# Glaine®

Recombinant Insulin Glargine Injection (r-DNA origin)
100 IU/ml
Solution for injection in a 3ml pre-filled pen, For SC use only
Each ml contains:
Insulin Glargine USP..... 100 IU
m-Cresol USP ..... 0.27% w/v as preservative
Zinc .....q.s.
Water for injection.....q.s.
If you have any problem reading the leaflet, please contact Vitane Pharmed.

**Drug Category**

Antidiabetic agent

Insulin Glargine injection (r-DNA 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. 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 hyperglycemia.

**General guidance for patient**

This medicine has been prescribed for your current disease, please do not use it in similar cases and do not recommend others, use this product. Read all of this leaflet carefully including the instructions for use Glaine®, before you start using this medicine because it contains important information for you.

**Dosage and Administration:** Drug dosage is prescribed by the physician with respect to patient's metabolic needs, eating habits, and other variables of his/her lifestyle. However, the usual drug dosage is as follows:

Insulin Glargine is given subcutaneously once daily. 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 administrated 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.bIn 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 the increase susceptibility to hypo or hyperglycemia. Any change of Insulin dose should be made cautiously and only under medical supervision.

**Changing over to Insulin Glargine:** The initial dose of Insulin Glargine should be determined individually, depending on the desired blood glucose levels. If changing from a treatment regimen with an intermediate- or long- acting Insulin to a regimen with Insulin Glargine, the amount and timing of short- acting Insulin or fast -acting Insulin analogue or the dose of any oral antidiabetic drug may need to be adjusted. A close metabolic monitoring under medical supervision is recommended during change over and in the initial weeks thereafter. With improved metabolic control and resultant increase in Insulin sensitivity (reduced Insulin requirements), further adjustment of the dose of Insulin Glargine and other Insulin or oral antidiabetic agents in the regimen may become necessary. Insulin Glargine must not be diluted or mixed with any other Insulin or solution. If Insulin Glargine is diluted or mixed, the solution may become cloudy and the pharmacokinetic / pharmacodynamics profile (e.g. onset of action, time to peak effect) of Insulin Glargine and/or the mixed Insulin may be altered in an unpredictable manner.

If you have missed a dose of Insulin Glargine or if you have not injected enough Insulin, your blood sugar level may become too high (hyperglycemia). Check your blood sugar frequently.

Do not take a double dose to make up for a forgotten dose.

**Warning and Precautions**

**Pediatric use:** Insulin Glargine can be administered to children aged 6 years and older. Safety and efficacy have not been established in children less than 6 years old.

**Geriatric use:** Compared to the entire study population, patients 65 years and older had an expected higher incidence of cardiovascular events in the Insulin Glargine and NPH human Insulin- treated groups. Because hypoglycemia (low blood sugar) may be more difficult to detect in the elderly, the initial dose, dose increments, and maintenance dose should be conservative to minimize the chance of hypoglycemic reactions.

**Pregnancy:** To date, studies have not been done in humans. Women with diabetes or a history of gestational diabetes must be educated about the necessity of maintaining good glycemic control before conception and during pregnancy to improve fetal outcome. Insulin requirements often are decreased during the first trimester and increased during the second and third trimesters and rapidly decline after delivery. Careful blood glucose control is essential in such patients.

FDA Pregnancy Category C

**Breast-feeding:** It is not known whether Insulin Glargine is distributed into breast milk. Women who are breast-feeding may require consultation with physician and adjustments in their dosages of Insulin Glargine or/ and in their meal plans.

Insulin Glargine is not intended for intravenous administration. Intravenous administration of the usual subcutaneous dose could result in severe hypoglycemia.

**Renal function impairment:** In patients with renal impairment, Insulin requirements may be diminished.

**Hepatic function impairment:** In patients with severe hepatic impairment, Insulin requirements may be diminished due to the reduced capacity for gluconeogenesis and reduced metabolism.

**Contraindications:** Talk to your doctor if you are:

-Hypersensitive to Insulin Glargine, any of its excipients or other medicines and foods
-Renal or hepatic function impaired

**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).

You should contact your doctor for advice on driving if:

- You have frequent episodes of hypoglycemia,
- The first warning symptoms which help you to recognize hypoglycemia are reduced or absent Intercurrent conditions and patient monitoring: Insulin requirements may be altered during intercurrent conditions such as illness, infection emotional disturbances, mood swing or stress

The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition:

- Blood glucose concentration (Monitoring essential as a guide to therapeutic efficacy)
- Glycosylated hemoglobin (hemoglobin A1C) determinations (periodic monitoring recommended to assess long-term glycemic control)

**Treatment of overdose & Hypoglycemia:**

An excess of Insulin relative to food intake, energy expenditure or both may lead to severe and sometimes long- term and life- threatening hypoglycemia.

