SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

WOSULIN-30/70 (Recombinant DNA Origin), 100 IU / mL

[30% Insulin Human Regular and 70% Isophane Insulin Human Suspension (r-DNA origin)]

Biphasic Isophane Insulin Injection, BP Recombinant DNA origin.

Monocomponent Insulin

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 Qualitative Declaration

Each mL contains:

Insulin Human USP 100 IU

(30% Regular Insulin Human neutral and 70% Isophane Insulin)

m-Cresol USP 0.16% w/v as preservative

Phenol USP 0.065 w/v as preservative

Water for Injection USP q.s.

2.2 Quantitative Declaration

Sr. No.	Ingredients	Specifications	Theoretical quantity per mL	Reason for inclusion
1.	Insulin Human (Recombinant)	USP	100 IU	Active
2.	Disodium hydrogen phosphate anhydrous	USP	2.08 mg	Buffering agent
3.	Glycerol (98%)	USP	16.32 mg	Isotonic agent
4.	Zinc oxide (as Zinc)	USP	0.025 mg	Stabilizer
5.	m-Cresol	USP	1.60 mg	Preservative
6.	Phenol	USP	0.65 mg	Preservative
7.	Protamine sulphate	USP	0.259 mg	Complexing agent
8.	Sodium hydroxide	USP	q.s. to pH	pH modifier
9.	Hydrochloric acid	USP	q.s. to pH	pH modifier
10.	Water for Injection	USP	q.s. to 1 mL	Vehicle

q.s.: Quality Sufficient, IU: International Unit, mg: Milligram

3. PHARMACEUTICAL FORM

Suspension for Injection

4. CLINICAL PARTICULAR

4.1 Therapeutic Indications

WOSULIN-30/70 is indicated for the following:

- Treatment of all patients with type 1 diabetes.
- Treatment of patients with type 2 diabetes who are not adequately controlled by diet and / or oral hypoglycemic agents.
- Treatment of Gestational diabetes.

4.2 Posology and method of administration

Route of administration: Subcutaneous Injection

The dosage of WOSULIN-30/70 is determined by the physician, as per the needs of the patient. With WOSULIN-30/70 vial, it is important to use a syringe that is marked for the desired strength, for e.g. U-40 or U-100 insulin preparations. Failure to use the proper syringe can lead to a mistake in dosage, causing serious problems such as severe hypoglycemia or hyperglycemia. The average range of total daily insulin requirement for maintenance in type 1 diabetic patients ranges between 0.5 and 1.0 IU / kg. Further, in insulin resistance, the daily requirement of insulin may be substantially higher.

In patients with type 2 diabetes, the requirements of insulin are lower i.e. approximately 0.3-0.6 IU / kg / day. Individualize and adjust the dosage of Wosulin30/70 based on the individual's metabolic needs, blood glucose monitoring results and glycemic control goal. Dosage adjustments may be needed with changes in physical activity, changes in meal patterns (i.e., macronutrient content or timing of food intake), and changes in renal or hepatic function or during acute illness.

WOSULIN-30/70 is administered subcutaneously in the abdominal wall, the thigh, gluteal region or the deltoid region.

To avoid lipodystrophy, the site of injection should be frequently changed. Any injection of insulin should be followed by a meal or snack containing carbohydrates within 30 minutes.

Adjustment of dosage may be necessary if patients undertake increased physical activity or change their usual diet.

4.3 Contraindications

WOSULIN-30/70 is contraindicated in the following conditions

Hypoglycemia

Hypersensitivity to insulin or any other component of the formulation.

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, isophane, 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 hypoglycemic 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, eg, by intensified insulin therapy, may lose some or all of the warning symptoms of hypoglycemia and should be advised accordingly. Other conditions which may make the early warning symptoms of hypoglycemia different or less pronounced include long duration of diabetes, diabetic nerve disease, or medications such as beta-blockers. Uncorrected hypoglycemic and hyperglycemic 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 hyperglycemia and diabetic ketoacidosis; conditions which are potentially lethal.
Treatment with human insulin may cause formation of antibodies, but titers 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.

