SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF DRUG PRODUCT

Insuget-R Regular (Human Insulin - rDNA origin) Injection 100 IU/mL

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of injection contains:
Human Insulin E. Ph 100IU (rDNA origin)

3. PHARMACEUTICAL FORM

A colorless liquid, free from turbidity and foreign matter; filled in a sterilized glass vial USP type I with yellow color flip off seal and cream color rubber.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Insuget is indicated for the treatment of:

- Patients with Type I diabetes mellitus.
- Patients with Type II diabetes mellitus either alone or in combination with oral anti-diabetic agents.
- Patients with gestational diabetes.
- The emergency management of diabetic ketoacidosis.

4.2 Dosage and Administration

The type of formulation, its dose and the frequency of administration should be determined by the physician, according to the needs suitable to the patient. The dose should be adjusted as necessary according to the results of regular monitoring of glucose concentrations in the blood glucose (or occasionally urine concentrations). A total close in excess of about 80 units daily would be unusual and may indicate the presence of a form of Insulin resistance. The average daily requirement for diabetes therapy ranges between 0.5 and 0.1 IU/kg, depending on the individual needs of the patient. Optimized metabolic control, including glucose monitoring, is therefore recommended during insulin treatment.
In geriatric patients, the primary aim of treatment may be relief of symptoms and avoidance of hypoglycemic events. Insuget-R Regular may be taken 1 to 4 times daily, before meals and possibly at bedtime. Regular (or rapid-acting) insulin should be administered 30 to 45 minutes before a meal. It can be mixed in the same syringe with intermediate-acting insulins, but in such situations, the regular insulin is drawn first. Insuget-R Regular should be given by subcutaneous injection but may, although not recommended, also be given by intramuscular injection. It may also be administered intravenously. Insuget-R Regular is administered into the thigh or abdominal wall. If convenient, the gluteal region or deltoid region may be used.

Ketoacidosis:
Only Insuget-R Regular insulin should be used. Treatment includes adequate fluid replacement, usually by infusing sodium chloride 0.9% initially and the administration of potassium salts to prevent or correct hypokalemia. Insulin should be given by continuous intravenous infusion, if possible, although other routes have also been used. Insulin can also be given by intramuscular injection. In adults an initial loading dose of 20 units is followed by 6 units every hour until the blood glucose concentration falls to 10mmoL per litre, when the dose is given every 2 hours.

Since insulin normally corrects hyperglycemia before ketosis it is usually necessary to continue administration of insulin once normoglycemia has been achieved but to change the rehydration fluid to glucose-saline so that the additional glucose prevents the development of hypoglycemia.

4.3 Contraindications

- Patients with Hypoglycaemia.
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1, unless used as part of a desensitisation programme.
- Patients in coma due to Hyperglycaemia.
- Under no circumstances should this be given intravenously.

4.4 Special Warnings and Special Precautions for use

- 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.

- Care is also necessary during excessive exercise. Hypoglycemia caused by metabolic effects and increased insulin absorption is the usual response, but hyperglycemia may sometimes occur. Adjustment of insulin dosage may also be necessary if patients change their level of physical activity or change their usual diet.

- The use of insulin necessitates monitoring of therapy, such as the testing of blood or urine for glucose concentrations and the urine for ketones, by the patient.

- Local reactions, characterised hypersensitivity may produce urticaria, angioedema and very rarely anaphylactic reactions. If continued therapy with insulin is essential, hypersensitization procedures may need to be performed.

-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, mixture), 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 hypoglycaemic 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, e.g., by intensified insulin therapy, may lose some or all the warning symptoms of hypoglycaemia and should be advised accordingly. Other conditions which may make the early warning symptoms of hypoglycaemia different or less pronounced include long duration of diabetes, diabetic nerve disease, or medications such as beta blockers. Uncorrected

hypoglycaemic and hyperglycaemic 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 hyperglycaemia and diabetic ketoacidosis: conditions which are potentially lethal.

-Treatment with human insulin may cause formation of antibodies, but titres of antibodies are lower than those to purified animal insulin.

4.5 Drug Interactions

-Beta blocking agent may mask the symptoms of hypoglycemia. Some of the drugs leading to reduced insulin requirement: Oral hypoglycemic agents (OHA), octreotide, monoamine oxidase inhibitor (MAOI), non-selective beta blocking agents, angiotensin converting enzyme (ACE) inhibitors, salicylates, alcohol and alcohol steroids. Some of the drugs leading to the increase insulin requirement: Oral contraceptives, thiazides, glucocorticoids, thyroid hormones and sympathomimetics, danazol etc.

-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 human insulin 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.

4.6 Pregnancy and Lactation

It is essential to maintain good control of the insulin treated (insulin-dependent or gestational diabetes) patient throughout pregnancy. Insulin requirements usually fall during the first trimester and increase during the second and third trimesters. Patients with diabetes should be advised to inform their doctors if they are pregnant or are contemplating pregnancy. Careful monitoring of glucose control, as wellas general health, is essential in pregnant patients with diabetes. Patients with diabetes who are lactating may require adjustments in insulin dose and/or diet.

4.7 Undesirable Effects

Very Common

Hypoglycaemia is the most frequent undesirable effect of insulin therapy that a patient with diabetes may suffer. Severe hypoglycaemia may lead to loss of consciousness, and in extreme cases, death. No specific frequency for hypoglycaemia is presented, since hypoglycaemia is a result of both the insulin dose and other factors e.g. a patient`s level of diet and exercise.

