SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Wosulin R 100 IU/mL solution for injection in Cartridge

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 Qualitative Declaration

Each mL contains:

Insulin Human USP	100 IU
m-Cresol USP	0.25% as
Water for Injection USP	preservative q.s.

1 mL solution contains 100 international units of insulin human*.
1 Cartridge contains 3 mL equivalent to 300 international units.
*Insulin human is produced in *Hansenula polymorpha* by recombinant DNA technology.

2.2 Quantitative Declaration

S. No.	Ingredients	Reference	Unit composition formula (Qty./mL)	Reason for inclusion
1	Insulin Human (r-DNA)	USP	100 IU	Active Ingredients
2	Citric acid monohydrate	USP	0.0021 mg	Buffering agent
3	Glycerol	USP	16.32 mg	Isotonic agent
4	Zinc (as Zinc Oxide)	USP	0.025 mg	Stabilizer
5	m-Cresol	USP	2.50 mg	Preservative
6	Tri-sodium citrate dihydrate	USP	0.19 mg	pH modifier
7	Sodium Hydroxide	USP	q.s. to pH	Buffering agent
8	Hydrochloric Acid	USP	q.s. to pH	pH modifier
9	Water for Injection	USP	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

3. PHARMACEUTICAL FORM

Solution for subcutaneous injection.

The solution is clear, colourless and aqueous.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

WOSULIN-R is indicated for treatment of diabetes mellitus.

4.2 Posology and method of administration

- **Route of Administration: Subcutaneous Injection**

Posology

The potency of human insulin is expressed in international units.

WOSULIN-R dosing 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 international unit/kg/day.

Adjustment of dose may be necessary if patients undertake increased physical activity, change their usual diet or during concomitant illness.

Special populations

Elderly (≥ 65 years old)

WOSULIN-R can be used in elderly patients.

In elderly patients, glucose monitoring should be intensified and the insulin dose adjusted on an individual basis.

Renal and hepatic impairment

Renal or hepatic impairment may reduce the patient's insulin requirements.

In patients with renal or hepatic impairment, glucose monitoring should be intensified and the human insulin dose adjusted on an individual basis.

Paediatric population

WOSULIN-R can be used in children and adolescents.

Transfer from other insulin medicinal products

When transferring from other insulin medicinal products, adjustment of the WOSULIN-R dose and the dose of the basal insulin may be necessary.

Close glucose monitoring is recommended during the transfer and in the initial weeks thereafter (see section 4.4).

Method of administration

WOSULIN-R is a fast-acting human insulin and may be used in combination with intermediate or long-acting insulin medicinal products.

WOSULIN-R is administered subcutaneously by injection in the abdominal wall, the thigh, the gluteal region or the deltoid region. Injection into a lifted skin fold minimises the risk of unintended intramuscular injection.

The needle should be kept under the skin for at least 6 seconds to make sure the entire dose is injected. Injection sites should always be rotated within the same region in order to reduce the risk of lipodystrophy. Subcutaneous injection into the abdominal wall ensures a faster absorption than other injection sites. The duration of action will vary according to the dose, injection site, blood flow, temperature and level of physical activity.

An injection should be followed within 30 minutes by a meal or snack containing carbohydrates.

Due to the risk of precipitation in pump catheters, WOSULIN-R should not be used in insulin pumps for continuous subcutaneous insulin infusion.

Intravenous use

If necessary, WOSULIN-R can be administered intravenously. This should be carried out by healthcare professionals.

For intravenous use, infusion systems with WOSULIN-R at concentrations from 0.05 international unit/ml to 1.0 international unit/ml human insulin in the infusion fluids 0.9% sodium chloride, 5% dextrose and 10% dextrose with 40 mmol/l potassium chloride using polypropylene infusion bags, are stable at room temperature for approximately 24 hours. Although stable over time, a certain amount of insulin will initially be adsorbed to the material of the infusion bag. Monitoring of blood glucose is necessary during the insulin infusion.

For detailed user instructions, please refer to the package leaflet.

