X	Proposed truth_v1_	X	Internal reviewer_DS__	☐	Medical reviewer___IJ___
X	Internal creator_MH_	☐	Approval for Submission Date _____	☐	Marketing reviewer_____

BASAGLAR KWIKPEN
Insulin glargine

1. NAME OF THE MEDICINAL PRODUCT
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 6.1.

3. PHARMACEUTICAL FORM
Solution for injection. (injection) in pre-filled pen (KwikPen).
Clear, colourless solution.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
For the treatment of adults, adolescent, and children of 6 years or above with diabetes mellitus, where treatment with insulin is required.

4.2 Posology and method of administration
Posology
BASAGLAR contains insulin glargine, an insulin analogue and has a prolonged duration of action.
BASAGLAR should be administered once daily at any time but at the same time each day.
The dose regimen (dose and timing) should be individually adjusted. In patients with type 2 diabetes mellitus, 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 5.1).

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

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.

Renal impairment
In patients with renal impairment, insulin requirements may be diminished due to reduced insulin metabolism.
The effect of renal impairment on the pharmacokinetics of BASAGLAR has not been studied.

Hepatic impairment
In patients with hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism.
The effect of hepatic impairment on the pharmacokinetics of BASAGLAR has not been studied.

Paediatric population
Safety and efficacy of insulin glargine have been established in adolescents and children aged 6 years and older. Currently available data are described in sections 4.8, 5.1 and 5.2.

Switch from other insulins to BASAGLAR
When changing from a treatment regimen with an intermediate or long-acting insulin to a regimen with 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).

If converting from Lantus to BASAGLAR, the initial dose can be made on a unit-to-unit basis.

Switch from twice daily NPH insulin to BASAGLAR
To reduce the risk of nocturnal and early morning hypoglycaemia, patients who are changing their basal insulin regimen from a twice daily NPH insulin to a once daily regimen with BASAGLAR should reduce their daily dose of basal insulin by 20-30 % during the first weeks of treatment.

Switch from insulin glargine 300 units/ml to BASAGLAR
BASAGLAR and Lantus XR (insulin glargine 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 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.

As with other insulin analogues, patients with high insulin doses because of antibodies to human insulin may experience an improved insulin response with BASAGLAR.

Close metabolic monitoring is recommended during the transition 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 hypoglycaemia or hyperglycaemia (see section 4.4). The dose and time of administration should be determined by the physician.

Method of administration
BASAGLAR is administered subcutaneously.

BASAGLAR 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 hypoglycaemia.

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 the same region in order to reduce the risk of lipodystrophy and cutaneous amyloidosis (see section 4.4 and 4.8).

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 consistency.
The insulin label must always be checked before each injection to avoid medication errors between BASAGLAR and other insulins.

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

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

Instructions for Use/Handling

To prevent the possible transmission of disease, each pen must be used by one patient only, even if the needle is changed.

Before using BASAGLAR solution for injection in a pre-filled pen, the instructions for use included in the package leaflet must be read carefully.

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use
BASAGLAR is not the insulin of choice for the treatment of diabetic ketoacidosis. Instead, regular insulin administered intravenously is recommended in such cases.

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

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.

Hypoglycaemia

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

Particular caution should be exercised, and intensified blood glucose monitoring is advisable in patients in whom hypoglycaemic episodes might 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 hypoglycaemia) as well as in patients with proliferative retinopathy, particularly if not treated with photocoagulation (risk of transient amaurosis following hypoglycaemia).

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

- in whom glycaemic control is markedly improved,
- in whom hypoglycaemia develops gradually,
- who are elderly,
- after transfer from animal insulin to human insulin,
- in whom an autonomic neuropathy is present,
- with a long history of diabetes,
- suffering from a psychiatric illness,
- receiving concurrent treatment with certain other medicinal products (see section 4.5).

Such situations may result in severe hypoglycaemia (and possibly loss of consciousness) prior to the patient's awareness of hypoglycaemia.

The prolonged effect of subcutaneous insulin glargine may delay recovery from hypoglycaemia.

If normal or decreased values for glycated haemoglobin are noted, the possibility of recurrent, unrecognised (especially nocturnal) episodes of hypoglycaemia must be considered.

Adherence of the patient to the dose and dietary regimen, correct insulin administration and awareness of hypoglycaemia symptoms are essential to reduce the risk of hypoglycaemia. Factors increasing the susceptibility to hypoglycaemia require particularly close monitoring and may necessitate dose adjustment. These include:

- change in the injection area,
- improved insulin sensitivity (e.g., by removal of stress factors),
- unaccustomed, increased or prolonged physical activity,
- intercurrent illness (e.g. vomiting, diarrhoea),
- inadequate food intake,
- missed meals,

- alcohol consumption,
- certain uncompensated endocrine disorders, (e.g. in hypothyroidism and in anterior pituitary or adrenocortical insufficiency),
- concomitant treatment with certain other medicinal products.

Injection technique

Patients 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 glycaemic 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 hypoglycaemia. Blood glucose monitoring is recommended after the change in the injection site, and dose adjustment of antidiabetic medications may be considered.

Intercurrent illness

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

Insulin antibodies

Insulin administration may cause insulin antibodies to form. In rare cases, the presence of such insulin antibodies may necessitate adjustment of the insulin dose in order to correct a tendency to hyper- or hypoglycaemia (see section 5.1).

Medication errors

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

Combination of BASAGLAR with pioglitazone

Thiazolidinediones (TZDs), which are peroxisome proliferator-activated receptor (PPAR)-gamma agonists, can cause dose-related fluid retention, particularly when used in combination with insulin. Fluid retention may lead to or exacerbate heart failure. Patients treated with insulin, including BASAGLAR, and a PPAR-gamma agonist should be observed for signs and symptoms of heart failure. If heart failure develops, it should be managed according to current standards of care, and discontinuation or dose reduction of the PPAR-gamma agonist must be considered.

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

Hypokalemia
All insulin products, including BASAGLAR, cause a shift in potassium from the extracellular to intracellular space, possibly leading to hypokalemia. Untreated hypokalemia may cause respiratory paralysis, ventricular arrhythmia, and death. Monitor potassium levels in patients at risk for hypokalemia if indicated (e.g., patients using potassium-lowering medications, patients taking medications sensitive to serum potassium concentrations).

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

4.5 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-glucose-lowering effect and increase susceptibility to hypoglycaemia include oral antidiabetic medicinal products, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, pentoxifylline, propoxyphene, salicylates, somatostatin anologues and sulphonamide antibiotics.

Substances that may reduce the blood-glucose-lowering effect include corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, oestrogens, progestogens, phenothiazine derivatives, somatropin, sympathomimetic medicinal products (e.g. epinephrine [adrenaline], salbutamol, 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 hypoglycaemia, which may sometimes be followed by hyperglycaemia.

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation may be reduced or absent.

4.6 Fertility, pregnancy and lactation
Pregnancy
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.

Animal data do not indicate reproductive toxicity.

The use of 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 hyperglycaemia. Insulin requirements may decrease during the first trimester and generally increase during the second and third

trimesters. Immediately after delivery, insulin requirements decline rapidly (increased risk of hypoglycaemia). Careful monitoring of glucose control is essential.

Breast-feeding
It is unknown whether insulin glargine is excreted in human milk. No metabolic effects of ingested insulin glargine on the breast-fed newborn/infant are anticipated since insulin glargine as a peptide is digested into amino acids in the human gastrointestinal tract.

Breast-feeding women may require adjustments in insulin dose and diet.

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

4.7 Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or using machines).

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. It should be considered whether it is advisable to drive or operate machines in these circumstances.

4.8 Undesirable effects

Summary of safety profile
Hypoglycaemia (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 4.4).

Tabulated list of adverse reactions
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; very rare: <1/10,000 and not known (cannot be estimated from the available data).

