APPROVED PACKAGE INSERT

BIOSULIN RANGE: PROPOSED PACKAGE INSERT

SCHEDULING STATUS:

S3

PROPRIETARY NAMES (AND DOSAGE FORMS):

BIOSULIN R (Solution for Injection)

BIOSULIN N (Suspension for Injection)

BIOSULIN L (Suspension for Injection)

BIOSULIN 30/70 (Suspension for Injection)

COMPOSITION:

BIOSULIN (-R, -N, -L, -30/70) contains biosynthetic human insulin (recombinant DNA origin) 100 I.U./ml. Details of **BIOSULIN R, -N, -L** and -**30/70** composition are as follows:

Preservative and type of biosynthetic Insulin

BIOSULIN preparation	**Type of biosynthetic Insulin (rDNA)**	**Preservatives**
BIOSULIN R	Soluble (short-acting)	m-cresol 0,25 % *m/v*
BIOSULIN N	Isophane suspension (Intermediate-acting)	m-cresol 0,16 % *m/v* phenol 0,065 % *m/v*
BIOSULIN L	Zinc suspension (Intermediate-acting)	Methylparaben 0,1 % *m/v*
BIOSULIN 30/70	30 % soluble 70 % Isophane (Biphasic)	m-cresol 0,16 % *m/v* phenol 0,065 % *m/v*

Other inactive ingredients are:

BIOSULIN R: Glycerin, 10 % hydrochloric acid solution and 10 % sodium hydroxide solution.

BIOSULIN N: Glycerin, protamine sulphate, zinc oxide, 10 % hydrochloric acid solution and 10 % sodium hydroxide solution.

BIOSULIN L: Zinc oxide, 10 % hydrochloric acid solution and 10 % sodium hydroxide solution.

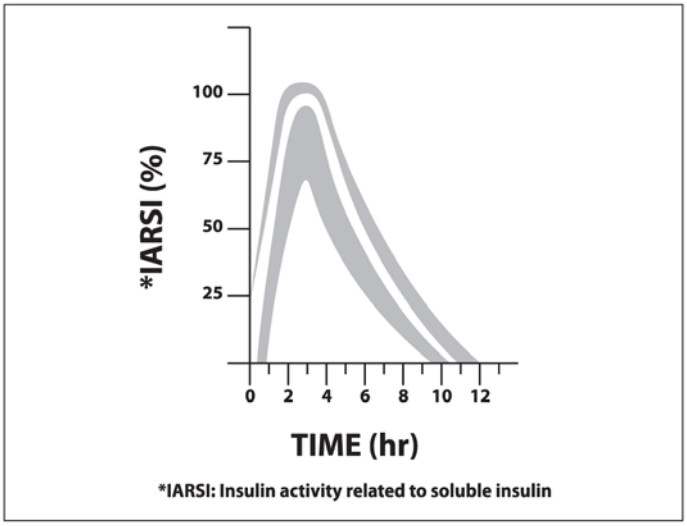
BIOSULIN 30/70: Glycerin, protamine sulphate, zinc oxide, 10 % hydrochloric acid solution and 10 % sodium hydroxide solution.

PHARMACOLOGICAL CLASSIFICATION:

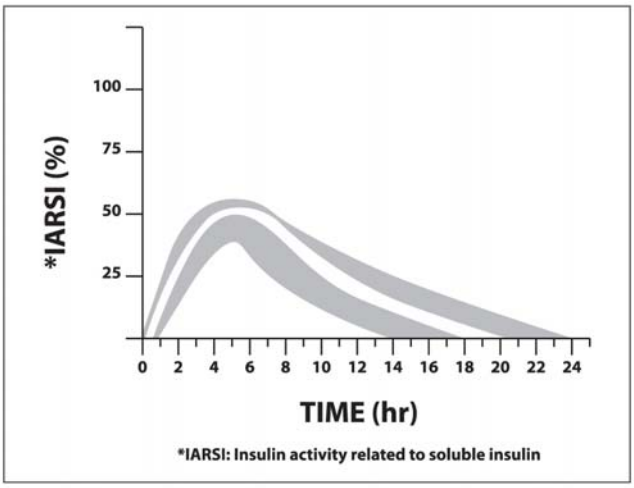
A 21.1 Insulin preparations.

