Insulin Glargine

Basagine®

100Units/mL Solution for injection (SC), 3mL Vial

Antidiabetic

Description:
Insulin Glargine (Basagine®) is a solution for injection used as antidiabetic agent. Insulin Glargine (Basagine®) is a biosynthetic long-acting, human insulin analogue administered subcutaneously to lower the excess blood-glucose-level. It is synthesized by using recombinant DNA technology and a special laboratory strain of non-pathogenic *Escherichia coli*. Insulin Glargine differs from human insulin in that the amino acid asparagine at position A21 is replaced by glycine and two arginines are added to the C-terminus of the B-chain. Chemically, it is 21^{A} -Gly-30^{B}a-L-Arg-30^{B}b-L-Arg-human insulin and has the molecular formula $C_{267}H_{404}N_{72}O_{78}S_6$.

Formulation:
Insulin Glargine (Basagine®) is available as solution for injection for subcutaneous administration as:
Insulin Glargine (Basagine®) 100Units/ mL:
Each mL contains:
Insulin Glargine (r-DNA origin) ... 100 Units (3.64mg)
Preservative: Metacresol... 0.27% w/v

CLINICAL PHARMACOLOGY
Mechanism of Action
The primary activity of insulin glargine is the regulation of glucose metabolism. It inhibits hepatic glucose production and lowers blood glucose level by enhancing peripheral glucose uptake especially by skeletal muscle and fat. It also inhibits lipolysis in the adipocyte, inhibits proteolysis and enhances protein synthesis. 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 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.

PHARMACOKINETICS
Absorption and Bioavailability
Following subcutaneous injection, absorption of insulin glargine is slower and more prolonged compared with that of isophane (NPH) human insulin; the serum concentration-time profile for insulin glargine is relatively constant over 24 hours. After subcutaneous injection of 0.3 units/kg insulin glargine in patients with type 1 diabetes, a relatively constant concentration/time profile has been demonstrated. The duration of action after abdominal, deltoid, or thigh subcutaneous administration is almost similar.
Insulin glargine injected once daily will reach steady state levels in 2-4 days after first dose.

Metabolism
Insulin glargine is partly metabolized in the subcutaneous depot at the carboxyl terminus of the B-Chain to form the active metabolites i.e. M1 (21^{A} -Gly-insulin and M2 (21A-Gly-des-30^{B}-Thr-insulin) having similar *invitro* activity to insulin.

Special Population
Age, Race and Gender
Age, race and gender did not show difference in safety and efficacy between insulin glargine and NPH human insulin.

Renal & Hepatic Insufficiency
The effect of the renal & hepatic insufficiency on the pharmacokinetics of Insulin Glargine rDNA origin has not been studied. However, some studies with human insulin have shown increased circulating levels of insulin in patients with renal & hepatic failure. Careful glucose monitoring and dose adjustments may be necessary in patients with renal & hepatic dysfunction.

INDICATIONS
Insulin Glargine (Basagine®) is indicated to improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus.

DOSAGE AND ADMINISTRATION
Dosing
Insulin Glargine (Basagine®) is a recombinant human insulin analogue for once daily subcutaneous administration with potency that is approximately the same as the potency of human insulin. Insulin Glargine (Basagine) exhibits a relatively constant glucose-lowering profile over 24 hours that permits once-daily dosing.
Insulin Glargine (Basagine®) may be administered at any time during the day. Insulin Glargine (Basagine®) should be administered subcutaneously once a day at the same time every day. The dose of Insulin glargine must be individualized based on clinical response. Blood glucose monitoring is essential in all patients receiving insulin therapy. Patients adjusting the amount or timing of dosing with Insulin Glargine (Basagine®), should only do so under medical supervision with appropriate glucose monitoring.
In patients with type 1 diabetes, Insulin Glargine (Basagine®) must be used in regimens with short-acting insulin.
The intended duration of activity of Insulin Glargine is dependent on injection into subcutaneous tissue. Insulin Glargine should not be administered intravenously or via an insulin pump. Intravenous administration of the usual subcutaneous dose could result in severe hypoglycemia As with all insulins, injection sites should be rotated within the same region (abdomen, thigh, or deltoid) from one injection to the next to reduce the risk of lipodystrophy.

Initiation therapy:
The recommended starting dose of Insulin Glargine (Basagine®) in patients with type 1 diabetes should be approximately one-third of the total daily insulin requirements. Short-acting, pre-meal insulin should be used to satisfy the remainder of the daily insulin requirements. The recommended starting dose of Insulin Glargine (Basagine®) in patients with type 2 diabetes who are not currently treated with insulin is 10 units (or 0.2 Units/kg) once daily, which should subsequently be adjusted to the patient's needs.
The dose of Insulin Glargine (Basagine®) should be adjusted according to blood glucose measurements. The dosage of Insulin Glargine (Basagine®) should be individualized under the supervision of healthcare provider in accordance with the needs of the patient.

