



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

Rx

Insulin Injection IP Soluble Insulin, Neutral

Insugen - R Refil®

इन्सुजेन - आर रीफिल

3 mL Cartridges

100
IU/mL

Solution for injection in a cartridge for S.C. use only.

Insugen-R Refil® (Regular) is soluble short acting insulin in a cartridge.

Insugen-R Refil® (Regular) 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 (Human Insulin of recombinant DNA Origin),
m-cresol USP 0.25% w/w
Water for injections IP q.s.

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

Pharmaceutical form

Solution for injection in a cartridge.

Insugen-R Refil® cartridge contains sterile, clear solution 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. In geriatric patients, the primary aim of treatment may be relief of symptoms and avoidance of hypoglycaemic events.

Insugen-R Refil® is administered subcutaneously into the thigh or abdominal wall, before meals, 1 to 2 times daily depending upon the requirement of the individual. If convenient, the gluteal region or deltoid region may be used. Subcutaneous injection into the abdominal wall results in faster absorption than from other injection sites. Injection into a lifted skin fold minimises the risk of an intramuscular injection. **Insugen-R Refil®** cartridges may be also used along with INSUPen EZ® and INSUPen Pro® to administer **Insugen-R Refil®** intravenously but it should be an exception only in situations where vials are not available. In this case **Insugen-R Refil®** should be drawn into an insulin syringe, provided air is avoided, or infused with an infusion system. This procedure should only be carried out by health care professionals.

Injection sites should be rotated within an anatomic region, and also amongst various other sites in order to avoid lipodystrophy. An injection should be followed within 30 minutes by a meal or snack containing carbohydrates. In patients with diabetes mellitus, optimised glycaemic control delays the onset of late diabetic complications. Close blood glucose monitoring is therefore recommended.

Instructions to be given to the patient on how to handle Insugen-R Refil® cartridge

1. The **Insugen-R 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 a patient is using another type of insulin cartridge besides **Insugen-R Refil®** cartridge, two different INSUPen EZ® and INSUPen Pro® should be used for the respective insulins.
3. The **Insugen-R Refil®** cartridges is for single person use only.
4. **Insugen-R Refil®** cartridges should not be refilled.

Before using **Insugen-R Refil®** cartridge

- Check the label to make sure it is the right type of insulin.
- Remove the cartridge from the blisterpack 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.
- Cartridges containing **Insugen-R Refil®** do not require resuspension and should only be used if it is clear, colourless, with no visible solid particles and if it is of water-like appearance.
- 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® and INSUPen Pro® 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-R 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 may be a risk of leakage of insulin.
- If it has not been stored properly or if it has been frozen.
- If the liquid appears white and cloudy or has some suspended particles.

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 appropriately. Store **Insugen-R Refil®** cartridge in INSUPen EZ® and INSUPen Pro® without any 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 breathing.

Never use **Insugen-R 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-R Refil®** is a clear solution of human insulin. Never use **Insugen-R Refil®** cartridges if the liquid appears white and cloudy or has some visible suspended particles.

Insugen-R 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 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-R 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 R 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 considered.

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 for 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



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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 nocturnal 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: insulin and analogues for injection, fast-acting, insulin (human).

ATC code: A10AB01

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 suppression of glucose output from the liver. 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), which is why considerable intra- and inter-patient variability is seen.

An average action profile after subcutaneous injection of Insugen-R Refil®:

Onset of action : Within ½ hour
Maximum peak effect : Between 2 and 4 hours
Duration of action : 4 to 6 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
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)
Water for injections.

Incompatibilities

Insulin products should only be added to compounds with which it is known to be compatible. Insulin solutions should not be added in infusion fluids. Medicinal products added to the insulin solution may cause degradation of the insulin, e.g. if the medicinal products contain thiols or sulphites.

Shelf life: Please refer to carton/label

Storage and precautions

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

The solution 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-R Refil®** cartridge out of reach of children.

Do not use frozen **Insugen-R 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.

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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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