PHARMACOLOGICAL ACTION:

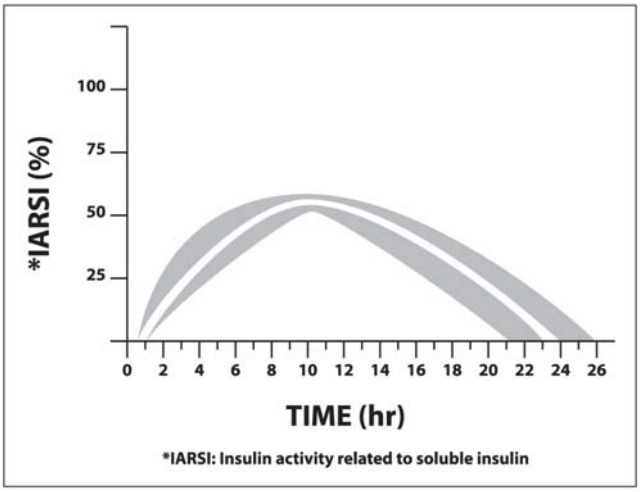
Biosynthetic insulin replaces the insufficient section of insulin by the β-cells of the pancreas. Typical activity profiles (glucose utilization curves) following the subcutaneous injection of the different **BOSULIN** preparations are illustrated below by the white lines within the shaded areas. The shaded areas illustrate the variations that a patient may experience in timing and/or intensity of insulin activity. The time course of action of insulin may vary considerably between patients and from time to time in the same patient. Dose, site of injection, blood supply, temperature and physical activity determine the duration of action of biosynthetic insulin.



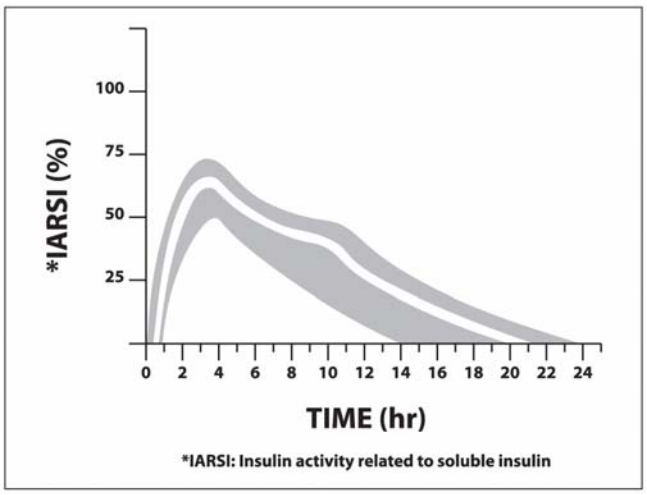
BIOSULIN R



BIOSULIN N



BIOSULIN L



BIOSULIN 30/70

INDICATIONS:

BIOSULIN (-R, -N, -L & -30/70), is indicated for the treatment of diabetes mellitus.

CONTRAINDICATIONS:

BIOSULIN is contraindicated in patients with:

- Hypoglycaemia.
- Hypersensitivity to any of the ingredients.

WARNINGS AND SPECIAL PRECAUTIONS:

Under no circumstances should BIOSULIN N, -L or -30/70 be given intravenously.

Transferring a patient to another type or brand of insulin should be done under strict medical supervision as this may result in the need for a change in dosage. There have been no reports of hypoglycaemia, sometimes with decreased warning symptoms, in patients changing from animal source insulin to human insulin. When changing from animal (especially bovine insulin) to human insulin, a reduction in insulin dosage may be required.

BIOSULIN R solution should be clear and colourless or almost colourless. Do not use **BIOSULIN R** solution if it appears cloudy, thickened or if solid particles are visible.