Fluid retention and heart failure with concomitant use of PPAR-gamma agonists: Thiazolidinediones (TZDs), which are peroxisome proliferator-activated receptor (PPAR)-gamma agonists, 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 WOSULIN-R, 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.

4.5 Interactions with other medicaments and other forms of Interaction

Insulin requirements may be increased by medications with hyperglycemic activity such as corticosteroids, isoniazid, certain lipid-lowering drugs (e.g. niacin), estrogens, oral contraceptives, phenothiazines, and thyroid replacement therapy.
Insulin requirements may be decreased in the presence of drugs with hypoglycemic activity, such as oral hypoglycemic agents, salicylates, sulfa antibiotics, certain antidepressants (monoamine oxidase inhibitors), certain angiotensin converting enzyme inhibitors, beta adrenergic blockers, inhibitors of pancreatic function (e.g. octreotide), and alcohol. Beta adrenergic blockers may mask the symptoms of hypoglycemia in some patients.

Renal Impairment: The requirements for insulin may be reduced in patients with renal impairment.

Hepatic Impairment: Although impaired hepatic function does not affect the absorption or disposition of WOSULIN-30/70, careful glucose monitoring and dose adjustments of insulin may be necessary.

4.6 Pregnancy and Lactation

Pregnancy: There are no restrictions on the use of insulin during pregnancy since insulin does not cross the placental barrier. Published studies with human insulins suggest that optimizing overall glycemic control, including postprandial control, before conception and during pregnancy improves fetal outcome. Although the fetal complications of maternal hyperglycemia have been well documented, fetal toxicity also has been reported with maternal hypoglycemia. Insulin requirements usually fall during the first trimester and increase during the second and third trimesters. Careful monitoring of the patient is required throughout pregnancy. During the perinatal period, careful monitoring of infants born to mothers with diabetes is warranted.

Nursing Mothers: There are no restrictions on the use of insulin in lactating mothers as insulin treatment of nursing mothers does not involve any risk to the baby. However, caution should be exercised when administered to nursing mothers and the dosage of insulin may be reduced.

4.7 Effects on ability to drive and use machines

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

Patients should therefore be advised to avoid hypoglycemia during driving. This is particularly significant in patients who have reduced awareness of the warning signs of hypoglycemia or have frequent episodes of hypoglycemia.

4.8 Undesirable effects

The most commonly seen adverse reaction with WOSULIN-30/70 are:

a. Hypoglycemia: Hypoglycemia is one of the most common adverse effects seen with the use of any type of insulin including human insulin. This can occur because of the following:

- Use of too much insulin
- Missed meal / delayed meal
- Intercurrent infection or illness
- Strenuous exercise

Diseases of the adrenal, pituitary, or thyroid gland, or progression of kidney or liver disease may also lead to hypoglycemia.

Concomitant administration with other drugs that lower blood glucose such as oral hypoglycemics, salicylates (for example, aspirin), sulfa antibiotics, and certain antidepressants may lead to hypoglycemia.

Concomitant consumption of alcoholic beverages may also lead to hypoglycemia. Symptoms of mild to moderate hypoglycemia may occur suddenly and can include: Sweating; dizziness; palpitation; tremor; hunger; restlessness; tingling in the hands, feet, lips, or tongue; lightheadedness; inability to concentrate; headache; drowsiness; sleep disturbances; anxiety; blurred vision; slurred speech; depressive mood; irritability; abnormal behavior; unsteady movement; personality changes.

Signs of severe hypoglycemia can include:

Disorientation; unconsciousness; seizures; death.

Therefore, it is important that assistance be obtained immediately.

Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as long duration of diabetes, diabetic nerve disease, coadministration of medications such as beta-blockers, change in insulin preparations, or intensified control (3 or more insulin injections per day) of diabetes.

