SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT:

BIOSULIN R (Insulin Injection, Soluble Ph. Eur. 100 IU/ml, 10 ml Vial)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Label Claim: Each ml contains:

• Human Insulin Ph. Eur…….……..……..100 IU

• Meta-cresol USP (as preservative) .....0.25% w/v

• Water for Injection USP. ……q.s.

3. PHARMACEUTICAL FORM

Solution for Injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

BIOSULIN R is indicated for the treatment of patients with diabetes mellitus who require insulin for the maintenance of normal glucose homeostasis.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION:

Posology

The dosage should be determined by the physician, according to the requirement of the Patient, considering your blood glucose values, age, daily activities etc. the time course of action of an insulin preparation may vary considerably in different individuals or at different times in the same individuals. Therefore, the dosage schedule will be individualized for you. You must, therefore, follow your doctors' instructions carefully.

Pediatric Population:

No data are available.

Method of administration

Biosulin R should be given by subcutaneous injection but may, although not recommended, also be given by intramuscular injection. It may also be administered intravenously. Subcutaneous administration should be in the upper arms, thighs, buttocks or abdomen. Use of injection sites should be rotated so that the same site is not used more than approximately once a month in order to reduce the risk of lipodystrophy and cutaneous amyloidosis (see section 4.4 and 4.8). After any insulin injection, the injection site should not be massaged. Patients must be educated to use proper injection techniques. Each pack contains a patient information leaflet with instructions on how to inject insulin.

4.3 CONTRAINDICATIONS

Hypoglycaemia.

Hypersensitivity to insulin or any of its excipients listed in section 6.1.

4.4 SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE

Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (soluble, NPH, lente, etc.), species (animal, human, human insulin analogue), and/or method of manufacture (recombinant DNA versus animal-source insulin) may result in the need for a change in dosage.

Some patients taking human insulin may require a change in dosage from that used with animal-source insulins. If an adjustment is needed, it may occur with the first dose or during the first several weeks or months.

A few patients who experienced hypoglycaemic reactions after transfer to human insulin have reported that the early warning symptoms were less pronounced or different from those experienced with their previous animal insulin. Patients whose blood glucose is greatly improved, e.g., by intensified insulin therapy, may lose some or all of the warning symptoms of hypoglycaemia and should be advised accordingly. Conditions which may make the early warning symptoms of hypoglycaemia different or less pronounced include long duration of diabetes, intensified insulin therapy, diabetic nerve disease, or medications such as beta-blockers. Uncorrected hypoglycaemic and hyperglycaemic reactions can cause loss of consciousness, coma or death. The use of dosages which are inadequate, or discontinuation of treatment, especially in insulin-dependent diabetics, may lead to hyperglycaemia and diabetic ketoacidosis, conditions which are potentially lethal.

If hypersensitivity reactions occur, treatment should be discontinued and monitored depending upon the recommendation of standard care until symptoms and signs resolve.

Treatment with human insulin may cause formation of antibodies, but titters of antibodies are lower than those to purified animal insulin.

Insulin requirements may change significantly in diseases of the adrenal, pituitary, or thyroid glands, and in the presence of renal or hepatic impairment. Insulin requirements may be increased during illness or emotional disturbances.

Adjustment of insulin dosage may also be necessary if patients change their level of physical activity or change their usual diet.

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 site, and dose adjustment of antidiabetic medications may be considered.

Combination of human insulin 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 human insulin 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.

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

A number of medicinal products are known to interact with glucose metabolism and therefore the physician should be consulted when using other medications in addition to human insulin The physician must therefore take possible interactions into account and should always ask his patients about any medicinal products they take.

Insulin requirements may be increased by substances with hyperglycaemic activity, such as glucocorticoids, thyroid hormones, growth hormone, danazol, beta2-sympatomimetics (such as ritodrine, salbutamol, and terbutaline), thiazides.

Insulin requirements may be reduced in the presence of substances with hypoglycaemic activity, such as oral hypoglycaemic (OHA), salicylates (for example, acetylsalicylic acid), certain antidepressants (monoamine oxidase inhibitors), certain angiotensin-converting enzyme (ACE) inhibitors (captopril, enalapril), angiotensin II receptor blockers, non-selective beta-blocking agents, and alcohol.

Somatostatin analogues (octreotide, lanreotide) may both decrease or increase insulin dose requirements.

4.6 PREGNANCY AND LACTATION:

It is essential to maintain good control of the insulin-treated patient throughout pregnancy. Insulin requirements usually fall during the first trimester and increase during the second and third trimesters. Patients with diabetes should be advised to inform their doctors if they are pregnant or are contemplating pregnancy.

Careful monitoring of glucose control, as well as general health, is essential in pregnant patients with diabetes.

There are no restrictions on treatment of diabetes with insulin during pregnancy, as insulin does not pass the placental barrier. Both hypoglycaemia and hyperglycemias, 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.

After delivery, insulin requirements return rapidly to pre-pregnancy values. Insulin treatment of the nursing mother presents no risk to the baby. However, the dosage may need to be adjusted.