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

MedDRA system organ classes	**Very common**	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not known**
Immune system disorders						
Allergic reactions				X		
Metabolism and nutrition disorders						
Hypoglycaemia	X					
Nervous system disorders						
Dysgeusia					X	

Eyes disorders						
Visual impairment				X		
Retinopathy				X		
Skin and subcutaneous tissue disorders						
Lipohypertrophy		X				
Lipoatrophy			X			
Cutaneous						X
Musculoskeletal and connective tissue disorders						
Myalgia					X	
General disorders and administration site conditions						
Injection site reactions		X				
Oedema				X		

Description of selected adverse reactions

Metabolism and nutrition disorders
Severe hypoglycaemic attacks, especially if recurrent, may lead to neurological damage. Prolonged or severe hypoglycaemic episodes may be life-threatening. In many patients, the signs and symptoms of neuroglycopenia are preceded by signs of adrenergic counter-regulation. Generally, the greater and more rapid the decline in blood glucose, the more marked is the phenomenon of counter-regulation and its symptoms.

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

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

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

Skin and subcutaneous tissue disorders
Lipodystrophy and cutaneous amyloidosis may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions (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 oedema particularly if previously poor metabolic control is improved by intensified insulin therapy.

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system in http://e-meso.pom.go.id/ or via Adverse Drug Reaction (ADR) form (Formulir Kuning MESO).

4.9 Overdose
Symptoms
Insulin overdose may lead to severe and sometimes long-term and life-threatening hypoglycaemia.

Management
Mild episodes of hypoglycaemia can usually be treated with oral carbohydrates. Adjustments in dose of the medicinal product, meal patterns, or physical activity may be needed.

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

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Drugs used in diabetes, insulins and analogues for injection, long-acting. ATC Code: A10AE04.

BASAGLAR is a biosimilar medicinal product.

Mechanism of action
Insulin glargine is a human insulin analogue designed to have a low solubility at neutral pH. It is completely soluble at the acidic pH of the BASAGLAR injection solution (pH 4). After injection into the subcutaneous tissue, the acidic solution is neutralised leading to formation of micro-precipitates from which small amounts of insulin glargine are continuously released, providing a smooth, peakless, predictable concentration/time profile with a prolonged duration of action.

Insulin glargine is metabolised into 2 active metabolites M1 and M2 (see section 5.2).

Insulin receptor binding
In vitro studies indicate that the affinity of insulin glargine and its metabolites M1 and M2 for the human insulin receptor is similar to the one of human insulin.

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

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

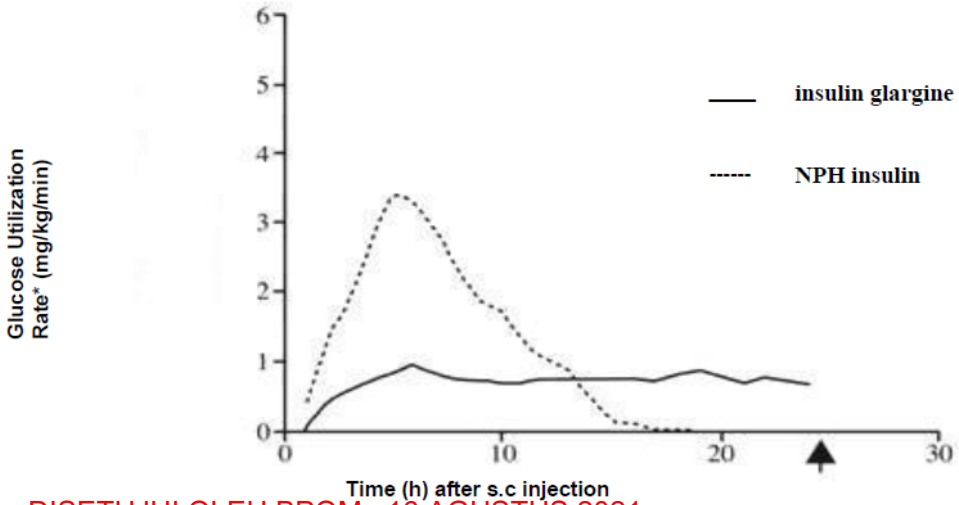
Pharmacodynamic effects
The primary activity of insulin, including insulin glargine, is regulation of glucose metabolism. Insulin and its analogues lower blood glucose levels by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. 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 euglycaemic clamp studies in healthy subjects or in patients with type 1 diabetes, the onset of action of subcutaneous insulin glargine was slower than with human NPH insulin, its effect profile was smooth and peakless, and the duration of its effect was prolonged.

The following graph shows the results from a study in patients:

Figure 1: Activity profile in patients with type 1 diabetes



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

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

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

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 Study (ETDRS) scale was investigated by fundus photography. No significant difference was seen in the progression of diabetic retinopathy when insulin glargine was compared to NPH insulin.

The ORIGIN (Outcome Reduction with Initial Glargine INtervention) study was a multicenter, randomised, 2x2 factorial design study conducted in 12,537 participants at high cardiovascular (CV) risk with impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) (12% of participants) or type 2 diabetes mellitus treated with ≤1 antidiabetic oral agent (88% of participants). Participants were randomised (1:1) to receive insulin glargine (n=6,264), titrated to reach FPG ≤95 mg/dL (5.3 mM), or standard care (n=6,273).

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

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

Insulin glargine did not alter the relative risk for CV disease and CV mortality when compared to standard of care. There were no differences between insulin glargine and standard care for the two co-

primary outcomes; for any component endpoint comprising these outcomes; for all-cause mortality; or for the composite microvascular outcome.

Mean dose of insulin glargine by study end was 0.42 U/kg. At baseline, participants had a median HbA1c value of 6.4% and median on-treatment HbA1c values ranged from 5.9 to 6.4% in the insulin glargine group, and 6.2% to 6.6% in the standard care group throughout the duration of follow-up. The rates of severe hypoglycaemia (affected participants per 100 participant years of exposure) were 1.05 for insulin glargine and 0.30 for standard care group and the rates of confirmed non-severe hypoglycaemia were 7.71 for insulin glargine and 2.44 for standard care group. Over the course of this 6-year study, 42% of the insulin glargine group did not experience any hypoglycaemia.

At the last on-treatment visit, there was a mean increase in body weight from baseline of 1.4 kg in the insulin glargine group and a mean decrease of 0.8 kg in the standard care group.

Paediatric population

In a randomised, controlled clinical study, paediatric patients (age range 6 to 15 years) with type 1 diabetes (n=349) were treated for 28 weeks with a basal-bolus insulin regimen where regular human insulin was used before each meal. Insulin glargine was administered once daily at bedtime and NPH human insulin was administered once or twice daily. Similar effects on glycohaemoglobin and the incidence of symptomatic hypoglycaemia were observed in both treatment groups, however fasting plasma glucose decreased more from baseline in the insulin glargine group than in the NPH group. There was less severe hypoglycaemia in the insulin glargine group as well. One hundred forty three of the patients treated with insulin glargine in this study continued treatment with insulin glargine in an uncontrolled extension study with mean duration of follow-up of 2 years. No new safety signals were seen during this extended treatment with insulin glargine.

A crossover study comparing insulin glargine plus lispro insulin to NPH plus regular human insulin (each treatment administered for 16 weeks in random order) in 26 adolescent type 1 diabetic patients aged 12 to 18 years was also performed. As in the paediatric study described above, fasting plasma glucose reduction from baseline was greater in the insulin glargine group than in the NPH group. HbA_{1c} changes from baseline were similar between treatment groups; however blood glucose values recorded overnight were significantly higher in the insulin glargine/ lispro group than the NPH/regular group, with a mean nadir of 5.4 mM vs. 4.1 mM. Correspondingly, the incidences of nocturnal hypoglycaemia were 32 % in the insulin glargine / lispro group vs. 52 % in the NPH/ regular group.