The use of preparations of WOSULIN-30/70 should minimize the incidence of adverse effects associated with the use of animal insulins.

b. Oedema:

Oedema and refraction anomalies may occur upon initiation of insulin therapy. These symptoms are usually of a transitory nature. Insulin may cause sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

c. Hyperglycemia and ketoacidosis:

In patients with insulin-dependent diabetes, prolonged hyperglycemia can result in diabetic acidosis. The first symptoms of diabetic acidosis usually come on gradually, over a period of hours or days, and include a drowsy feeling, flushed face, thirst, loss of appetite, and fruity odor on the breath. With acidosis, urine tests show large amounts of glucose and acetone. Heavy breathing and a rapid pulse are more severe symptoms. If uncorrected, prolonged hyperglycemia or diabetic acidosis can result in loss of consciousness or death. Therefore, it is important that one should obtain medical assistance immediately.

d. Allergy to Insulin:

Systemic Allergy: Less common, but potentially more serious, is generalized allergy to insulin, which 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.

Local Allergy: Patients occasionally experience redness, swelling, and itching at the site of injection of insulin. This condition called local allergy, usually clears up in a few days to a few weeks. In some instances, this condition may be related to factors other than insulin, such as irritants in the skin cleansing agent.

e. Lipoatrophy and lipodystrophy:

Lipodystrophy occurs at the site of injection after long usage. However, this is less common with the newer preparations of insulin.

f. Insulin resistance:

When insulin requirement is increased (> 200 IU / day), insulin resistance is said to have developed. The following are the different grades of insulin resistance: Acute:
Acute insulin resistance develops rapidly and is usually a short term problem. It usually occurs due to an underlying infection, trauma, surgery and emotional stress. Treatment is to overcome the precipitating factor and to give high doses of regular insulin.

Chronic: This type of insulin resistance is generally seen in patients treated for years with conventional preparations of beef or pork insulins and it is more common in patients with Type 2 diabetes. Development of such a type of insulin resistance is an indication for switching patients to the newer preparations of insulin. After instituting the newer preparations, insulin requirement gradually declines over weeks and months and majority of patients stabilize at approximately 60 IU / day.

g. Hypokalemia:

Insulin stimulates potassium movement into the cells, possibly leading to hypokalemia, that left untreated may cause respiratory paralysis, ventricular arrhythmia, and death. Since intravenously administered insulin has a rapid onset of action, increased attention to hypokalemia is necessary. Therefore, potassium levels must be monitored closely when WOSULIN-R or any other insulin is administered intravenously. Use caution in patients who may be at risk for hypokalemia (e.g., patients using potassium-lowering medications, patients taking medications sensitive to serum potassium concentrations).

i. Tabulated list of adverse reactions

The adverse reactions listed below are classified according to MedDRA frequency and System Organ Class. Frequency categories are defined according to the following convention: Very common (> 1/10); common (> 1/100 to < 1/10); uncommon (> 1/1,000 to < 1/100); rare (> 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

Immune system disorders	Uncommon - Urticaria, rash Very rare - Anaphylactic reactions*

Metabolism and nutrition disorders	Very common - Hypoglycaemia
Nervous system disorders	Uncommon - Peripheral neuropathy (painful neuropathy)*
Eye disorders	Very rare - Refraction disorders Uncommon - Diabetic retinopathy*
Skin and subcutaneous tissue disorders	Uncommon - Lipodystrophy
General disorders and administration site conditions	Uncommon - Injection site reactions
	Uncommon - Oedema

*Not known: Anaphylactic reactions, Peripheral neuropathy (painful neuropathy) and Diabetic retinopathy.

As per the routine Pharmacovigilance plan, the Company will continue to monitor for any new safety information that may alter the benefit-risk profile of Wosulin 30-70 and duly take necessary steps with any new specific information that may become available.

4.9 Overdose

Hypoglycemia may occur as a result of an excess of insulin relative to food intake, energy expenditure, or both. Mild episodes of hypoglycemia usually can be treated with oral glucose. It is therefore recommended that the diabetic patient constantly carries some sugar lumps, sweets, biscuits, or sugary fruit juice. Adjustments in drug dosage, meal patterns, or exercise, may be needed.