4.7 UNDESIRABLE EFFECTS

Hypoglycaemia is the most frequent undesirable effect of insulin therapy that a patient with diabetes may suffer. Severe hypoglycaemia may lead to loss of consciousness, and in extreme cases, death. No specific frequency for hypoglycaemia is presented, since hypoglycaemia is a result of both the insulin dose and other factors e.g., a patient's level of diet and exercise.

Local allergy in patients is common Redness, swelling, and itching can occur at the site of insulin injection. This condition usually resolves in a few days to a few weeks. In some

instances, local reactions may be related to factors other than insulin, such as irritants in the skin cleansing agent or poor injection technique.

Systemic allergy, which is very rare but potentially more serious, is a generalized allergy to insulin. It may cause rash over the whole body, shortness of breath, wheezing, reduction in blood pressure, fast pulse, or sweating. Severe cases of generalized allergy may be life-threatening. In the rare event of a severe allergy to Insulin, treatment is required immediately. A change of insulin or desensitization may be required.

Lipodystrophy at the injection site is uncommon (≥ 1/1,000 to < 1/100).

Skin and subcutaneous tissue disorders: Frequency "unknown": Cutaneous amyloidosis

Skin and subcutaneous tissue disorders:

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 (See section 4.4).

Cases of oedema have been reported with insulin therapy, particularly if previous poor metabolic control is improved by intensified insulin therapy.

4.8 OVERDOSE

Insulin has no specific overdose definitions, because serum glucose concentrations are a result of complex interactions between insulin levels, glucose availability and other metabolic processes. Hypoglycaemia may occur as a result of an excess of insulin relative to food intake and energy expenditure.

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 hypoglycaemia can be accomplished by intramuscular or subcutaneous administration of glucagon, followed by oral carbohydrate when the patient recovers sufficiently. Patients who fail to respond to glucagon must be given glucose solution intravenously.

If the patient is comatose, glucagon should be administered intramuscularly or subcutaneously. However, glucose solution must be given intravenously if glucagon is not available, or if the

patient fails to respond to glucagon. The patient should be given a meal as soon as consciousness is recovered. Sustained carbohydrate intake and observation may be necessary because hypoglycaemia may occur after apparent clinical recovery. Upon regaining consciousness, administration of oral carbohydrate is recommended for the patient in order to prevent relapse.

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group Insulins and analogues for injection, fast-acting, insulin (human). ATC code A10AB01.

BIOSULIN R is rapidly acting human insulin preparation.

In addition insulin has 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 uptake, while decreasing glycogenolysis, gluconeogenesis, ketogenesis, lipolysis, protein catabolism and amino acid output.

Soluble Insulin is a buffered neutral pH solution of unmodified insulin stabilized by a small amount of zinc. At the concentration of the injectable solution, the insulin molecules self aggregate to form hexamers around zinc ions. After S.C injection, insulin monomers are released gradually by dilution, so that absorption occurs slowly. Peak action is produced only after 2-3 hours and action continues up to 6-8 hours. The absorption pattern is also affected by dose; higher doses act longer.

5.2 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.

5.3 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.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS:

Metacresol (Distilled)

Glycerine

Water for Injection

10% Hydrochloric Acid Solution

10% Sodium Hydroxide Solution

6.2 INCOMPATIBILITIES:

BIOSULIN R preparations should not be mixed with insulin's produced by other manufacturers or with animal insulin preparations.

6.3 SHELF LIFE

24 Months from the date of Manufacturing. 28 days after first use.

6.4 SPECIAL PRECAUTIONS FOR STORAGE:

BIOSULIN R preparation can be stored for two years in the temperature 2-8℃. Do not Freeze them. Once the cartridge is opened, the preparation can be stored for 28 days in the temperature below 30℃. Insulin should not be used after expiry date. BIOSULIN R preparation must be protected from light. Store out of reach of children.

6.5 NATURE AND CONTENTS OF CONTAINER:

10 ml, glass vial USP type I with a rubber stopper on top and sealed with aluminium seal.

6.6 INSTRUCTIONS FOR USE AND HANDLING:

Do not reuse needles. Dispose of the needle in a responsible manner. Needles and pens must not be shared. Vials can be used until empty, then properly discard. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

a) Preparing a dose

Vials containing Biosulin R formulation do not require resuspension and should only be used if it is clear, colourless, with no solid particles visible and if it is of water-like appearance.

b) Injecting a dose

Inject the correct dose of insulin, as directed by your doctor or diabetes specialist nurse. Use of the injection sites should be rotated so that the same is not used more than approximately once a

month. Each pack contains a patient information leaflet with instructions on how to inject insulin.

7. MARKETING AUTHORISATION HOLDER

CORPORATE ADDRESS:

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Tel 91-22-27402331

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8. NUMBER(S) IN THE NATIONAL REGISTER OF FINISHED PHARMACEUTICAL PRODUCTS

BIO/INDIA/377

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION.

14th May, 2018

10. DATE OF REVISION OF THE TEXT

12th July, 2023