FRONT

100 IU/mL
For Subcutaneous Use Only

Insulin Glargine Injection USP

Recombinant DNA Origin

GLARITUS®

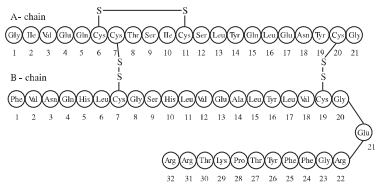
3 mL Cartridge I 10 mL Vial

COMPOSITION
Each mL contains:
Insulin Glargine USP ..... 100 IU
m-Cresol USP ..... 0.27 % w/v as preservative
Water for injection USP ..... q.s.
Zinc (as Zinc Chloride) 30 µg, Glycerol (85%) 20 mg, Glycine 1mg (for Vial pack only), Hydrochloric Acid q. s. to pH and Sodium Hydroxide q. s. to pH.

Pharmacotherapeutic group: Anti-diabetic agent (Long acting human insulin analogue).
ATC (Anatomical Therapeutic Chemical) Classification Code: A10AE04

DESCRIPTION
GLARITUS (insulin glargine injection) is a sterile clear and colourless solution of insulin glargine for subcutaneous use. Insulin glargine is a recombinant human insulin analog that is a long-acting, parenteral blood-glucose-lowering agent. Insulin glargine has low aqueous solubility at neutral pH. At pH 4 insulin glargine is completely soluble. After injection into the subcutaneous tissue, the acidic solution is neutralized, leading to formation of microprecipitates from which small amounts of insulin glargine are slowly released, resulting in a relatively constant concentration/time profile over 24 hours with no pronounced peak. This profile allows once daily dosing as basal insulin. GLARITUS is produced by recombinant DNA technology utilizing a non-pathogenic laboratory strain of Escherichia coli as the production organism. 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, insulin glargine is 21-Gly-30^{b}-a-L-Arg-30^{a}-b-L-Arg-human insulin and has the empirical formula $C_{267}H_{404}N_{72}O_{78}S_6$ and a molecular weight of 6063. Insulin glargine has the following structural formula:



CLINICAL PHARMACOLOGY
Mechanism of Action
The primary activity of insulin, including insulin glargine, is regulation of glucose metabolism. Insulin and its analogs lower blood glucose by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin inhibits lipolysis and proteolysis, and enhances protein synthesis.
Pharmacodynamics
The glucose-lowering effect on a molar basis (i.e., when given at the same doses) of intravenous insulin glargine is approximately the same as that for human insulin. Insulin Glargine differs because of its unique structure providing a smooth and peakless profile with a prolonged duration of action of 24 hours (end of observation period) compared to 14.5 hours for NPH human Insulin. The onset of action of Insulin Glargine is slower than NPH human Insulin.
The duration of action of insulin glargine after abdominal, deltoid, or thigh subcutaneous administration is reportedly similar. The time course of action of insulins, including GLARITUS, may vary between individuals and within the same individual.
Comparative Pharmacodynamics of Glaritus® with Lantus®
Pharmacodynamics of insulin glargine from Glaritus® was compared with that from Lantus® in two separate studies – one in healthy volunteers (n=40 in two-way cross-over design) and second in patients of type 1 diabetes mellitus (n = 111 in parallel group design) with successful achievement of bioequivalence of Glaritus® to Lantus® as displayed in the tables below.

Table 1: Pharmacodynamic comparison of Glaritus® to Lantus® in healthy volunteers

Pharmacodynamic Parameter	Geometric LSM		T/R Ratio	90% CI of T/R
	Glaritus® (T, N=69)	Lantus® (R, N=65)		
GIR_{max} (mg/kg/min, mean)	1.82	1.85	0.98	0.87 to 1.11
$AUC_{0-t_{clamp}}$ (h*mg/kg/min, mean)	20.99	21.63	0.97	0.83 to 1.14
GIR_T_{max} (hours, median)	12.83	12.83	12.83	P value 0.74