5.2 Pharmacokinetic properties

Absorption

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

After subcutaneous injection in diabetic patients, insulin glargine is rapidly metabolised 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 insulin glargine.

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

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

Paediatric population

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.

5.3 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.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Zinc oxide
Metacresol
Glycerol
Hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities
This medicinal product must not be mixed with other medicinal products.

6.3 Shelf life
2 years.

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.

6.4 Special precautions for storage

Before use

Store in a refrigerator (2°C - 8°C).

Do not freeze.

Do not store BASAGLAR next to the freezer compartment or a freezer pack.

Keep the pre-filled pen in the outer carton in order to protect from light.

In use

For storage conditions after first opening of this medicinal product, see section 6.3.

6.5 Nature and contents of container

3 mL solution in a cartridge (type 1 colourless glass) with a plunger (halobutyl rubber) and a disc seal (laminate of polyisoprene and halobutyl rubber) with aluminium seal.

The cartridge is sealed in a disposable pen injector.

Pack of 5 pens.
Needles are not included in the pack.

6.6 Special precautions for disposal and other handling

BASAGLAR must not be mixed with any other insulin or medicinal products or diluted. Mixing or diluting can change its time/action profile and mixing can cause precipitation.

Inspect the cartridge before use. It must only be used if the solution is clear, colourless, with no solid particles visible, and if it is of water-like consistency. Since BASAGLAR is a solution, it does not require re-suspension before use.

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 and other insulins (see section 4.4).

The patient should be advised to read the instructions for use included in the package leaflet carefully before using BASAGLAR solution for injection in pre-filled pen.

7. PRESENTATION

BASAGLAR KWIKPEN 100 IU/ml, Box 5 prefilled pens @ 3 mL Reg. No.: DKI2088802243A1

HARUS DENGAN RESEP DOKTER

Manufactured by
Eli Lilly Italia S.p.A.,
Via Gramsci, 731 – 733
50019 Sesto Fiorentino – Italy

Assembled, packed and released by:
Lilly France, S.A.S
F-67640 Fegersheim, France

Registered by:
PT Pyridam Farma Tbk.
Kabupaten Cianjur, Indonesia.

X	Proposed truth_v1	X	Internal reviewer__DS__	X	Medical reviewer___IJ___
X	Internal creator_MH_		Approval for Submission		Marketing reviewer_____
			Date _____		

BASAGLAR KWIKPEN 100 unit /ml

Insulin glargine

Larutan injeksi di dalam pen yang sudah terisi (*pre-filled pen*)

Bacalah seluruh leaflet ini dengan saksama termasuk Petunjuk Penggunaan (*Instruction for Use*) BASAGLAR KWIKPEN sebelum Anda mulai menggunakan obat ini karena leaflet ini berisikan informasi penting untuk Anda.

- Simpanlah leaflet ini. Anda mungkin perlu untuk membacanya kembali suatu saat nanti.
- Jika Anda memiliki pertanyaan lebih lanjut, hubungi dokter, apoteker atau perawat.
- Obat ini diresepkan hanya untuk Anda. Jangan memberikannya kepada orang lain karena bisa jadi akan mencelakakan mereka, walaupun gejala penyakit yang mereka derita sama dengan Anda.
- Jika Anda merasakan adanya efek samping, sampaikan kepada dokter, apoteker atau perawat Anda. Ini termasuk jika Anda mungkin mengalami efek samping yang tidak tercantum di leaflet ini pada bagian 4.

Informasi apa saja yang terdapat pada leaflet ini

1. Apakah BASAGLAR dan kegunaannya

BASAGLAR mengandung insulin glargine. Sebuah insulin buatan yang sangat menyerupai dengan insulin manusia.

BASAGLAR digunakan untuk terapi diabetes melitus pada orang dewasa, remaja dan anak-anak di atas 6 tahun ketika terapi dengan insulin diperlukan.

Diabetes mellitus adalah suatu penyakit dimana tubuh Anda tidak dapat memproduksi insulin dalam jumlah yang cukup atau adanya ketidakmampuan insulin untuk mengkontrol kadar gula dalam darah. Insulin glargine memiliki aksi yang lama/ panjang dan stabil dalam menurunkan kadar gula darah.

2. Apa saja yang perlu Anda ketahui sebelum menggunakan BASAGLAR

Jangan menggunakan BASAGLAR

Jika Anda alergi terhadap insulin glargine atau bahan-bahan tambahan lainnya (tercantum pada bagian 6).

Peringatan dan Perhatian
Hubungi dokter, apoteker atau perawat Anda sebelum menggunakan BASAGLAR.
Ikuti dengan baik petunjuk cara pemakaian, pengawasan/ monitoring (tes darah dan urin), pola makan dan aktivitas fisik (pekerjaan fisik dan olahraga) yang disampaikan oleh dokter.

Jika kadar gula darah Anda terlalu rendah (hipoglikemia), ikuti petunjuk penanganan hipoglikemia (terdapat dalam kotak di bagian akhir leaflet ini).

Melakukan Perjalanan
Sebelum bepergian, konsultasikan terlebih dahulu dengan dokter Anda. Anda dapat membicarakan hal-hal berikut:
- ketersediaan insulin Anda di negara yang akan Anda kunjungi,
- pasokan insulin, alat suntik, dll
- cara penyimpanan insulin yang benar selama bepergian,
- pengaturan waktu makan dan penyuntikan insulin selama bepergian,
- kemungkinan efek yang timbul akibat perubahan zona waktu,
- kemungkinan adanya resiko kesehatan baru di negara yang akan dikunjungi,
- apa yang harus Anda lakukan pada keadaan darurat ketika Anda merasa tidak sehat atau menjadi sakit.

Penyakit dan Luka
Pada keadaan berikut, penanganan diabetes Anda mungkin akan memerlukan banyak perhatian (contohnya penyesuaian dosis insulin, tes darah dan urin):
- Jika Anda sedang sakit atau memiliki luka serius maka kadar gula darah Anda dapat meningkat (hiperglikemia).
- Jika Anda tidak makan dengan cukup maka kadar gula darah Anda dapat menjadi terlalu rendah (hipoglikemia)

Pada kebanyakan kejadian Anda akan membutuhkan bantuan dokter. **Pastikan Anda menghubungi dokter dengan segera.**

Jika Anda memiliki diabetes tipe 1 (diabetes mellitus yang tergantung pada insulin), jangan hentikan penggunaan insulin Anda dan lanjutkan konsumsi karbohidrat yang cukup. Selalu sampaikan kepada orang yang merawat Anda bahwa Anda memerlukan insulin.

Pengobatan dengan insulin dapat menyebabkan tubuh memproduksi antibodi terhadap insulin (zat yang bekerja melawan insulin). Namun, sangat jarang hal ini membutuhkan perubahan pada dosis insulin Anda.

Beberapa pasien dengan diabetes tipe 2 yang sudah berlangsung lama dan memiliki sakit jantung atau riwayat stroke yang diobati dengan pioglitazone dan insulin, mengalami perkembangan gagal jantung. Informasikan kepada dokter Anda sesegera mungkin jika Anda mengalami gejala gagal jantung seperti napas pendek yang tidak biasa atau peningkatan berat badan yang cepat atau terjadinya pembengkakan lokal (udem).

Obat-obatan Lain dan BASAGLAR

Beberapa obat dapat menyebabkan perubahan kadar gula darah (penurunan, peningkatan atau keduanya, tergantung pada kondisi). Pada setiap kejadian, mungkin diperlukan penyesuaian dosis insulin Anda untuk mencegah kadar gula darah menjadi terlalu rendah ataupun terlalu tinggi. Berhati-hatilah ketika Anda memulai atau menghentikan konsumsi obat-obatan yang lain.

