PROCEDURE FOR INSULIN ADMINISTRATION

1. Inspect the vial of WOSULIN-R for any crystallization, clumping or discolouration. If present, discard and open a new vial.

2. Wash your 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.

6. Insert needle into vial and push plunger to empty the air into the vial.

7. 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 reassured that injecting air in the sub-cutaneous tissue does no harm other than decreasing the intended dose.

8. Lightly pinch up the skin; holding the syringe like a pencil.

9. Insert the needle to the hub and push the plunger slowly. Wait for 5 seconds & pull out the syringe.

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

Your Daily Insulin Intake Calendar

DATE	INSULIN DOSE	TIME	BRAND

DATE	INSULIN DOSE	TIME	BRAND

Page 4

Rx

For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

Insulin Injection I.P. (r-DNA origin)

WOCKHARDT

Wosulin® R

40 IU/ml | 10ml

REGULAR
(SOLUBLE / NEUTRAL)
Monocomponent
Insulin Human

For (SC) (IM) (IV) use only

1. Generic Name

Insulin Injection I.P. (r-DNA origin) 40 IU/mL
Regular (Soluble / Neutral)
Monocomponent Insulin Human

2. Qualitative and quantitative composition

Each mL contains
Human Insulin I.P. .....40 IU
m-Cresol U.S.P. .....0.25% w/v
(as preservative)
Water for Injections I.P. .....q.s

3. Dosage form and strength

It is a 10 ml multi-dose vial containing 40 IU/mL regular human insulin injection for subcutaneous, intramuscular and intravenous use.

4. Clinical particulars

4.1 Therapeutic indication

Regular human insulin Injection is indicated for the following:

- For the treatment of type-I diabetes mellitus
- For the treatment of type-II diabetes who are not adequately controlled by diet and or oral hypoglycaemic agent
- For the initial stabilization of Type II diabetes patients with diabetic ketoacidosis, hyperosmolar non-ketotic syndrome and in diabetes during pregnancy.

4.2 Posology and method of administration

Subcutaneous (SC)

WOSULIN-R is usually given SC three or more times daily before meals. The dosage and timing of WOSULIN-R should be individualized and determined in accordance with the needs of the patient. WOSULIN-R may also be used in combination with oral antihyperglycemic agents or longer-acting insulin products to suit the needs of the individual patients with diabetes. The injection of WOSULIN-R should be followed by a meal within approximately 30 minutes of administration. The average range of total daily insulin requirement for maintenance therapy in insulin-treated patients without severe insulin resistance lies between 0.5 and 1 unit/kg/day. However, in pre-pubertal children it usually varies from 0.7 to 1 unit/kg/day, but can be much lower during the period of partial remission. In situations of insulin resistance, e.g. during puberty or due to obesity, the daily insulin requirement may be substantially higher. The average range of total insulin requirement for maintenance in type 1 diabetic patients ranges between 0.5 to 1 IU/kg. In patients with type 2 diabetes, the requirements of insulin are lower i.e. approximately 0.3-0.6 IU/kg/day. WOSULIN-R may be administered by SC injection in the abdominal wall, the thigh, the gluteal region or in the upper arm. SC injection into the abdominal wall ensures a faster absorption than from other injection sites. Injection into a lifted skin fold minimizes the risk of intramuscular injection. Injection sites should be rotated within the same region. As with all insulin, the duration of action will vary according to the dose, injection site, blood flow, temperature, and level of physical activity.

Intravenous (IV)

IV administration of WOSULIN-R is possible under medical supervision with close monitoring of blood glucose and potassium levels to avoid hypoglycemia and hypokalemia. For IV use, WOSULIN-R should be used at concentrations from 0.1 unit/mL to 1 unit/mL in infusion systems with the infusion fluids 0.9% sodium chloride using polyvinyl chloride infusion bags.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Never use WOSULIN-R if it has become viscous (thickened) or cloudy; use it only if it is clear and colorless. WOSULIN-R should not be used after the printed expiration date.

Mixing of Insulins

- WOSULIN-R is short-acting and is often used in combination with intermediate- or long-acting insulins.
- The order of mixing and brand or model of syringe should be specified by the physician.
- A U-40 insulin syringe should always be used. Failure to use the correct syringe can lead to dosage errors.
- In general, when an intermediate-acting insulin (e.g., NPH insulin isophane suspension) is mixed with short-acting soluble insulin (e.g., regular), the short-acting insulin should be drawn into the syringe first.

4.3 Contraindications

WOSULIN-R is contraindicated during episodes of hypoglycemia and in patients hypersensitive to WOSULIN-R or any of its excipients.

4.4 Special warnings and precautions for use

Needles or syringes must never be reused or shared between patients. Sharing poses a risk for transmission of blood-borne pathogens.

