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

This package insert is continually updated: Please read carefully before using a new

Recombinant Human Monocomponent Insulin

INSUTAGE®

COMPOSITION

INSUTAGE® R

Insulin Injection Soluble I.P. 100 IU/ml
Each ml contains:

Insulin Human I.P. (Human Insulin of rDNA Origin)	100 IU
Metacresol USP (as preservative)	0.25% w/v
Water for Injection I.P.	q.s.

INSUTAGE® 30/70

Biphasic Isophane Insulin Injection I.P.100 IU/ml
Each ml contains:

Human Insulin I.P.: (30% as Soluble Insulin Injection and 70% as Isophane Insulin Injection) (Human Insulin of rDNA Origin)	100 IU
Metacresol USP (as preservative)	0.16% w/v
Phenol I.P. (as preservative)	0.065% w/v
Water for Injection I.P.	q.s.

QUALITATIVE & QUANTITATIVE COMPOSITION:

1 ml contains 100 IU of human insulin (produced in *E.coli* by recombinant DNA technology)
One cartridge contains 3 ml equivalent to 300 IU of human insulin.

DOSAGE FORM:

INSUTAGE® R: Solution for Injection
INSUTAGE® 30/70: Suspension for Injection

DESCRIPTION

INSUTAGE® cartridge contains insulin produced by recombinant DNA technology using a special non-disease producing strain of *Escherichia coli* bacteria. The insulin molecule in **INSUTAGE®** cartridge is mono component and is identical to natural human insulin in composition and in three-dimensional confirmation. **INSUTAGE® R** is a short acting human insulin. **INSUTAGE® 30/70** is a mixture of insulin soluble insulin 30% and isophane insulin 70%.

CLINICAL PARTICULARS

THERAPEUTIC INDICATIONS

INSUTAGE® is indicated for the treatment of patient with diabetes mellitus, maintain normal glucose homeostasis in patient with diabetes.

POSOLOGY AND ADMINISTRATION

Posology

The dosage is determined by the physician according to the needs of the patient.

Method of administration

INSUTAGE® cartridge preparations are for subcutaneous injection. For self-administration by patients, the subcutaneous route is preferred. **INSUTAGE® R** cartridge is generally administered 15-30 minutes before a meal, and **INSUTAGE® 30/70** cartridges are usually administered 30-60 minutes before a meal.
Shake gently before use.
Formulation should not be administered intravenously.
Do not mix **INSUTAGE® 30/70** with other insulin or diluents.

CONTRAINDICATIONS

- Hypoglycemia (low blood sugar)
- Hypersensitivity to human insulin or any of the excipients
- Intravenous administration of insulin suspensions

SPECIAL WARNING AND PRECAUTIONS

Any change of insulin cartridge (e.g., Brand, source, purity, strength) should be made with caution and only under medical supervision. Dose adjustments may be required. Appropriate testing should be conducted prior to initiation of **INSUTAGE®** cartridge treatment in patients who have previously developed generalized allergic reactions to insulin preparations.

The requirement of insulin may be affected by high fever; severe infection; emotional stress; gastrointestinal disorders, especially nausea, vomiting and diarrhea; pituitary, adrenal or thyroid gland disorders. The usual dose should be reviewed by a doctor in these conditions, and the patient should monitor glucose levels in blood/urine frequently.

The most frequent adverse reactions experienced by insulin users is hypoglycemia (Low blood sugar). If this condition is severe, immediate medical help is necessary.

Early warning symptoms of hypoglycemia may be less pronounced or different under certain conditions e.g. changing form animal insulin to human insulin, long duration or diabetes, diabetic or neuropathy, use of betablockers. The onset and intensity of the symptoms may vary between patients. If such symptoms occur frequently, even if they are mild, patients should seek medical advice to change the insulin dose or diet. If uncertain about the symptoms, the patient should learn to monitor the level of glucose in blood and urine frequently to familiarize themselves with the symptoms of hypoglycemia.

