Appendix VI

5.2 SUMMARY OF PRODUCT CHARACTERISTICS (PRODUCT DATA SHEET)

1. NAME OF THE MEDICINAL PRODUCT

1.1 Name of the Product:
Wosulin-R (Recombinant DNA Origin) (100 IU / mL)
Insulin Human Injection USP
Human Recombinant (r-DNA) Insulin Regular (Soluble/Neutral)

1.2 Strength: 100 IU/mL

1.3 Pharmaceutical Dosage Form: Injectable

2. QUALITY AND QUANTITATIVE COMPOSITION

2.1 Qualitative Declaration
Each mL contains:
Insulin Human USP 100 IU
m-Cresol USP : 0.25% as preservative
Water for Injection USP: q.s.

2.2 Quantitative Declaration

S. No.	Ingredients	Reference	Unit composition formula (Qty./mL)	Reason for inclusion
01	Insulin Human (r-DNA)	IP/USP/Ph.Eur.	102.5 IU*	Active Ingredients
02	Citric acid monohydrate	IP/USP/Ph.Eur.	0.0021 mg	Buffering agent
03	Glycerol	IP/USP/Ph.Eur.	16.32 mg	Isotonic agent
04	Zinc (as Zinc Oxide)	IP/USP/Ph.Eur.	0.025 mg	Stabilizer
05	m-Cresol	USP/Ph.Eur.	2.50 mg	Preservative
06	Sodium Hydroxide	IP/USP/Ph.Eur.	0.19 mg	pH modifier
07	Tri-sodium citrate dihydrate	IP/USP/Ph.Eur.	0.19 mg	Buffering agent
08	Hydrochloric Acid	IP/USP/Ph.Eur.	0.00035 mL	pH modifier
09	Water for Injection	IP/USP/Ph.Eur.	q.s. to 1 mL	Vehicle

Note:
1. The amount of Zinc Oxide added to the formulation is dependent on the amount of zinc in the Human Insulin used. The target amount for Zinc in the formulation is 25 µg per 100 IU Insulin.
2. Trace amount of Citric Acid and Tri-sodium citrate dehydrate may be added to facilitate dissolution.
3. *2.5%.overages

3. PHARMACEUTICAL FORM

Injectable: A Clear, Colourless or almost colourless liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

WOSULIN-R 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.
- For the initial stabilization of diabetes in patients with diabetic ketoacidosis, hyperosmolar non-ketotic syndrome and during periods of stress such as severe infections and major surgery in diabetic patients.
- Treatment of Gestational diabetes

4.2 Posology and method of administration

The dosage of WOSULIN-R is determined by the physician, as per the need of the patient. Usual insulin dose may be affected by changes in food, activity, or work schedule. Therefore carefully follow doctor's instructions. With WOSULIN-R, it is important to use a syringe that is marked for the desired strength, 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.

WOSULIN-R is usually administered subcutaneously in the abdominal wall, the thigh, the gluteal region or the deltoid region. Intramuscular injections are possible under guidance by a physician.

Intravenous administrations are suitable only for vial products and should be carried out under the guidance of a physician. To avoid lipodystrophy, the site of subcutaneous 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-R is contraindicated in the following conditions

- Hypoglycemia
- Hypersensitivity to insulin

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,

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.

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 of insulin may be reduced in patients with renal impairment

Hepatic Impairment:
Although impaired hepatic function does not affect the absorption or disposition of WOSULIN-R, 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

Most commonly seen adverse reaction with WOSULIN-R are:

1. 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, co-administration of medications such as beta-blockers, change in insulin preparations, or intensified control (3 or more insulin injections per day) of diabetes. If the blood glucose is below your normal fasting glucose, you should consider eating or drinking sugar containing foods to treat your hypoglycemia. Mild to moderate hypoglycemia may be treated by eating foods or drinks that contain sugar. Patients should always carry a quick source of sugar, such as candy or glucose tablets. More severe hypoglycemia may require assistance of another person. The use of preparations of WOSULIN-R should minimize the incidence of adverse effects associated with the use of animal insulins

2. Oedema :

Oedema and refraction anomalies may occur upon initiation of insulin therapy. These symptoms are usually of a transitory nature.

3. 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 of 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.

4. Allergy to Insulin :

a) 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.

b) 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. I n some instances, this condition may be related to factors other than insulin, such as irritants in the skin cleansing agent.

5. Lipoatrophy and lipodystrophy

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

6. 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 y ears 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.

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 carry 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

Like all other insulins, the glucose lowering effect of WOSULIN-R 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-R is dependent on the dose, site of injection, blood supply, temperature, and physical activity

An average action profile after subcutaneous injection indicates:

Onset - within 30 minutes, Peak levels attained between 1-3 hours, Duration of action - approximately 4-6 hours.

5.3 Preclinical 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

Citric Acid Monohydrate, Glycerol, Zinc Oxide, m-Cresol, Sodium Hydroxide, Tri-Sodium Citrate Dihydrate, Hydrochloric Acid, and Water for Injection.

6.2 Incompatibilities

None known

6.3 Shelf Life

24 months from the date of manufacturing

6.4 Special precautions for storage

WOSULIN-R 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 upto six weeks. Do not expose to excessive heat or direct sunlight. WOSULIN-R must be kept out of reach of children. Insulin preparations, which have been frozen, must not be used. WOSULIN-R solutions should not be used if they do not appear water-clear and colourless. Once opened (when the stopper or seal has been punctured with a needle), WOSULIN-R is kept at room temperature. Cold insulin can be irritating to inject. Thus, patients should be asked to roll the vial in their hands 10 times 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 clear, colorless or almost colorless 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.

3 mL filled in a glass cartridge pasted with printed sticker label. 1 cartridge blister packed in a printed carton with literature insert.

6.6 Instruction for use and handling

1. Inspect the vial for any crystallization, clumping or discolouration. If present, discard and open new vial.

2. Wash hands.

3. Roll vial 10 times; excess agitation can damage insulin and cause precipitation.

4. Wipe top of the bottle with alcohol or cotton ball soaked in alcohol

5. Push plunger up and then down to the number of units to be drawn up. Insert needle into vial and push plunger to empty the air into the vial.

6. Push plunger down to the prescribed number of units. Draw 1 – 2 units extra to make up for insulin bubbles to be pushed out. Every patient should be re-assured that injecting air in the sub-cutaneous tissue does no harm other than decreasing the intended dose.

7. Lightly pinch up the skin; holding the syringe like pencil, insert the needle to the hub and push the plunger slowly. Wait for 5 seconds and pull out the syringe.

8. Do not massage the area. Note any back leakage of insulin.

7. MARKETING AUTHORISATION HOLDER

M/s. Wockhardt Limited

8. MARKETING AUTHORISATION NUMBER(S)

AD/004

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

April 12, 2004