More severe episodes of hypoglycemia with coma, seizure, or neurologic impairment may be treated with intramuscular / subcutaneous glucagon or concentrated intravenous glucose. Glucose must also be given intravenously, if the patient does not respond to glucagon within 10 to 15 minutes. Sustained carbohydrate intake and observation may be necessary because hypoglycemia may recur after apparent clinical recovery.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco therapeutic group: Insulin and analogues, biphasic insulin preparations.
ATC code: A10AD01

Like all other insulins, the glucose lowering effect of WOSULIN-30/70 is due to the facilitated uptake of glucose in body tissues. This uptake occurs following the binding of insulin to its receptors present in the muscle and adipose tissue. The blood glucose lowering effect of insulin also occurs due to the simultaneous inhibition of glucose output from the liver.

5.2 Pharmacokinetic properties

Insulin has a half- life of a few minutes in the blood stream. Consequently, the time course of action of any insulin may vary considerably in different individuals or at different times in the same individual. As with all insulin preparations, the intensity and duration of action of WOSULIN-30/70 is dependent o n the dose, site of injection, blood supply, temperature, and physical activity.

An average action profile after subcutaneous injection indicates:

- Onset within 0.5 hours.
- Peak levels attained between 2-12 hours
- Duration of action approximately 18-24 hours

5.3 Pre-clinical safety data

Wosulin is human insulin produced by recombinant technology. No serious events have been reported in sub-chronic toxicology studies. Human insulin was not mutagenic in a series of *in vitro* and *in vivo* genetic toxicity assays.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sr No	Excipients	Specification
1	Disodium hydrogen phosphate anhydrous	USP
2	Glycerol (98%)	USP
3	Zinc oxide (as Zinc)	USP
4	m-Cresol	USP
5	Phenol	USP
6	Protamine sulphate	USP
7	Sodium hydroxide	USP
8	Hydrochloric acid	USP
9	Water for Injection	USP

USP: United States national formulary

6.2 Incompatibilities

None known

6.3 Shelf Life

36 months from the date of manufacturing

6.4 Special precautions for storage

WOSULIN-30/70 should be stored in a refrigerator (2°C to 8°C) but not allowed to freeze. When in use, vials may be kept at room temperature (15°C to 25°C) for up to six weeks. Do not expose to excessive heat or direct sunlight. WOSULIN-30/70 must be kept

out of reach of children.

Insulin preparations, which have been frozen, must not be used.
Once opened (when the stopper or seal has been punctured with a needle), insulin is kept at room temperature. Cold insulin can be irritating to inject. Patients should be asked to roll the vial in their hands 10 times for mixing the suspension prior to drawing it up in the syringe after allowing the vial to sit for 30 minutes at room temperature if the vial is stored in the refrigerator.

6.5 Nature and contents of container

A white or almost white suspension which on standing deposits white or almost white sediment and leaves a colorless or almost colorless supernatant liquid.

10 mL filled in a glass vial with bromobutyl plug and flip off seal. Vial is pasted with printed label. 1 vial packed in a printed carton with literature insert.

6.6 Instruction for use and handling 10 mL

Multi-Dose Vial (MDV)

i. Wash your hands. Carefully shake or roll WOSULIN-30/70 insulin vial 10 times to completely mix the insulin.
ii. Inspect the vial. WOSULIN-30/70 should appear uniformly cloudy or milky. The insulin injection should not be used if there is anything unusual in the appearance.
iii. When using a new vial, flip off the plastic protective cap, but do not remove the stopper. The tip of the vial should be wiped with an alcohol swab.
iv. Draw air into the syringe equal to your insulin dose
v. Insert needle into vial through rubber top and push plunger to empty the air into the vial.
vi. Turn the bottle and syringe upside down. Hold the bottle and syringe firmly in one hand and shake gently. Making sure the tip of the needle is in the insulin; withdraw the correct dose of insulin into the syringe.
vii. Before removing the needle from the vial, check the insulin syringe for air bubbles, which reduce the amount of insulin in it. If bubbles are present, hold the syringe straight up and tap its side until the bubbles float to the top. Push them out with the plunger and withdraw the correct dose again.
viii. Lightly pinch up the skin; holding the syringe like a pencil.
ix. Insert the needle into the skin and push the plunger slowly. Make sure the needle is all the way in.
x. Wait for 5 seconds and pull out the syringe. Do not rub the area.

7. Applicant/ Manufacturer

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