Table 2: Pharmacodynamic comparison of Glaritus® to Lantus® in Type 1 Diabetic patients (After exclusion of outlier values)

Pharmacodynamic Parameter	Geometric LSM		T/R Ratio	90% CI of T/R
	Glaritus® (T, N=94)	Lantus® (R, N=94)		
$AUC_{0-t_{clamp}}$ (h*mg/min, mean)	1310.36	1377.55	95.1	85.3 to 106.1
GIR_{max} (hours, mean)	109.27	112.81	96.9	89.9 to 104.4

Pharmacokinetics
Absorption And Bioavailability
After subcutaneous injection of Insulin Glargine, the Insulin serum concentrations indicate a slower, more prolonged absorption and a lack of a peak in comparison to NPH human Insulin. Concentrations are thus consistent with the time profile of the pharmacodynamics activity of Insulin Glargine.
Metabolism And Elimination
A reported metabolism study in humans indicates that insulin glargine is partly metabolized at the carboxyl terminus of the B chain in the subcutaneous depot to form two active metabolites with in vitro activity similar to that of human insulin, M1 (21A-Gly-insulin) and M2 (21A-Gly-des-30b-Thr-insulin). Unchanged drug and these degradation products are also present in the circulation.
Special Populations
Age, Race, And Gender
Effect of age, race, and gender on the pharmacokinetics of GLARITUS has not been evaluated. However, in reported clinical studies in adults and pediatric patients, subgroup analyses based on age, race, and gender did not show differences in safety and efficacy between insulin glargine and NPH insulin.
Obesity
Effect of Body Mass Index (BMI) on the pharmacokinetics of GLARITUS has not been evaluated.

INDICATIONS
GLARITUS is indicated to improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus.
Limitations Of Use
GLARITUS is not recommended for the treatment of diabetic ketoacidosis.

DOSAGE AND ADMINISTRATION
Important Administration Instructions
- Administer GLARITUS subcutaneously once daily at any time of day but at the same time every day.
- Prior to initiation of GLARITUS, train patients on proper use and injection technique.
- Patient should follow the Instructions for Use of pen device to correctly administer GLARITUS from cartridge.
- Administer GLARITUS subcutaneously into the abdominal area, thigh, or deltoid, and rotate injection sites within the same region from one injection to the next to reduce the risk of lipodystrophy [see **ADVERSE REACTIONS**].
- Visually inspect GLARITUS cartridges for particulate matter and discoloration prior to administration. Only use if the solution is clear and colorless with no visible particles.
- Refrigerate unused (unopened) GLARITUS cartridges.
- Do not administer intravenously or via an insulin pump.
- Do not dilute or mix GLARITUS with any other insulin or solution.
- The cartridges to be used in pen device are for single patient use only [see **WARNINGS AND PRECAUTIONS**].

General Dosing Instructions
- Individualize and adjust the dosage of GLARITUS based on the individual's metabolic needs, blood glucose monitoring results and glycemic control goal.
- Dosage adjustments may be needed with changes in physical activity, changes in meal patterns (i.e., macronutrient content or timing of food intake), during acute illness, or changes in renal or hepatic function. Dosage adjustments should only be made under medical supervision with appropriate glucose monitoring [see **WARNINGS AND PRECAUTIONS**].

Initiation Of GLARITUS Therapy
Type 1 Diabetes
- In patients with type 1 diabetes, GLARITUS must be used concomitantly with short-acting insulin. The recommended starting dose of GLARITUS in patients with type 1 diabetes should be approximately one-third of the total daily insulin requirements. Short-acting, prompt insulin should be used to satisfy the remainder of the daily insulin requirements.

Type 2 Diabetes
- The recommended starting dose of GLARITUS in patients with type 2 diabetes who are not currently treated with insulin is 0.2 units/kg or up to 10 units once daily. One may need to adjust the amount and timing of short- or rapid-acting insulins and dosages of any oral anti-diabetic drugs.

