Version number: LG01-PI-07

date: 2022.05.16

Insulin Glargine Injection

DRUG NAME

Generic name: Insulin Glargine Injection

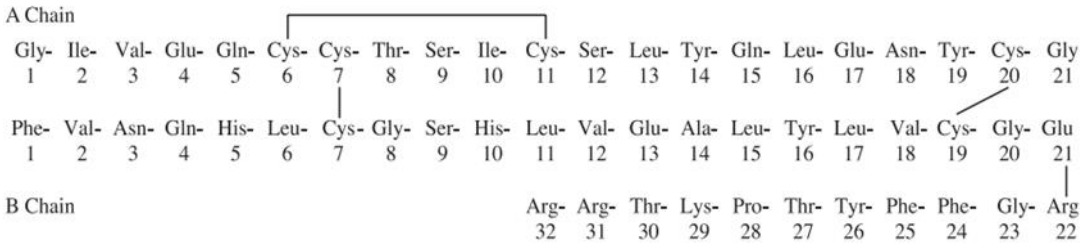
Trade name: Basalin®

COMPOSITION

Active ingredient: Insulin Glargine

Chemical name: 21^{A}-Gly-30^{B}a-L-Arg-30^{B}b-L-Arg-human insulin

Chemical structural formula:



Molecular formula: $C_{267}H_{404}N_{72}O_{78}S_6$

Molecular weight: 6063 Da

Excipient: Zinc chloride, M-cresol, Glycerol, Sodium hydroxide (for pH adjustment), Hydrochloric acid (for pH adjustment), Water for injections

DESCRIPTION

Clear, colorless, sterile solution filled in colorless and transparent cartridge

INDICATION

Basalin is indicated to improve glycemic control in adults with type 1 and type 2 diabetes mellitus.

STRENGTHS

100 units/mL in 3-mL cartridge

DOSAGE AND ADMINISTRATION

Usage

Basalin is administered subcutaneously.

Basalin should not be administered intravenously. The prolonged duration of action of Basalin 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 Basalin. Injection sites must be rotated within a given injection area from one injection to the next in order to reduce the risk of lipodystrophy and cutaneous amyloidosis.

Basalin must not be mixed with any other insulin or diluted. Mixing or diluting can change its time/action profile and mixing can cause precipitation.

Wipe the skin with an alcohol swab to clean the injection site. Let the injection site dry before you inject your dose.

Please bring Basalin to room temperature before use and follow the injection steps described below:

(1) Check the insulin to make sure it is clear and colorless. Do not use Basalin if it is colored or cloudy, or if you see particles in the solution.

(2) Please refer to the relevant reusable pen package insert, when using Basalin in conjunction with a reusable pen.

(3) Basalin is injected under the skin (subcutaneously) of your upper arm, thigh, or stomach area (abdomen). Wipe the skin with an alcohol swab to clean the injection site. Let the injection site dry before injection. Rotate injection sites within the same region from one injection to the next to reduce the risk of lipodystrophy and localised cutaneous amyloidosis.

(4) Pinch the skin of the injection site with your fingers and puncture the needle. After the pusher is pushed to the end, keep the needle under the skin for a few seconds to ensure that the correct dose is injected, then pull out the needle, and gently press the injection site with the sterile cotton ball for a few seconds, but do not rub the injection site to avoid damage to the subcutaneous tissue or cause the exudation of Basalin.

Dosage

Basalin has a prolonged duration of action, and should be administered subcutaneously once daily at any time but at the same time each day.

Individualize and adjust the dosage of Basalin based on the individual's metabolic needs, blood glucose monitoring results and glycemic control goal. The dose regimen (dose and timing) should be individually adjusted. In patients with type 2 diabetes mellitus, Basalin can also be given together with orally active antidiabetic medicinal products.

Switch from other insulins to Basalin

When switching from a treatment regimen with an intermediate or long-acting insulin to a regimen with Basalin, 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 Basalin

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 Basalin should reduce their daily dose of basal insulin by 20-30% during the first weeks of treatment.

Patients with high insulin doses because of antibodies to human insulin may experience an improved insulin response with Basalin.

Close metabolic monitoring is recommended during the switch and in the initial weeks thereafter.

