# BIOCON FORMULATIONS
MASTER PROOF OF APPROVED PRINTED **VIAL LEAFLET** ART WORK
**Insugen®-R 100 IU/mL, 10 mL** FOR COLOUR COPY

## (FOR MALAYSIA INDIA MFG BBL) ANNEXURE-4 [Ref. No. : S2/BF/QA/SOP/0018]
ARTWORK CODE: **BF2128/XX**

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

Biocon Biologics

DUOPHARMA

# Insugen®-R (Regular)

Insulin, Human of recombinant DNA Origin.

100 IU/mL
10 ml vials

## Insulin Injection, Soluble

Solution for injection Subcutaneous or intravenous use only

**NAME OF THE MEDICINAL PRODUCT**

**INSUGEN®-R (REGULAR)**
(Insulin Injection, Soluble 100 IU/mL)

**COMPOSITION**
Each mL contains
Insulin, Human Ph.Eur. 100 IU
(Insulin Human of recombinant DNA origin)
m-Cresol Ph.Eur. 0.25% w/v
Water for injection Ph.Eur. q.s.
One IU (International Unit) of insulin is equivalent to 0.035 mg of human insulin.
Each 10 mL vial contains solution for injection, equivalent to 1000 IU.
For a full list of excipients, see section **List of Excipients.**
Insulin human, rDNA is produced by recombinant DNA technology in *Pichia pastoris*.

**PHARMACEUTICAL FORM**
Solution for injection in a vial.
A colourless liquid, free from turbidity and foreign matter. During storage, traces of very fine sediment may be deposited.

**PHARMACOLOGICAL PROPERTIES**
Pharmacotherapeutic group: Insulins and analogues for injection, fast-acting, insulin (human), ATC code: A10AB01.
INSUGEN®-R has been developed as a similar biological medicinal product to Actrapid®.

**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®-R is a fast-acting insulin. Onset of action is within 0.5 hours, reaches a maximum peak effect within 1.5 and 3.5 hours and the entire duration of action is upto 7 to 8 hours.

**Pharmacodynamic properties**
Insulin, a hormone secreted by the beta cells of the pancreas, plays an essential role in controlling the metabolism and storage of carbohydrates, fat, and protein. Insulin is secreted in response to a rise in blood glucose (sugar). Insulin lowers blood glucose by facilitating 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 between meals. 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 variants are seen.

Clinical efficacy of INSUGEN®-R plus INSUGEN®-N was evaluated in comparison with Actrapid® plus Insulatard® in a randomized, open-label, two-phase, 48-week, phase 3 study in type 1 diabetes mellitus (T1DM) patients (Study INSUGCT300509). During the first 24-week comparative phase, patients received INSUGEN®-R plus INSUGEN®-N or Actrapid® plus Insulatard® whereas, in the subsequent 24-week non-comparative phase, patients who received Actrapid® plus Insulatard® were switched to receive INSUGEN®-R plus INSUGEN®-N. During the study, efficacy of INSUGEN®-R plus INSUGEN®-N was similar to Actrapid® plus Insulatard® with respect to changes in glycosylated hemoglobin (HbA1C), fasting plasma glucose, 7-point capillary blood glucose levels and prandial as well as basal insulin dose. Switching the patients from Actrapid® plus Insulatard® to INSUGEN®-R plus INSUGEN®-N had no effect on efficacy.
Overall, INSUGEN®-R and INSUGEN®-N were individually similar to Actrapid® and Insulatard® in efficacy.

**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 is reached within 1.5 to 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 2 to 5 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**
The potency of human insulin is expressed in international units (IU).

***Dosage***
Dosage is individual and determined in accordance with the needs of the patient. It can be used alone or in combination with intermediate-acting or long-acting insulin before a meal or a snack.
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.