Sampaikan kepada dokter atau apoteker jika Anda sedang, akhir-akhir ini atau mungkin akan mengkonsumsi obat-obatan lain. Sebelum mengkonsumsi suatu obat tanyakan kepada dokter Anda apakah obat tersebut dapat mempengaruhi kadar gula darah dan tindakan apa, jika ada, yang perlu dilakukan.

Obat-obatan yang dapat menyebabkan kadar gula darah menurun (hipoglikemia) antara lain:
- semua obat diabetes lainnya,
- *angiotensin converting enzyme* (ACE) *inhibitors* (digunakan untuk mengobati kondisi jantung tertentu atau tekanan darah tinggi),
- disopyramide (digunakan untuk mengobati kondisi jantung tertentu),
- fluoxetine (digunakan untuk mengobati depresi),
- fibrates (digunakan untuk menurunkan kadar lemak darah yang tinggi),
- *monoamine oxidase (MAO) inhibitors* (digunakan untuk mengobati depresi),
- pentoxifylline, propoxyphene, salisilat (seperti aspirin, digunakan untuk meringankan nyeri dan menurunkan demam),
- analog somatostatin (seperti octreotide, digunakan untuk mengobati kondisi tidak biasa dimana Anda memproduksi hormon pertumbuhan terlalu banyak),
- antibiotik sulphonamide.

Obat-obatan yang dapat menyebabkan kadar gula darah meningkat (hiperglikemia) antara lain:
- kortikosteroid (seperti ‘kortison’ yang digunakan untuk mengobati kondisi inflamasi),
- danazol (obat yang beraksi pada proses ovulasi),
- diazoxide (digunakan untuk mengobati tekanan darah tinggi),
- diuretik (digunakan untuk mengobati tekanan darah tinggi atau retensi cairan yang berlebihan),
- glucagon (hormon pankreas yang digunakan untuk mengobati hipoglikemia yang parah),
- isoniazid (digunakan untuk mengobati tuberculosis/ TBC),
- estrogen dan progestogen (seperti yang terdapat pada obat kontrasepsi),
- derivatif phenothiazine (digunakan untuk mengobati gangguan psikiatrik),
- somatropin (hormon pertumbuhan),
- obat-obatan simpatomimetik (seperti epinefrin [adrenalin], salbutamol, terbutalin yang digunakan untuk mengobati asma),
- hormon tiroid (digunakan untuk mengobati kelainan kelenjar tiroid),
- obat-obatan antipsikotik atipikal (seperti clozapine, olanzapine),
- *protease inhibitors* (digunakan untuk mengobati HIV).

Kadar gula darah dapat menurun atau meningkat jika Anda mengkonsumsi:
- *beta-blockers* (digunakan untuk mengobati tekanan darah tinggi),
- klonidin (digunakan untuk mengobati tekanan darah tinggi),
- garam lithium (digunakan untuk mengobati gangguan psikiatrik).

Pentamidine (digunakan untuk mengobati beberapa infeksi yang disebabkan oleh parasit) dapat menyebabkan hipoglikemia yang terkadang diikuti oleh hiperglikemia.

Beta-blockers seperti halnya obat-obatan *sympatholytic* lainnya (seperti klonidin, *guanethidine*, dan reserpin) dapat memperlemah atau menekan secara keseluruhan gejala peringatan pertama yang dapat membantu Anda mengenali hipoglikemia.
Jika Anda tidak yakin apakah Anda sedang mengkonsumsi salah satu obat-obatan di atas, tanyakanlah kepada dokter atau apoteker.

BASAGLAR dan Alkohol
Kadar gula darah Anda dapat naik atau juga turun ketika Anda mengkonsumsi minuman beralkohol.

Kehamilan dan Menyusui
Mintalah nasihat kepada dokter atau apoteker sebelum mengkonsumsi obat apapun.
Informasikan kepada dokter Anda jika Anda berencana untuk hamil, atau jika Anda sedang hamil. Dosis insulin Anda mungkin perlu diubah selama masa kehamilan dan sesudah melahirkan. Pengendalian diabetes yang seksama dan pencegahan hipoglikemia, adalah penting untuk kesehatan bayi Anda.
Jika Anda sedang menyusui, konsultasikan kepada dokter Anda karena Anda mungkin perlu untuk menyesuaikan dosis insulin dan pola makan.

Mengendarai dan Mengoperasikan Mesin
Kemampuan Anda untuk berkonsentrasi atau bereaksi dapat berkurang jika:
- Anda mengalami hipoglikemia (kadar gula darah rendah),
- Anda mengalami hiperglikemia (kadar gula darah tinggi),
- Anda memiliki masalah dengan penglihatan.

Ingatlah hal ini pada segala situasi dimana Anda dapat membahayakan diri sendiri dan orang lain (seperti mengendarai kendaraan atau mengoperasikan mesin). Anda harus menghubungi dokter untuk mendapatkan nasihat dalam mengemudi jika:
- Anda sering mengalami kejadian hipoglikemia,
- gejala peringatan pertama yang membantu Anda mengenali terjadinya hipoglikemia berkurang atau hilang.

Informasi Penting Mengenai Beberapa Komposisi BASAGLAR
Obat ini mengandung kurang dari 1 mmol (23 mg) natrium per dosis, yang mana secara esensial obat ini ‘bebas-natrium’.

3. Bagaimana cara menggunakan BASAGLAR

Selalu gunakan obat ini tepat seperti yang dokter jelaskan kepada Anda. Cek kembali kepada dokter atau apoteker jika Anda merasa tidak yakin.

Walaupun BASAGLAR mengandung zat aktif yang sama dengan Lantus XR (insulin glargine 300 unit/mL), obat-obat ini tidak dapat menjadi substitusi antara satu sama lain. Perubahan dari satu terapi insulin ke yang lain memerlukan resep dokter, pengawasan medis dan pemeriksaan gula darah. Silakan konsultasikan dengan dokter Anda untuk informasi lebih lanjut.

Dosis
Berdasarkan gaya hidup Anda, hasil tes kadar gula darah (glukosa) dan penggunaan insulin sebelumnya, dokter akan:
- menentukan seberapa banyak BASAGLAR per hari yang Anda butuhkan dan pada jam berapa,
- menyampaikan kapan Anda perlu mengecek kadar gula darah, dan apakah Anda perlu untuk melakukan tes urin,
- menyampaikan kapan Anda boleh menyuntikkan dosis BASAGLAR yang lebih tinggi atau lebih rendah.

BASAGLAR adalah insulin kerja panjang. Dokter dapat meminta Anda untuk menggunakannya dalam kombinasi dengan insulin kerja pendek atau dengan obat tablet yang digunakan untuk mengobati kadar gula darah tinggi.
Banyak faktor yang dapat mempengaruhi kadar gula darah. Anda perlu untuk mengetahui hal ini agar dapat bertindak dengan tepat untuk perubahan kadar gula darah Anda dan untuk mencegahnya menjadi terlalu tinggi atau terlalu rendah. Perhatikan informasi pada kotak di akhir bagian leaflet ini untuk informasi lebih lanjut.

Penggunaan pada Anak-anak dan Remaja
BASAGLAR dapat digunakan pada remaja dan anak-anak berusia 6 tahun ke atas. Gunakan obat ini persis seperti yang dikatakan dokter Anda.

Frekuensi Penyuntikan
Anda perlu 1 injeksi BASAGLAR setiap harinya, pada waktu yang sama.

Cara Penyuntikan
BASAGLAR disuntikkan di bawah kulit. JANGAN suntikkan BASAGLAR pada vena, karena akan mengubah mekanisme aksi dan dapat menyebabkan hipoglikemia.

Dokter akan menunjukkan kepada Anda area kulit mana saja untuk penyuntikan BASAGLAR. Ubahlah area penyuntikan (di sekitar area yang dianjurkan) untuk setiap injeksi.

