

INFORMATION FOR THE PHYSICIAN

HUMULIN[®] R REGULAR INSULIN HUMAN INJECTION, USP (rDNA ORIGIN) 100 UNITS PER ML (U-100)

DESCRIPTION

Humulin[®] R U-100 is a polypeptide hormone structurally identical to human insulin synthesized through rDNA technology in a special non-disease-producing laboratory strain of *Escherichia coli* bacteria. Humulin R U-100 has the empirical formula C₂₅₇H₃₈₃N₆₅O₇₇S₆ and a molecular weight of 5808.

Humulin R U-100 is a sterile, clear, aqueous, and colorless solution that contains human insulin (rDNA origin) 100 units/mL, glycerin 16 mg/mL and metacresol 2.5 mg/mL, endogenous zinc (approximately 0.015 mg/100 units) and water for injection. The pH is 7.0 to 7.8. Sodium hydroxide and/or hydrochloric acid may be added during manufacture to adjust the pH.

Adequate insulin dosage permits patients with diabetes to effectively utilize carbohydrates, proteins and fats. Regardless of dose strength, insulin enables carbohydrate metabolism to occur and thus to prevent the production of ketone bodies by the liver. Some patients develop severe insulin resistance such that daily doses of several hundred units of insulin or more are required.

CLINICAL PHARMACOLOGY

Regulation of glucose metabolism is the primary activity of insulin. Insulin lowers blood glucose by stimulating peripheral glucose uptake by skeletal muscle and fat, 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 Humulin R U-100, 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, Humulin R U-100 restores their ability to metabolize carbohydrates, proteins and fats.

As with all insulin preparations, the duration of action of Humulin R U-100 is dependent on dose, site of injection, blood supply, temperature, and physical activity.

Humulin R U-100 is human insulin with a short duration of action. With subcutaneous use, the pharmacologic effect of Humulin R U-100 begins approximately 30 minutes (range: 10 to 75 minutes) after administration of doses in the 0.05 to 0.4 units/kg range. The effect is maximal at approximately 3 hours (range: 20 minutes to 7 hours) and terminates after approximately 8 hours (range: 3 to 14 hours). With intravenous use, the pharmacologic effect of Humulin R U-100 begins at approximately 10 to 15 minutes and terminates at a median time of approximately 4 hours (range: 2 to 6 hours) after administration of doses in the range of 0.1 to 0.2 units/kg. The time course of action of any insulin may vary considerably in different individuals or at different times in the same individual.

CLINICAL STUDIES

Subcutaneous use of Humulin R U-100

A 48-month multicenter, open-label, single-arm study was conducted in insulin-naïve patients with type 1 or type 2 diabetes (N=129) to assess the safety and efficacy of Humulin R U-100. Humulin R U-100 and Humulin[®] N (alone or in combination) were administered by

subcutaneous injection. Eighty-four percent of patients were Caucasian. Fifty-seven percent of the patients were male. The mean age was 45 years (range: 4 to 83 years). The average weight was 72 kg.

Total mean (\pm SD) glycohemoglobin improved from baseline to endpoint (baseline: $14.3 \pm 3.1\%$, endpoint: $10.1 \pm 2.8\%$). Hemoglobin A_{1c} was not measured in this study. At baseline, patients weighed 72 ± 23 kg; at endpoint mean weight was 80 ± 22 kg. At endpoint, mean (\pm SD) total daily insulin doses for Humulin R U-100 were 0.18 ± 0.17 units/kg. At 48 months, 16 patients (21%) reported hypoglycemia. During the study, 4 patients experienced diabetic ketoacidosis.

Intravenous use of Humulin R U-100

The intravenous administration of Humulin R U-100 was tested in 21 patients with type 1 diabetes. The patients' usual doses of insulin were temporarily held, and blood glucose concentrations were maintained at a range of 200 – 260 mg/dL for one to three hours during a run-in phase of intravenous Humulin R U-100 followed by a 6-hour assessment phase. During the assessment phase patients received intravenous Humulin R at an initial dose of 0.5 U/h, adjusted to maintain blood glucose concentrations near normoglycemia (100 to 160 mg/dL).

The mean blood glucose levels during the assessment phase for patients on Humulin R U-100 therapy are summarized below in Table 1. All patients achieved near normoglycemia during the 6-hour assessment phase. At the endpoint, blood glucose was within the target range (100 to 160 mg/dL) for 20 of 21 patients treated with Humulin R U-100. The average time (\pm SE) required to attain near normoglycemia was 161 ± 14 minutes for Humulin R U-100.