Some symptoms of hypoglycemia include: anxiety; blurred vision; cold sweats; coma; confusion; cool; pale skin; difficulty in concentrating; dizziness; drowsiness; excessive hunger; fast heartbeat; headache; nausea; nightmares; restless sleep; seizures; shakiness; difficulty in speech ; tingling in the hands; feet; lips or tongue. Mild hypoglycemia without neurologic symptoms or loss of consciousness should be treated with immediate ingestion of glucose and adjustments to medication dosage and/or meal plan.

**Hypoglycemia and treatment:** Hypoglycemia with some signs such as: anxiety, blurred vision, cold sweats, coma, confusion, cool, pale skin, difficulty in concentrating, dizziness, drowsiness, excessive hunger, fast heartbeat, headache, nausea, nightmares, restless sleep, seizures, shakiness, difficulty in speech, tingling in the hands and feet, lips or tongue. Severe hypoglycemia including coma, seizure, or other neurologic impairment requires immediate emergency medical assistance. The patient should immediately be given intramuscular or subcutaneous glucagon, or intravenous glucose, and observed because relapse may occur following apparent clinical recovery. 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. Patients in whom intentional overdose is confirmed or suspected should be referred for psychiatric consultation.

**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.

In patients with insulin-dependent diabetes, these side-effects occur at the time of shortage of insulin and excessive increase of blood sugar, which may in turn happen because of forgetting the injection time, inadequate insulin injection, excessive consumption of sugar-containing food materials, fever, or infection. Its symptoms include drowsiness, blurry vision, thirst, or lack of appetite. The symptoms of acidosis exacerbation are shortness of breath and high pulse which may lead to coma or death if not being medically taken care of. Thus, the immediate medical actions are necessary. Insulin Glargine is not the Insulin of choice for the treatment of diabetic ketoacidosis. Short- acting intravenous (IV) Insulin is the preferred treatment.

**Drug interactions**

A number of substances affect glucose metabolism and may require Insulin or other drugs dose adjustment.

Drugs that may enhance the blood glucose lowering effect and susceptibility to hypoglycemia include: oral antidiabetic agents, (ACE) inhibitors, pentoxifylline, perhexiline, disopyramide, fibrates, fluoxetine, Monoamine oxidase (MAO) inhibitors, dextropropoxyphene, salicylates, and sulfonamide antibiotics

Drugs that may reduce the blood glucose lowering effect and susceptibility to hyperglycemia include: corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, contraceptives, phenothiazine derivatives, somatropin, sympathomimetic agents (e.g. epinephrine (adrenaline), salbutamol, terbutaline), thyroid hormones, protease inhibitors and atypical antipsychotic medications (e.g. olanzapine and clozapine)

Beta- adrenergic blocking agents, clonidine, lithium salts or alcohol may either potentiate or weaken the blood glucose lowering effect of Insulin. Pentamidine may cause hypoglycemia, which may be sometimes followed by hyperglycemia.

In addition, under the influence of sympatholytic medicinal products such as beta- adrenergic blocking agents, clonidine, guanethidine and reserpine, some of the symptoms of hypoglycemia may be masked and in this condition, detecting hypoglycemia is difficult. Inform your physician in case of using other drugs.

**Side/Adverse Effects**

Like all medicines, this medicine can cause side effects, although not everybody gets them. If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate) - not necessarily inclusive:

**Hypoglycemia:** 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.

Note: Recovery from hypoglycemia may be delayed because Insulin Glargine has a long duration of effect.

Systemic Allergy: Less common, but potentially more serious, is generalized allergy to Insulin, which may cause rash over the whole body, decrease in blood pressure; rapid pulse; shortness of breath; sweating. Severe cases of generalized allergy may be life-threatening.Those indicating need for medical attention only if they continue or are bothersome

**Injection site pain & Allergy:** This pain reaction is usually mild and did not result in discontinuation of therapy. Patients occasionally experience itching, redness, or swelling at injection site 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.

**Edemas:** Edema with signs: (bloating or swelling of face, hands, lower legs, and/or feet; rapid weight gain)

**Injection site reactions:** As with any Insulin therapy, lipodystrophy (depression of the skin) or lipohypertrophy (thickening of the skin) may occur at the injection site and delay Insulin absorption. These reactions usually resolve in a few days to a few weeks.

