Biocon

℞ Biphasic Isophane Insulin Injection IP

100 IU/mL

Insugen®- 50/50 (Biphasic)

इन्सुजेन -५०/५०

Insugen®-50/50 (Biphasic)
(Human Insulin of recombinant DNA Origin)

COMPOSITION
Each mL contains
Human Insulin IP 100 IU
(50% as soluble insulin injection and 50% as Isophane insulin injection)
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 0.035mg of human insulin.

Each 10 mL vial contains suspension for injection, equivalent to 1000 IU.
For a full list of excipients, see section **List of excipients**.

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 combined with fast-acting, insulin (human).

ATC Code: A10AD01

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®-50/50 (Biphasic) is a dual-acting insulin.

Onset of action is within ½ hour, reaches a maximum peak effect within 2-8 hours and the entire duration of action is up to 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 absorption profile is due to the product being a mixture of insulin products with fast and protracted absorption respectively. The maximum plasma concentration of the fast-acting insulin is reached within 1.5-2.5 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 disulfide 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 ($t_{½}$) 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 $t_{½}$ of a few minutes). Trials have indicated a $t_{½}$ of about 5-10 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
Treatment of diabetes mellitus.

Posology and Method of Administration
Insugen®-50/50 (Biphasic) is a dual-acting insulin. It is biphasic formulation containing both fast-acting and intermediate-acting insulin.

Premixed insulin products are usually given once or twice daily when a rapid initial effect together with a more prolonged effect is desired.

Dosage
Dosage 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/day. 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.

In patients with diabetes mellitus optimised glycaemic control delays the onset of late diabetic complications. Close blood glucose monitoring is therefore recommended.

An injection should be followed within 30 minutes by a meal or snack containing carbohydrates.

Dosage adjustment
Concomitant illness, especially infections and feverish conditions, usually increases the patient's insulin requirement.

Renal or hepatic impairment may reduce insulin requirement.

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 (see section **Special Warnings and Precautions for Use**).

Administration
For subcutaneous use. Insulin suspensions are never to be administered intravenously.

Insugen®-50/50 (Biphasic) 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.

Instructions to be given to the patient
Before injecting this insulin,

1. Disinfect the rubber stopper with an alcohol swab.
2. 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.
3. Draw air into the syringe, in the same amount as the volume of insulin to be injected
4. Inject the air into the vial: push the needle through the rubber stopper and press the plunger.
5. Turn the vial and syringe upside down.
6. Draw the correct dose of insulin into the syringe.
7. Pull the needle out of the vial.
8. Make sure that there is no air left in the syringe: point the needle upwards and push the air out.
9. Check you have the right dose.
10. Inject straight away.

Contraindications
Hypersensitivity to the active substance or to any of the excipients (see section **List of Excipients**).
Hypoglycaemia.

Special Warnings and Precautions for Use
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, 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 may occur if the insulin dose is too high in relation to the insulin requirement (see sections **Undesirable Effects** and **Overdose**).

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.

Usual warning symptoms may disappear in patients with longstanding diabetes.

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®-50/50 (Biphasic)**, it may occur with the first dose or during the first several weeks or months.

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®-50/50 (Biphasic).**

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.

Before traveling between different time zones, the patient should be advised to consult the physician, since this may mean that the patient has to take insulin and meals at different times.

Insulin suspensions are not to be used in insulin infusion pumps.

The insulin vials have a protective colour-coded, tamper proof plastic cap, which must be removed before insulin can be withdrawn. The patient should be instructed not to use the vial if the plastic cap is loose or missing and return to the pharmacy.

Always use a syringe that is marked for U-100 insulin. Using a syringe other than U-100 insulin syringe may lead to administration of wrong dose of insulin that could lead to blood sugar levels that are too low or too high. Always use a new needle and syringe each time you give **Insugen®-50/50 (Biphasic)** injection.

Insugen®-50/50 (Biphasic) contains metacresol, which may cause allergic reactions.
Combination of **Insugen®-50/50 (Biphasic)** with pioglitazone
Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for development of cardiac heart failure. This should be kept in mind if treatment with the combination of pioglitazone and **Insugen®-50/50 (Biphasic)** is considered. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs.

Drug Interactions
A number of medicinal products are known to interact with glucose metabolism. The physician must therefore take possible interactions into account and should always ask his patients about any medicinal products they take.

The following substances may reduce insulin requirement:
Oral hypoglycaemic agents (OHA), monoamine oxidase inhibitors (MAOI), non-selective betablocking agents, angiotensin converting enzyme (ACE) inhibitors, salicylates, alcohol, anabolic steroids and sulphonamides.

The following substances may increase insulin requirement:
Oral contraceptives, thiazides, glucocorticoids, thyroid hormones and beta-sympathomimetics, growth hormone and danazol.

Beta-blocking agents may mask the symptoms of hypoglycaemia and delay recovery from hypoglycaemia.

Octreotide/lanreotide may both decrease and increase insulin requirement.

Alcohol may intensify and prolong the hypoglycaemic effect of insulin.

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®-50/50 (Biphasic)** 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. 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 **biphasic insulin** 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)
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. 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): 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 re actions): 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)
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, 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 to 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®-50/50 (Biphasic)** vial from the refrigerator it is recommended to allow the vial to reach room temperature (not above 25°C) before resuspending the insulin as instructed for first time use.
Keep out of reach of children.
Insulin suspensions should not be used if they do not appear uniformly white and cloudy after resuspension.
Any unused product or waste material should be disposed of in accordance with local requirements.

Nature and Contents of Container
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 package insert.

Pack sizes: 1 × 10 mL

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

BF1001/05

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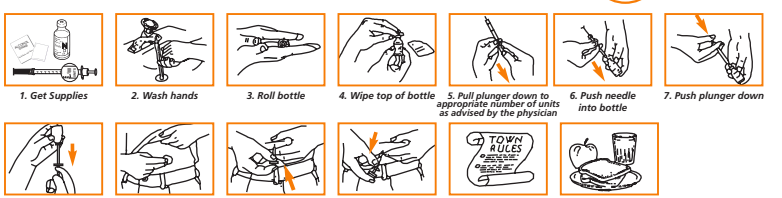
In case of any product related complaints or adverse events related to Biocon products, Call Toll Free No.: **1800-102-9465** OR visit our website **www.biocon.com** and fill voluntary reporting form available under 'Report Adverse Events/Side Effects and Product Complaints' and send the duly filled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

Drawing and Self-Injecting Insulin



1. Get Supplies
2. Wash hands
3. Roll bottle
4. Wipe top of bottle
5. Pull plunger down to appropriate number of units as advised by the physician
6. Push needle into bottle
7. Push plunger down
8. Pull plunger down to appropriate number of units as advised by the physician
9. Pick injection site Wipe with Alcohol Swab
10. Pinch up skin Push needle into skin Push plunger in
11. Pull needle out
12. Dispose syringe safely Check your town rules
13. Eat after appropriate interval