:

- Select a new Needle.
- Pull off the Paper Tab from the Outer Needle Shield.

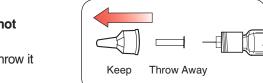


Step 3:

 Push the capped Needle straight onto the Pen and twist the Needle on until it is tight.



- Pull off the Outer Needle Shield. Do not
- throw it away. Pull off the Inner Needle Shield and throw it



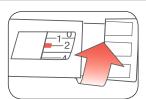
Priming your Pen

Prime before each injection.

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

Step 5:

• To prime your Pen, turn the Dose Knob to select 2 units.



 Hold your Pen with the Needle pointing up. Tap the Cartridge Holder gently to collect air bubbles at the top.

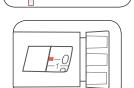


 Continue holding your Pen with Needle pointing up. Push the Dose Knob in until it stops, and "0" is seen in the Dose Window. Hold the Dose Knob in and count to 5 slowly. You should see insulin at the tip of the



- If you **do not** see insulin, repeat the priming steps, but not more than 4 times.

- If you **still do not** see insulin, change the Needle and repeat the priming steps. Small air bubbles are normal and will not affect your dose.



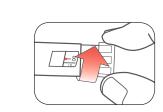
Selecting your dose

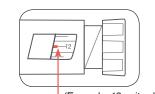
- You can give from 1 to 80 units in a single injection.
- If your dose is more than 80 units, you will need to give more than one injection.
- If you need help deciding how to divide up your dose, ask your healthcare provider.
- You should use a new Needle for each injection and repeat the priming step.

Step 8:

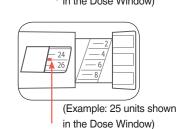
 Turn the Dose Knob to select the number of units you need to inject. The Dose Indicator should line up with your dose.

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





(Example: 12 units shown in the Dose Window)



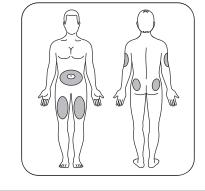
- The Pen will not let you dial more than the number of units left in the Pen.
- If you need to inject more than the number of units left in the Pen, you may either:
- inject the amount left in your Pen and then use a new Pen to give the rest of your dose, or
- get a new Pen and inject the full dose.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

Giving your injection

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

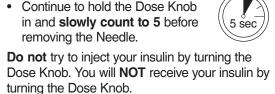
Choose your injection site.

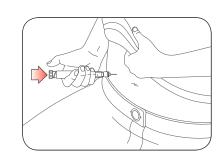
- Insulin Glargine (Basaglar® KwikPen) is injected under the skin (subcutaneously) of your stomach area, buttocks, upper legs or upper arms.
- Wipe the skin with an alcohol swab, and let the injection site dry before you inject your dose.



Step10:

- Insert the Needle into your skin.
- Push the Dose Knob all the way in.
- Continue to hold the Dose Knob in and **slowly count to 5** before removing the Needle.





Step 11:

- Pull the Needle out of your skin.
- A drop of insulin at the Needle tip is normal. It will not affect your dose.
- Check the number in the Dose Window
- If you see "0" in the Dose window, you have received the full amount you dialed.
- If you do not see "0" in the Dose window, do not redial. Insert the needle into your skin
- and finish your injection. - If you **still** do not think you received the full amount you dialed for your injection, do not **start over or repeat that injection.** Monitor your blood glucose as instructed by your
- healthcare provider. - If you normally need to give 2 injections for your full dose, be sure to give your second

The plunger only moves a little with each injection, and you may not notice that it moves.

If you see blood after you take the Needle out of your skin, press the injection site lightly with a piece of gauze or an alcohol swab. **Do not** rub the area.

After your injection

Step 12:

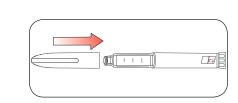
Carefully replace the Outer Needle Shield.



- Unscrew the capped Needle and dispose of it as described below (see **Disposing of Pens and Needles** section).
- Do not store the Pen with the Needle attached to prevent leaking, blocking the Needle, and air from entering the Pen.



 Replace the Pen Cap by lining up the Cap Clip with the Dose Indicator and pushing straight on.



Disposing of Pens and Needles

- Put used Needles in a sharps container or a hard plastic container with a secure lid. **Do not** throw needles directly into your household trash.
- The used Pen may be discarded in your household trash after you have removed the Needle.
- **Do not** recycle the filled sharps container.
- Ask your healthcare provider about options to dispose of the sharps container properly.
- The directions regarding needle handling are not intended to replace local, healthcare provider or institutional policies.

Storing your Pen

Unused Pens

In-use Pen

- Store unused Pens in the refrigerator at 2°C to 8°C.
- **Do not** freeze Insulin Glargine (Basaglar® KwikPen). **Do not** use if it has been frozen. • Unused Pens may be used until the expiration date printed on the Label, if the Pen has

been kept in the refrigerator.

• Store the Pen you are currently using at room temperature (up to 30°C) and away from

• Throw away the Pen you are using after 28 days, even if it still has insulin left in it.

Keep your Pen and Needles out of the sight and reach of children.

General information about the safe and effective use of your Pen

- Do not use your Pen if any part looks broken or damaged.
- Always carry an extra Pen in case yours is lost or damaged.

Troubleshooting

- If you cannot remove the Pen Cap, gently twist the cap back and forth, and then pull the cap straight off.
- If the Dose Knob is hard to push:
- Pushing the Dose Knob more slowly will make it easier to inject.

Your Needle may be blocked. Put on a new Needle and prime the Pen.

You may have dust, food, or liquid inside the Pen. Throw the Pen away and get a new

Imported and Distributed by: Zuellig Pharma Corporation Km. 14 West Service Rd.

Document Revision Date: October 2022

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23/11/2022 06:11

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