Bagaimana Cara Menangani BASAGLAR KwikPen
BASAGLAR KwikPen adalah pen sekali pakai yang sudah terisi/ terpasang dengan insulin glargine.

Baca dengan saksama "BASAGLAR KwikPen Instruction for Use" termasuk di dalam leaflet ini. Anda harus menggunakan pen seperti yang dijelaskan di *Instruction for Use*.

Jarum yang masih baru harus dipasangkan sebelum setiap kali pemakaian. Hanya pergunakan jarum yang sesuai dengan BASAGLAR KWIKPEN (lihat pada BASAGLAR KwikPen *Instruction for Use*).

Tes keamanan harus dilakukan sebelum setiap penyuntikan.

Perhatikan cartridge yang terpasang sebelum Anda menggunakan pen. Jangan gunakan BASAGLAR KwikPen jika Anda mendapati ada partikel di dalam larutan. Hanya gunakan BASAGLAR KwikPen jika larutannya jernih, tidak berwarna dan seperti air. Jangan kocok atau mencampurnya sebelum digunakan.

Untuk mencegah kemungkinan penyebaran penyakit, setiap pen harus digunakan hanya untuk 1 pasien, walaupun jika jarumnya sudah diganti.

Pastikan tidak terdapat alkohol atau disinfektan lain atau zat lain yang mengkontaminasi larutan insulin.

Selalu gunakan pen baru jika Anda mendapati kadar gula darah Anda memburuk oleh sebab yang tidak diketahui. Jika Anda mengira Anda bermasalah dengan BASAGLAR KwikPen, hubungi dokter, apoteker atau perawat Anda.

Pen yang sudah kosong tidak boleh diisi ulang dan harus dibuang dengan benar.

Jangan gunakan BASAGLAR KwikPen jika rusak atau tidak bekerja dengan baik, pen tersebut harus dibuang dan diganti dengan KwikPen baru untuk digunakan.

Pertukaran Insulin
Anda harus selalu memeriksa label insulin sebelum setiap penyuntikan untuk menghindari tertukarnya BASAGLAR dan insulin lainnya.

Jika Anda Menggunakan BASAGLAR Lebih Banyak dari Seharusnya
- Jika Anda menyuntikkan BASAGLAR terlalu banyak dari dosis seharusnya, kadar gula darah Anda dapat menjadi terlalu rendah (hipoglikemia). Periksa kadar gula darah Anda secara teratur. Secara umum, untuk mencegah terjadinya hipoglikemia Anda harus makan lebih banyak makanan dan memantau kadar gula darah Anda. Informasi penanganan hipoglikemia dapat Anda baca pada bagian akhir leaflet ini.

Jika Anda Lupa Menggunakan BASAGLAR
- Jika Anda lupa menyuntikkan 1 dosis BASAGLAR atau jika Anda menyuntikkan dalam jumlah kurang, kadar gula darah Anda dapat menjadi terlalu tinggi (hiperglikemia). Periksa kadar gula darah Anda secara teratur. Informasi penanganan hiperglikemia dapat Anda baca pada bagian akhir leaflet ini.
- Jangan menyuntikkan dosis ganda sebagai kompensasi untuk dosis yang telah lupa disuntikkan.

Jika Anda Berhenti Menggunakan BASAGLAR
Hal ini dapat menyebabkan hiperglikemia berat (kadar gula darah yang sangat tinggi) dan ketoasidosis (penumpukan asam di dalam darah karena tubuh akhirnya memecah lemak, bukan gula). Jangan hentikan penggunaan BASAGLAR tanpa memberitahukan kepada dokter Anda.

Jika Anda memiliki pertanyaan lebih lanjut mengenai cara penggunaan obat ini, hubungi dokter, apoteker atau perawat Anda.

4. Efek Samping yang Mungkin Timbul

Seperti halnya semua obat, obat ini dapat menimbulkan efek samping, meskipun tidak setiap orang mengalaminya.

Jika Anda melihat tanda-tanda gula darah Anda terlalu rendah (hipoglikemia), segera lakukan tindakan untuk meningkatkan kadar gula darah Anda. Hipoglikemia (gula darah rendah) bisa menjadi sangat serius dan sangat umum terjadi pada pengobatan dengan insulin (dapat mempengaruhi lebih dari 1 dari 10 orang). Gula darah rendah berarti tidak ada cukup gula dalam darah Anda. Jika kadar gula darah Anda turun terlalu rendah, Anda bisa pingsan (menjadi tidak sadarkan diri). Hipoglikemia yang serius dapat menyebabkan kerusakan otak dan dapat mengancam jiwa. Untuk informasi lebih lanjut, lihat kotak di akhir leaflet ini.

Reaksi alergi yang parah (jarang, dapat mempengaruhi hingga 1 dari 1.000 orang) - tanda-tandanya bisa termasuk reaksi kulit berskala besar (ruam dan gatal di seluruh tubuh), pembengkakan kulit atau selaput lendir yang parah (angiooedema), sesak napas, penurunan tekanan darah dengan detak jantung yang cepat dan berkeringat. Reaksi alergi yang parah terhadap insulin dapat mengancam jiwa. Beri tahu dokter segera jika Anda melihat tanda-tanda reaksi alergi yang parah.

Perubahan kulit pada lokasi penyuntikan Jika Anda menyuntikkan insulin di tempat yang sama terlalu sering, kulit mungkin akan menyusut (lipoatrofi, dapat mempengaruhi hingga 1 dari 100 orang) atau menebal (lipohipertrofi, dapat mempengaruhi hingga 1 dari 10 orang). Juga dapat terjadi benjolan di bawah kulit yang disebabkan oleh penumpukan protein yang disebut amiloid (amiloidosis kulit, tidak diketahui seberapa sering hal ini terjadi). Insulin mungkin tidak akan bekerja dengan baik. Ganti lokasi penyuntikan setiap kali akan menyuntik untuk membantu mencegah perubahan kulit seperti tersebut di atas.

Efek samping yang biasa terjadi (dapat timbul hingga 1 dari 10 orang)

- **Reaksi pada kulit dan alergi pada tempat penyuntikan**

Tanda-tandanya meliputi memerah, rasa sakit intens yang tidak biasa ketika penyuntikan, gatal, ruam, bengkak atau inflamasi. Reaksi tersebut dapat menyebar di sekitar lokasi penyuntikan. Kebanyakan reaksi minor terhadap insulin biasanya akan hilang dalam beberapa hari atau beberapa minggu.

Efek samping yang jarang terjadi (dapat timbul hingga 1 dari 1.000 orang)

Reaksi pada mata

Perubahan (perbaikan atauperburukan) pada kontrol kadar gula darah dapat mengganggu penglihatan Anda untuk sementara waktu. Jika Anda menderita *proliferative retinopathy* (suatu penyakit mata yang terkait dengan diabetes) serangan hipoglikemia berat dapat menyebabkan kehilangan penglihatan sementara.

Gangguan umum

Pada kejadian yang jarang, pengobatan dengan insulin dapat juga menyebabkan penimbunan air di tubuh untuk sementara, ditandai dengan pembengkakan pada betis dan pergelangan kaki.

Efek samping yang sangat jarang terjadi (dapat timbul hingga 1 dari 10.000 orang)
Pada kejadian yang sangat jarang, *dysgeusia* (gangguan pengecapan rasa) dan *myalgia* (nyeri otot) dapat timbul.

Penggunaan pada anak-anak dan remaja
Secara umum, efek samping yang terjadi pada anak-anak dan remaja berumur hingga 18 tahun kurang lebih sama dengan yang terjadi pada dewasa.

Keluhan akan reaksi pada lokasi penyuntikan (nyeri, reaksi lainnya) dan reaksi kulit (merah, *urticaria*) dilaporkan lebih sering terjadi pada anak-anak dan remaja berusia hingga 18 tahun daripada pada dewasa.