With improved metabolic control and resulting increase in insulin sensitivity, a further adjustment in dose regimen may become necessary. Dose adjustment may also be required, for example, if the patient's weight or life-style changes, change of timing of insulin dose or other circumstances arise that increase susceptibility to hypo- or hyperglycaemia.

Due to limited experience, the safety and effectiveness of insulin glargine in the following patient groups need to be evaluated:

Children, and patients with liver damage, patients with moderate or severe renal impairment.

ADVERSE REACTIONS

Tabulated list of adverse reactions

The following related adverse reactions from clinical investigations 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).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

MedDRA system organ classes	**Very common**	**Common**	**Uncommon**	**Rare**	**Very rare**
Immune system disorders				Allergic reactions	
Metabolism and nutrition disorders	Hypoglycaemia				
Nervous system disorders					Dysgeusia
Eyes disorders				Visual impairment Retinopathy	
Skin and subcutaneous tissue disorders		Lipohypertrophy	Lipoatrophy		
Musculoskeletal and connective tissue disorders					Myalgia
General disorders and		Injection site reactions		Oedema	

administration site conditions					

Hypoglycemia

Hypoglycemia may occur if the insulin dose is too high and/or uncoordinated diet and exercise in relation to the insulin requirement.

Metabolism and nutrition disorders

Severe hypoglycaemic attacks, especially if recurrent, may lead to neurological damage. Prolonged or severe hypoglycaemic episodes may be life-threatening.

In many patients, the signs and symptoms of neuroglycopenia are preceded by signs of adrenergic counter-regulation. Generally, the greater and more rapid the decline in blood glucose, the more marked is the phenomenon of counter-regulation and its symptoms.

Immune system disorders

Immediate-type allergic reactions to insulin are rare. Such reactions to insulin (including insulin glargine) or the excipients may, for example, be associated with generalised skin reactions, angio-oedema, bronchospasm, hypotension and shock, and may be life-threatening.

Insulin treatment may induce production of insulin antibodies. According to the foreign literature, in clinical studies, antibodies that cross-react with human insulin and Basalin were observed with the same frequency in both NPH-insulin and Basalin treatment groups. In rare cases, due to the presence of insulin antibodies, it may necessitate to adjust insulin dose in order to correct a tendency of hyperglycemia or hypoglycemia.

Eyes disorder

A marked change in glycemic control may cause temporary visual impairment, due to temporary alteration in the turgidity and refractive index of the lens.

Long-term improved glycemic control decreases the risk of progression of diabetic retinopathy. However, intensification of insulin therapy with abrupt improvement in glycemic control may be associated with temporary worsening of diabetic retinopathy. In patients with proliferative retinopathy, particularly if not treated with photocoagulation, severe hypoglycemic episodes may result in transient amaurosis.

Skin and subcutaneous tissue disorders

Lipodystrophy may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent lipoatrophy or lipohypertrophy.

General disorders and administration site conditions

Injection site reactions include redness, pain, itching, hives, swelling, or inflammation. Most minor reactions to insulins at the injection site usually resolve in a few days to a few weeks.

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

Cardiovascular risk

According to the literature, the Outcome Reduction with Initial Glargine Intervention trial (i.e., ORIGIN) was an open-label, randomized, 2-by-2, factorial design study. One intervention in ORIGIN compared the effect of Insulin Glargine to standard care on major adverse cardiovascular outcomes in 12,537 participants ≥50 years of age with abnormal glucose levels (i.e., impaired fasting glucose [IFG] and/or impaired glucose tolerance [IGT]) or early type 2 diabetes mellitus and established cardiovascular (i.e., CV) disease or CV risk factors at baseline.

The objective of the trial was to demonstrate that Insulin Glargine use could significantly lower the risk of major cardiovascular outcomes compared to standard care. Two coprimary composite cardiovascular endpoints were used in ORIGIN. The first coprimary endpoint was the time to first occurrence of a major adverse cardiovascular event defined as the composite of CV death, nonfatal myocardial infarction and nonfatal stroke. The second coprimary endpoint was the time to the first occurrence of CV death or nonfatal myocardial infarction or nonfatal stroke or revascularization procedure or hospitalization for heart failure.