***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**).

**Method of Administration**
INSUGEN®-R is usually administered subcutaneously into the abdominal wall. The thigh, the gluteal region or the deltoid region may also be used.
INSUGEN®-R can be administered intravenously, which should only be carried out by a physician. Subcutaneous injection into the abdominal wall results in a faster absorption than from other injection sites. Injection into a lifted skin fold minimises the risk of an intramuscular injection.
Injection sites should always be rotated within the same region in order to reduce the risk of lipodystrophy and cutaneous amyloidosis.
An injection should be ideally but not always, followed within 30 minutes by a meal or a snack containing carbohydrates.
As with all insulin medicinal products, the duration of action will vary according to the dose, injection site, blood flow, temperature and level of physical activity.
INSUGEN®-R vials are for use with insulin syringes with a corresponding unit scale that is marked U-100. 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. Disinfect the rubber stopper with an alcohol swab.
2. Visually inspect the vial to ensure that there are no suspended impurities.
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**
INSUGEN®-R is contraindicated for use in patients with:
- Hypersensitivity to the active substance or to any of the excipients (see section **List of Excipients**).
- 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.

***Hyperglycaemia***
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 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 sections **Side Effect** and **Overdose**).
Omission of a meal or unplanned, strenuous physical exercise may lead to hypoglycaemia. In case of hypoglycaemia or if hypoglycaemia is suspected **INSUGEN®-R** must not be injected. After stabilisation of patient's blood glucose adjustment of the dose should be considered (see sections **Side Effect** and **Overdose**).
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.
Concomitant illness, especially infections and feverish conditions, usually increases the patient's insulin requirement. Concomitant diseases in the kidney, liver or affecting the adrenal, pituitary or thyroid gland can require changes in the insulin dose.

***Transfer from other Insulin Medicinal Products***
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 dose. If an adjustment is needed when switching the patients to **INSUGEN®-R**, it may occur with the first dose or during the first several weeks or months.
When patients are transferred between different types of insulin medicinal products, the early warning symptoms of hypoglycaemia may change or become less pronounced than those experienced with their previous insulin.
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.

***Injection Site 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®-R**.
Due to the risk of precipitation in pump catheters, INSUGEN®-R should not be used in insulin pumps for continuous subcutaneous insulin infusion.

***Skin and subcutaneous tissue disorders***
Patients must be instructed to perform continuous rotation of the injection site to reduce the risk of developing lipodystrophy and cutaneous amyloidosis. There is a potential risk of delayed insulin absorption and worsened glycaemic control following insulin injections at sites with these reactions. A sudden change in the injection site to an unaffected area has been reported to result in hypoglycaemia. Blood glucose monitoring is recommended after the change in the injection and dose adjustment of antidiabetic medications may be considered.

***Combination of INSUGEN®-R 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®-R 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.

***Others***
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.



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

Biocon Biologics

DUOPHARMA

Insugen®-R (Regular)

Insulin, Human of recombinant DNA Origin.

100 IU/mL
10 ml vials

Insulin Injection, Soluble

Solution for injection Subcutaneous or intravenous use only

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®-R** injection.
INSUGEN-R contains metacresol, which may cause allergic reactions.

**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**
***Pregnancy***
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 blood glucose 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.

***Lactation***
There is no restriction on treatment with **INSUGEN®-R** during breast-feeding. Insulin treatment of the nursing mother presents no risk to the baby. However, the INSUGEN®-R 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.

**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. 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.
Safety data for INSUGEN®-R plus INSUGEN®-N was generated in a randomized, open-label, two-phase, 48-week, phase 3 study in T1DM patients (Study INSUGCT300509). Incidence of treatment-emergent adverse events (TEAEs), severe adverse events and serious adverse events were similar for INSUGEN®-R plus INSUGEN-N and Actrapid® plus Insulatard® during the study. There were no notable clinically significant differences when patients switched from Actrapid® plus Insulatard® to INSUGEN®-R plus INSUGEN®-N.
The TEAEs occurring in ≥2% of patients in either treatment group during the study are described below:
*General disorders and administration site conditions:* asthenia and pyrexia
*Nervous system disorders:* headache
*Infections and infestations:* nasopharyngitis, influenza, tonsillitis, upper respiratory tract infection and urinary tract infection
*Skin and subcutaneous tissue disorders:* hyperhidrosis
*Musculoskeletal and connective tissue disorders:* back pain and pain in extremity
*Metabolism and nutrition disorders:* dyslipidemia, hypercholesterolemia and hypoglycemia
*Injury, poisoning and procedural complications:* excoriation
*Renal and urinary disorders:* ketonuria and proteinuria
*Respiratory, thoracic and mediastinal disorders:* cough
*Vascular disorders:* hypertension
The following side effects and their frequencies have been observed under treatment with INSUGEN®-R. The assessment of side effects is based on the following frequency data: uncommon (≥1/1,000 to <1/100). Isolated spontaneous cases are presented as very rare defined as <1/10,000 including isolated reports.
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Nervous system disorders
Uncommon - Peripheral neuropathy
Fast improvement in blood glucose control may be associated with a condition termed "acute painful neuropathy", which is usually reversible.