Pelaporan efek samping
Jika Anda mengalami suatu efek samping, sampaikan kepada dokter atau apoteker Anda. Pelaporan ini termasuk untuk efek samping yang mungkin terjadi yang tidak tercantum dalam leaflet ini. Dengan melaporkan efek samping, Anda dapat ikut membantu penyediaan informasi terkait keamanan obat ini.

5. Bagaimana cara menyimpan BASAGLAR

Jauhkan obat ini dari jangkauan dan pandangan anak-anak.

Jangan gunakan obat ini setelah melewati tanggal kadaluwarsa yang tercantum pada karton dan label yang dinyatakan oleh istilah “EXP”. Tanggal kadaluwarsa ini merujuk pada tanggal terakhir dari bulan yang disebutkan.

Pen yang belum digunakan
Simpan di dalam lemari es (2°C - 8°C). Jangan dibekukan.
Jangan letakkan BASAGLAR berdekatan dengan perangkat pembeku *(freezer)* atau *freezer pack*.
Simpanlah *pre-filled pen* di dalam kemasan kartonnya untuk melindungi dari cahaya.

Pen yang sedang digunakan
Pen yang sedang digunakan atau yang dibawa sebagai cadangan boleh disimpan selama maksimal 28 hari pada suhu hingga 30°C dan dijauhkan dari panas atau cahaya langsung. Pen yang sedang digunakan tidak boleh disimpan di dalam lemari es. Jangan gunakan pen ketika sudah melebihi waktu 28 hari. Tutup pen harus dikembalikan pada tempatnya setiap kali setelah penyuntikan untuk melindunginya dari cahaya.

Jangan buang obat melalui saluran pembuangan air di rumah atau limbah rumah tangga. Tanyakan kepada apoteker bagaimana cara membuang obat jika Anda tidak lagi menggunakannya. Hal ini akan membantu untuk melindungi lingkungan.

6. Isi Kemasan dan Informasi Lainnya

Apakah Kandungan BASAGLAR
- Zat aktifnya adalah insulin glargine. Setiap milliliter larutan injeksi mengandung 100 unit zat aktif insulin glargine (setara dengan 3.64 mg).

- Komposisi lainnya: seng oksida, metacresol, gliserol, natrium hidroksida (perhatikan bagian 2 “informasi penting mengenai beberapa komposisi BASAGLAR”), asam hidroklorat dan air khusus untuk injeksi.

Seperti Apakah BASAGLAR dan Isi dalam Kemasannya
BASAGLAR KwikPen 100 units/mL merupakan larutan injeksi yang jernih dan tidak berwarna di dalam pen yang sudah terisi (*pre-filled* pen).
Setiap pen mengandung larutan injeksi sebesar 3 mL (setara dengan 300 unit).

Kemasan yang Tersedia
BASAGLAR KwikPen 100 IU/ml, Dus, 5 pre-filled pens @ 3 mL.
Reg. No.: DKI2088802243A1

HARUS DENGAN RESEP DOKTER

Dibuat oleh:
Eli Lilly Italia S.p.A.,
Via Gramsci, 731 – 733
50019 Sesto Fiorentino – Italy

Dirakit, dikemas dan dirilis oleh:
Lilly France, S.A.S
F-67640 Fegersheim, Perancis

Didaftarkan oleh:
PT Pyridam Farma Tbk.
Kabupaten Cianjur, Indonesia

HIPERGLIKEMIA DAN HIPOGLIKEMIA

Selalu bawalah gula (minimal 20 gram) bersama Anda.

Bawalah beberapa informasi/ penanda bahwa Anda adalah penderita diabetes.

HIPERGLIKEMIA (kadar gula darah tinggi)

Jika kadar gula darah Anda terlalu tinggi (hiperglikemia), kemungkinan Anda menyuntikkan insulin dalam jumlah yang kurang.

Mengapa Hiperglikemia Terjadi?
Contohnya adalah sebagai berikut:
- Anda belum menyuntikkan insulin atau menyuntikkan dalam jumlah yang kurang, atau insulin Anda berkurang efektivitasnya, misalnya dikarenakan penyimpanan yang kurang benar,
- pen insulin Anda tidak bekerja dengan benar,
- Anda tidak/ kurang berolahraga seperti biasanya, Anda sedang dalam kondisi stress (tekanan emosional, ketegangan), atau Anda sedang mengalami luka, operasi, infeksi atau demam,
- Anda sedang atau telah mengkonsumsi obat-obatan lain (lihat pada bagian 2, “Obat-obatan lain dan BASAGLAR”).

Gejala Peringatan Hiperglikemia
Haus, peningkatan keinginan untuk buang air kecil, kelelahan, kulit kering, wajah memerah, kehilangan nafsu makan, tekanan darah rendah, detak jantung cepat, dan terdapat glukosa & badan keton di urin. Sakit perut, napas yang cepat dan dalam, mengantuk atau bahkan kehilangan kesadaran merupakan tanda dari suatu keadaan yang serius (ketoasidosis) akibat dari kekurangan insulin.

Apa yang Harus Anda Lakukan Jika Anda Mengalami Hiperglikemia?
Periksa kadar gula darah dan kadar keton urin Anda sesegera mungkin ketika gejala-gejala di atas muncul. Hiperglikemia atau ketoasidosis berat harus dirawat oleh dokter, pada umumnya di rumah sakit.

HIPOGLIKEMIA (kadar gula darah rendah)
Jika kadar gula darah turun terlalu banyak Anda dapat kehilangan kesadaran. Hipoglikemia yang serius dapat menyebabkan serangan jantung atau kerusakan otak dan dapat mengancam nyawa. Anda diharapkan dapat mengenali gejala ketika kadar gula darah Anda turun tajam sehingga Anda dapat mengambil tindakan yang tepat.

Mengapa Hipoglikemia Terjadi?
Contohnya adalah sebagai berikut:
- Anda menyuntikkan insulin terlalu banyak,
- Anda melewatkan waktu makan atau menundanya,
- Anda makan tidak dalam jumlah yang cukup, atau memakan makanan yang mengandung karbohidrat kurang dari biasanya (gula dan bahan serupa disebut dengan karbohidrat; akan tetapi pemanis buatan BUKAN karbohidrat),

- Anda kehilangan karbohidrat karena muntah atau diare,
- Anda meminum minuman beralkohol, terlebih ketika Anda tidak makan dalam jumlah yang cukup,
- Anda berolahraga melebihi biasanya atau melakukan aktifitas fisik yang berbeda,
- Anda sedang dalam masa pemulihan luka atau operasi atau tekanan lainnya,
- Anda sedang dalam masa penyembuhan dari suatu penyakit atau demam,
- Anda mengkonsumsi atau berhenti meminum obat-obatan yang lain (lihat pada bagian 2, "Obat-obatan lain dan BASAGLAR").

Hipoglikemia Biasanya Juga Muncul Jika
- Anda baru saja memulai pengobatan dengan insulin atau berganti sediaan insulin yang lain (ketika mengganti sediaan insulin basal sebelumnya menjadi BASAGLAR, hipoglikemia, jika muncul, lebih sering muncul di pagi hari daripada malam),
- kadar gula darah Anda hampir normal atau tidak stabil,
- Anda mengubah area kulit dimana Anda menyuntikkan insulin (sebagai contoh dari paha ke lengan atas),
- Anda menderita penyakit ginjal atau hati berat, atau penyakit lainnya seperti hipotiroid.

Gejala Peringatan Hipoglikemia
- *Pada tubuh*
Contoh gejala yang menunjukkan bahwa kadar gula darah Anda turun secara tajam atau terlalu banyak: berkeringat, kulit yang basah atau berkeringat, cemas, detak jantung cepat, tekanan darah tinggi, palpitasi dan detak jantung tak beraturan. Gejala-gejala ini sering timbul sebelum adanya gejala kadar gula darah yang rendah di otak.