WOSULIN-R cartridge

Administration with a pen device

WOSULIN-R cartridge is designed to be used with insulin delivery pen devices.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and special precautions for use

Before travelling between different time zones, the patient should seek the doctor's advice since this may mean that the patient has to take the insulin and meals at different times.

Hyperglycaemia

Inadequate dosing or discontinuation of treatment, especially in type 1 diabetes, may lead to hyperglycaemia and diabetic ketoacidosis. Usually, the first symptoms of hyperglycaemia develop 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

Omission of a meal or unplanned strenuous physical exercise may lead to hypoglycaemia. Hypoglycaemia may occur if the insulin dose is too high in relation to the insulin requirement. In case of hypoglycaemia or if hypoglycaemia is suspected, WOSULIN- R must not be injected. After stabilisation of the patient's blood glucose, adjustment of the dose should be considered.

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.

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.

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, origin (animal insulin, human insulin or insulin analogue) and/or method of manufacture (recombinant DNA versus animal source insulin) may result in a need for a change in dose. Patients transferred to WOSULIN-R from another type of insulin may require an increased

number of daily

injections or a change in dose from that used with their usual insulin medicinal products. If an adjustment is needed, it may occur with the first dose or during the first few weeks or months.

Injection site reactions

As with any insulin therapy, injection site reactions may occur and include pain, redness, hives, inflammation, bruising, swelling and itching. Continuous rotation of the injection site within a given area reduces the risk of developing these reactions. Reactions usually resolve in a few days to a few weeks. On rare occasions, injection site reactions may require discontinuation of WOSULIN-R.

Combination of WOSULIN-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 WOSULIN-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.

4.5 Interactions with other medicaments and other forms of Interaction

A number of medicinal products are known to interact with glucose metabolism.
The following substances may reduce the patient's insulin requirement:
Oral antidiabetic medicinal products, monoamine oxidase inhibitors (MAOI), betablockers, angiotensin converting enzyme (ACE) inhibitors, salicylates, anabolic steroids and sulfonamides.
The following substances may increase the patient's insulin requirement:
Oral contraceptives, thiazides, glucocorticoids, thyroid hormones, sympathomimetics, growth hormone and danazol.
Beta-blockers may mask the symptoms of hypoglycaemia.
Octreotide/lanreotide may either increase or decrease the insulin requirement.
Alcohol may intensify or reduce the hypoglycaemic effect of insulin.

4.6 Fertility, 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.

Fertility: Animal reproduction studies with human insulin have not revealed any adverse effects on fertility.

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

Summary of the safety profile

The most frequently reported adverse reaction during treatment is hypoglycaemia. The frequencies of hypoglycaemia vary with patient population, dose regimens and level of glycaemic control, please see Description of selected adverse reactions below. At the beginning of the insulin treatment, refraction anomalies, oedema and injection site reactions (pain, redness, hives, inflammation, bruising, swelling and itching at the injection site) may occur. These reactions are usually of a transitory nature. Fast improvement in blood glucose control may be associated with acute painful neuropathy, which is usually reversible. Intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy, while long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy.

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

* see Description of selected adverse reactions.

Description of selected adverse reactions

Anaphylactic reactions

The occurrence of generalised hypersensitivity reactions (including generalised skin rash, itching, sweating, gastrointestinal upset, angioneurotic oedema, difficulty in breathing, palpitation and reduction in blood pressure) is very rare but can potentially be life threatening.

Hypoglycaemia

The most frequently reported adverse reaction is hypoglycaemia. It may occur if the insulin dose is too high in relation to the insulin requirement. Severe hypoglycaemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death. The symptoms of hypoglycaemia usually occur suddenly. They may include cold sweats, cool pale skin, fatigue, nervousness or tremor, anxiousness, unusual tiredness or weakness, confusion, difficulty in concentrating, drowsiness, excessive hunger, vision changes, headache, nausea and palpitation.

In reported studies, the frequency of hypoglycaemia varied with patient population, dose regimens and level of glycaemic control.

Lipodystrophy

Lipodystrophy (including lipohypertrophy, lipoatrophy) may occur at the injection site. Continuous rotation of the injection site within the particular injection area reduces the risk of developing these reactions.

