For the use of only a registered medical practitioner or hospital or laboratory

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Isophane Insulin Injection IP

Biocon

40 IU/mL

INSUGEN® - N (NPH)

इन्सुजेन - एन

10 mL

COMPOSITION
Each mL contains
Human Insulin IP 40 IU
(Human Insulin of recombinant DNA origin)
m-Cresol USP 0.16% w/v
Phenol IP 0.065% w/v
Water for injection IP q.s.
One IU (International Unit) of insulin is equivalent to 0.035 mg of human insulin.

For a full list of excipients, see **List of excipients** section.

PHARMACEUTICAL FORM
Suspension for injection in a vial.
Cloudy white aqueous suspension.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic Properties
Pharmacotherapeutic group: Insulins and analogues for injection, intermediate-acting, insulin (human).
ATC code: A10AC01
Mechanism of Action
The blood glucose lowering effect of insulin is due to the facilitated uptake of glucose following binding of insulin to receptors on muscle and fat cells and to the simultaneous inhibition of glucose output from the liver.
INSUGEN®-N is a long-acting insulin. After a subcutaneous (SC) injection, the onset of action is within 1½ hours, reaches a maximum effect within 4 to 12 hours and the entire duration of action is approximately 24 hours.

Pharmacokinetic Properties
Insulin in the blood stream has a half-life of a few minutes. Consequently, the time-action profile of an insulin preparation is determined solely by its absorption characteristics.
This process is influenced by several factors (e.g. insulin dosage, injection route and site, thickness of subcutaneous fat, type of diabetes). The pharmacokinetics of insulin products are therefore affected by significant intra- and inter-individual variation.
Absorption
The maximum plasma concentration of the insulin is reached within 2 to18 hours after subcutaneous administration.
Distribution
No profound binding to plasma proteins, except circulating insulin antibodies (if present) has been observed.
Metabolism
Human insulin is reported to be degraded by insulin protease or insulin-degrading enzymes and possibly protein disulphide isomerase. A number of cleavage (hydrolysis) sites on the human insulin molecule have been proposed; none of the metabolites formed following the cleavage are active.
Elimination
The terminal half-life is determined by the rate of absorption from the subcutaneous tissue. The terminal half-life ($t_{1/2}$) is therefore a measure of the absorption rather than of the elimination *per se* of insulin from plasma (insulin in the blood stream has a $t_{1/2}$ of a few minutes). Trials have indicated a $t_{1/2}$ of about 5 to 10 hours.

Preclinical Safety Data
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

CLINICAL PARTICULARS
Therapeutic Indications
INSUGEN®-N for the treatment of diabetes mellitus in patients who requires injectable insulin.