Eye disorders
Uncommon side effect - Refraction disorders
Refraction anomalies may occur upon initiation of insulin therapy. These symptoms are usually of transitory nature.
Very rare side effect- 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
Uncommon - Lipodystrophy
Not known - Cutaneous amyloidosis
Lipodystrophy and cutaneous amyloidosis may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions.

General disorders and administration site conditions
Uncommon - Injection site reactions
Injection site reactions (redness, swelling, itching, pain and haematoma at the injection site) may occur during treatment with insulin. Most reactionsare transitory and disappear during continued treatment.
Uncommon - Oedema
Oedema may occur upon initiation of insulin therapy. These symptoms are usually of transitory nature.
Immune system disorders
Uncommon - Urticaria, rash.
Very rare - 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 with glucagon (0.5 to 1 mg) given intramuscularly or subcutaneously by a trained person, or with 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, Zinc Oxide, Hydrochloric acid, Sodium Hydroxide, Water for injections.
**Incompatibilities**
Insulin products should only be added to compounds with which it is known to be compatible.
**Shelf Life**
Refer to label/ carton.
**Interchangeability and Automatic Substitution**
INSUGEN®-R has been developed as a similar biological medicinal product to Actrapid® and has been shown to have a comparable quality, safety and efficacy profile to Actrapid®. Therefore, interchangeability with the reference product Actrapid® may be considered if this is in agreement with the treating physician. However, automatic substitution (i.e. the practice by which a different product to that specified on the prescription is dispensed to the patient without the prior informed consent of the treating physician) and active substance-based prescription cannot apply to biologicals, including biosimilars. Such a differentiating approach towards biologicals ensures that treating physicians can make informed decision about treatments is in the interest of patient's safety.
**Storage and Precautions**
Store in a refrigerator at temperature between 2°C and 8°C.
Do not freeze. Do not store **INSUGEN®-R** in or too near the freezer section or cooling element.
Keep the vial in the outer carton in order to protect from light.
Protect from excessive heat and sunlight.
In-use Instruction: Do not refrigerate. Do not freeze. **Insugen®-R** vials that are in use can be kept at a temperature (not above 30°C) for up to 42 days.
Keep INSUGEN®-R out of reach of children.
*Jauhi daripada kanak-kanak.*
**Special Precautions for Disposal and Other Handling**
Insulin products which have been frozen must not be used.
After removing INSUGEN®-R vial from the refrigerator it is recommended to allow the vial to reach room temperature not above 30°C for first time use.
Never use INSUGEN®-R, if the solution is not clear, colourless and aqueous or if it shows cloudiness or any suspended matter.
The patient should be advised to discard the needle and syringe after each injection.
Any unused product or waste material should be disposed of in accordance with local requirements.
**Nature and Contents of Container**
**INSUGEN®-R** is supplied 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 package insert.
**Pack sizes:** 1×10 mL

**Product Registration Holder:**
**Biocon Sdn. Bhd.**
No.1, Jalan Bioteknologi 1,
Kawasan Perindustrian SiLC,
79200 Iskandar Puteri, Johor, Malaysia.

**Manufactured & Released by:**
**Biocon Biologics Limited,**
Block No. B1, B2, B3, Q13 of Q1 and W20 & Unit S18,
1st Floor, Block B4, Special Economic Zone,
Plot No.2, 3, 4 & 5 Phase IV, Bommasandra-Jigani Link Road,
Bommasandra Post, Bengaluru - 560 099, India.

**Imported & Marketed by:**
**Duopharma Marketing Sdn. Bhd.**
Lot No. 2, 4, 6, 8 & 10,
Jalan P/7, Section 13,
Bangi Industrial Estate,
43650 Bandar Baru Bangi,
Selangor Darul Ehsan, Malaysia.

Revision Date: **January 2023**

BF2128/XX



Size : 110 (W) x 180 (H) mm
Folding Size : 23 (W) x 110 (H) mm
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