Participants were randomized to either Insulin Glargine (N=6264) titrated to a goal fasting plasma glucose of ≤95 mg/dL or to standard care (N=6273). Anthropometric and disease characteristics were balanced at baseline. The mean age was 64 years and 8% of participants were 75 years of age or older. The majority of participants were male (65%). Fifty-nine percent were Caucasian, 25% were Latin, 10% were Asian and 3% were Black. The median baseline BMI was 29 kg/m^2. Approximately 12% of participants had abnormal glucose levels (IGT and/or IFG) at baseline and 88% had type 2 diabetes. For patients with type 2 diabetes, 59% were treated with a single oral antidiabetic drug, 23% had known diabetes but were on no antidiabetic drug and 6% were newly diagnosed during the screening procedure. The mean HbA1c (SD) at baseline was 6.5% (1.0). Fifty-nine percent of participants had had a prior cardiovascular event and 39% had documented coronary artery disease or other cardiovascular risk factors.

Vital status was available for 99.9% and 99.8% of participants randomized to Insulin Glargine and standard care respectively at end of trial. The median duration of follow-up was 6.2 years (range: 8 days to 7.9 years). The mean HbA1c (SD) at the end of the trial was 6.5% (1.1) and 6.8% (1.2) in the Insulin Glargine and standard care group respectively. The median dose of Insulin Glargine at end of trial was 0.45 U/kg. Eighty-one percent of patients randomized to Insulin Glargine were using Insulin Glargine at end of the study. The mean change in body weight from baseline to the last treatment visit was 2.2 kg greater in the Insulin Glargine group than in the standard care group. The rates of severe hypoglycaemia (affected participants per 100 participant years of exposure) were 1.05 for insulin glargine and 0.30 for standard care group and the rates of confirmed non-severe hypoglycaemia were 7.71 for insulin glargine and 2.44 for standard care group. Over the course of this 6-year study, 42% of the insulin glargine group did not experience any hypoglycaemia.

Overall, the incidence of major adverse cardiovascular outcomes was similar between groups. All-cause mortality was also similar between groups.

Cardiovascular Outcomes in ORIGIN – Time to First Event Analyses

	Insulin Glargine N=6264	Standard Care N=6273	Insulin Glargine vs Standard Care
	n (Events per 100 PY)	n (Events per 100 PY)	Hazard Ratio (95% CI)
Coprimary endpoints			
CV death, nonfatal myocardial infarction, or nonfatal stroke	1041 (2.9)	1013 (2.9)	1.02 (0.94, 1.11)
CV death, nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure or revascularization procedure	1792 (5.5)	1727 (5.3)	1.04 (0.97, 1.11)
Components of coprimary endpoints			
CV death	580	576	1.00 (0.89, 1.13)
Myocardial Infarction (fatal or non-fatal)	336	326	1.03 (0.88, 1.19)
Stroke (fatal or non-fatal)	331	319	1.03 (0.89, 1.21)
Revascularizations	908	860	1.06 (0.96, 1.16)
Hospitalization for heart failure	310	343	0.90 (0.77, 1.05)

CONTRAINDICATIONS

Hypersensitivity to insulin glargine or to any of the excipients listed in ***COMPOSITION***.

PRECAUTIONS

Basalin must not be mixed with any other insulin or diluted, and make sure no other substance inside injector before use.

The long action of Basalin is related to the release rate of insulin after subcutaneous injection. Severe hypoglycemia may occur in case of intravenous injection. Do not intravenously inject Basalin.

Basalin is not the insulin choice for the treatment of diabetic ketoacidosis. Instead, regular insulin administration is recommended in such cases. The insulin dose of patients with renal impairment may be reduced due to reduced insulin metabolism. In the elderly, progressive deterioration of renal function may lead to a steady decrease in insulin requirements.

The insulin dose of patients with hepatic impairment may be reduced due to lower gluconeogenesis ability and reduced insulin metabolism.

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.

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.

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 Basalin, 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.

Combination of insulin glargine with pioglitazone

Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially for patients with risk factors for development of cardiac heart failure. This should be kept in mind if treatment with the combination of pioglitazone and Basalin is considered.

If pioglitazone is used in combination with Basalin, symptoms and signs of heart failure such as weight gain and edema should be observed. If any deterioration in cardiac symptoms occurs, pioglitazone should be discontinued.

Effect 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.

