Biocon

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

100 IU/mL

℞

Biphasic Isophane Insulin Injection IP

Insugen-30/70 Refil®

इन्सुजेन -३०/७० रीफिल

3 mL Cartridges

4264

Suspension for injection in a cartridge, for S.C. use only.

Insugen-30/70 Refil® is a mixture of biphasic isophane insulin injection, containing 30% of short acting (regular) insulin solution and 70% intermediate-acting isophane (NPH) insulin suspension.

Insugen-30/70 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
Human insulin IP 100 IU
(30% as soluble Insulin Injection and 70% as isophane Insulin Injection)
(Human Insulin of recombinant DNA Origin)
m-cresol USP 0.16% w/v
Phenol IP 0.065% w/v
Water for injections IP q.s.

One IU (International Unit) of insulin is equivalent to 0.035 mg of human insulin.

Pharmaceutical form
Suspension for injection in a cartridge.
Insugen-30/70 Refil® cartridge contains sterile, cloudy, white, aqueous suspension of human insulin.

Indications:
For the treatment of diabetes mellitus in patients who requires injectable insulin.

Dosage and administration
Dosage is individualised and determined by the physician in accordance with the needs of the patient. The average daily insulin requirement for diabetes therapy ranges between 0.3 and 1.0 IU/kg, depending on the individual metabolic status and glycaemic control.

Insugen-30/70 Refil®, a premixed insulin is usually given once or twice daily, administered subcutaneously. It should be given, preferably just before meals when a rapid initial effect together with a more prolonged effect is desired.

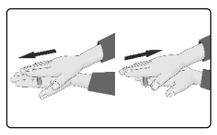
Insugen-30/70 Refil® cartridge injection should be ideally but not always followed within 30 minutes by a meal or a snack containing carbohydrates. Injection sites should be rotated within an anatomic region in order to avoid lipodystrophy. In patients with diabetes mellitus, optimised glucose control delays the onset and slows the progression of late diabetic complications. Regular blood glucose monitoring on the advice of the treating clinician, is therefore recommended.
Insugen-30/70 Refil® cannot be given intravenously.

Instructions to be given to the patient on how to handle Insugen-30/70 Refil® cartridge
1. The **Insugen-30/70 Refil®** cartridges are designed to be used with INSUPen EZ® and INSUPen Pro®. Detailed instruction accompanying the INSUPen EZ® and INSUPen Pro® should be followed.
2. If a patient is using another type of insulin cartridge besides **Insugen-30/70 Refil®** cartridge, two different INSUPen EZ® and INSUPen Pro® should be used for the respective insulins.
3. The **Insugen-30/70 Refil®** cartridge is for single person use only.
4. **Insugen-30/70 Refil®** cartridges should not be refilled.

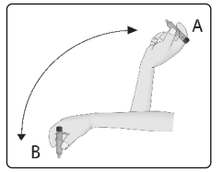
Before using **Insugen-30/70 Refil®** cartridge
- Check the label to make sure it is the right type of insulin.
- Remove the cartridge from the blister pack by pushing through the foil side of the packaging.
- Do check the cartridge, including the plunger stopper. Do not use it if any damage is seen or if there is a gap between the plunger and the label band.
- 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 the cartridge after taping; this small air bubble will not affect your dose.
- 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.
- Detailed instruction accompanying the INSUPen EZ® must be followed.
- Use a medicinal swab to disinfect the rubber membrane.
- To prevent contamination always use a new pen needle for each injection.

Do not use Insugen-30/70 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 properly or if it has been frozen.
- If it is not uniformly white and cloudy, when resuspended.

Before inserting a 3 mL cartridge into your INSUPen EZ® and INSUPen Pro® for the first time:
1. Roll the **Insugen-30/70 Refil®** cartridge between your palms 10 times. These steps should be done with the 3 mL cartridge in a flat (horizontal) position.
2. Then turn the cartridge up and down between positions A and B (see Figure) so the glass bead moves from one end of the cartridge to the other. Do this at least 10 times. Repeat the rolling and turning steps until the insulin looks uniformly white and cloudy. Resuspending is easier when the insulin is at room temperature. Complete the other stages of injection without delay.
3. Do not force the dose knob. Check for the desired units of insulin left in the cartridge before resuspending. If there are less than desired units left, use a new cartridge.



How to inject this insulin
1. Inject the insulin under the skin. Use the injection technique described in the INSUPen EZ® and INSUPen Pro® manual.
2. Keep the needle under the skin for at least 10 seconds to make sure that the full dose has been delivered.
3. After each injection be sure to remove and discard the needle and store **Insugen-30/70 Refil®** cartridge in INSUPen EZ® and INSUPen Pro® without a needle attached. Otherwise, the liquid may leak out which can cause inaccurate dosing.



Contraindications
Hypoglycaemia.
Hypersensitivity to human insulin or any of the excipients.

Warnings and precautions for use
Inadequate dosage or discontinuation of treatment, especially in type 1 diabetes, may lead to hyperglycaemia and diabetic ketoacidosis. 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 the breath.

Never use **Insugen-30/70 Refil®** cartridge after the expiry date printed on the pack.

Cartridges should only be used in combination with products that are compatible with them and allow the cartridge to function safely and effectively. **Insugen-30/70 Refil®** is a cloudy, white, aqueous suspension of human insulin. Never use **Insugen-30/70 Refil®** cartridge if the liquid is not white and uniformly cloudy after gentle rolling. Any unused product or waste material should be disposed of in accordance with local requirements.
Insugen-30/70 Refil® contains m-cresol , which may cause Type IV (delayed hypersensitivity) allergic reactions.