Common

Local allergy in patients is common. Redness, swelling, and itching can occur at the site of insulin injection. This condition usually resolves in a few days to a few weeks. In some instances, local reactions may be related to factors other than insulin, such as irritants in the skin cleansing agent or poor injection technique.

Uncommon

Lipodystrophy at the injection site is uncommon.

4.8 Overdosage

Insulin has no specific overdose definitions, because serum glucose concentrations are a result of complex interactions between insulin levels, glucose availability and other metabolic processes. Hypoglycaemia may occur as a result of an excess of insulin relative to food intake and energy expenditure. Hypoglycaemia may be associated with listlessness, confusion, palpitations, headache, sweating and vomiting. Mild hypoglycaemic episodes will respond to oral administration of glucose or sugar products. Correction of moderately severe hypoglycaemia can be accomplished by intramuscular or subcutaneous administration of glucagon, followed by oral carbohydrate when the patient recovers sufficiently. Patients who fail to respond to glucagon must be given glucose solution intravenously. If the patient is comatose, glucagon should be administered intramuscularly or subcutaneously. However, glucose solution must be given intravenously, if glucagon is not available or if the patient fails to respond to glucagon. The patient should be given a meal as soon as consciousness is recovered. Sustained carbohydrate intake and observation may be necessary because hypoglycaemia may occur after apparent clinical recovery.

4.9 Effects **on ability to drive and use machines**

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery). Patients should be advised to take precautions to avoid hypoglycaemia whilst driving, this is particularly important in those who have reduced or absent awareness of the warning signs of hypoglycaemia or have frequent episodes of hypoglycaemia. The advisability of driving should be considered in these circumstances.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

The major effects of insulin on carbohydrate homoeostasis following its binding to specific cell-surface receptors on insulin-sensitive tissues, notably the liver, muscles and adipose tissue. It inhibits hepatic glucose production and enhances peripheral glucose disposal thereby reducing blood-glucose concentration. It also inhibits lipolysis thereby preventing the formation of ketone bodies.

5.2 Pharmacokinetic properties

Absorption
Insulin is fairly rapidly absorbed from subcutaneous tissue following injection. Insulin in the blood stream has a half-life of a few minutes. The rate of absorption from different anatomical sites may be different depending on local blood flow, with absorption from the abdomen being faster than that from the arm and that from the arm faster than from buttock or thigh. Absorption may also be increased by exercise. The absorption of insulin after intramuscular administration is more rapid than that following subcutaneous administration.

Distribution
If no circulating insulin-binding antibodies are present, insulin will distribute as free insulin in the plasma and then diffuse into other compartments.

Metabolism & Excretion
Insulin is rapidly metabolized, mainly in the liver but also in the kidneys and muscle tissue. In the kidneys it is reabsorbed in the proximal tubule and either returned to venous blood or metabolized, with only a small amount excreted unchanged in the urine.

Patients with Special population
Careful glucose monitoring and dose adjustments of insulin, including Human Insulin - rDNA origin, may be necessary in patients with renal or hepatic dysfunction.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Meta-Cresol, Glycerin, Zinc Oxide, Water for Injection, Hydrochloric Acid and Sodium Hydroxide.

6.2 Incompatibilities

In general terms insulin should only be added to compounds with which it is known to be compatible. Insulin suspensions should not be added in infusion fluids.

6.3 Shelf-life

2 Years
The expiration date refers to the product correctly stored in the required conditions.

6.4 Special precautions for storage

Store between 2 - 8℃. Do not freeze.
Do not expose to excessive heat and direct sunlight.
Once in use, the vial can be kept at room temperature (up to 25℃) for up to 6 weeks. Do not use beyond this period.

6.5 Nature and contents of container

Insuget-R Regular Injection 100 IU/mL (Human Insulin - rDNA origin) is available in 10mL vials in packs of 1’s (1 vial in a unit carton) along with a package insert.

6.6 Instructions for use/handling

- Care should be taken when injecting any Insuget-R Regular Injection 100 IU/mL. The

injection site should not be massaged. Patients must be educated to use proper injection techniques.

- Before injecting the insulin:
- Disinfect the rubber stopper.
- Roll the vial between the palms of the hands, making sure that there are no suspended impurities. For Insuget-R Regular Injection 100 IU/mL the liquid should be uniformly white and cloudy.
- Draw into the syringe the same amount of air as the dose of insulin to be injected.
- Inject the air into the vial.
- Turn the vial and syringe upside down and draw the correct insulin dose into the syringe. Withdraw the needle and expel the air from the syringe and check that the dose is correct.
- Inject immediately.
- Do not use if the insulin substance (white material) remains at the bottom after mixing. Do not use if there are changes in the insulin after mixing. Do not use if solid white particles stick to the bottom or wall of the bottle, giving it a frosted appearance. Injection sites should be rotated within an anatomic region in order to avoid lipodystrophy. An injection should be followed within 30 minutes by a meal or a snack containing carbohydrates.
- Injection sites should be rotated within an anatomic region in order to avoid lipodystrophy. An injection should be followed within 30 minutes by a meal or a snack containing carbohydrates.
- Keep out of reach of children.
- Shake gently before use.
- To be sold on prescription of a registered medical practitioner only.

7. APPLICANT/HOLDER OF CERTIFICATE OF PRODUCT REGISTRATION

Getz Pharma (Pvt.) Limited
29-30/27, Korangi
Industrial Area Karachi
74900, Pakistan Tel:
(92-21) 111-111-511
Fax: (92-21) 35057592