USE FOR PREGNANT WOMEN AND NURSING MOTHERS

Ask your doctor or pharmacist for advice taking any medicine

Pregnancy

According to the literature, 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 Basalin 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. 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 hypoglycemia). Careful monitoring of glucose control is essential.

Breast-feeding

Patients with diabetes who are breast-feeding may require adjustments in insulin dose, diet or both.

PEDIATRIC USE

The safety and efficacy of Basalin have not been established in children. No data are available.

GERIATRIC USE

In the elderly, progressive deterioration of renal function may lead to a steady decrease in insulin requirements.

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.

OVERDOSAGE

Insulin overdose may lead to severe and sometimes long-term and life-threatening hypoglycemia.

Mild episodes of hypoglycemia can usually be treated with oral carbohydrates or sugary substances (such as biscuits, juice, candy, etc.). 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 hypoglycemia may recur after apparent clinical recovery.

PHARMACODYNAMICS

Pharmacology

Insulin glargine is a human insulin analog produced by recombinant DNA technology. Like other insulins, insulin glargine's primary function is regulation of glucose metabolism by stimulating glucose uptake in peripheral tissues, especially by muscles and fat, and by inhibiting hepatic glucose production. Simultaneously insulin glargine inhibits lipolysis of adipocytes and proteolysis, and enhance protein synthesis.

Genetic toxicity

Insulin glargine was not mutagenic in tests for detection of gene mutations in bacteria and mammalian cells (Ames and HGPRT-test) and in tests for detection of chromosomal aberrations (cytogenetics in vitro in V79 cells and in vivo in Chinese hamsters).

Reproductive toxicity

Female rats were injected subcutaneously with insulin glargine from before mating to pregnancy, the dose reached 0.36mg/kg/d, pregnant rabbits were injected subcutaneously with 0.072mg/kg/d during organogenesis, which is respectively about 7 times and 2 times recommended human subcutaneous starting dose of 10U/d (0.008mg/kg/d), the effect of insulin glargine on rats and rabbits is not significantly different from human insulin. In the high-dose group, 5 out of 2 litters of rabbits showed ventricular dilatation. Fertility and early embryonic development were not abnormal.

In the combined test of rat fertility and prenatal and postpartum, rats were injected subcutaneously with insulin glargine 0.36mg/kg/d, calculated as mg/m^2, which is 7 times the recommended human subcutaneous starting dose of 10U/d (0.008mg/kg /d), it can be seen that the dose-related maternal toxicity caused by hypoglycemia, including death. Consequently, a reduction of the rearing rate occurred in the high-dose group only. Similar effects were observed with NPH insulin.

Carcinogenesis

In mice and rats, standard two-year carcinogenicity studies with insulin glargine were performed at doses up to 0.455 mg/kg, which was approximately 5 and 10 times the recommended human subcutaneous starting dose of 10U/day (0.008 mg/kg/d). Histiocytomas were found at injection sites in male rats and mice in acid vehicle containing groups and are considered a response to chronic tissue irritation and inflammation in rodents. These tumors were not found in female animals, in saline control, or insulin comparator groups using a different vehicle.

PHARMACOKINETICS

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.

After subcutaneous injection in diabetic patients, insulin glargine is rapidly metabolized at the carboxyl terminus of the Beta chain to form 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 Basalin. The pharmacokinetic and pharmacodynamic findings indicate that the effect of the subcutaneous injection with Basalin 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 Basalin.

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.

STORAGE

Unopened cartridges

Store in a refrigerator (2°C -8°C)
Do not freeze or place next to freezer compartment or a freezer pack.
Keep the cartridge in the outer carton in order to protect from light.

In-use cartridges

The medicinal product may be stored for maximum of 4 weeks not above 25 °C and away from direct heat or direct light.

PACKAGE

Cartridge, compound aluminum cap, brominated butyl rubber stopper, 1 cartridge/box

SHELF LIFE

Unopened cartridges

36 months

In-use cartridges

28 days

MANUFACTURER

Name: Gan & Lee Pharmaceuticals

Address: No. 8 Nanfeng West 1st Street, Huoxian, Tongzhou District, Beijing, China.

Postal code: 101109

Tel/Fax: +86 800 810 5020, +86 10 6050 4998

Http://www.ganlee.com