Posology and Method of Administration
INSUGEN®-N is a long-acting insulin.
Dosage
Dosing is individual and determined in accordance with the needs of the patient. The individual insulin requirement is usually between 0.3 and 1.0 IU/kg per day depending upon the metabolic status and glycaemic control. The daily insulin requirement may be higher in patients with insulin resistance (e.g. during puberty or due to obesity) and lower in patients with residual, endogenous insulin production.
The physician determines whether one or several daily injections are necessary. **INSUGEN®-N** may be used alone or mixed with fast-acting insulin. In intensive insulin therapy the suspension may be used as basal insulin (evening and/or morning injection) with fast-acting insulin given at meals.
In patients with diabetes mellitus, optimised glycaemic control delays the onset of late diabetic complications. Close blood glucose monitoring is therefore recommended.
Dosage Adjustment in Special Populations
Renal and Hepatic Impairment
Renal or hepatic impairment may reduce insulin requirement. As with all insulin medicinal products, in patients with renal or hepatic impairment, glucose monitoring should be intensified and the human insulin dose should be adjusted on an individual basis.
Paediatrics
In general, paediatric patients with type 1 diabetes are more susceptible to hypoglycaemia than adult patients with type 1 diabetes. As in adults, the dosage of insulin must be individualized in paediatric patients based on metabolic needs and frequent monitoring of blood glucose.
Geriatrics
Use caution in patients with advanced age, due to the potential for decreased renal function in this population.
Transfer from other insulin medicinal products
Adjustment of dosage may also be necessary if patients change physical activity or their usual diet. Dosage adjustment may be necessary when transferring patients from one insulin preparation to another. Close glucose monitoring is recommended during the transfer and in the initial weeks thereafter (see **Special Warnings and Precautions for Use** section).
Others
Concomitant illness, especially infections and feverish conditions, usually increases the patient's insulin requirement.
Method of Administration
INSUGEN®-N is used for subcutaneous use only. Insulin suspensions are never to be administered intravenously.
INSUGEN®-N is administered subcutaneously in the thigh or abdominal wall. If convenient, the gluteal region or the deltoid region may also be used. Subcutaneous injection into the abdominal wall ensures a faster absorption than from other injection sites.
Injection into a lifted skin fold minimises the risk of unintended intramuscular injection.
The needle should be kept under the skin for at least 6 seconds to make sure the entire dose is injected. If blood appears after the needle has been withdrawn, press the injection site lightly with a finger. Injection sites should be rotated within an anatomic region in order to avoid lipodystrophy.
The vials are for use with insulin syringes with a corresponding unit scale.
When two types of insulin are mixed, draw the amount of fast-acting insulin first, followed by the amount of long-acting insulin.
Instructions to be given to the patient
Before injecting this insulin,
1. Wash hands with soap and water.
2. Disinfect the rubber stopper with an alcohol swab.
3. Roll the vial between the palms of the hands until the liquid is uniformly white and cloudy. Resuspending is easier if the insulin has reached room temperature.
4. Draw air into the syringe, in the same amount as the volume of insulin to be injected.
5. Inject the air into the vial: push the needle through the rubber stopper and press the plunger.
6. Turn the vial and syringe upside down.
7. Draw the correct dose of insulin into the syringe.
8. Pull the needle out of the vial.
9. Make sure that there is no air left in the syringe: point the needle upwards and push the air out.
10. Check you have the right dose.
11. Inject the insulin into the subcutaneous tissue.

Contraindications
INSUGEN-N is contraindicated in the patients with:
- Hypersensitivity to the active substance or to any of the excipients (see **List of Excipients** section).
- Hypoglycaemia.

