GLARITUS ®
Recombinant Insulin Glargine Injection 100 lU/ml

Read all of this leaflet carefully before you start taking GLARITUS ®

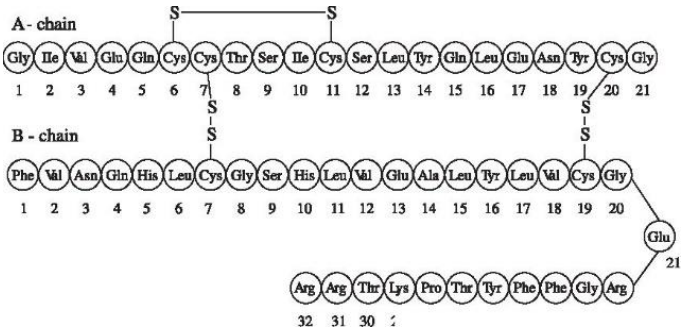
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, health care provider or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm Them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this
- Leaflet, please tell your doctor, health care provider or pharmacist.

In this leaflet:

a) What Is GLARITUS ®And What It Is Used For

Insulin Glargine Injection (rDNA origin} is a recombinant human insulin analogue produced by Recombinant DNA technology. 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 empirical formula $C_{267}H_{404}N_{72}O_{78}S_6$ and a molecular weight of 6063. It has the following structural formula:



Insulin glargine is a novel recombinant human insulin analogue, equipotent to human insulin. It exhibits a peakless glucose-lowering profile with a prolonged duration of action.

Pharmacodynamics

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.

Insulin Glargine differs from other insulins because its unique structure provides 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.
In clinical studies, intravenous Insulin Glargine and human insulin have been shown to be equipotent when given at the same doses. The onset of action of Insulin Glargine is slower than NPH human insulin.
The effect profile of Insulin Glargine is smooth and peakless, and the duration of its effect is prolonged compared to NPH human insulin.

Pharmacokinetics
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 action profile of the pharmacodynamics activity of Insulin Glargine.
Insulin Glargine is a human insulin analogue that has been designed to have low solubility at neutral pH. At pH 4, the pH of the Insulin
Glargine injection solution, it is completely soluble. After injection into the subcutaneous tissue, the acidic solution is neutralised, leading to formation of microprecipitates from which small amounts of Insulin Glargine are continuously released, providing a smooth, peakless, predictable time/concentration profile and a prolonged duration of action. This allows once daily dosing to meet a patient's basal insulin needs.

Insulin Glargine is partly degraded in the subcutaneous depot at the carboxyl terminus of the B chain to form the active metabolites, with similar in vitro activity to insulin.

Insulin Glargine is an insulin analogue indicated for once-daily subcutaneous administration in the treatment of type 1 or type 2 diabetes mellitus patients who require insulin for the control of hyperglycaemia.

b) Before you take or use GLARITUS ®.

Insulin Glargine is not intended for intravenous administration.
Intravenous administration of the usual subcutaneous dose could result in severe hypoglycaemia. Insulin Glargine is not the Insulin of choice for the treatment of diabetic ketoacidosis. Instead, intravenous regular Insulin is recommended in such cases.
Renal Impairment
In patients with renal impairment, Insulin requirements may be diminished. In the elderly, progressive deterioration of renal function may lead to a steady decrease in Insulin requirements.
Hepatic Impairment
In patients with severe hepatic impairment, Insulin requirements may
be diminished due to reduced capacity for gluconeogenesis and reduced Insulin metabolism.
Intercurrent Conditions
Insulin requirements may be altered during intercurrent conditions such as illness, emotional disturbances or stress.

Use in Pregnancy
To date, no relevant clinical trial data are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal or foetal development, parturition or postnatal development.
It is essential for patients with pre-existing or gestational diabetes to maintain good metabolic control throughout pregnancy. Insulin requirements may decrease during the first trimester, increase during the second and third trimesters and rapidly decline after delivery. Careful blood glucose control is essential in such patients.
Effects on the ability to drive and use machines:
The patient's ability to concentrate and react may be impaired as a result of hypoglycemia. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery).
Patients should therefore be advised to avoid hypoglycemia during driving. This is particularly significant in patients who have reduced awareness of the warning signs of hypoglycemia or have frequent episodes of hypoglycemia.

Drug Interactions
A number of substances affect glucose metabolism and may require insulin dose adjustment. Substances that may enhance the blood glucose lowering effect and susceptibility to hypoglycaemia include: oral antidiabetic agents, ACE inhibitors, pentoxifylline, perhexiline, disopyramide, fibrates, fluoxetine, MAO inhibitors, dextropropoxyphene, salicylates, sulphonamide antibiotics.
Substances that may reduce the blood glucose lowering effect and susceptibility to hyperglycaemia include: corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, oral contraceptives, phenothiazine derivatives, somatotrophin, sympathomimetic agents (eg epinephrine [adrenaline], salbutamol, terbutaline), thyroid hormones, protease inhibitors and atypical antipsychotic medications (eg olanzapine and clozapine).
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 be sometimes 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

c) How to take or use GLARITUS ®.

Insulin Glargine is given subcutaneously once a day. It may be administered at any time during the day, however, at the same time every day. It is not intended for intravenous administration.
The desired blood glucose levels as well as the doses and timing of Insulin Glargine, must be determined and adjusted individually by the physician.