Table 1: Mean Blood Glucose Concentrations (mg/dL) during Intravenous Infusions of Humulin R U-100

Time from Start of Infusion (min)	Mean Blood Glucose (mg/dL) Intravenous ^a
0	220 ± 11
30	204 ± 17
60	193 ± 18
120	172 ± 28
180	153 ± 30
240	139 ± 24
300	131 ± 22
360	128 ± 18

^a Results shown as mean \pm Standard Deviation.

INDICATIONS AND USAGE

Humulin R U-100 is indicated as an adjunct to diet and exercise to improve glycemic control in adults and children with type 1 and type 2 diabetes mellitus.

Humulin R U-100 may be administered intravenously under proper medical supervision in a clinical setting for glycemic control (*see* DOSAGE AND ADMINISTRATION *and* Storage).

CONTRAINDICATIONS

Humulin R U-100 is contraindicated during episodes of hypoglycemia and in patients hypersensitive to Humulin R U-100 or any of its excipients.

WARNINGS

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 Humulin R U-100, 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.

PRECAUTIONS

Hypoglycemia

Hypoglycemia is the most common adverse reaction of all insulin therapies, including Humulin R U-100. Severe hypoglycemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or death. Severe hypoglycemia requiring the assistance of another person and/or parenteral glucose infusion or glucagon administration has been observed in clinical trials with insulin, including trials with Humulin R U-100.

As with all insulin preparations, the time course of Humulin R U-100 action may vary in different individuals or at different times in the same individual and is dependent on dose, site of injection, blood supply, temperature, and physical activity.

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 (*see* PRECAUTIONS, Drug Interactions).

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 Humulin R U-100 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. Early signs of diabetic ketoacidosis include glycosuria and ketonuria. Polydipsia, polyuria, loss of appetite, fatigue, dry skin, abdominal pain, nausea and vomiting and compensatory tachypnea come on gradually, usually over a period of some hours or days, in conjunction with hyperglycemia and ketonemia. Severe sustained hyperglycemia may result in hyperosmolar coma or death.

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 Humulin R U-100 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).

Hypersensitivity and Allergic Reactions

Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products, including Humulin R U-100 (*see* ADVERSE REACTIONS).

Localized reactions and generalized myalgias have been reported with the use of metacresol as an injectable excipient.

Renal or Hepatic Impairment

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

Drug Interactions

Some medications may alter insulin requirements and the risk for hypoglycemia and hyperglycemia (*see* ADVERSE REACTIONS, Drug Interactions).

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. Female patients should be advised to tell their physician if they intend to become, or if they become pregnant.

Studies show that endogenous insulin only crosses the placenta in minimal amounts. While there are no adequate and well-controlled studies in pregnant women, an extensive body of published literature demonstrates the maternal and fetal benefits of insulin treatment in patients with diabetes during pregnancy. Humulin R is a recombinant human insulin that is identical to the endogenous hormone; therefore, reproduction and fertility studies were not performed in animals.

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. In a study of eight preterm infants between 26 to 30 weeks gestation, enteral administration of Humulin R did not result in hypoglycemia. Good glucose control supports lactation in patients with diabetes. Patients with diabetes who are lactating may require adjustments in insulin dose and/or diet.

ADVERSE REACTIONS

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
- 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
- depressed mood
- irritability
- abnormal behavior
- unsteady movement
- personality changes

Signs of severe hypoglycemia can include:

- disorientation
- seizures

- unconsciousness
- death
- coma

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 Precautions

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.

Drug 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 Humulin R U-100 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.

OVERDOSAGE

Excess insulin may cause hypoglycemia 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.

DOSAGE AND ADMINISTRATION

Humulin R U-100, when used subcutaneously, is usually given three or more times daily before meals. The dosage and timing of Humulin R U-100 should be individualized and determined, based on the physician's advice, in accordance with the needs of the patient. Humulin R U-100 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 Humulin R U-100 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. Initial dosages for patients with diabetes are often lower, e.g., 0.2 to 0.4 units/kg/day.

Humulin R U-100 may be administered by subcutaneous injection in the abdominal wall, the thigh, the gluteal region or in the upper arm. Subcutaneous 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 administration of Humulin R U-100 is possible under medical supervision with close monitoring of blood glucose and potassium levels to avoid hypoglycemia and hypokalemia.