Changing To GLARITUS From Other Insulin Therapies
- If changing patients from once daily insulin glargine 300 Units/mL to once daily GLARITUS, the recommended initial GLARITUS dose is 80% of the insulin glargine 300 Units/mL dose that is being discontinued. This dose reduction will lower the likelihood of hypoglycemia.
- If changing from a treatment regimen with an intermediate- or long-acting insulin to a regimen with GLARITUS, a change in the dose of the basal insulin may be required and the amount and timing of the shorter-acting insulins and doses of any oral antidiabetic drugs may be needed to be adjusted.
- If changing patients from once-daily NPH insulin to once-daily GLARITUS, the recommended initial GLARITUS dose is the same as the dose of NPH that is being discontinued.
- If changing patients from twice-daily NPH insulin to once-daily GLARITUS, the recommended initial GLARITUS dose is 80% of the total NPH dose that is being discontinued. This dosage reduction will lower the likelihood of hypoglycemia.

CONTRAINDICATIONS
GLARITUS is contraindicated
- During episodes of hypoglycemia.
- In patients with hypersensitivity to GLARITUS or one of its excipients.

WARNINGS AND PRECAUTIONS
Never Share A GLARITUS Cartridge Or Needle Between Patients
GLARITUS cartridges must never be shared between patients, even if the needle is changed. Patients using GLARITUS must never reuse or share needles with another person. Sharing poses a risk for transmission of blood-borne pathogens.
Hyperglycemia Or Hypoglycemia With Changes In Insulin Regimen
Changes in insulin strength, manufacturer, type, or method of administration may affect glycemic control and predispose to hypoglycemia or hyperglycemia. These changes should be made cautiously and only under close medical supervision, and the frequency of blood glucose monitoring should be increased. For patients with type 2 diabetes, dosage adjustments of concomitant oral and anti-diabetic products may be needed.
Hypoglycemia
Hypoglycemia is the most common adverse reaction associated with insulin, including GLARITUS. Severe hypoglycemia can cause seizures, may be life-threatening or cause death. Hypoglycemia can impair concentration ability and reaction time; this may place an individual and others at risk in situations where these abilities are important (e.g., driving or operating other machinery).
Hypoglycemia can happen suddenly and symptoms may differ in each individual and change over time in the same individual. Symptomatic awareness of hypoglycemia may be less pronounced in patients with longstanding diabetes, in patients with diabetic nerve disease, in patients using medications that block the sympathetic nervous system (e.g., beta-blockers), or in patients who experience recurrent hypoglycemia.
Risk Factors For Hypoglycemia
The risk of hypoglycemia after an injection is related to the duration of action of the insulin and, in general, is highest when the glucose lowering effect of the insulin is maximal. As with all insulin preparations, the glucose lowering effect time course of GLARITUS may vary in different individuals or at different times in the same individual and depends on many conditions, including the area of injection as well as the injection site blood supply and temperature. Other factors which may increase the risk of hypoglycemia include changes in meal pattern (e.g., macronutrient content or timing of meals), changes in level of physical activity, or changes to co-administered medication. Patients with renal or hepatic impairment may be at higher risk of hypoglycemia.