Any change in insulin should be made cautiously and only under medical supervision. Changes in insulin strength, manufacturer, type (e.g., regular, NPH, analog, etc.), species, or method of administration may result in the need for a change in dosage.

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.

Hypoglycemia: Hypoglycemia is the most common adverse reaction of all insulin therapies, including WOSULIN-R. Severe hypoglycemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or death.

Adjustment of dosage of any insulin may be necessary if patients change their physical activity or their usual meal plan. Insulin requirements may be altered during illness, emotional disturbances, or other stresses. Concomitant antihyperglycemic agents may need to be adjusted. The timing of hypoglycemia usually reflects the time-action profile of the administered insulin formulations. Other factors such as changes in food intake (e.g., amount of food or timing of meals), injection site, exercise, and concomitant medications may also alter the risk of hypoglycemia. As with all insulins, use caution in patients with hypoglycemia unawareness and in patients who may be predisposed to hypoglycemia (e.g., the pediatric population and patients who fast or have erratic food intake). The patient's ability to concentrate and react may be impaired as a result of hypoglycemia. This may present a risk in situations where these abilities are especially important, such as driving or operating other machinery.

Hyperglycemia, Diabetic Ketoacidosis, and Hyperosmolar Non-Ketotic Syndrome: Hyperglycemia, diabetic ketoacidosis, or hyperosmolar coma may develop if the patient takes less WOSULIN-R than needed to control blood glucose levels. This could be due to increases in insulin demand during illness or infection, neglect of diet, omission or improper administration of prescribed insulin doses or use of drugs that affect glucose metabolism or insulin sensitivity.

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. 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).

Hypersensitivity and Allergic Reactions: Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products, including WOSULIN-R. Localized reactions and generalized myalgias have been

Page 1

reported with the use of metacresol as an injectable excipient.

4.5 Drugs interactions

A number of substances affect glucose metabolism and may require insulin dose adjustment and particularly close monitoring.

Drugs that may increase the blood-glucose-lowering effect of WOSULIN-R and susceptibility to hypoglycemia: Oral antihyperglycemic agents, salicylates, sulfa antibiotics, certain antidepressants (monoamine oxidase inhibitors, selective serotonin reuptake inhibitors [SSRIs]), pramlintide, disopyramide, fibrates, fluoxetine, propoxyphene, pentoxifylline, ACE inhibitors, angiotensin II receptor blocking agents, beta-adrenergic blockers, inhibitors of pancreatic function (e.g., octreotide), and alcohol.

Drugs that may reduce the blood-glucose-lowering effect: Corticosteroids, isoniazid, certain lipid-lowering drugs (e.g., niacin), estrogens, oral contraceptives, phenothiazines, danazol, diuretics, sympathomimetic agents, somatropin, atypical antipsychotics, glucagon, protease inhibitors and thyroid replacement therapy.

Drugs that may increase or decrease blood-glucose-lowering effect: Beta-adrenergic blockers, clonidine, lithium salts, and alcohol. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.

Drugs that may mask the signs of hypoglycemia: Beta-adrenergic blockers, clonidine, guanethidine, and reserpine.

4.6 Use in special populations

Renal or Hepatic Impairment: Frequent glucose monitoring and insulin dose reduction may be required in patients with renal or hepatic impairment.

Use in Pregnancy: Pregnancy Category B. All pregnancies have a background risk of birth defects, miscarriage, or other adverse outcome regardless of drug exposure. This background risk is increased in pregnancies complicated by hyperglycemia and is decreased with good glucose control. It is important for patients to maintain good control of diabetes before conception and during pregnancy. Special attention should be paid to diet, exercise and insulin regimens. Insulin requirements may decrease during the first trimester, usually increase during the second and third trimesters, and rapidly decline after delivery. Careful monitoring is essential in these patients. Therefore, female patients should be advised to tell their physicians if they intend to become, or if they become pregnant while taking WOSULIN-R. While there are no adequate and well-controlled studies of WOSULIN-R in pregnant women, evidence from published literature suggests that good glycemic control in patients with diabetes during pregnancy provides significant maternal and fetal benefits.

Labor and Delivery: Careful glucose monitoring and management of patients with diabetes during labor and delivery are required.

Nursing Mothers: Endogenous insulin is present in human milk. Insulin orally ingested is degraded in the gastrointestinal tract. No adverse reactions have been associated with infant exposure to insulin through the consumption of human milk. Good glucose control supports lactation in patients with diabetes. Women with diabetes who are lactating may require adjustments in their insulin dose.

Pediatric Use: Safety and effectiveness of WOSULIN-R in patients less than 18 years of age has not been established.