Special Warnings and Precautions for Use
Before travelling between different time zones, the patient should be advised to consult the physician, since the patient may have to take insulin and meals at different times.
Always use a new needle and syringe each time you take **INSUGEN®-N** injection to prevent contamination.
Missed dose/change of insulin
In case of missed dose, measure the blood glucose and add a dose of regular insulin if glucose levels are too high. Otherwise, it is recommended to wait for the next scheduled dose. Any change of dose or transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (fast-, dual-, long-acting insulin etc.), origin (animal, human or analogue insulin) and/or method of manufacture (recombinant DNA versus animal source insulin) may result in a need for a change in dosage. If an adjustment is needed when switching the patients to **INSUGEN®-N**, it may occur with the first dose or during the first several weeks or months.
A few patients who have experienced hypoglycaemic reactions after transfer from animal source insulin have reported that early warning symptoms of hypoglycaemia were less pronounced or different from those experienced with their previous insulin.
Hyperglycaemia
Inadequate dosage or discontinuation of treatment, especially in type 1 diabetes, may lead to hyperglycaemia. Usually, the first symptoms of hyperglycaemia set in gradually, over a period of hours or days. They include thirst, increased frequency of urination, nausea, vomiting, drowsiness, flushed dry skin, dry mouth, and loss of appetite as well as acetone odour of breath. In type 1 diabetes, untreated hyperglycaemic events eventually lead to diabetic ketoacidosis, which is potentially lethal.
Hypoglycaemia
Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement (see **Undesirable Effects** and **Overdose** sections).
Omission of a meal or unplanned, strenuous physical exercise may lead to hypoglycaemia. Patients whose blood glucose control is greatly improved e.g. by intensified insulin therapy, may experience a change in their usual warning symptoms of hypoglycaemia and should be advised accordingly. Intravenously administered insulin has a more rapid onset of action than subcutaneously administered insulin, requiring more close monitoring for hypoglycaemia.
As with all insulins, use caution in patients with hypoglycaemia unawareness and in patients who may be predisposed to hypoglycaemia (e.g. patients who are fasting or have erratic food intake, paediatric patients, and the elderly). The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia. This may present a risk in situations where these abilities are especially important, such as driving or operating other machinery (see **Effects on Ability to Drive and Use Machines** section).
Usual warning symptoms may disappear in patients with long-standing diabetes.
Hypokalaemia
All insulins, including **INSUGEN®-N**, cause a shift in potassium from the extracellular to intracellular space, possibly leading to hypokalaemia that, if left untreated, may cause respiratory paralysis, ventricular arrhythmia, and death. Use caution in patients who may be at risk for hypokalaemia (e.g., patients using potassium-lowering medications and patients taking medications sensitive to serum potassium concentrations).
Hypersensitivity reactions
Local reactions
As with any insulin therapy, injection site reactions may occur and include pain, itching, hives, swelling and inflammation. Continuous rotation of the injection site within a given area may help to reduce or prevent these reactions. Reactions usually resolve in a few days to a few weeks. On rare occasions, injection site reactions may require discontinuation of **INSUGEN®-N.**
Systemic reactions
Severe, life-threatening, generalized allergy, including anaphylaxis may occur with any insulin, including **INSUGEN®-N.** Generalized allergy to insulin may manifest as a whole body rash (including pruritus), dyspnea, wheezing, hypotension, tachycardia, or diaphoresis. **INSUGEN®-N** contains metacresol, which may cause allergic reactions.
Mixing of insulins
If soluble insulin is mixed with NPH human insulin, regular soluble insulin should be drawn into the syringe first and the mixture should be injected immediately after mixing. Insulin mixtures should not be administered intravenously.
Due to the risk of precipitation in pump catheters, **INSUGEN®-N** should not be used in insulin pumps for continuous subcutaneous insulin infusion.
Fluid retention and heart failure with concomitant use of PPAR-gamma agonists
Thiazolidinediones (TZDs), which are peroxisome proliferator-activated receptor (PPAR)-gamma agonists 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 **INSUGEN®-N**, and a PPAR-gamma agonist should be observed for signs and symptoms of heart failure. If heart failure develops, it should be managed according to current standards of care, and discontinuation or dose reduction of the PPAR-gamma agonist must be considered.
Special Populations
As with other insulins, the dose requirements for **INSUGEN®-N** may be reduced in patients with renal or hepatic impairment.
Dose adjustment for **INSUGEN®-N** is recommended in paediatrics and geriatrics (see **Posology and Method of Administration** section).

Drug Interactions
A number of medications affect glucose metabolism that may require insulin dose adjustment and particularly close monitoring for hypoglycaemia or worsening glycaemic control.
The following are examples of medications that may increase the blood glucose-lowering effect of insulin and increase susceptibility to hypoglycaemia: oral antidiabetic medications, pramlintide acetate, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, propoxyphene, salicylates, somatostatin analogs (e.g., octreotide), and sulfonamide antibiotics.
The following are examples of medications that may reduce the blood glucose-lowering effect of insulin, leading to worsening of glycemic control: corticosteroids, niacin, danazol, diuretics, sympathomimetic agents (e.g., epinephrine, salbutamol, terbutaline), isoniazid, phenothiazine derivatives, somatropin, thyroid hormones, estrogens, progestogens (e.g., in oral contraceptives), and atypical antipsychotics.
Beta-blockers, clonidine, and lithium salts may either potentiate or weaken the blood glucose lowering effect of insulin.
Alcohol can increase susceptibility to hypoglycaemia.
Pentamidine may cause hypoglycaemia, which may sometimes be followed by hyperglycaemia.
The signs of hypoglycaemia may be reduced or absent in patients taking sympatholytic medications such as beta-blockers, clonidine, guanethidine, and reserpine.

Pregnancy and Lactation
There are no restrictions on treatment of diabetes with insulin during pregnancy, as insulin does not pass the placental barrier.
Both hypoglycaemia and hyperglycaemia, which can occur in inadequately controlled diabetes therapy, increase the risk of malformations and death *in utero*. Intensified control in the treatment of pregnant women with diabetes is therefore recommended throughout pregnancy and when contemplating pregnancy.
Insulin requirements usually fall in the first trimester and subsequently increase during the second and third trimesters. After delivery, insulin requirements return rapidly to pre-pregnancy values.
Insulin treatment of the nursing mother presents no risk to the baby. However, the **INSUGEN®-N** dosage may need to be adjusted.