Converting to Insulin Glargine (Basagine®) from other insulin therapies
If changing from a treatment regimen with an intermediate-or long-acting insulin to a regimen with Insulin Glargine (Basagine®), the amount and timing of shorter-acting insulins and doses of any oral antidiabetic drugs may need to be adjusted.

- If transferring patients from once-daily NPH insulin to once-daily Insulin Glargine (Basagine®), the recommended initial Insulin Glargine dose is the same as the dose of Insulin Glargine that is being discontinued.
- If transferring patients from twice-daily NPH insulin to once-daily Insulin Glargine (Basagine®), the recommended initial Insulin Glargine dose is 80% of the total NPH dose that is being discontinued. This dose reduction will lower the likelihood of hypoglycemia.

ADVERSE REACTIONS
Very Common:
Hypoglycemia is the most frequently occurring undesirable effect of insulin therapy that a patient with diabetes may suffer.

Common:
Lipohypertrophy, injection site reactions such as redness, pain, itching, swelling or inflammation.

Uncommon:
Lipoatrophy

Rare:
Allergic reaction, visual impairment, retinopathy, edema (insulin may cause sodium retention and edema particularly if previously poor metabolic control is improved by intensified insulin therapy.

Very Rare:
Myalgia, Dysgeusia

CONTRAINDICATIONS
Insulin Glargine (Basagine®) must not be used in patients hypersensitive to Insulin glargine or any of its excipients.

WARNINGS AND PRECAUTIONS
Dosage adjustment and monitoring
Glucose monitoring is essential for all patients receiving insulin therapy. Changes to an insulin regimen should be made cautiously and only under medical supervision.

Changes in insulin strength, manufacturer, type, or method of administration may result in the need for a change in insulin dose or an adjustment in concomitant oral anti-diabetic treatment.

As with all insulin preparations, the time course of action for Insulin Glargine (Basagine) may vary in different individuals or at different times in the same individual and is dependent on many conditions including the local blood supply, local temperature, and physical activity.

Administration
Do not administer Insulin Glargine intravenously or via an insulin pump. The intended duration of activity of Insulin Glargine is dependent on injection into subcutaneous tissue.
Intravenous administration of the usual subcutaneous dose could result in severe hypoglycaemia.
Do not dilute or mix Insulin Glargine with any other insulin or solution. If Insulin Glargine is diluted or mixed, the solution may become cloudy, and the pharmacokinetic or pharmacodynamic profile (e.g., onset of action, time to peak effect) of Insulin Glargine and the mixed insulin may be altered in an unpredictable manner.

Hypoglycemia
Hypoglycemia is the most common adverse reaction of insulin, including Insulin Glargine. The risk of hypoglycemia increases with intensive glycemic control. Patients must be educated to recognize and manage hypoglycemia. Severe hypoglycemia can lead to unconsciousness or convulsions and may result in temporary or permanent impairment of brain function or death. The timing of hypoglycemia usually reflects the time-action profile of the administered insulin formulations. Other factors

such as changes in food intake (e.g., amount of food or timing of meals), exercise, and concomitant medications may also alter the risk of hypoglycemia.
The prolonged effect of subcutaneous Insulin Glargine may delay recovery from hypoglycemia. Patients being switched from twice daily NPH insulin to once-daily Insulin Glargine should have their initial Insulin Glargine dose reduced by 20% from the previous total daily NPH dose to reduce the risk of hypoglycemia.
As with all insulins, use caution in patients with hypoglycemia unawareness and in patients who may be predisposed to hypoglycemia (e.g., the pediatric population and patients who fast or have erratic food intake).
The patient's ability to concentrate and react may be impaired as a result of hypoglycemia. This may present a risk in situations where these abilities are especially important, such as driving or operating other machinery.
Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as longstanding diabetes, diabetic neuropathy, use of medications such as betablockers, or intensified glycemic control. These situations may result in severe hypo glycaemia (and, possibly, loss of consciousness) prior to the patient's awareness of hypoglycemia.

Hypersensitivity and allergic reactions
Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products, including Insulin Glargine.

Renal impairment
Due to its long duration of action, Insulin Glargine is not recommended during periods of rapidly declining renal function because of the risk for prolonged hypoglycemia.
Although studies have not been performed in patients with diabetes and renal impairment, a reduction in the Insulin Glargine dose may be required in patients with renal impairment because of reduced insulin metabolism, similar to observations found with other insulins.