Geriatric Use: The effect of age on the pharmacokinetics and pharmacodynamics of WOSULIN-R has not been studied. Patients with advanced age using any insulin, including WOSULIN-R, may be at increased risk of hypoglycemia due to co-morbid disease and polypharmacy.

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

Hypoglycemia: Hypoglycemia is one of the most frequent adverse events experienced by insulin users. Symptoms of mild to moderate hypoglycemia may occur suddenly and can include sweating, drowsiness, dizziness, sleep disturbances, palpitation, anxiety, tremor, blurred vision, hunger, slurred speech, restlessness, depressed mood, tingling in the hands, feet, lips, or tongue, irritability, lightheadedness, abnormal behavior, inability to concentrate, unsteady movement, headache and personality changes. Signs of severe hypoglycemia can include disorientation, seizures, unconsciousness, coma and death.

Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as long duration of diabetes, autonomic diabetic neuropathy, use of medications such as beta-adrenergic blockers, changing insulin preparations, or intensified control (3 or more insulin injections per day) of diabetes. Without recognition of early warning symptoms, the patient may not be able to take steps to avoid more serious hypoglycemia. Patients who experience hypoglycemia without early warning symptoms should monitor their blood glucose more frequently, especially prior to activities such as driving. Mild to moderate hypoglycemia may be treated by eating foods or taking drinks that contain sugar. Patients should always carry a quick source of sugar, such as hard candy, non-diet carbohydrate-containing drinks or glucose tablets.

Hypokalemia: See section 4.4 Special warnings and precautions for use

Lipodystrophy: Administration of insulin subcutaneously can result in lipoatrophy (depression in the skin) or lipohypertrophy (enlargement or thickening of tissue).

Allergy

Local Allergy – Patients occasionally experience erythema, local edema, and pruritus at the site of injection. This condition usually is self-limiting. In some instances, this condition may be related to factors other than insulin, such as irritants in the skin cleansing agent or poor injection technique.

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 (anaphylaxis) may be life threatening.

Weight Gain: Weight gain can occur with some insulin therapies and has been attributed to the anabolic effects of insulin and the decrease in glycosuria.

Peripheral Edema: Insulin may cause sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

Immunogenicity: Development of antibodies that react with human insulin have been observed with all insulin, including WOSULIN R.

4.9 Overdose

Excess insulin may cause hypoglycaemia and hypokalemia, particularly after intravenous administration. 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. Adjustments in drug dosage, meal patterns, or exercise may be needed. More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/ subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycemia may recur after apparent clinical recovery. Hypokalemia must be corrected appropriately.

5. Pharmacological properties

5.1 Mechanism of Action

Regulation of glucose metabolism is the primary activity of insulin. Insulin lowers blood glucose by stimulating peripheral glucose uptake by skeletal muscle and fat following binding the insulin receptors, and by inhibiting hepatic glucose production. Insulins inhibit lipolysis, proteolysis, and gluconeogenesis, and enhance protein synthesis and conversion of excess glucose into fat. Administered insulin, including WOSULIN-R, substitutes for inadequate endogenous insulin secretion and partially corrects the disordered metabolism and inappropriate hyperglycemia of diabetes mellitus, which are caused by either a deficiency or a reduction in the biologic effectiveness of insulin. When administered in appropriate doses at prescribed intervals to patients with diabetes mellitus, WOSULIN-R restores their ability to metabolize carbohydrates, proteins and fats.

5.2 Pharmacodynamic properties

The prime activity of insulin is the regulation of glucose metabolism. 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.

5.3 Pharmacokinetic properties

As with all insulin preparations, the duration of action of WOSULIN-R is dependent on dose, site of injection, blood supply, temperature, and physical activity. WOSULIN-R is human insulin with a short duration of action. With

Page 2

subcutaneous use, the pharmacologic effect of WOSULIN-R begins approximately 30 minutes after administration. The effect is maximal at approximately 1-3 hours and terminates after approximately 4-6 hours. With intravenous use, the pharmacologic effect of WOSULIN-R begins at approximately 10 to 15 minutes and terminates at a median time of approximately 4 hours after administration. The time course of action of any insulin may vary considerably in different individuals or at different times in the same individual.

6. Nonclinical properties

6.1 Animal Toxicology

Single dose toxicity – There were no signs of toxicity in Swiss albino mice and Sprague Dawley rats treated at the dose level of 24IU/kg body weight of subcutaneous injections of regular human insulin.

Repeated dose toxicity - There were no signs of toxicity in Swiss albino mice and Sprague Dawley rats during a period of 28 days with subcutaneous injections of regular human insulin.

Dermal Toxicity - There were no signs of dermal irritation or skin sensitization in New Zealand white rabbits and Duncan Hartley guinea pigs with topical testing of regular human insulin.