Patients who intend to travel across more than two time zones should consult their doctor concerning adjustments in insulin injection schedule.

Exercise may lower the body's requirement for insulin during and for some time after the activity. It may also speed up onset of the effect of an insulin dose, especially if the area of injection site is involved. Patients should discuss with the doctor concerning changes in dosing regimen to accommodate exercise e.g., not to inject **INSUTAGE®** cartridge into a thigh before running.

Combination of human insulin with thiazolidinediones
Cases of cardiac failure have been reported with the usage of thiazolidinediones in combination with insulin, especially in patients with multiple risk factors predisposing to cardiac heart failure. If treatment in combination of insulin and pioglitazone is considered patients should be observed for signs and symptoms of heart failure, weight gain and edema. Discontinue thiazolidinediones, if any deterioration in cardiac symptoms occurs.

Avoid sharing of needles or syringes between patients in order to avoid transmission of blood-borne pathogens.

MyStar® pens to be used with **INSUTAGE®** cartridges. The cartridges should be used in conjunction with **MyStar®** reusable insulin pen and should not be used with any other reusable pen as the dosing accuracy has not been established with other pens.

DRUG INTERACTIONS

Drugs interacting with human insulin may increase the risk of hypoglycemia or may decrease the blood glucose lowering effect of human insulin or may increase/decrease blood glucose lowering effect of human insulin or may blunt the signs and symptoms of hypoglycemia.

The following substances may interact the patient's insulin preparations:
Oral hypoglycemics, beta-blockers, ACE inhibitors, MAO inhibitors (antidepressants), methyldopa, salicylates, alcohol, anabolic steroids, sulfonamide antibiotics, tetracycline, antibacterial quinolones, alpha-adrenalin, isoniazid phenothiazides, beta-2 stimulants (such as salbutamol, terbutaline), lithium salts, clonidine.

USE IN SPECIFIC POPULATION

Use in Renal and Hepatic impairment: Insulin is metabolized mainly in liver and kidneys. Its duration of action is prolonged in patients with kidney or liver impairment. Dose reduction of **INSUTAGE®** is required in these patients.

Use in Pregnancy: It is essential to maintain continuous good control of glycaemia among diabetics requiring insulin throughout the pregnancy as hyperglycemia may harm the foetus. Management of the condition may be more difficult since insulin requirement changes during pregnancy. Patients who are pregnant or planning to become pregnant should consult the doctor.

Use in Lactation: There are no restrictions on treatment of diabetes with **INSUTAGE®** during lactation. Insulin treatment of the nursing mother is not expected to affect the baby. However, the dosages of **INSUTAGE®** may need to be adjusted.

Use in Geriatrics: Patients with advanced age using any insulin, including **INSUTAGE®** may be at risk of hypoglycemia due to co-morbid disease and polypharmacy.

EFFECT ON PATIENT'S ABILITY TO DRIVE AND USE MACHINE:

Patient's ability to concentrate and react may be impaired as a result of hypoglycemia. This may constitute risk in situations where these abilities are of special importance (e.g. car driving or operating machine).

Advise patients for taking precautions to avoid hypoglycemia while doing activities like driving or operating machinery, importantly in particular to those who lack awareness of the warning sign of hypoglycemia or have frequent episodes of hypoglycemia.

UNDESIRABLE EFFECTS

Hypoglycemia

Symptoms of hypoglycemia usually occur suddenly. They may include hyperhydrosis, dizziness, trembling, sensation of hunger, anxiety, tingling sensation in hands, feet, lips or tongue, concentration disturbance, sleepiness, sleep disturbances, loss of self-control, dilation of the pupils, visual disorders, speech disturbances, irritability.

Severe hypoglycemia may lead to unconsciousness and may result in temporary or permanent impairment of brain function or even death.

Hypokalemia: Human insulin can cause a shift in potassium from the extracellular to intracellular space, leading to hypokalemia.