BIOSULIN N, -L and -**30/70** suspensions should look uniformly milky after gentle shaking. If a deposit of solid particles remains on the bottom or wall of the cartridge/vial or if there are clumps floating in the insulin after the cartridge/vial has been rotated or carefully shaken, such cartridges/vials of **BIOSULIN N, -L** and -**30/70** suspensions should not be used. If the **BIOSULIN N, -L** and -**30/70** suspension is clear and remains clear after the cartridge/vial is rotated or carefully shaken, it should also not be used.

Special Precautions:

Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for the development of cardiac failure. (See **INTERACTIONS**).

Patients which are using the combination should be monitored for the signs and symptoms of heart failure, weight gain and oedema.

Should any deterioration in the cardiac status occur, in patients using both **BIOSULIN** and pioglitazone, pioglitazone use should be discontinued.

Hypoglycaemia is the most frequent complication of **BIOSULIN** therapy. However, some patients, such as the elderly, those with tightly controlled diabetes or those with longstanding diabetes, may experience the typical early warning signs of a hypoglycaemic attack.

BIOSULIN dosage may need to be altered under certain circumstances. Doses may have to be increased during infection, emotional stress, accidental or surgical trauma and puberty, and decreased in patients with impaired renal or liver function. Adjustment of dosage may be necessary during increased physical activity or a change in the usual diet. Patients who use **BIOSULIN** require regular monitoring of therapy. This may be performed by testing the blood or urine for glucose concentrations and testing urine for ketones.

INTERACTIONS:

An increased risk of cardiac failure has been observed when pioglitazone is used in combination with insulin in the treatment of patients with type 2 diabetes, especially in those with predisposing factors.

Many medicines affect blood glucose concentrations and may alter **BIOSULIN** requirements.

BIOSULIN requirements may be decreased by ACE inhibitors, alcohol, anabolic steroids, aspirin, beta-blockers (which may also mask the warning signs of hypoglycaemia), disopyramide, fenfluramine, guanethidine, some MAOIs (monoamine oxidase inhibitors), mebendazole, octreotide, some tetracyclines and amitriptyline.

BIOSULIN requirements may increase with chlordiazepoxide, chlorpromazine, some calcium channel blockers such as dilitiazem or nifedipine, corticosteroids, diazoxide, lithium thiazide diuretics and thyroid hormones.

The use of cyclophosphamide, isoniazid and oral contraceptives may lead to increased or decreased **BIOSULIN** requirements.

PREGNANCY AND LACTATION:

It is essential to maintain good control of the diabetic patient throughout pregnancy and, therefore, diabetic patients should be advised to inform their doctor if they are pregnant or contemplating pregnancy. During pregnancy, **BIOSULIN** requirements usually decrease during the first trimester and increase during the latter two trimesters. Patients with diabetes who are lactating may require adjustment of **BIOSULIN** dose, diet or both.

DOSAGE AND DIRECTIONS FOR USE:

The healthcare professional should determine the dosage and type of **BIOSULIN** according to the requirements of the patient.

Patients should use a syringe marked for use with an insulin preparation that contains 10 units per ml, since use of an incorrect syringe could lead to dosage errors.

BIOSULIN R may be administered by subcutaneous, intramuscular or intravenous injection. **BIOSULIN N, -L** and -**30/70** should only be administered via subcutaneous or intramuscular injection.

Appropriate sites for subcutaneous injection are the upper arm, thigh, buttock or abdomen. It is important to educate patients regarding the use of proper injection techniques.

Mixing of insulin:

Many insulin regimens involve the use of short-acting soluble insulin together with intermediate-acting insulin or a mixed insulin zinc suspension. On the advice of a physician **BIOSULIN R** (from vials) may be mixed with longer-acting insulin such as **BIOSULIN N** or -**L** (from vials) as required, usually twice daily. The shorter acting **BIOSULIN R** should be drawn into the syringe first to prevent the longer-acting insulin contaminating the vial. It is recommended that patients inject immediately after mixing. Such mixtures must not be administered intravenously.

Since **BIOSULIN 30/70** is a ready-made mixture, patients do not need to mix insulins. It is usually given twice daily with about two-thirds of the total daily requirement administered before breakfast and the remaining third administered before the evening meal.

