Biocon

For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

100 IU/mL

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Insulin Glargine Injection (rDNA)

4268

BASALOG Refil®
बेसल्लौग रीफिल

3 mL Cartridges

Insulin Glargine is a recombinant. Human insulin analogue that is a long acting (up to 24 hour duration of action) parenteral blood-glucose-lowering agent.

Solution for injection in a cartridge, for subcutaneous use only.
BASALOG Refil® 3 mL cartridges are available in the strength of 100 IU/mL for use with INSUPen EZ® and INSUPen Pro® (re-usable injector) only.

Composition:
Each mL contains
Insulin Glargine (rDNA) 100 IU
m-Cresol..2.7 mg (as preservative)
Excipients q.s.
(Each 100 units is equivalent to 3.64 mg insulin glargine)

Pharmaceutical form
A clear colorless solution for injection in cartridge.

Description:
Insulin glargine differs from human insulin 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.

Therapeutic Indications
For the treatment of adults, adolescents and children of 2 years of above with diabetes mellitus, where treatment with insulin is required.

Dosage and method of administration:
Insulin glargine is an analogue of human insulin which exhibits a relatively constant glucose lowering profile over 24 hours that permit once daily dosing. Potency of insulin glargine is approximately the same as human insulin.

BASALOG Refil® is recommended for once daily subcutaneous administration and may be administered at any time during the day. However, once started it should be administered at the same time every day. For patients requiring change in dosing and timing with **BASALOG Refil®** see Warnings and Precautions. **BASALOG Refil®** is not recommended for intravenous administration (see precautions). Intravenous administration of the usual subcutaneous dose could result in severe hypoglycaemia. The desired blood glucose levels as well as the doses and timing of other anti-diabetic medications must be determined individually. Blood glucose monitoring is recommended for all patients with diabetes.

The prolonged duration of action of **BASALOG Refil®** is dependent on injection into subcutaneous space. As with all insulins, injection sites within an injection area (abdomen, thigh, or deltoid) must be rotated from one injection to the next.

In published clinical studies, there was no relevant difference in insulin glargine absorption after abdominal, deltoid, or thigh subcutaneous administration. As for all insulins, the rate of absorption, and consequently the onset and duration of action, may be affected by exercise and other variables.

BASALOG Refil® is not the insulin of choice for treatment of diabetes ketoacidosis. An intravenous short-acting insulin is the preferred treatment**.**

Initiation of BASALOG Refil® therapy:
Depending on the need of basal insulin appropriate amount of **BASALOG Refil®** should be used as a basal insulin component and the post prandial insulin requirements should be taken care of by using short acting/rapid acting premeal insulin.
Based on published information the recommended starting dose for type-2 diabetic patients who are not on insulin is 10 IU once daily on average and subsequently adjusted according to the patient's need to a total daily dose ranging from 2 to 100 IU, however doses need to be individualized by the prescriber for a particular patient.

Paediatric use:
Insulin glargine can be administered to children ≥ 2 years of age. Administration to children <2 years has not been studied.

Geriatric use:
In elderly patients with diabetes, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycaemic reactions. Hypoglycaemia may be difficult to recognize in the elderly.

Changeover to BASALOG Refil®.
If changing from a treatment regimen with an intermediate or long-acting insulin to a regimen with **BASALOG Refil®** the amount and timing of short-acting insulin or fast-acting insulin analogue or dose of any oral anti-diabetic drug may need to be adjusted.

Based on the published clinical studies it is recommended that:
- If transferring patients from once-daily NPH insulin to once-daily **BASALOG Refil®** the recommended initial glargine dose should be the same as the dose of NPH that is being discontinued.
- If transferring patients from twice-daily NPH insulin to once-daily **BASALOG Refil®**, the recommended initial **BASALOG Refil®** dose should be 80% of the total NPH dose i.e. being discontinued. This dose reduction will lower the likelihood of hypoglycaemia.