For intravenous use, Humulin R U-100 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 Humulin R U-100 if it has become viscous (thickened) or cloudy; use it only if it is clear and colorless. **Humulin R U-100 should not be used after the printed expiration date.**

Mixing of Insulins

- Humulin R U-100 should only be mixed as directed by the physician.
- Humulin R U-100 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-100 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.

Storage

Not in-use (unopened): Humulin R U-100 vials not in-use should be stored in a refrigerator (2° to 8°C [36° to 46°F]), but not in the freezer.

In-use (opened): The Humulin R U-100 vial currently in-use can be kept unrefrigerated as long as it is kept as cool as possible [below 30°C (86°F)] away from heat and light. In-use vials must be used within 31 days or be discarded, even if they still contain Humulin R U-100.

Admixture: Infusion bags prepared with Humulin R U-100 as indicated under DOSAGE AND ADMINISTRATION are stable when stored in a refrigerator (2° to 8°C [36° to 46°F]) for 48 hours and then may be used at room temperature for up to an additional 48 hours.

Do not use Humulin R U-100 after the expiration date stamped on the label or if it has been frozen.

HOW SUPPLIED

Humulin R U-100, Regular, insulin human injection, USP (rDNA origin), 100 units/mL, is supplied as follows:

10 mL vials

NDC 0002-8215-01 (HI-210)

Marketed by: Lilly USA, LLC, Indianapolis, IN 46285, USA

www.lilly.com

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PATIENT INFORMATION

HUMULIN[®] R REGULAR INSULIN HUMAN INJECTION, USP (rDNA ORIGIN) 100 UNITS PER ML (U-100)

WARNINGS

THIS LILLY HUMAN INSULIN PRODUCT DIFFERS FROM ANIMAL-SOURCE INSULINS BECAUSE IT IS STRUCTURALLY IDENTICAL TO THE INSULIN PRODUCED BY YOUR BODY'S PANCREAS AND BECAUSE OF ITS UNIQUE MANUFACTURING PROCESS.

ANY CHANGE OF INSULIN SHOULD BE MADE CAUTIOUSLY AND ONLY UNDER MEDICAL SUPERVISION. CHANGES IN STRENGTH, MANUFACTURER, TYPE (E.G., REGULAR, NPH, ANALOG), SPECIES, OR METHOD OF MANUFACTURE MAY RESULT IN THE NEED FOR A CHANGE IN DOSAGE.

SOME PATIENTS TAKING HUMULIN[®] (HUMAN INSULIN, rDNA ORIGIN) MAY REQUIRE A CHANGE IN DOSAGE FROM THAT USED WITH OTHER INSULINS. IF AN ADJUSTMENT IS NEEDED, IT MAY OCCUR WITH THE FIRST DOSE OR DURING THE FIRST SEVERAL WEEKS OR MONTHS.

Humulin R may cause serious side effects, including:

- **swelling of your hands and feet**
- **heart failure.** Taking certain diabetes pills called thiazolidinediones or “TZDs” with Humulin R may cause heart failure in some people. This can happen even if you have never had heart failure or heart problems before. If you already have heart failure it may get worse while you take TZDs with Humulin R. Your healthcare provider should monitor you closely while you are taking TZDs with Humulin R. Tell your healthcare provider if you have any new or worse symptoms of heart failure including:
 - shortness of breath
 - swelling of your ankles or feet
 - sudden weight gain

Treatment with TZDs and Humulin R may need to be adjusted or stopped by your healthcare provider if you have new or worse heart failure.

DIABETES

Insulin is a hormone produced by the pancreas, a large gland that lies near the stomach. This hormone is necessary for the body's correct use of food, especially sugar. Diabetes occurs when the pancreas does not make enough insulin to meet your body's needs.

To control your diabetes, your doctor has prescribed injections of insulin products to keep your blood glucose at a near-normal level. You have been instructed to test your blood regularly for glucose. Studies have shown that some chronic complications of diabetes such as eye disease, kidney disease, and nerve disease can be significantly reduced if the blood sugar is maintained as close to normal as possible. Proper control of your diabetes requires close and constant cooperation with your doctor. Despite diabetes, you can lead an active and healthy life if you eat a balanced diet, exercise regularly, and take your insulin injections as prescribed by your doctor.

Always keep an extra supply of insulin as well as a spare syringe and needle on hand. Always wear diabetic identification so that appropriate treatment can be given if complications occur away from home.