Carcinogenicity and impairment of fertility- Carcinogenicity and fertility studies were not performed in animals.

Mutagenicity - Human insulin was not mutagenic in mammalian cells and tested negative in the Ames bacterial reverse mutation assay with and without activation.

7. Description

WOSULIN-R is a polypeptide hormone, structurally identical to human insulin. Human insulin is produced by recombinant DNA technology synthesized in a special non-disease-producing laboratory strain of the yeast Hansenula polymorpha. This special host cell line has been genetically altered by the addition of the gene for human insulin production.

8. Pharmaceutical particulars

8.1 Incompatibilities

These medicinal products should not be mixed with any other insulin or any other medicinal product.

8.2 Shelf-life

Shelf-life of Pack: 10 ml Multi-dose Vial: 30 months.

8.3 Packaging information

PACK: WOSULIN-R 40 IU/ml - 10 ml Multi-dose Vial

8.4 Storage and handing instructions

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 up to 30°C for up to four 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). Do not use WOSULIN-R after the expiration date stamped on the label or if it has been frozen.

9. Patient Counselling Information

Important Risks and Adverse drug reactions

Never Share a Wosulin R vial or syringe between patients

Advise patients using Wosulin R, not to share needles, syringes, or DispoPen with another person. Sharing poses a risk for transmission of blood-borne pathogens.

Hypoglycemia

Inform patients that hypoglycemia is the most common adverse reaction with insulin. Instruct patients on self-management procedures including glucose monitoring, proper injection technique, and management of hypoglycemia and hyperglycemia, especially at initiation of Wosulin R therapy. Instruct patients on handling of special situations such as illness, stress, or emotional disturbances, an inadequate or skipped insulin dose, inadvertent administration of an increased insulin dose, inadequate food intake, and skipped meals,

Instruct patients on the management of hypoglycemia. Advise patients to regularly carry some sugar lumps, sweets, biscuits, or sugary fruit juice to mitigate symptoms of hypoglycemia. Inform patients that their ability to concentrate and react may be impaired as a result of hypoglycemia. Advise patients who have frequent hypoglycemia or reduced or absent warning signs of hypoglycemia to use caution when driving or operating machinery. [see Special warnings and precautions for use(4.4)].

Hypoglycemia due to Medication Errors

Instruct patients that hypoglycemia may occur as a result of an excess of insulin relative to food intake, energy expenditure, or both. Instruct patients to always check the insulin label before each injection to avoid mix-ups between insulin products.

Hypersensitivity Reactions

Advise patients that hypersensitivity reactions can occur with Wosulin. Inform patients on the symptoms of hypersensitivity reactions and advice the patient to discontinue Wosulin and to seek medical attention if they occur [see Undesirable effects (4.8)].

Use in Special Population

Pregnant females

Advise pregnant patients that insulin requirements usually fall during the first trimester and increase during second and third trimesters of pregnancy. Careful monitoring is required throughout pregnancy. During the perinatal period, careful monitoring of infants born to mothers with diabetes is warranted.

Nursing Mothers

Advise the nursing mothers that dosage of insulin may be reduced.

Renal and Hepatic Impairment

Advise the patients that dosage of insulin may be reduced and these patients are at increased risk of hypoglycemia thus requiring frequent blood glucose monitoring.

Administration Instructions

Instruct the patient to never use Wosulin R vial if it is frozen. Advise patients 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). Advise the patients on proper and safe disposal of the needle [see Instructions for use].

Storage and Handling

Instruct the patient that Wosulin R vial which is not in use, should be stored in a refrigerator (2°C to 8°C) and should never be kept in the freezer compartment.

Instruct the patient that when in use, Wosulin R vial may be carried at room temperature up to 30°C for up to 4 weeks.

10. Details of manufacturer

Manufactured in India by
WOCKHARDT LIMITED
Biotech Park, H-14/2 MIDC,
Waluj, Aurangabad 431136 Maharashtra State

11. Details of permission or licence number with date

Manufacturing License No: AD/004

12. Date of revision

Dec/2019.

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Page 3

PATIENT'S INFORMATION AND RECORD

Points you should know :

- Remember the brand name and type of insulin prescribed.
- Never expose insulin to extreme temperatures.
- Use only the right concentration of the insulin prescribed (40 IU or 100 IU) with the right syringe.
- The insulin vials have a protective colour-coded cap which must be removed before use. If the plastic cap is loose or missing, return the vial to the pharmacy.
- WOSULIN is free from, Insulin derived from Animals.

L.I.No.m-SS1141
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Pantone 101 C

Size 180 x 160 mm
SIZE AFTER FOLDING 90 x 20 mm

Pantone 101 C

Size 180 x 160 mm
SIZE AFTER FOLDING 90 x 20 mm