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Risk Mitigation Strategies For Hypoglycemia
Patients and caregivers must be educated to recognize and manage hypoglycemia. Self-monitoring of blood glucose plays an essential role in the prevention and management of hypoglycemia. In patients at higher risk for hypoglycemia and patients who have reduced symptomatic awareness of hypoglycemia, increased frequency of blood glucose monitoring is recommended.
The long-acting effect of GLARITUS may delay recovery from hypoglycemia.
Medication Errors
Accidental mix-ups among insulin products, particularly between long-acting insulins and rapid-acting insulins, have been reported. To avoid medication errors between GLARITUS and other insulins, instruct patients to always check the insulin label before each injection.
Hypersensitivity And Allergic Reactions
Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products, including insulin glargine. If hypersensitivity reactions occur, discontinue insulin glargine; treat per standard of care and monitor until symptoms and signs resolve. Insulin glargine is contraindicated in patients who have had hypersensitivity reactions to insulin glargine or one of the excipients.
Hypokalemia
All insulin products, including GLARITUS, 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).
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 GLARITUS, 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 GLARITUS 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.
All pregnancies have a background risk of birth defects, loss, or other adverse outcome regardless of drug exposure. This background risk is increased in pregnancies complicated by hyperglycemia and may be decreased with good metabolic control. It is essential for patients with diabetes or history of gestational diabetes to maintain good metabolic control before conception and throughout pregnancy. In patients with diabetes or gestational diabetes, insulin requirements may decrease during the first trimester, generally increase during the second trimester, and rapidly decline after delivery. Careful monitoring of glucose control is essential in these patients. Therefore, female patients should be advised to tell their physicians if they intend to become, or if they become pregnant while taking GLARITUS.
Nursing Mothers
Endogenous insulin is present in human milk; 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 GLARITUS is administered to a nursing women. Use of GLARITUS 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 insulin glargine have been established in pediatric patients (age 2 to 15 years) with type 1 diabetes in reported clinical studies. The safety and effectiveness of insulin glargine in pediatric patients younger than 2 years of age with type 1 diabetes and pediatric patients with type 2 diabetes have not been established.
The dosage recommendation when changing to GLARITUS in pediatric patients (age 2 to 15 years) with type 1 diabetes is the same as that described for adults [see DOSAGE AND ADMINISTRATION]. As in adults, the dosage of GLARITUS must be individualized in pediatric patients (age 2 to 15 years) with type 1 diabetes based on clinical response and frequent monitoring of blood glucose.
In the reported pediatric clinical study, pediatric patients (age 2 to 15 years) with type 1 diabetes had a higher incidence of severe symptomatic hypoglycemia compared to the adults in studies with type 1 diabetes.
Geriatric Use
Caution should be exercised when GLARITUS 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.
Hepatic Impairment
The effect of hepatic impairment on the pharmacokinetics of GLARITUS has not been studied. Frequent glucose monitoring and dose adjustment may be necessary for GLARITUS in patients with hepatic impairment.
Renal Impairment
The effect of renal impairment on the pharmacokinetics of GLARITUS has not been studied. Some studies with human insulin have shown increased circulating levels of insulin in patients with renal failure. Frequent glucose monitoring and dose adjustment may be necessary for GLARITUS in patients with renal impairment.
Obesity
Subgroup analyses based on BMI in reported controlled clinical studies, did not show differences in safety and efficacy between insulin glargine and NPH.

ADVERSE REACTIONS
The following adverse reactions are discussed elsewhere:
- Hypoglycemia [see WARNINGS AND PRECAUTIONS]
- Hypersensitivity and allergic reactions [see WARNINGS AND PRECAUTIONS]
- Hypokalemia [see WARNINGS AND PRECAUTIONS].

Peripheral Edema
Some patients taking insulin glargine have experienced sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy.
Lipodystrophy
Administration of insulin subcutaneously, including insulin glargine, has resulted in lipoatrophy (depression in the skin) or lipohypertrophy (enlargement or thickening of tissue) in some patients.
Insulin Initiation And Intensification Of Glucose Control
Intensification or rapid improvement in glucose control has been associated with a transitory, reversible ophthalmologic refraction disorder, worsening of diabetic retinopathy, and acute painful peripheral neuropathy. However, long-term glycemic control decreases the risk of diabetic retinopathy and neuropathy.
Weight Gain
Weight gain has occurred with some insulin therapies including insulin glargine and has been attributed to the anabolic effects of insulin and the decrease in glucosuria.
Allergic Reactions
Local Allergy
As with any insulin therapy, patients taking GLARITUS may experience injection site reactions, including redness, pain, itching, urticaria, edema, and inflammation.
Systemic Allergy
Severe, life-threatening, generalized allergy, including anaphylaxis, generalized skin reactions, angioedema, bronchospasm, hypotension, and shock may occur with any insulin, including insulin glargine and may be life threatening.
Immunogenicity
As with all therapeutic proteins, there is potential for immunogenicity. All insulin products can elicit the formation of insulin antibodies. The presence of such insulin antibodies may increase or decrease the efficacy of insulin and may require adjustment of the insulin dose.
Medication errors have been reported in which other insulins, particularly rapid-acting insulins, have been accidentally administered instead of insulin glargine. To avoid medication errors between GLARITUS and other insulins, patients should be instructed to always verify the insulin label before each injection.
Other adverse event reported in patients administered with insulin glargine include upper respiratory tract infection, peripheral edema, hypertension, influenza, sinusitis, cataract, bronchitis, arthralgia, pain in extremity, back pain, cough, urinary tract infection, diarrhea, depression, headache, accidental injury, infection and retinal vascular disorder.