With Insulin, it is important to use a syringe that is marked for the desired strength, e.g. U-40. Failure to use the proper syringe can lead to a mistake in dosage, causing serious problems such as severe hypoglycemia.
Insulin is usually administered in the abdominal wall, the thigh, the gluteal region or the deltoid region. Although absorption of Insulin Glargine does not differ between the injection sites, as with all Insulins, injection sites must be rotated from one injection to the next to avoid
lipodystrophy.
The average range of total daily Insulin requirement for maintenance in type 1 diabetic patients ranges between 0.5 and 1.0 IU/kg. Further, in Insulin resistance, the daily requirement of Insulin may be substantially higher. In patients with type 2 diabetes, the requirements of Insulin are lower i.e. approximately 0.3-0.6 IU/kg/day.
Dose adjustment may be required, if patients undertake increased physical activity or change their usual diet or if the patient's weight or lifestyle change or other circumstances arise that increase susceptibility to hypo or hyperglycaemia. Any change of Insulin dose should be made cautiously and only under medical supervision.

d) Possible side effects

The adverse events most commonly associated with human Insulin therapy include the following:

Hypoglycaemia

Hypoglycemia is the most common adverse effect of Insulin. The incidence of hypoglycemia in regimens that include Insulin Glargine is significantly reduced compared with regimens containing NPH human Insulin. The time of occurrence of hypoglycemia depends on the action profile of the Insulin and may, therefore, change when the treatment regimen is changed. While switching from twice daily NPH to once daily Glargine the dose of Glargine should be adjusted to avoid hypoglycemia.

Oedema

Insulin may cause sodium retention and oedema, particularly if previously poor metabolic control is improved by intensified Insulin therapy.

Hyperglycemia and Ketoacidosis

In patients with Insulin-dependent diabetes, prolonged hyperglycemia can result in diabetic acidosis. If uncorrected, prolonged hyperglycemia or diabetic acidosis can result in loss of consciousness or death.
Therefore, it is important that one should obtain medical assistance immediately.

Allergic Reactions

Local Allergy: Patients occasionally experience redness, swelling, and itching at the site of injection of Insulin. This condition called local allergy, usually clears up in a few days to a few weeks. In some instances, this condition may be related to factors other than Insulin, such as irritants in the skin cleansing agent.
Systemic Allergy: Less common, but potentially more serious, is generalized allergy to Insulin, which may cause rash over the whole body, shortness of breath, wheezing, reduction in blood pressure, fast pulse, or sweating. Severe cases of generalized allergy may be life threatening.

Injection site reactions

As with any Insulin therapy, lipodystrophy may occur at the injection site and delay Insulin absorption. Other injection site reactions with Insulin therapy include redness, pain, itching, hives, swelling and inflammation. Most minor reactions to Insulins usually resolve in a few days to a few weeks.

Insulin resistance

When Insulin requirement is increased (> 200 IU / day), Insulin resistance is said to have developed.

Antibody Production

Insulin administration may cause the formation of antibodies to Insulin. In rare cases, the presence of such Insulin antibodies may necessitate adjustment of the Insulin dose in order to correct a tendency to hyperglycaemia or hypoglycaemia.

Other

A marked change in glycaemic control may cause temporary visual impairment, due to temporary alteration in the turgidity and refractive index of the lens. Intensification of Insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy.

e) How to store GLARITUS ®.

Glaritus Cartridge which is not in use should be stored in a refrigerator (2° to 8°C) but not allowed to freeze. When in use, Cartridge may be used in Glaritus Pen or may be carried at room temperature (up to 25°C) for up to 4 weeks.

Do not expose to excessive heat or direct sunlight. Insulin Glargine Cartridge and dispopens 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 Insulin Glargine Dispo Pen and Cartridge

Insulin Glargine Dispo Pen and Cartridge should never be used after the expiry date.

Handling of Insulin Glargine Dispo Pen

Components

a. Dose Dialler
b. Dose Display Window
c. Dose Indicator
d. Glaritus DispoPen Body
e. Glaritus Cartridge
f. Cartridge Holder
g. Glaritus DispoPen Cap
h: Needle
i: Outer Protective Flap
j: Outer Protective Cap
k: Plunger

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Handling of dispopen
Getting started
a. Remove the DispoPen cap and check that the DispoPen contains the correct type of Insulin, i.e. Insulin Glargine.

Priming and injection
b. Remove the outer protective flap of the needle and firmly screw it onto the threads at the end of the cartridge holder.

c. Remove the outer protective cap and the needle cap from the needle.

d. It is important to prime the DispoPen before use to remove any air that may be inside the needle. Dial 2 units with the help of Dose Dialler. The dose display window shows the units of insulin dialled.

e. Hold Insulin Glargine DispoPen with the needle pointing upwards and tap the cartridge gently with the finger few times. Press the plunger all the way in.
Repeat steps d and e till a drop of insulin appears at the needle tip, ensuring the expulsion of air. Insulin Glargine DispoPen is now ready for use.

f. Check that the dose dialler is set to zero. Dial the number of units that need to be injected.

g. Insert the needle at the site of injection using the technique recommended by your doctor.

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h. Deliver the dose by pushing the plunger all the way in. The dose display window reads 0, this confirms that you have injected the right amount of insulin.

i. Count till 10 and remove the needle from the skin. Reattach the white outer protective needle cap and remove the needle. Replace the DispoPen cap on to the DispoPen. Dispose off the needle in the recommended way.

f) Further information

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

Presentation:
GLARITUS® Cartridge 3ml
GLARITUS® 10mL vial
GLARITUS® Dispo Pen

M. L. No. AD/004
Manufactured in India by WOCKHARDT LIMITED
Biotech Park, H-14/2 MlDC, Waluj, Aurangabad 431 136