REGULAR HUMAN INSULIN

Description

Humulin is synthesized in a special non-disease-producing laboratory strain of *Escherichia coli* bacteria that has been genetically altered to produce human insulin. Humulin R [Regular insulin human injection, USP (rDNA origin)] consists of zinc-insulin crystals dissolved in a clear fluid. It takes effect within 30 minutes and has a duration of activity of approximately 4 to 12 hours. 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 duration of action of Humulin R is dependent on dose, site of injection, blood supply, temperature, and physical activity. Humulin R is a sterile solution and is for subcutaneous injection. It should not be used intramuscularly. The concentration of Humulin R is 100 units/mL (U-100).

Identification

Human insulin from Eli Lilly and Company has the trademark Humulin. Your doctor has prescribed the type of insulin that he/she believes is best for you.

DO NOT USE ANY OTHER INSULIN EXCEPT ON YOUR DOCTOR'S ADVICE AND DIRECTION.

Always check the carton and the bottle label for the name and letter designation of the insulin you receive from your pharmacy to make sure it is the same as prescribed by your doctor. There are two Humulin R formulations: Humulin R U-100 and Humulin R U-500. Make sure that you have the formulation prescribed by your doctor.

Always check the appearance of your bottle of Humulin R before withdrawing each dose. Humulin R is a clear and colorless liquid with a water-like appearance and consistency. Do not use Humulin R:

- if it appears cloudy, thickened, or slightly colored, or
- if solid particles are visible.

If you see anything unusual in the appearance of Humulin R solution in your bottle or notice your insulin requirements changing, talk to your doctor.

Storage

Not in-use (unopened): Humulin R U-100 bottles not in-use should be stored in a refrigerator (36° to 46°F [2° to 8°C]), but not in the freezer.

In-use (opened): The Humulin R U-100 bottle you are currently using can be kept unrefrigerated as long as it is kept as cool as possible [below 86°F (30°C)] away from heat and light. In-use bottles must be used within 31 days or be thrown out, even if they still contain Humulin R U-100.

Do not use Humulin R after the expiration date stamped on the label or if it has been frozen.

DOSAGE

Your doctor has told you which insulin to use, how much, and when and how often to inject it. Because each patient's diabetes is different, this schedule has been individualized for you.

Your usual dose of Humulin R may be affected by changes in your diet, activity, or work schedule. Carefully follow your doctor's instructions to allow for these changes. Other things that may affect your Humulin R dose are:

Illness

Illness, especially with nausea and vomiting, may cause your insulin requirements to change. Even if you are not eating, you will still require insulin. You and your doctor should establish a sick day plan for you to use in case of illness. When you are sick, test your blood glucose frequently. If instructed by your doctor, test your ketones and report the results to your doctor.

Pregnancy

Good control of diabetes is especially important for you and your unborn baby. Pregnancy may make managing your diabetes more difficult. If you are planning to have a baby, are pregnant, or are nursing a baby, talk to your doctor.

Medication

Insulin requirements may be increased if you are taking other drugs with blood-glucose-raising activity, such as oral contraceptives, corticosteroids, or thyroid replacement therapy. Insulin requirements may be reduced in the presence of drugs that lower blood glucose or affect how your body responds to insulin, such as oral antidiabetic agents, salicylates (for example, aspirin), sulfa antibiotics, alcohol, certain antidepressants and some kidney and blood pressure medicines. Your healthcare provider may be aware of other medications that may affect your diabetes control. Therefore, always discuss any medications you are taking with your doctor.

Before you use Humulin R, tell your healthcare provider if you:

- take any other medicines, especially ones commonly called TZDs (thiazolidinediones).
- have heart failure or other heart problems. If you have heart failure, it may get worse while you take TZDs with Humulin R.

Exercise

Exercise may lower your body's need for insulin during and for some time after the physical activity. Exercise may also speed up the effect of an insulin dose, especially if the exercise involves the area of injection site (for example, the leg should not be used for injection just prior to running). Discuss with your doctor how you should adjust your insulin regimen to accommodate exercise.

Travel

When traveling across more than 2 time zones, you should talk to your doctor concerning adjustments in your insulin schedule.