DRUG INTERACTIONS
Drugs That May Increase the Risk of Hypoglycemia
Drugs: Antidiabetic agents, ACE inhibitors, angiotensin II receptor blocking agents, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, pentoxifylline, pramlintide, propoxyphene, salicylates, somatostatin analogs (e.g., octreotide), and sulfonamide antibiotics.
Intervention: Dose reductions and increased frequency of glucose monitoring may be required when insulin glargine is co-administered with these drugs.
Drugs That May Decrease the Blood Glucose Lowering Effect of GLARITUS
Drugs: Atypical antipsychotics (e.g., olanzapine and clozapine), corticosteroids, danazol, diuretics, estrogens, glucagon, isoniazid, niacin, oral contraceptives, phenothiazines, progestogens (e.g., in oral contraceptives), protease inhibitors, somatropin, sympathomimetic agents (e.g., albuterol, epinephrine, terbutaline), and thyroid hormones.
Intervention: Dose increases and increased frequency of glucose monitoring may be required when insulin glargine is co-administered with these drugs.
Drugs That May Increase or Decrease the Blood Glucose Lowering Effect of GLARITUS
Drugs: Alcohol, beta-blockers, clonidine, and lithium salts. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.
Intervention: Dose adjustment and increased frequency of glucose monitoring may be required when insulin glargine is co-administered with these drugs.
Drugs That May Blunt Signs and Symptoms of Hypoglycemia
Drugs: beta-blockers, clonidine, guanethidine, and reserpine.
Intervention: Increased frequency of glucose monitoring may be required when insulin glargine is co-administered with these drugs.

OVERDOSAGE
Excess insulin administration may cause hypoglycemia and hypokalemia. 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. Hypokalemia must be corrected appropriately.
It is therefore recommended that the diabetic patient constantly carry some sugar lumps, sweets, biscuits, or sugary fruit juice. Adjustments in drug dosage, meal patterns, or exercise, may be needed.

STORAGE
GLARITUS cartridge and vial which is not in use should be stored in a refrigerator (+2° to +8° C) but not allowed to freeze.

Cartridge: Once opened, Glaritus Cartridge should be stored at temperature not above 30 °C for up to 4 weeks.
Vial: Once opened, Glaritus Vial should be stored at temperature not above 30 °C for up to 6 weeks.

Do not expose to excessive heat or direct sunlight. GLARITUS must be kept out of reach of children.

Insulin glargine must only be used if the solution is clear and colourless with no particles visible.

Insulin glargine must not be mixed with any other Insulin nor be diluted. Mixing or diluting can change its time/action profile and mixing can cause precipitation.

Remove the needle from the Pen after each injection, otherwise temperature changes may cause liquid to leak out of the needle and the Insulin concentration may increase.
Do not refill the GLARITUS cartridges and vials.
GLARITUS cartridge and vial should never be used after the expiry date.

PACK PRESENTATION
Cartridge: 3 mL Multi-Dose Cartridge - 1 x 5 Monocartons in a polybag
Vial: 10 mL Multi-Dose Vial - 1 x 10 Monocartons in a polybag

SHELF LIFE
36 Months

CONDITIONS OF SUPPLY
Prescription only medicine

Manufactured by:
WOCKHARDT LIMITED.
Biotech Park, H-14/2, MIDC, Waluj, Aurangabad - 431136, Maharashtra State, India

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