Peripheral Edema: Human insulin may cause sodium retention and edema, particularly, if previously poor metabolic control is improved by intensified insulin therapy.

Weight Gain: Weight gain can occur with insulin therapy, including human insulin and has been attributed to the anabolic effects of insulin.

Lipodystrophy: Other adverse events that occasionally occur during treatment with biosynthetic insulin are: allergy to insulin, insulin resistance, post-insulin Lipodystrophy (atrophy or over growth of fat tissue in the area of injection). However, lipodystrophy may be minimized by rotating the site of injection. Patients should inform their doctor if they experience any adverse reaction while using the product.

Localized Cutaneous Amyloidosis (LCA): LCA at the injection has occurred. Hyperglycemia has been reported with repeated insulin injections into areas of localized cutaneous amyloidosis; hypoglycemia has been reported with a sudden change to an unaffected injection site.

Immunogenicity: As with all therapeutic peptides, insulin administration may cause anti-insulin antibodies to form. The incidence of antibody formation with human insulin is unknown.

To report any suspected undesirable/adverse effects, contact Sanofi India Limited at PV.India@sanofi.com or Tel: +91-22-2803 2000 (Select IVRS option 03)

OVERDOSE

Overdose causes hypoglycemia and hypokalemia.

Treatment of mild to moderate hypoglycemia: If the patient is conscious and co-operative, a readily available sugar-containing food (or small quantity of glucose powder) should be offered. This should then be followed by a longer acting carbohydrate (such as a sandwich or dried fruit).

Treatment of severe hypoglycemia: Glucagon is generally used for treating hypoglycemia outside hospital.

For adults and children 5 years and above who are unable to take oral food or fluids the dose of glucagon is 1 mg injected subcutaneously or intramuscularly. If intravenous access is available, 20 to 30 ml glucose 50% should be administered through a securely positioned catheter.

For children under 5 years, the dose of glucagons is 0.5 mg injected intramuscularly or subcutaneously followed by oral feeding when conscious. If intravenous access is available, a 2 ml/kg bolus 10% glucose solution should be given, followed by 0.1 ml/kg/minute until the patients is fully conscious.

PHARMACOLOGICAL PROPERTIES

Mechanism of action: Insulin lowers blood glucose by stimulating peripheral glucose uptake by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin inhibits lipolysis and proteolysis and enhance protein synthesis.

The administration of appropriate doses of insulin to patients with diabetes mellitus along with controlled diet and exercise, temporarily restores their ability to metabolize carbohydrates, fats and proteins, store glycogen in the liver, and convert glucose to fat. When given to a diabetic patient at appropriate doses and dosage intervals, the blood glucose level is maintained within a reasonable range, urine remains relatively free from glucose and ketone bodies, and diabetic complications like acidosis and coma are prevented.

Pharmacodynamics:
Pharmacotherapeutic group:
INSUTAGE® Regular short acting insulin,
INSUTAGE® 30/70: Mixture of intermediate acting insulin with short acting insulin.
The primary activity of insulin Human r-DNA is the regulation of glucose metabolism.
In addition, insulins have several anabolic and anti-catabolic actions on a variety of different tissues. Within muscle tissue this includes increasing glycogen, fatty acid, glycerol and protein synthesis and amino acid output.

Pharmacokinetics
In healthy subjects, approximately 5% of Insulin is bound to plasma proteins. Insulin can also be detected in cerebrospinal fluid at a concentration of approximately 25% of total serum insulin concentration.

Insulin is metabolized by the liver and kidneys, and to a lesser extent in fat and muscle tissue. It is eliminated by the kidneys, and minute quantities are also eliminated in bile. The elimination half-life is approximately 4 minutes. Hepatic or renal impairment, which is often associated with ageing patients, may delay insulin elimination.