A program of close metabolic monitoring under medical supervision is recommended during transfer and the initial weeks thereafter. The amount and timing of short-acting insulin or fast acting insulin analogue may be need to be adjusted. This is particularly true for patients with acquired antibodies to human insulin needing high-insulin doses and occurs with all insulin analogues. Dose adjustment of insulin glargine and other insulins or oral anti-diabetes drugs may be required; for example, if the patients timing of dosing, weight or lifestyle changes, or other circumstances arise that increase susceptibility to hypoglycaemia or hyperglycaemia. The dose may also have to be adjusted during intercurrent illness (see precautions).

Instructions to be given to the patients on how to handle **BASALOG Refil®** cartridge
1. The **BASALOG Refil®** cartridges are designed to be used with INSUPen EZ® and INSUPen Pro® detailed instruction accompanying the INSUPen EZ® and INSUPen Pro® must be followed.
2. If the patient is treated with **BASALOG Refil®** cartridge and another insulin cartridge, two INSUPen EZ® and INSUPen Pro®should be used, one for each type of insulin.
3. The **BASALOG Refil®** cartridges are for single person use only, and should not be shared with anyone else.
4. The **BASALOG Refil®** cartridges are not to be refilled.

Before using BASALOG Refil® cartridge
- Check the label to make sure it is the right type of Insulin.
- Remove the cartridge from the blister pack by pushing through the foil side of the packaging.
- Appearance of air bubble is a normal phenomenon, vigorous shaking immediately before the dose is administered may also result in the formation of air bubbles which could cause dosage errors; in that case tap the container gently with your finger a small air bubble may remain in cartridge after taping; this small air bubbles will not affect your dose.
- Detailed instruction accompanying the INSUPen EZ® and INSUPen Pro® must be followed.
- If your INSUPen EZ® and INSUPen Pro® with the cartridge inside is in cold storage, take it out 1 to 2 hours before you inject to allow it to warm up. Cold insulin is more painful to inject.
- To prevent contamination always use a new pen needle for each injection.

Do not use BASALOG Refil® cartridge
- In insulin infusion pumps.
- If the cartridge or the INSUPen EZ® and INSUPen Pro® containing the cartridge is dropped, damaged or crushed there is a risk of leakage of insulin.
- If it has not been stored correctly or it has been frozen.
- If the liquid appears cloudy, colored or has some suspended matter.

Preparation and Handling:
BASALOG Refil®should be inspected visually prior to administration. **BASALOG Refil®** must only be used if the solution is clear and colorless with no visible particles.

Mixing and diluting:
BASALOG Refil® must not be diluted or mixed with any other insulin or solution.

Contraindications:
BASALOG Refil® is contraindicated in patients hypersensitive to the active substances to any of the excipients.

Warnings:
Hypoglycaemia is the most common adverse effect of insulin, including insulin glargine. As with all insulins, the timings of hypoglycaemia may differ among various insulin formulations. Glucose monitoring is recommended for all patients with diabetes.

Any change of insulin should be made cautiously and only under medical supervision. Change in insulin strength. timing of dosing, manufacturer, type (e.g. regular, NPH or insulin analogues, species (animal, human, or method of manufacture (recombinant DNA versus animal source insulin) may result in the need for a change in dosage Concomitant oral anti-diabetic treatment may need to be adjusted.

BASALOG Refil®contains m-cresol, which may cause Type IV (delayed hypersensitivity) allergic reactions.

Precautions:
General:
Patients must be advised that the **BASALOG Refil®**must NOT be diluted or mixed with any other insulin or solution. Patients should be instructed on self-management procedure including glucose monitoring, proper injection technique, hypoglycaemia and hyperglycaemia management. Patients must be instructed on handling of special situation such as inter current conditions (illness, stress or emotional disturbance), an inadequate or skipped insulin dose, inadvertent administration of an increased insulin dose, inadequate food intake, or skipped meals. As with all patients who have diabetes, the ability to concentrate and or react may be impaired as a result of hypoglycaemia or hyperglycaemia. Patients with diabetes should be advised to inform their healthcare professional if they are pregnant or contemplating pregnancy.