Paediatric population

Based on reported studies and published literature, the frequency, type and severity of adverse reactions observed in the paediatric population do not indicate any differences to the broader experience in the general population.

Other special populations

Based on reported studies and published literature, the frequency, type and severity of adverse reactions observed in elderly patients and in patients with renal or hepatic impairment do not indicate any differences to the broader experience in the general population.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

National Pharmacovigilance and Drug Safety Centre (NPC)

- Fax: +966-11-205-7662
- Call NPC at +966-11-2038222, Exts: 2317-2356-2353-2354-2334-2340.
- Toll free phone: 8002490000
- E-mail: npc.drug@sfda.gov.sa
- Website: www.sfda.gov.sa/npc

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 R and duly take necessary steps with any new specific information that may become available.

4.9 Overdose

A specific overdose of insulin cannot be defined, however, hypoglycaemia may develop over sequential stages if too high a dose relative to the patient's requirement is administered:

- Mild hypoglycaemic episodes can be treated by oral administration of glucose or sugary products. It is therefore recommended that the diabetic patient always carries sugar-containing products.
- 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 healthcare professional. Glucose must be given intravenously, if the patient does not respond to glucagon within 10 to 15 minutes.

Upon regaining consciousness, administration of oral carbohydrates is recommended for the patient in order to prevent a relapse.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes. Insulins and analogues for injection, fast-acting, insulin (human). ATC code: A10AB01.

Mechanism of action and pharmacodynamic effects

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.

WOSULIN-R is a fast-acting insulin.

Onset of action is within ½ hour, reaches a maximum effect within 1–3 hours and the entire duration of action is approximately 4–6 hours.

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.

No profound binding to plasma proteins, except circulating insulin antibodies (if present) has been observed for human insulin.

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.

Paediatric population

The limited available reported data suggest that the pharmacokinetic profile of human insulin in children and adolescents may be similar to that in adults. However, there were differences between age groups in C_{max}, stressing the importance of individual dose titration.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on reported conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

S. No.	Excipients	Specifications
1.	Citric Acid Monohydrate	USP
2.	Glycerol	USP
3.	Zinc Oxide	USP
4.	m-Cresol	USP
5.	Sodium Hydroxide	USP
6.	Tri-Sodium Citrate Dihydrate	USP
7.	Hydrochloric Acid	USP
8.	Water For Injection	USP

6.2 Incompatibilities

Insulin medicinal products should only be added to compounds with which it is known to be compatible. Medicinal products added to the insulin solution may cause degradation of the insulin, e.g. if the medicinal products contain thiols or sulfites.

6.3 Shelf Life

36 months from the date of manufacturing

6.4 Special precautions for storage

Before opening: Store in a refrigerator (2°C - 8°C). Do not freeze.
During use or when carried as a spare: Store below 25°C. Do not freeze. WOSULIN-R cartridge can be stored for maximum of 4 weeks.
Keep the cartridge in the outer carton in order to protect from light.

6.5 Nature and contents of container

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 Special precautions for disposal and other handling

Do not use this medicinal product if you notice that the solution is not clear, colourless and aqueous.
WOSULIN-R which has been frozen must not be used.
The patient should be advised to discard the needle and syringe after each injection.
Any unused medicinal product or waste material should be disposed of in accordance

with local requirements.
Needles, syringes, cartridges and pen devices must not be shared.
The cartridge must not be refilled.
In case of emergency in current WOSULIN-R users (hospitalisation or insulin pen malfunction), WOSULIN-R can be withdrawn with an UI00 insulin syringe from a cartridge.

7. MARKETING AUTHORISATION HOLDER

M/s. Wockhardt Limited, Biotech Park, H-14/2, MIDC, Waluj, Aurangabad - 431136, India

8. NAME AND ADDRESS OF APPLICANT

M/s. Wockhardt Limited, Wockhardt Towers, Bandra Kurla Complex, G Block BKC, Bandra Kurla Complex, Bandra East, Mumbai, Maharashtra 400051