Continuous rotation of the injection site will also minimize this reaction.

Cutaneous amyloidosis is a skin reaction at the injection site, in which case it accumulates an abnormal protein (called amyloid) in the skin. If this is the case, consult your doctor.

**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 hyperglycemia or hypoglycemia.

A marked change in glycemic 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 glycemic control may be associated with temporary worsening of diabetic retinopathy.

Pharmacodynamics

Like other types of Insulin, the primary action of Insulin Glargine is to regulate glucose metabolism. Also, Insulin and its analogues lower the blood glucose concentration by stimulating peripheral glucose uptake, especially by skeletal, muscle and fat, and by inhibiting hepatic glucose production. Insulin also inhibits lipolysis in adipocytes, inhibits proteolysis, and enhances protein synthesis. Insulin Glargine differs from other Insulins because its unique structure provides a smooth and peakless effect 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.

**Pharmacokinetics**

After subcutaneous injection of Insulin Glargine, the Insulin serum concentration indicates 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 pharmacodynamic activity of Insulin Glargine. Insulin Glargine was formulated to have a low aqueous solubility at neutral pH. The Insulin Glargine solution has a pH of 4, and at this pH, it 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, providing a smooth, peakless, predictable time/ concentration profile and a prolonged duration of action. This allows once daily dosing-relatively constant concentration over 24 hours- to meet a patient's basal Insulin needs. There is no pronounced peak with Insulin Glargine.

Like other Insulins, the time course of action of Insulin Glargine may vary between individuals and within the same individual. In contrast to other Insulin products, the duration of action of Insulin Glargine was similar after subcutaneous injection into abdominal, deltoid, or thigh areas.

**Storage**

Store unopened pens in the refrigerator between 2 and 8 °C. Discard if it has been frozen. Keep Insulin pen in the outer carton in order to protect from light. If refrigeration is not possible, in use pen can be kept unrefrigerated for up to 28 days away from direct heat and light, as long as the temperature is not above 25 °C. In use pens, whether or not refrigerated, must be used within a 28- day period or they must be discarded. Insulin Glargine must be kept out of reach of children. Do not use this medicine after the expiry date. The expiry date refers to the last day of that month

**Signs of Drug Decay**

Insulin Glargine must only be used if the solution is clear and colorless with no particles visible.The bulk of relevant information regarding this drug product is mentioned in the leaflet. In order to gain more information, please contact the physician, pharmacist, or medical centers.

**Packaging**

Each box contains 5 pre- filled pens along with 3ml solution and one leaflet.

Introduction: Please read this manual completely and follow the directions carefully before using your pen, even if you have used a similar injection pen device before.

Important information:

-Only use pen after you have received adequate training from your healthcare professional.
-Always dispose of pen in compliance with local regulations after you have used it.
-Always use a new pen needle for each injection.
-Always keep the cap on the pen when it is not in use.
-Prior to using the pen always check if the proper pen with the correct drug is chosen.
-Always check the expiry date before use.
-Pen is a multiple-dose, variable-dose, prefilled disposable injection pen.
-To clean your pen a moist cloth is sufficient.
-Replace the pen needle after every use and do not store the pen with attached pen needle.

**Technical characteristics:**

Pen can deliver doses between 10 µl (microliter) and 600 µl in 10 µl increments.


**Read the instructions for use before using pen:**

-If the following instructions are not observed, there is a risk of receiving an incorrect dose of medication.
-If you have any doubts about your health, please consult your healthcare professional immediately.

Please follow the instructions for use for pen and only use the pen as directed by your healthcare professional.

**To ensure correct handling:**

-Children shall only use pen for self-injection if they have reached the age of 7 years and are supervised by trained adults experienced in its use.
-Pen must not be used by blind or visually handicapped patients without assistance from appropriately trained persons.
- Store pen out of the reach of children and any other persons who are not acquainted with how to handle it properly.
- If you do not understand or are unable to perform a step that is described in the operating instructions, contact your healthcare professional.