Hepatic impairment
Due to its long duration of action, Insulin Glargine is not recommended during periods of rapidly declining hepatic function because of the risk for prolonged hypoglycemia.
Although studies have not been performed in patients with diabetes and hepatic impairment, a reduction in the Insulin Glargine dose may be required in patients with hepatic impairment because of reduced capacity for gluconeogenesis and reduced insulin metabolism, similar to observations found with other insulins.

Drug interaction
Some medications may alter insulin requirements and subsequently increase the risk for hypoglycemia or hyperglycemia.

Fluid retention and heart failure with concomitant use of PPAR-gamma agonists
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 Insulin Glargine, 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.

USE IN SPECIFIC POPULATIONS
Pregnancy
There are no well-controlled clinical studies of the use of Insulin Glargine in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is essential for patients with diabetes or a history of gestational diabetes to maintain good metabolic control before conception and throughout pregnancy. Insulin requirements may decrease during the first trimester, generally increase during the second and third trimesters, and rapidly decline after delivery. Careful monitoring of glucose control is essential in these patients.

Nursing Mothers
It is unknown whether insulin glargine is excreted in human milk. Because many drugs, including human insulin, are excreted in human milk, caution should be exercised when Insulin Glargine is administered to a nursing woman. Use of Insulin Glargine is compatible with breastfeeding, but women with diabetes who are lactating may require adjustments of their insulin doses.

Pediatric Use
The safety and effectiveness of subcutaneous injections of Insulin Glargine have been established in pediatric patients (age 6 to 15years) with type 1 diabetes. Insulin Glargine has not been studied in pediatric patients younger than 6 years of age with type 1diabetes. Insulin Glargine has not been studied in pediatric patients with type 2 diabetes.

Geriatric Use
Caution should be exercised when it 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.

DRUG INTERACTIONS
A number of drugs affect glucose metabolism and may require insulin dose adjustment and particularly close monitoring.
The following are examples of drugs that may increase the blood-glucose-lowering effect of insulins including Insulin Glargine and, therefore, increase the susceptibility to hypoglycemia: oral anti-diabetic products, pramlintide, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, propoxyphene, pentoxifylline, salicylates, somatostatin analogs, and sulfonamide antibiotics.
The following are examples of drugs that may reduce the blood-glucose-lowering effect of insulins including Insulin Glargine: corticosteroids, niacin, danazol, diuretics, sympathomimetic agents (e.g., epinephrine, albuterol, terbutaline), glucagon, isoniazid, phenothiazine derivatives, somatropin, thyroid hormones, estrogens, progestogens (e.g., in oral contraceptives), protease inhibitors and atypical antipsychotic medications (e.g. olanzapine and clozapine).
Beta-blockers, clonidine, lithium salts, and alcohol may either potentiate or weaken the blood glucose-lowering effect of insulin. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.
The signs of hypoglycemia may be reduced or absent in patients taking sympatholytic drugs such as beta-blockers, clonidine, guanethidine, and reserpine.

OVERDOSAGE
An excess of insulin relative to food intake, energy expenditure, or both may lead to severe and sometimes prolonged and life-threatening hypoglycemia. Mild episodes of hypoglycemia can usually be treated with oral carbohydrates. Adjustments in drug dosage, meal patterns, or exercise may be needed.
More severe episodes of hypoglycemia with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. After apparent clinical recovery from hypoglycemia, continued observation and additional carbohydrate intake may be necessary to avoid recurrence of hypoglycemia.

STORAGE CONDITIONS
Store in a refrigerator (2℃ - 8℃).
Do not freeze.
Protect from heat and sunlight.
Once opened, the vial may be used for up to four weeks when stored below 25℃. Do not use beyond this period. Solution for subcutaneous injection only.

Keep out of reach of children.

AVAILABILITY
In a box of I-PVC tray containing 3mL solution in 5mL USP Type I clear glass vial with cream color rubber stopper and aluminum seal with purple color flip off cap.

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

For suspected adverse drug reaction, report to FDA: www.fda.gov.ph

REGISTRATION NUMBER
BR-1154.

DATE OF FIRST AUTHORIZATION / RENEWAL OF AUTHORIZATION
03 June, 2016.

DATE OF REVISION OF PACKAGING INSERT
20 Aug, 2016.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

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www.getzpharma.com
A member of The Getz Group, USA.
PH-200008909

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Imported by: Getz Pharma (Phils.) Inc., 2/F Tower 1, The Rockwell Business Center, Ortigas Ave., Pasig City, Philippines.