COMMON PROBLEMS OF DIABETES

Hypoglycemia (Low Blood Sugar)

Hypoglycemia (too little glucose in the blood) is one of the most frequent adverse events experienced by insulin users. It can be brought about by:

1. **Missing or delaying meals.**
2. Taking too much insulin.
3. Exercising or working more than usual.
4. An infection or illness associated with diarrhea or vomiting.
5. A change in the body's need for insulin.
6. Diseases of the adrenal, pituitary, or thyroid gland, or progression of kidney or liver disease.
7. Interactions with certain drugs, such as oral antidiabetic agents, salicylates (for example, aspirin), sulfa antibiotics, certain antidepressants and some kidney and blood pressure medicines.
8. Consumption of alcoholic beverages.

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
- depressed mood
- irritability
- abnormal behavior
- unsteady movement
- personality changes

Signs of severe hypoglycemia can include:

- disorientation
- seizures

- unconsciousness
- 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, use of medications such as beta-blockers, changing insulin preparations, or intensified control (3 or more insulin injections per day) of diabetes.

A few patients who have experienced hypoglycemic reactions after transfer from animal-source insulin to human insulin have reported that the early warning symptoms of hypoglycemia were less pronounced or different from those experienced with their previous insulin.

Without recognition of early warning symptoms, you may not be able to take steps to avoid more serious hypoglycemia. Be alert for all of the various types of symptoms that may indicate hypoglycemia. Patients who experience hypoglycemia without early warning symptoms should monitor their blood glucose frequently, especially prior to activities such as driving. 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 hard candy or glucose tablets. More severe hypoglycemia may require the assistance of another person. Patients who are unable to take sugar orally or who are unconscious require an injection of glucagon or should be treated with intravenous administration of glucose at a medical facility.

You should learn to recognize your own symptoms of hypoglycemia. If you are uncertain about these symptoms, you should monitor your blood glucose frequently to help you learn to recognize the symptoms that you experience with hypoglycemia.

If you have frequent episodes of hypoglycemia or experience difficulty in recognizing the symptoms, you should talk to your doctor to discuss possible changes in therapy, meal plans, and/or exercise programs to help you avoid hypoglycemia.

Hyperglycemia (High Blood Sugar) and Diabetic Ketoacidosis (DKA)

Hyperglycemia (too much glucose in the blood) may develop if your body has too little insulin. Hyperglycemia can be brought about by any of the following:

1. Omitting your insulin or taking less than your doctor has prescribed.
2. Eating significantly more than your meal plan suggests.
3. Developing a fever, infection, or other significant stressful situation.

In patients with type 1 or insulin-dependent diabetes, prolonged hyperglycemia can result in DKA (a life-threatening emergency). The first symptoms of DKA 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 DKA, blood and urine tests show large amounts of glucose and ketones. Heavy breathing and a rapid pulse are more severe symptoms. If uncorrected, prolonged hyperglycemia or DKA can lead to nausea, vomiting, stomach pain, dehydration, loss of consciousness, or death. Therefore, it is important that you obtain medical assistance immediately.

Lipodystrophy

Rarely, administration of insulin subcutaneously can result in lipodystrophy (seen as an apparent depression of the skin) or lipohypertrophy (seen as a raised area of the skin). If you notice either of these conditions, talk to your doctor. A change in your injection technique may help alleviate the problem.

Allergy

Local Allergy — Patients occasionally experience redness, swelling, and itching at the site of injection. 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 or poor injection technique. If you have local reactions, talk to your doctor.

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. If you think you are having a generalized allergic reaction to insulin, call your doctor immediately.

ADDITIONAL INFORMATION

Information about diabetes may be obtained from your diabetes educator.

Additional information about diabetes and Humulin can be obtained by calling The Lilly Answers Center at 1-800-LillyRx (1-800-545-5979) or by visiting www.LillyDiabetes.com.

Marketed by: Lilly USA, LLC, Indianapolis, IN 46285, USA

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INSTRUCTIONS FOR INSULIN VIAL USE

NEVER SHARE NEEDLES AND SYRINGES.

Correct Syringe Type

Doses of insulin are measured in **units**. U-100 insulin contains 100 units/mL (1 mL=1 cc). With Humulin R, it is important to use a syringe that is marked for U-100 insulin preparations. Failure to use the proper syringe can lead to a mistake in dosage, causing serious problems for you, such as a blood glucose level that is too low or too high.

Syringe Use

To help avoid contamination and possible infection, follow these instructions exactly.

Disposable syringes and needles should be used only once and then discarded by placing the used needle in a puncture-resistant disposable container. Properly dispose of the puncture-resistant container as directed by your Health Care Professional.