Effects on Ability to Drive and Use Machines
The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a 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 or have frequent episodes of hypoglycaemia. The advisability of driving should be considered in these circumstances.

Undesirable Effects
As for other insulin products, in general, hypoglycaemia is the most frequently occurring undesirable effect. Weight gain is common when taking insulin. It may occur if the insulin dose is too high in relation to the insulin requirement. In clinical trials and during marketed use, the frequency varies with patient population and dose regimens. Therefore, no specific frequency can be presented. Severe hypoglycaemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death. Frequencies of adverse drug reactions from clinical trials that are considered related to insulin isophane are listed below. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.
Side effects reported uncommonly (≥1/1,000 to <1/100)
Diabetic retinopathy
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.
Skin and subcutaneous tissue disorders
Lipodystrophy may occur at the injection site as a consequence of failure to rotate injection sites within an area.
General disorders and administration site conditions (Injection site reactions)
Injection site reactions (redness, swelling, itching, pain and haematoma at the injection site) may occur during treatment with insulin. Most reactions are transitory and disappear during continued treatment.
Oedema
Oedema may occur upon initiation of insulin therapy. These symptoms are usually of transitory nature.
Immune system disorders
Urticaria, rash
Side effects reported very rarely (<1/10,000)
Nervous system disorders (Peripheral neuropathy)
Fast improvement in blood glucose control may be associated with a condition termed "acute painful neuropathy", which is usually reversible.
Eye disorders (Refraction disorders):
Refraction anomalies may occur upon initiation of insulin therapy. These symptoms are usually of transitory nature.
Anaphylactic reactions
Symptoms of generalised hypersensitivity may include generalised skin rash, itching, sweating, gastrointestinal upset, and angioneurotic oedema, difficulties in breathing, palpitation, reduction in blood pressure and fainting/loss of consciousness. Generalised hypersensitivity reactions are potentially life-threatening.

Overdose
A specific overdose of insulin cannot be defined. However, hypoglycaemia may develop over sequential stages:
- Mild hypoglycaemic 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 also 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.

PHARMACEUTICAL PARTICULARS
List of Excipients
Glycerol, Metacresol, Hydrochloric acid, Sodium hydroxide, Protamine Sulphate, Zinc Oxide, Liquid Phenol, Dibasic sodium phosphate, Water for Injection.

Incompatibilities
Insulin products should only be added to compounds with which it is known to be compatible.
Insulin suspensions should not be added in infusion fluids.

Shelf Life
Please refer to carton/label.

Storage and Precautions
Unopened vials: **Store in a refrigerator at temperature between 2°C and 8°C.** Do not freeze.
Do not store in or too near the freezer section or cooling element.
Vials during use: vials that are in use can be kept at a temperature not above 25°C up to 6 weeks. It should not be allowed to freeze.
Keep the vial in the outer carton in order to protect from light.
Protect from excessive heat and sunlight.
Keep out of reach of children.

Special Precautions for Disposal and Other Handling
Insulin preparations which have been frozen must not be used.
After removing **INSUGEN®-N** vial from the refrigerator it is recommended to allow the vial to reach room temperature (not above 25°C) before re-suspending the insulin as instructed for first time use.
Insulin suspensions should not be used if they do not appear uniformly white and cloudy after re-suspension.
Any unused product or waste material should be disposed of in accordance with local requirements.

Nature and Contents of Container
INSUGEN®-N is available as 10 mL glass vials (USP Type I) closed with bromobutyl rubber stopper and sealed with aluminium flip-off seal. These vials are packed in a carton along with prescribing information sheet.
Pack sizes: 1×10 mL

Marketed by:
Biocon Biologics India Limited
Biocon House, Semicon Park,
Electronics City, Phase - II,
Bengaluru - 560 100, India.

BF0958/05

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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**.

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Biocon

40 IU/mL

INSUGEN® - N (NPH)

इन्सुजेन - एन

10 mL