Missed dose
Timing of insulin doses is extremely important. The best approach is to measure blood glucose and add a dose of regular insulin if glucose levels are too high. Otherwise, wait for the next scheduled dose.

Stopping the drug
Do not stop taking insulin injections unless ordered by your doctor. Patients with diabetes are often given general instructions for modifying their insulin doses based on home blood glucose measurements.

Precautions while switching types of insulin
Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (rapid-acting insulin, intermediate acting insulin, long acting insulin etc.), species (animal, human insulin analogue) and/or method of manufacture (recombinant DNA versus animal source insulin) may result in the need for a change in the dose.

Patients switching to or from **Insugen-30/70 Refil®** cartridge may require a change in their usual insulin dosage. If an adjustment is needed, it may occur within the first few days to few weeks.

Patients whose blood glucose control has greatly improved e.g. by intensified insulin therapy, may experience a change in their usual warning symptoms of hypoglycaemia and should be advised accordingly.

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.

Changes in the dose requirement
Adjustment of dosage may also be necessary if patients increase their physical activities or change their usual diet. Concomitant illnesses, especially infections and other feverish conditions, usually increases the patient's insulin requirement. Alcohol may intensify and prolong the hypoglycaemic effect of insulin.

Drug interactions
A number of drugs are known to interact with insulin with respect to glucose metabolism. Possible interactions must therefore be taken into account by the physician.

Some of the drugs leading to reduced insulin requirement:
Oral hypoglycaemic agents (OHA), octreotide, monoamine oxidase inhibitors (MAOI), non selective beta blocking agents, angiotensin converting enzyme (ACE) inhibitors, salicylates, alcohol and anabolic steroids.

Some of the drugs leading to increased insulin requirement:
Oral contraceptives, thiazides, glucocorticoids, thyroid hormones, sympathomimetics, danazol, etc. Beta-blocking agents may mask the symptoms of hypoglycaemia and delay recovery from hypoglycaemia.

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 30/70 Refil, 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

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Pregnancy and lactation
There are no restrictions on the treatment of diabetes with insulin during pregnancy as insulin does not pass the placental barrier. In the treatment of pregnant women with diabetes, intensified control of blood sugar is recommended throughout pregnancy. The same type of control is recommended even in women contemplating pregnancy.

Requirements of insulin usually fall in the first trimester, and subsequently increase during the second and third trimesters.

Postpartum, insulin requirements return rapidly to pre-conception levels. There are no restrictions in insulin treatment while treating a lactating diabetic mother, as it involves no risk to the baby. Insulin requirements tend to be lower during breast feeding. Home glucose monitoring is important to avoid hypoglycaemia. However, the insulin dosage may need to be reduced.

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 hypoglycaemia. This may constitute a risk in situations where these abilities are of special importance (e.g. driving 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
Serious side 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. Symptoms of hypoglycaemia can be caused by the release of adrenaline, or by an inadequate supply of glucose to the brain. Mild hypoglycaemia may cause restless sleep, nightmares, or a cold sweat that awakens patients at night. With severe hypoglycaemia, lack of sufficient glucose to the brain may cause slurred speech, impaired concentration, confusion, seizures, coma, irreversible brain damage, and death.

Common side effects
Symptoms resulting from release of adrenaline are common manifestations of mild to moderate hypoglycaemia. They include cold sweats, anxiety, shakiness, hunger, rapid heartbeat, headache, and nervousness. Weight gain is common when taking insulin.

Less common side effects
Anaphylactic reactions and lipodystrophy may occur at the injection site as a consequence of failure to rotate injection sites within an area. Oedema may occur upon initiation of insulin therapy. These symptoms are usually of transitory nature.

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.

Pharmacological properties
Pharmacotherapeutic group: Insulins and analogues for injection, intermediate-acting combined with fast acting, insulin (human). ATC code: A10AD01

The blood glucose-lowering effect of insulin is due to the facilitated uptake of glucose following binding of insulin to receptors on cells that include muscle and fat cells, and supression of glucose output from the liver. Insulin in the blood stream has a half-life of 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, route of administration and site of injection), which is why considerable intra-and inter-patient variation is seen.

An average action profile after subcutaneous injection of Insugen-30/70 Refil®:
Onset of action : Within ½ hour
Maximum peak effect : Between 2 and 8 hours
Duration of action : Upto 24 hours
Preclinical safety data
The non clinical studies performed with the human recombinant insulin reveals no special hazard to humans. Human insulin was not mutagenic in a series of *in vitro* and *in vivo* genotoxicity assays.

Pharmaceutical particulars
List of excipients
Zinc oxide
Glycerol
m-cresol
Phenol
Dibasic sodium phosphate
Hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Protamine sulphate
Water for injections.
Incompatibilities
In general terms insulin 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
Store Insugen-30/70 Refil® cartridge in a refrigerator at temperature between 2°C and 8°C. It should not be allowed to freeze.

The container should be gently shaken before a dose is withdrawn.

The suspension can be kept at room temperature below 25°C up to 42 days once the cartridge has been put to use

Do not expose to excessive heat or direct sunlight.

Keep **Insugen-30/70 Refil®** cartridge out of reach of children.

Do not use frozen **Insugen-30/70 Refil®** cartridge.

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. 1x3 mL, 3x3 mL or 5x3 mL cartridges are packed in a carton.

Special precautions for disposal and handling
Any unused product or waste material should be disposed off in accordance with local requirements.

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

® - Registered trademark

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