Timing of insulin dosage is extremely important. The best approach is to measure blood glucose and add dose of regular insulin if glucose levels are too high. Otherwise, wait for next schedule dose. Do not stop taking insulin injections unless advised by your doctor.

Insulin glargine is not intended for intravenous administration. The prolonged duration of activity of insulin glargine is dependent on injection into subcutaneous tissue. Intravenous administration of the usual subcutaneous dose could result in severe hypoglycaemia. 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 pharmacodynamics/ pharmacokinetic 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. When insulin glargine and regular human insulin are mixed immediately before injection there is possibility of delayed onset of action and delayed time to maximum effect for regular human insulin. The total bioavailability of the mixture may also slightly decrease compared to separate injection of insulin glargine or regular human insulin as with all insulin preparation the time course of insulin glargine action may vary in different patients or at different times in the same patient and rate of absorption Is dependent on blood supply, temperature and physical activity. Insulin may cause sodium retention and oedema, particularly if previously poor metabolic control is improved by intensify insulin therapy.

Hypoglycaemia:
The time of occurrence of hypoglycemia depends on the action profile of the insulin used and may, therefore, change when the treatment regimen is changed. As with all insulins, particular caution should be excised in patients in whom sequelae of hypoglycemic episodes might be of particular clinical relevance; and intensified blood glucose monitoring is advisable. Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as long duration of diabetes, diabetes nerve disease, use of medications such as beta-blockers or intensified diabetes control. Such situations may result in sever hypoglycemia (and, possible, loss of consciousness) prior to patients awareness of hypoglycaemia. Compliance of the patients with the dosage in dietary regimen, correct insulin administration and awareness of hypoglycemia symptoms are essential to reduce risk.

Renal impairment:
BASALOG Refil® requirements may be diminished because of reduced insulin metabolism, based on observations with other insulins.

Hepatic Impairment:
BASALOG Refil® requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism, similar to other insulin.

Intercurrent conditions:
Intercurrent illness require intensive metabolic monitoring in many cases. A urine test for ketones is indicated, and often it is necessary to adjust the insulin dose. The insulin requirement is often increased in patients with type -1 diabetes, carbohydrate supplies must be maintained even if patients are able to eat only little or no food or are vomiting etc.,. In patients with Type-1 diabetes insulin must never be omitted entirely.

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.

Drug interactions:
A number of drugs are known to interact with insulin w.r.t. glucose metabolism and may require dose adjustment of insulin glargine.

Substances that may enhance the blood-glucose-lowering effects and increase susceptibility to hypoglycaemia include oral anti-diabetic agents, angiotensin converting enzymes (ACE- Inhibitors), disopyramide fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, pentoxifylline, propoxyphene, salicylates and sulfonamide antibiotics. Substances that may reduce blood-glucose-lowering effects include corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, oestrogens and progestrogens, phenothiazine derivatives, somatropin, sympathomimetic agents.(e.g. epinephrine(adrenaline), salbutamol, terbutaline), thyroid hormone atypical anti-psychotic 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, guanidine and

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reserpine, signs of adrenergic counter-regulation may be reduced or absent.

Fluid retention and heart failure with concomitant use of PPAR-gamma agonists
Thiazolidinediones (TZDs), which are peroxisome proliferator-activated receptor (PPAR)-gamma agonist including pioglitazone, 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 Basalog Refil, and 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 PPAR-gamma agonist must be considered.

Pregnancy and lactation
Pregnancy:
There are no well-controlled clinical studies of the use of insulin glargine in pregnant women. It is essential for patients with diabetes or a history of gestational diabetes to maintain good metabolic control before conception and throughout pregnancy. Insulin requirements may decrease during the first trimester, generally increase during the second and third trimesters and rapidly decline after delivery. Careful monitoring of glucose control is essential in such patients.