- *Pada otak*
Contoh gejala yang mengindikasikan kadar gula rendah di otak: sakit kepala, rasa lapar yang sangat, mual, muntah, kelelahan, mengantuk, gangguan tidur, gelisah, tindakan agresif, gangguan konsentrasi, gangguan bereaksi, depresi, kebingungan, gangguan berbicara (terkadang terjadi kehilangan kemampuan berbicara secara total), gangguan penglihatan, gemetar, kelumpuhan, sensasi geli (*paraesthesia*), kekebasan dan sensasi geli pada area mulut, pening, kehilangan pengendalian diri, tidak mampu merawat diri sendiri, kejang dan kehilangan kesadaran.

Gejala pertama yang merupakan penanda terjadinya hipoglikemia ("gejala peringatan") dapat berubah-ubah, melemah atau hilang jika
- Anda telah berusia lanjut, jika Anda menderita diabetes dalam waktu yang sudah lama atau jika Anda menderita suatu penyakit saraf (*diabetic autonomic neuropathy*),
- Anda baru saja mengalami hipoglikemia (misalnya sehari sebelumnya) atau hipoglikemia terjadi secara perlahan-lahan,
- Anda memiliki kadar gula darah yang hampir normal atau membaik,
- Anda baru saja berganti dari sediaan insulin hewan ke sediaan insulin manusia contohnya BASAGLAR,
- Anda sedang atau telah mengkonsumi obat-obatan lain (lihat pada bagian 2, "Obat-obatan Lain dan BASAGLAR").

Pada kejadian yang seperti tersebut di atas, Anda dapat mengalami hipoglikemia parah (bahkan pingsan) sebelum Anda menyadari apa yang terjadi. Harap kenali dengan baik gejala peringatan

Anda sendiri. Jika perlu, pemeriksaan kadar gula darah dengan lebih sering dapat membantu mengidentifikasi kejadian hipoglikemia ringan yang mungkin dapat saja terlewat. Jika Anda tidak yakin dalam mengenali gejala peringatan, hindari situasi (misalnya mengendarai kendaraan) yang dapat membahayakan diri Anda dan orang lain.

Apa Yang Harus Anda Lakukan Ketika Mengalami Hipoglikemia?

1. Jangan suntikkan insulin. Segera konsumsi 10 – 20 gram gula, seperti glukosa, gula pasir atau minuman manis. Perhatian: pemanis buatan dan makanan dengan pemanis buatan (seperti minuman untuk diet) tidak dapat membantu perawatan hipoglikemia.

2. Kemudian makanlah sesuatu yang memiliki efek jangka panjang dalam menaikkan kadar gula darah (contohnya roti atau pasta). Dokter atau perawat akan mendiskusikan hal ini dengan Anda sebelumnya.
   Pemulihan hipoglikemia dapat tertunda karena BASAGLAR memiliki masa kerja yang lama/ panjang.

3. Jika hipoglikemia muncul kembali, konsumsi gula 10 – 20 gram lagi.

4. Hubungi dokter dengan segera jika Anda tidak dapat mengontrol hipoglikemia Anda atau jika muncul kembali. Sampaikan kepada saudara, teman atau rekan kerja Anda hal berikut:

Jika Anda tidak dapat menelan atau tidak sadarkan diri, Anda membutuhkan suntikan glukosa atau glukagon (obat untuk meningkatkan kadar gula darah). Suntikan ini diperbolehkan meskipun kejadian hipoglikemia belum dipastikan.

Disarankan untuk segera memeriksa kadar gula darah setelah Anda mengkonsumsi glukosa untuk mengetahui apakah Anda mengalami hipoglikemia.

X	Proposed truth_v1	X	Internal reviewer__DS__		Medical reviewer___IJ____
X	Internal creator_MH_		Approval for Submission		Marketing reviewer_____
			Date _____		

Instructions for use

BASAGLAR™ KwikPen™

Insulin glargine (100 units/mL solution for injection in a pre-filled pen)

PLEASE READ THESE INSTRUCTIONS BEFORE USE

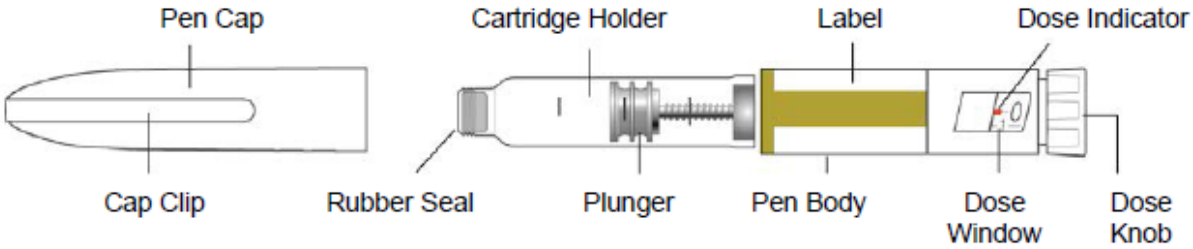
Read the instructions for use before you start using BASAGLAR KwikPen and each time you get another BASAGLAR KwikPen. There may be new information. This information does not take the place of talking to your healthcare professional about your medical condition or your treatment.

BASAGLAR™ KwikPen™ (“Pen”) is a disposable pen containing 300 units (3 mL) of insulin glargine. You can give yourself multiple doses using one Pen. The Pen dials 1 unit at a time. You can inject 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.

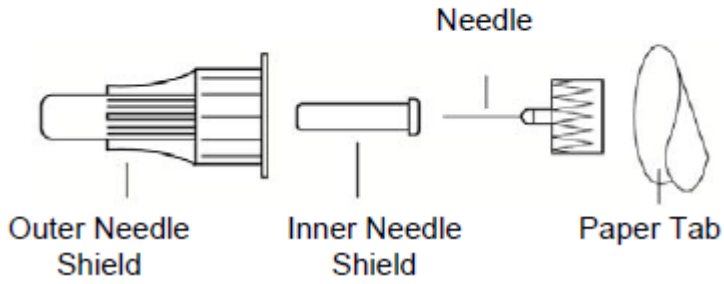
Do not share your pen with other people, even if the needle has been changed. Do not reuse or share needles with other people. You may give an infection to them or get an infection from them.

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



Pen Needle Parts
(Needles Not Included)



Dose Knob with green ring

How to recognize your Basaglar KwikPen:

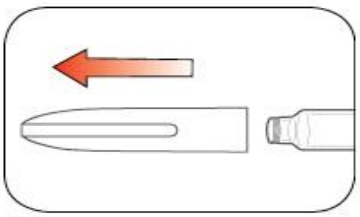
- Pen colour: Light grey
- Dose Knob: Light grey with green ring on the end
- Labels: Light grey with green color bars

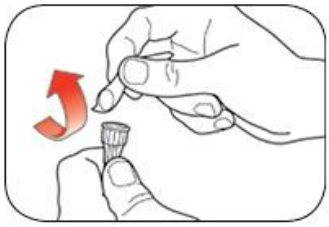
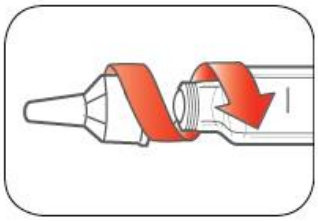
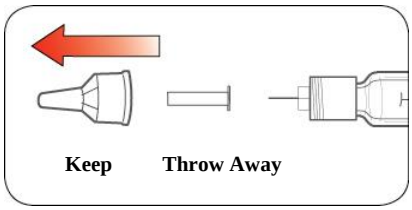
Supplies needed to give your injection:

- BASAGLAR KwikPen
- KwikPen compatible needle (BD [Becton, Dickinson and Company] pen needles recommended).
- Alcohol swab

Preparing your Pen

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

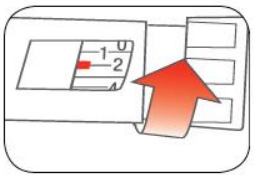
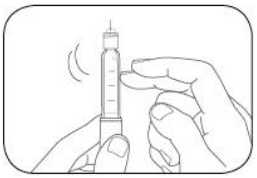
Step 1: • Pull the pen cap straight off. - Do not remove the pen label. • Wipe the rubber seal with an alcohol swab. BASAGLAR should look clear and colourless. **Do not** use if it is thick, cloudy, coloured, or has particles or clumps in it.	