**To ensure correct use:**

- Only use pen with the scope of treatment that has been prescribed for you by your healthcare professional.
- Follow the instructions issued by your healthcare professional concerning the parts of the body suitable for injection. Any changes must be made under the supervision of a healthcare professional.
- Before using the pen, inspect the pen visually to ensure it is not damaged.
- Avoid disease transmission by using the pen and the pen needles only for one person.
- Avoid bending or breaking off the pen needle.
- Do not change the injection angle once the pen needle has been inserted into the skin.
- Changing the angle can cause the pen needle to bend or break off. A bent or broken pen needle can remain stuck in the body or remain
- Completely under the skin. If a broken pen needle remains stuck in the body or remains under the skin, seek medical help immediately.
- Never subject the pen to extreme temperature, direct sunlight and very cold conditions.
- Do not drop the pen and do not knock it against hard surfaces. Otherwise a functional test must be performed prior to use the pen again.
- Do not immerse the pen in water or any other liquid. Generally handle the pen with care.
- Never use pen if you have doubts about its proper operation.
- Never apply excessive force to the pen.
- Never attempt to overcome a device-induced stoppage by applying force. The pen may be damaged and no longer operate properly.
- Never attempt to repair a damaged pen yourself. If pen is damaged, contact your Customer Service.

Audible and tactile indicators

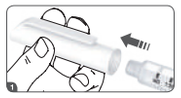
Your pen features audible and tactile indicators while setting the dose. For every drug unit that is added to the dose or corrected an audible click and tactile resistance is perceived.

**Compatible pen needles**

-Ypsomed Click fine® Needles
-BD Ultra- Fine® Needles

Dispose of pen after the cartridge is discharged. You can dispose of pen in accordance with local waste regulations or along with household waste.

**Important Information for use of pen:**

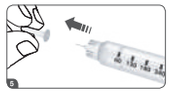


**1.** Pull off the pen cap.

**2.** Pull off the protective foil on the pen needle.


**3.** Click the pen needle onto the UnoPen®, keeping it straight.

**4.** Pull off the outer pen needle cap and keep for use after the injection.



**5.** Pull off the inner pen needle cap and dispose of it.
important: Prior to the first injection, the UnoPen® must be primed in order to remove air bubbles from the cartridge for accurate dosing and/or to ensure that the needle is not clogged.

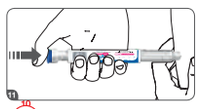
**6.** Select a dose of 2 units by turning the dose knob clockwise (2 clicks).
If necessary the selected dose can be corrected by turning the dose knob counter-clockwise.


**7.** Hold the pen in an upright position (pen needle pointing up). Tap slightly with your finger on the cartridge holder to allow potential air bubbles within the cartridge to rise up.
**Note:** Air bubbles are not always present. Nevertheless this step should be performed to check drug flow through the pen needle prior to each injection.

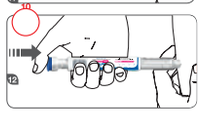
**8.** Press the push button all the way until a hard stop is felt to discharge the dose. Number '0' is visible in the display window and aligns with the dose indicator

**9.** Check whether a droplet of liquid shows at the tip of the pen needle. If no drops appear repeat steps 6–9 (Priming/functional test) until a drop appears. In case no drops emerge after 5 attempts, replace the pen needle (see step 13) and repeat the functional test (see steps 6–9).

**10.** . Turn the dose knob clockwise until the prescribed dose aligns with the dose indicator in the display window. If necessary the dose can be corrected by turning the dose knob counter-clockwise. Make sure not to press the push button while dialing the dose to avoid loss of drug.



**11.** Hold the pen so that the display window is visible during the injection. Insert the pen needle into the skin and press the push button all the way in until a hard stop is felt and the number '0' is visible in the display window and aligns with the dose indicator. Use the injection technique recommended by your doctor or healthcare professional.



**12.** When the complete dose has been delivered, keep the push button pressed for another 10 seconds. Then slowly remove the pen from the injection site at a 90° angle. Holding ensures a complete discharge of the drug dose. Do not tilt the pen during injection and removal from skin to avoid pen needle damage.

**13.** Replace the outer needle cap carefully. Unscrew the pen needle counter-clockwise and dispose of the pen needle safely in accordance with local regulations.

**14.** Firmly attach the pen cap to the pen for protection between injections

**Storage instruction**

If your pen is in cool storage, take it out 1 to 2 hours before you inject to allow it to warm up. Cold Insulin is more painful to inject.

Protect your pen from dust and dirt. Do not soak, wash or lubricate the pen as this may damage it. It should be handled with care. Avoid situations where pen might be damaged. If you are concerned that your pen may be damaged, use a new one.

**Reference**

United State Pharmacopeia Drug Information (USPDI)

30-Nov-2021

**Marketing Authorization Holder:** Vitane Pharmed
Under technical collaboration with Vitane Pharma GmbH, Germany
**Address:** Nazarabad Industrial Park, Nazarabad, Alborz, Iran
www.vitanepharmed.com

VITANE Quality to Life

ABT/CBLT-01