Nursing mothers:
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 insulin glargine is administered to a nursing woman. Use of insulin glargine is compatible with breastfeeding, but women with diabetes who are lactating may require adjustments of their insulin doses.

Effects on the ability to drive and use machines
The patient's ability to concentrate and react quickly may be impaired as a result of, for example, hypoglycaemia or hyperglycaemia or as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving car or operating machinery).
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 signs of hypoglycaemia. The feasibility of driving should be considered in these circumstances.

Undesirable effects:
In a clinical study done by Biocon the adverse events were similar in nature, frequency, and severity as compared to the reference product.
Hypoglycaemic events were the most common adverse events in both the treatment groups. Apart from hypoglycaemia, pyrexia was the next most common adverse event with three events in each study arm. Retinal adverse events reported in this study were comparable between the treatment groups. The abnormalities in the laboratory parameters were comparable between the two study arms and all of them were considered not clinically significant. Antibodies against Biocon's insulin glargine were observed with the same frequency as compared to the reference product.

Following are the adverse events reported in published literature for insulin glargine:
Hypoglycaemia:
Hypoglycaemia, in general the most frequent adverse reaction of insulin therapy, may occur if the insulin dose is too high in relation to the insulin requirement. As with all insulins, 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.

Eye disorders:
A marked change in glycaemic control may cause temporary visual impairment, due to temporary alteration in the turgidity and refractive index of the lens. Long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy. However, intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy. In patients with proliferative retinopathy, particularly if not treated with photocoagulation, severe hypoglycaemic episodes may result in transient amaurosis.

Injection site and allergic 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. Continuous rotation of the injection site within a given area may help to reduce or prevent these reactions. Most minor reactions to insulins usually resolve in a few days to a few weeks.
In published clinical studies, using regimens which included insulin glargine, injection site reactions were observed in 3-4% of patients. As, with any insulin therapy such reactions included redness, pain, itching, hives, swelling and inflammation. Most minor reactions to insulins usually resolve in a few days to a few weeks. Immediate-type allergic reactions are rare. Such reactions to insulin (including insulin glargine) or the excipients may, for example, be associate with generalized skin reactions, angioedema, bronchospasm, hypotension or shock or may be life threatening.

Immune system disorders:
Insulin administration may cause insulin antibodies to form.

Nervous system disorders: Dysgeusia (Taste disorders)

Musculoskeletal and connective tissue disorders: Myalgia

Overdose:
A specific overdose of insulin cannot be defined. However, hypoglycaemia may develop over sequential stages.
- Mild hypolycaemic episodes can be treated by oral administration of glucose or sugary products. It is therefore recommended that the diabetic patients carry some sugar lumps, sweets, biscuits or sugary fruit juice.
- Severe hypoglycaemic episodes, where the patient has become unconscious, can be treated by glucagon (0.5 to 1 mg) given intramuscularly or subcutaneously by a person who has received appropriate instruction or by glucose given intravenously by a medical professional. Glucose must be given intravenously if the patient does not respond to glucagon within 10 to 15 minutes.

Upon regaining consciousness, administration of oral carbohydrate is recommended for the patient in order to prevent relapse.

Pharmacological Properties
Pharmcotherapeutic group: insulin and analogues for injection, long-acting. ATC Code: A10AE04.

Mechanism of Action
Primary function of insulin, including insulin glargine, is regulation of glucose metabolism. Insulin and its analogues lower blood glucose levels by stimulating peripheral glucose uptake, primarily by skeletal muscle and fat, and by inhibiting hepatic glucose production. Anabolic functions of insulin include inhibition of lipolysis, inhibition of proteolysis, and enhancement of protein synthesis.

Pharmacodynamics:
Insulin glargine has low aqueous solubility at neutral pH. At pH 4, as in the insulin glargine injection solution, it is completely soluble. 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 slowly released, resulting in a relatively constant concentration/time profile over 24 hours with no pronounced peak. This allows once-daily dosing as a patient's basal insulin.