Administration using 10 ml vials and conventional insulin syringes:

Wash the hands. Remove the protective plastic cap on the vial. Use alcohol to wipe the exposed rubber top of the vial. Use the specified syringe and familiarise yourself with the distance the plunger needs to be drawn back corresponding to the quantity of **BIOSULIN** required.

Then, after ensuring that the plunger is not drawn out at all, pierce the rubber top with the syringe needle and turn the vial and syringe upside down. Next, draw back on the plunger slowly to withdraw the correct dose of **BIOSULIN**, while simultaneously avoiding drawing air

into the syringe. To avoid clogging the needle, inject the required amount of **BIOSULIN** promptly.

Administration using the Biosulin Pen device and cartridges;

Wash the hands. Follow the detailed instructions which are provided on the "Biosulin Pen Pack" leaflet, provided with your Biosulin Pen device.

General good and basic administration/injection practices to be followed using insulin from either the vials or the cartridges to be administered using the Biosulin Pen device

- CLEAN - Clean the skin where the injection is to be made. Inject the **BIOSULIN** as directed by a healthcare professional.
- DO NOT MASSAGE - The injection site should not be massaged after the injection.
- Patients should take care to ensure that a blood vessel is not entered when injecting **BIOSULIN N, -L** or -**30/70.**
- CHANGE INJECTION SITE - Since lipohypertrophy is associated with repeated injections at the same site, a different subcutaneous injection site should be used for each administration.

SIDE EFFECTS:

Immune system disorders:

Less frequent: Local or systemic hypersensitivity reactions. Systemic – generalised hypersensitivity reactions, which may cause urticaria, angioedema.

Very rarely: Anaphylactic reactions.

Metabolism and nutrition disorders:

Frequent: Hypoglycaemia, the symptoms of which include headache, visual disturbances such as blurred or double vision, slurred speech, paraesthesia of the mouth and fingers, alterations in behaviour, and impaired mental or intellectual ability, hunger, pallor, sweating, palpitations anxiety and tremulousness. If untreated hypoglycaemia may lead to convulsions and coma that should not be confused with hyperglycaemic coma.

Less frequent: Prolonged treatment may result in weight gain.

Skin and subcutaneous tissue disorders:

Frequent: Local or systemic hypersensitivity reactions. Local reactions, which are characterised by erythema and pruritis at the injection site and usually disappear with continued treatment/use.

General disorders and administration/injection site conditions:

Less frequent: Lipoatrophy or lipohypertrophy are associated with repeated subcutaneous insulin injections at the same site. Lipoatrophy appears to occur less frequently with purified insulins than with conventional insulins. Lipohypetrophy may usually be overcome by rotating the site of injection.

KNOWN SYMPTOMS OF OVER-DOSAGE AND PARTICULARS OF ITS TREATMENT:

Overdosage causes hypoglycaemia as described under **SIDE EFFECTS.** Hypoglycaemia in a conscious and co-operative patient is treated by administering sugar or glucose orally. In cases of hypoglycaemic coma, up to 50 ml of a 50 % solution of glucose should be administered intravenously or glucagon 0,5 to 1 mg should be administered subcutaneously, intramuscularly or intravenously.

IDENTIFICATION:

BIOSULIN R is a clear colourless liquid, free from turbidity and foreign matter.

BIOSULIN N, -L and -**30/70** are white suspensions which on standing deposit white sediment and leave an almost colourless supernatant liquid. The sediment is readily re-suspended on gentle shaking of the container.

PRESENTATION:

Single 10 ml clear glass vial or alternatively a carton containing five (5) 3 ml clear glass cartridges.

STORAGE INSTRUCTIONS:

Store in a refrigerator 2 °C to 8 °C, protected from light. Do not freeze.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS:

BIOSULIN R	37/21.1/0670
BIOSULIN N	37/21.1/0671
BIOSULIN L	37/21.1/0672
BIOSULIN 30/70	37/21.1/0673

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

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DATE OF PUBLICATION OF THE PACKAGE INSERT:

20 August 2015