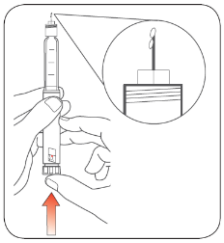
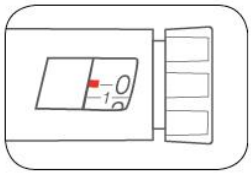
Step 2: Select a new needle. Pull off the paper tab from the outer needle shield.	
Step 3: Push the capped needle straight onto the pen and twist the needle on until it is tight.	
Step 4: Pull off the outer needle shield. Do not throw it away. Pull off the inner needle shield and throw it away.	

Priming your Pen

Prime before each injection.

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

Step 5: • To prime your pen, turn the dose knob to select 2 units.	
Step 6: • Hold your pen with the needle pointing up. Tap the cartridge holder gently to collect air bubbles at the top.	

Step 7: • Continue holding your pen with needle pointing up. Push the dose knob in until it stops, and "0" is seen in the dose window. Hold the dose knob in and count to 5 slowly. You should see insulin at the tip of the needle. - If you **do not** see insulin, repeat the priming steps, but not more than 4 times. - If you **still do not** see insulin, change the needle and repeat the priming steps. Small air bubbles are normal and will not affect your dose.	 

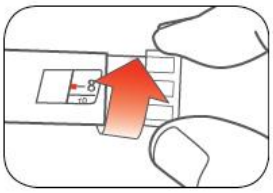
Selecting your dose

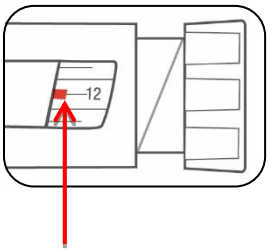
- You can give from 1 to 80 units in a single injection.
- If your dose is more than 80 units, you will need to give more than one injection.
  – If you need help deciding how to divide up your dose, ask your healthcare provider.
  – You should use a new needle for each injection and repeat the priming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

Step 8:

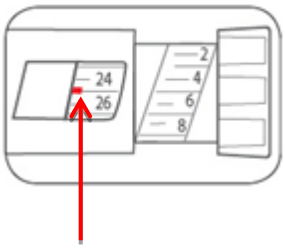
- Turn the dose knob to select the number of units you need to inject. The dose indicator should line up with your dose.
  - The Pen dials 1 unit a time
  - The Dose Knob clicks as you turn it.
  - **DO NOT** dial your dose by counting the clicks because you may dial the wrong dose
  - The dose can be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

- **Always check the number in the Dose Window to make sure you have dialed the correct dose**.





(Example: 12 units shown in the dose window)

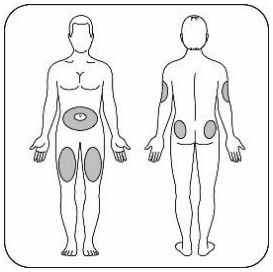
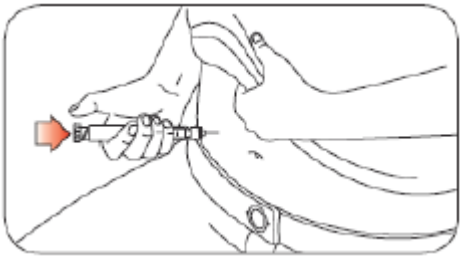
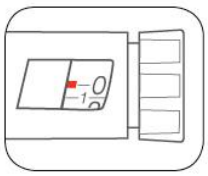


(Example: 25 units shown in the dose window)

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

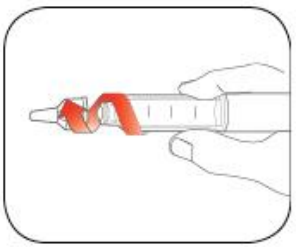
Giving your injection

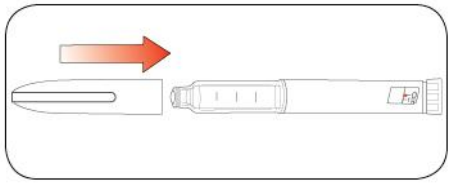
- Inject your insulin as your healthcare professional has shown you.
- Change (rotate) your injection site for each injection.
- **Do not** try to change your dose while injecting.

Step 9: Choose your injection site. • BASAGLAR is injected under the skin (subcutaneously) of your stomach area, buttocks, upper legs or upper arms. • Wipe the skin with an alcohol swab, and let the injection site dry before you inject your dose.	
Step 10: • Insert the needle into your skin. • Push the dose knob all the way in. • Continue to hold the dose knob in and **slowly count to 5** before removing the needle.  **Do not** try to inject your insulin by turning the Dose Knob. You will **NOT** receive your insulin by turning the Dose Knob.	
Step 11: • Pull the needle out of your skin. - A drop of insulin at the needle tip is normal. It will not affect your dose. • Check the number in the Dose Window - If you see “0” in the Dose window, you have received the full amount you dialed. - If you do not see “0” in the Dose window, do not redial. Insert the needle into your skin and finish your injection. - If you still do not think you received the full amount you dialed for your	

injection, do not start over or repeat that injection. Monitor your blood glucose as instructed by your healthcare provider. - If you normally need to give 2 injections for your full dose, be sure to give your second injection. The plunger only moves a little with each injection, and you may not notice that it moves. If you see blood after you take the Needle out of your skin, press the injection site lightly with a piece of gauze or an alcohol swab. **Do not** rub the area.	

After your injection

Step 12: Carefully replace the outer needle shield.	
Step 13: • Unscrew the capped needle and dispose of it as described below (see Disposing of Pens and Needles section). • Do not store the pen with the needle attached to prevent leaking, blocking of the needle, and air from entering the pen.	

Step 14: Replace the pen cap by lining up the cap clip with the dose indicator and pushing straight on.	

Disposing of Pens and Needles

- 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

- Store unused pens in the refrigerator at 36°F to 46°F (2°C to 8°C).
- **Do not** freeze BASAGLAR. **Do not** use if it has been frozen.
- Unused pens may be used until the expiration date printed on the label, if the pen has been kept in the refrigerator.

In-use pen

- The pen you are currently using should be stored at room temperature [up to 86°F (30°C)] and away from heat and light.
- Throw away the pen you are using after 28 days, even if it still has insulin left in it.

General information about the safe and effective use of your pen

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

Troubleshooting

- If you cannot remove the pen cap, gently twist the cap back and forth, and then pull the cap straight off.
- If the dose knob it is hard to push:
    - Pushing the dose knob more slowly will make it easier to inject.
    - Your needle may be blocked. Put on a new needle and prime the pen.

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

If you have any questions or problems with your BASAGLAR KwikPen, contact your healthcare provider for help.

PRESENTATION
BASAGLAR KWIKPEN 100 IU/ml, Box 5 prefilled pens @ 3 mL Reg. No.: DKIXXXXXX

HARUS DENGAN RESEP DOKTER

Manufactured by:
Eli Lilly Italia S.p.A.,
Via Gramsci, 731-733
50019 Sesto Fiorentino – Italy

Assembled, packed and released by:
Lilly France, S.A.S
F-67640 Fegersheim, France

Registered by:
PT Pyridam Farma Tbk.
Kabupaten Cianjur, Indonesia.

BASAGLAR KwikPen meets the current dose accuracy and functional requirements of ISO 11608-1:2012.