Glartus®

Insulin Glargine (rDNA)

FORMS AND PRESENTATION
Glartus®: 100 U/ml; Solution for subcutaneous injection; 1 or 2 Prefilled pen x 3ml.
COMPOSITION
Glartus®: Each 1 ml contains 100 units of Insulin Glargine (rDNA).
Excipients: Metacresol, Glycerin, Zinc chloride, Water for injection.
Hydrochloric acid and sodium hydroxide are added to adjust the final pH.
PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
Pharmacotherapeutic group: Drug used in diabetes, insulins and analogues for injection, long-acting.
ATC code: A10AE04.
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 Glartus® 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, peak less, predictable concentration/time profile with a prolonged duration of action.
Insulin glargine is metabolized into 2 active metabolites M1 and M2.
Insulin receptor binding: *In vitro* studies indicate that the affinity of insulin glargine and its metabolites M1 and M2 for the human insulin receptor is 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 Glartus® therapy, are considerably lower than the pharmacological concentrations required to activate the IGF-1 pathway.
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.
Pharmacokinetic properties
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.
Insulin glargine injected once daily will reach steady state levels in 2-4 days after the first dose.
When given intravenously the elimination half-life of insulin glargine and human insulin were comparable.
After subcutaneous injection of Glartus® in diabetic patients, insulin glargine is rapidly metabolized at the carboxyl terminus of the Beta chain with formation of two active metabolites M1 (21A-Gly-insulin) and M2 (21A - Gly - des- 30B-Thr-insulin). In plasma, the principal circulating compound is the metabolite M1. The exposure to M1 increases with the administered dose of Glartus®. The pharmacokinetic and pharmacodynamic findings indicate that the effect of the subcutaneous injection with Glartus® 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 Glartus®.
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.
INDICATIONS
Glartus® is used for the treatment of Diabetes mellitus in adults, adolescents and children of 2 years and above who require insulin.
CONTRAINDICATIONS
• During episodes of hypoglycemia.
• Patients sensitive to insulin glargine or other excipients in injection solution.
PRECAUTIONS
- Glartus® 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 hyper- 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 Glartus®, 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.
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.
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.
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 insulin glargine and other insulins.
Combination of Insulin Glargine with pioglitazone
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 the combination of pioglitazone and Insulin Glargine is considered, 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.
Excipients
This medicinal product contains less than 1 mmol (23 mg) sodium per dose, i.e. it is essentially 'sodium-free'.
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 use machines in these circumstances.
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 1000 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 Glartus® may be considered during pregnancy, if clinically needed.
It is essential for patients with pre-existing or gestational diabetes to maintain good metabolic control throughout pregnancy to prevent adverse outcomes associated with hyperglycemia. Insulin requirements may decrease during the first trimester and generally increase during the second and third trimesters. Immediately after delivery, insulin requirements decline rapidly (increased risk of 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 aminoacids 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.

DRUG INTERACTIONS

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 and sulfonamide antibiotics.
- Substances that may reduce the blood-glucose-lowering effect include corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, oestrogens and 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.

ADVERSE EFFECTS

The following related adverse reactions are listed below 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; not known: cannot be estimated from the available data).
Immune system disorders: allergic reactions (rare).
Metabolism and nutrition disorders: hypoglycaemia (very common).
Nervous system disorders: dysgeusia (very rare).
Eyes disorders: visual impairment, retinopathy (rare).
Skin and subcutaneous tissue disorders: lipohypertrophy (common); lipoatrophy (uncommon); cutaneous amyloidosis (not known).
Musculoskeletal and connective tissue disorders: myalgia (very rare).
General disorders and administration site conditions: injection site reactions (common); oedema (rare).

DOSAGE AND ADMINISTRATION

Dosage:
- Glartus® contains insulin glargine, an insulin analogue, and has a prolonged duration of action.
- Glartus® 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, Glartus® 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 Glartus® and are not the same as IU or the units used to express the potency of other insulin analogues

Special population
Elderly population (≥65 years old)
In the elderly, progressive deterioration of renal function may lead to a steady decrease in insulin requirements.
Renal impairment
In patients with renal impairment, insulin requirements may be diminished due to reduced insulin metabolism.
Hepatic impairment
In patients with hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism.
Paediatric population
Safety and efficacy of Glartus® have been established in adolescents and children aged 2 years and older. The dose regimen (dose and timing) should be individually adjusted.
Switch from other insulins to Glartus®:
When switching from a treatment regimen with an intermediate or long-acting insulin to a regimen with Glartus®, a change of the dose of the basal insulin may be required and the concomitant antidiabetic treatment may need to be adjusted (dose and timing of additional regular insulins or fast-acting insulin analogues or the dose of oral antidiabetic medicinal products).
Switch from twice daily NPH insulin to Glartus®:
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 Glartus® 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 Glartus®:
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 Glartus® should reduce their dose by approximately 20%. During the first weeks the reduction should be compensated by an increase in mealtime insulin, and a close metabolic monitoring is also recommended, after this period the regimen should be adjusted individually. Patients with high insulin doses because of antibodies to human insulin may experience an improved insulin response with Glartus®.

Method of administration:
- Glartus® is administered subcutaneously.
- Glartus® should not be administered intravenously. The prolonged duration of action of Glartus® 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 Glartus®. Injection sites must be rotated within a given injection area from one injection to the next.
- Glartus® must not be mixed with any other insulin or diluted. Mixing or diluting can change its time/action profile and mixing can cause precipitation.
Please recover insulin glargine's temperature to room temperature before use and follow the injection steps:

How to Use the Pen?

Step 1. Choose an injection site: Abdomen, thighs or upper arms.
These areas have more fat and fewer nerve endings.
Step 2. Get ready.
• Remove the pen cap with clean hands.
• Check the reservoir to make sure the insulin is clear and colorless and has no particles. If not, use another pen.
Step 3. Attach the needle.
• Wipe the pen tip with an alcohol swab.
• Remove the protective seal from the new needle, line the needle up straight with the pen, and put the needle on.
• After you have attached, take off the outer needle cap and save it.
• Remove the inner needle cap and throw it away.
Step 4. Perform a safety test.
• Dial a test dose of 2 units.
• Hold pen with the needle pointing up and lightly tap the insulin reservoir so the air bubbles rise to the top of the needle. This will help you get the most accurate dose.
• Press the injection button all the way in and check to see that insulin comes out of the needle. The dial will automatically go back to zero after you perform the test.
• If no insulin comes out, repeat the test 2 more times. If there is still no insulin coming out, use a new needle and do the safety test again.
Step 5. Select the dose.
• Make sure the window show '0' and then select the dose.
• Check if you have enough insulin in the reservoir.
Step 6. Inject your dose.
• Clean site with alcohol swab.
• Keep the pen straight, insert the needle into your skin.
• Use your thumb to press the injection button all the way down. When the number in the dose window return to '0' as you inject, slowly count to 10 before removing.
• Release the button and remove the needle from your skin.
Step 7. Remove the needle.
• After injecting, always remove the needle to prevent contamination and leaking.
• Put the outer needle cap back on the needle and pull the needle from pen.
• Throw needle away in a sharp container.
• Put the pen cap back on the pen.
To prevent the possible transmission of disease, each pen must be used by one patient only.

OVERDOSAGE

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.

STORAGE CONDITIONS

Unused Glartus® Pen should be stored at 2-8˚C.
Do not freeze.
Glartus® used pen could be kept at room temperature (between 20˚C and 25˚C) and should be used within 28 days.
Keep away from light and heat.

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Marketing Authorization Holder
Benta S.A.L. - Lebanon
Manufacturer
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