The various preparations of **INSUTAGE®** cartridge are formulated to provide short intermediate and biphasic therapeutic action. In clinical practice, the duration of **INSUTAGE®** cartridge action may vary from that specified below. As with all insulin preparations, variations between and within patients may occur depending upon injection site, dosage, diet, temperature and physical activity.

Presentation	Onset of effect	Maximum effect	Duration of effect
INSUTAGE® R	Within 30 minutes	1-3 hours	Up to 8 hours
INSUTAGE® 30/70	Within 30 minutes	2-8 hours	Up to 24 hours

NON-CLINICAL PROPERTIES:
In in vitro tests, including binding to insulin receptor sites and effects on growing cells, insulin Human r-DNA behaved in a manner that closely resembled human insulin. Acute, one month and twelve-month toxicology studies produced no significant toxicity findings.

Insulin Human r-DNA did not induce fertility impairment, embryo toxicity or teratogenicity in animal studies.

PHARMACEUTICAL PARTICULARS:
Incompatibilities
INSUTAGE® preparations should not be mixed with insulin produced by other manufacturers or with animal insulin preparations.

SHELF LIFE
Unused cartridge: 3 years at temperature of 2-8 °C
In Use/Opened Cartridge: 28 days at temperature up to 25 °C.

PACKAGING INFORMATION
3 ml USP Type I filled and sealed labelled Cartridge, such five labelled and Blistered cartridges are packed in printed carton along with a Product leaflet.

STORAGE CONDITIONS
INSUTAGE® preparation can be stored for three years at temperature of 2-8 °C. Do not freeze them.

INSUTAGE® cartridge should be used with a **MyStar®** insulin pen device.

Once the cartridge is opened, the preparation can be stored for 28 days at a temperature up to 25°C. Insulin should not be used after the expiry date. Please refer to expiry date on the carton/label.

Do not expose **INSUTAGE®** cartridge to excessive heat or direct sunlight.

INSUTAGE® cartridge must be kept out of reach of children.

PATIENT COUNSELLING INFORMATION
INSUTAGE® cartridge is designed to be used with **MyStar®** pen. The **MyStar®** pen is not designed to allow any other insulin to be mixed in its cartridge. **INSUTAGE®** cartridge must be rolled between the palms 10 times and inverted 180^0 for 10 times before inserting the **MyStar®** pen.

If the cartridge is already inside the pen, then the **MyStar®** pen must be rolled between the palms 10 times and inverted 180^0, 10 times before each injection so that the contents are uniformly mixed.

Visual inspection prior to Use: Before administration, examine the cartridge carefully to ensure uniform mixing and discard the cartridge if any crystallization, clump formation or discoloration of inside contents are noticed. **INSUTAGE®** R contains clear colour less solution.

When inserting **INSUTAGE®** cartridge for the first time in the **MyStar®** pen, disinfect the rubber surface of the cartridge with alcohol and shake the cartridge as directed above.

Before administration of **INSUTAGE®** cartridge through **MyStar®** pen, attach the needle to the pen and follow the instructions provided with the instrument to remove the air bubble, disinfect the hands and site of injection with alcohol and after adjusting the dose as advised by the doctor, administer the insulin appropriately. Do not apply heat or massage the area immediately after administration of dose. Detach the needle from the pen and dispose it off as recommended.

Never share **MyStar®** pen between patients.
Hyperglycemia or hypoglycemia Instruct patients on self-management procedures including glucose monitoring, proper injection technique, and management of hypoglycemia and hyperglycemia especially at initiation of **INSUTAGE®** therapy.
For further information, please *refer special warning and precaution section*.

Manufactured by: M. J. BIOPHARM PVT. LTD. L-7, MIDC Industrial area, Taloja, Tal-Panvel, Dist. Raigad, Maharashtra– 410 208.

Marketed by: Sanofi India Limited, Sanofi House, CT Survey No. 117-B, L&T Business Park, Saki Vihar Road, Powai, Mumbai – 400072

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