In published clinical studies, the glucose-lowering effect on a molar basis of intravenous insulin glargine was approximately similar to human insulin. In published euglycaemic clamp studies, both in healthy subjects or in patients with Type 1 diabetes, the onset of action of subcutaneous insulin glargine was slower than NPH human insulin. The effect profile of insulin glargine was relatively constant with no pronounced peak and the duration of its effect was prolonged compared to NPH human insulin.

Pharmacokinetics:
Absorption and bioavailability: Serum concentrations afetr subcutaneous injection of insulin glargine in healthy subjects and in patients with diabetes, indicated a slower, more prologed absorption and a relativel constant concentration/tiem profile over 24 hours, with no pronounced peak in comparison to NPH human insulin. In published studies, the duration of action was similar after subcutaneous administration in the abdomen, deltoid, or thigh.
Metabolism: In a published study in humans it wsa found that insulin glargine is partly metabolized at the carboxylterminus of the B chain in the subcutaneous depot to form two active metabolites with in vitro activity similar to that of insulin, M1 (21A-Gly-insulin) and M2 (21A Gly des 30B Thr insulin). Unchanged drug as well as these degradation products were present in the circulation.

Clinical studies- efficacy results:
Efficacy of Biocon's insulin glargine was assessed in a phase III study conducted by Biocon Limited to establish safety and non-inferiority (in comparison to reference product), with respect to decrease in HbA1C in patients with Type1 diabetes mellitus.
The results established non-inferiority of Biocon's insulin glargine compared to the reference product, with respect to change in HbA1C. The changes in FPG, PPG and seven-point glucose were comparable between the two study arms. The proportion of patients who achieved target HBa1c<7% was comparable between groups. Mean insulin dose was also comparable between the two arms. Compliance was good during the study, with average compliance >98% for both basal & pre meal soluble insulin was comparable for both study arms.
Overall the two study treatment were comparable with respect to efficacy.

Preclinical Safety Data
Based on published literature insulin glargine is reported to be non-mutagenic in a series of in vitro and in vivo genotoxicity assays.

Based on conventional non clinical (acute and repeat dose toxicity) studies performed with **BASALOG Refil®**, the non-clinical data reveals no special hazard for humans.

Pharmaceutical Particulars
List of Excipients
Zinc chloride
Glycerin
m-cresol
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)
Water for injection

Incompatibilities
In general terms insulin should only be added to compounds with which it is known to be compatible.

Shelf Life
Refer carton/label.
Never use **BASALOG Refil ®** after the expiry date printed on the pack.

Storage and Precautions:
Store BASALOG Refil® cartridge in a refrigerator at temperature between 2°C-8°C. It should not be allowed to freeze.

The solution can be kept at room temperature below 30°C (86°F) up to 28 days once the cartridge has been put to use.

Do not expose to excessive heat or direct sunlight.

Keep **BASALOG Refil®** cartridge out of reach of children.
Do not use frozen **BASALOG Refil®** cartridge.
DO NOT MIX WITH OTHER INSULINS OR SOLUTION.

Nature and contents of container:
The solution is presented in glass cartridge (USP Type 1). It is sealed using lined seals and plugged with plunger stopper 1x3ml, 3x3ml or 5x3ml cartridges are packed in a carton.
Special Precautions for Disposal and Other Handling
Any unused product or waste material should be disposed of in accordance with local regulations

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BF1047/04

Leaflet Revised **January 2020**

In case of any product related complaints or adverse events related to Biocon products, Call Toll Free No.: **1800-102-9465** OR visit our website **www.biocon.com** and fill voluntary reporting form available under 'Report Adverse Events/Side Effects and Product Complaints' and send the duly filled form to us at **drugsafety@biocon.com** For general queries regarding diabetes and its management, Call Toll Free No.: **1800-425-7667**.