Preparing the Dose

1. Wash your hands.
2. Inspect the insulin. Humulin R solution should look clear and colorless. Do not use Humulin R if it appears cloudy, thickened, or slightly colored, or if you see particles in the solution. Do not use Humulin R if you notice anything unusual in its appearance.
3. If using a new Humulin R bottle, flip off the plastic protective cap, but **do not** remove the stopper. Wipe the top of the bottle with an alcohol swab.
4. If you are mixing insulins, refer to the "Mixing Humulin R with Longer-Acting Human Insulins" section below.
5. Draw an amount of air into the syringe that is equal to the Humulin R dose. Put the needle through rubber top of the Humulin R bottle and inject the air into the bottle.
6. Turn the Humulin R bottle and syringe upside down. Hold the bottle and syringe firmly in one hand.
7. Making sure the tip of the needle is in the Humulin R solution, withdraw the correct dose of Humulin R into the syringe.
8. Before removing the needle from the Humulin R bottle, check the syringe for air bubbles. If bubbles are present, hold the syringe straight up and tap its side until the bubbles float to the top. Push the bubbles out with the plunger and then withdraw the correct dose.
9. Remove the needle from the bottle and lay the syringe down so that the needle does not touch anything.
10. If you do not need to mix your Humulin R with a longer-acting insulin, go to the "Injection Instructions" section below and follow the directions.

Mixing Humulin R with Longer-Acting Human Insulins

1. Humulin R should be mixed with longer-acting human insulins only on the advice of your doctor.
2. Draw an amount of air into the syringe that is equal to the amount of longer-acting insulin you are taking. Insert the needle into the longer-acting insulin bottle and inject the air. Withdraw the needle.
3. Draw an amount of air into the syringe that is equal to the amount of Humulin R you are taking. Insert the needle into the Humulin R bottle and inject the air, but **do not** withdraw the needle.
4. Turn the Humulin R bottle and syringe upside down.
5. Making sure the tip of the needle is in the Humulin R solution, withdraw the correct dose of Humulin R into the syringe.
6. Before removing the needle from the Humulin R bottle, check the syringe for air bubbles. If bubbles are present, hold the syringe straight up and tap its side until the bubbles float to the top. Push the bubbles out with the plunger and then withdraw the correct dose.

7. Remove the syringe with the needle from the Humulin R bottle and insert it into the longer-acting insulin bottle. Turn the longer-acting insulin 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 longer-acting insulin, withdraw the correct dose of longer-acting insulin.
8. Remove the needle from the bottle and lay the syringe down so that the needle does not touch anything.
9. Follow the directions under “Injection Instructions” section below.

Follow your doctor’s instructions on whether to mix your insulins ahead of time or just before giving your injection. It is important to be consistent in your method.

Syringes from different manufacturers may vary in the amount of space between the bottom line and the needle. Because of this, do not change:

- the sequence of mixing, or
- the model and brand of syringe or needle that your doctor has prescribed.

Injection Instructions

1. To avoid tissue damage, choose a site for each injection that is at least 1/2 inch from the previous injection site. The usual sites of injection are abdomen, thighs, and arms.
2. Cleanse the skin with alcohol where the injection is to be made.
3. With one hand, stabilize the skin by spreading it or pinching up a large area.
4. Insert the needle as instructed by your doctor.
5. Push the plunger in as far as it will go.
6. Pull the needle out and apply gentle pressure over the injection site for several seconds.
Do not rub the area.
7. Place the used needle in a puncture-resistant disposable container and properly dispose of the puncture-resistant container as directed by your Health Care Professional.

Patient Instruction for Use revised March 2011

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INFORMATION FOR THE PHYSICIAN

HUMULIN[®] R REGULAR U-500 (CONCENTRATED) INSULIN HUMAN INJECTION, USP (rDNA ORIGIN)

DESCRIPTION

Humulin R[®] U-500 is a polypeptide hormone structurally identical to human insulin synthesized through rDNA technology in a special non-disease-producing laboratory strain of *Escherichia coli* bacteria. Humulin R U-500 has the empirical formula $C_{257}H_{383}N_{65}O_{77}S_6$ and a molecular weight of 5808.

Humulin R U-500 is a sterile, clear, aqueous and colorless solution that contains human insulin (rDNA origin) 500 units/mL, glycerin 16 mg/mL, metacresol 2.5 mg/mL and zinc oxide to supplement the endogenous zinc to obtain a total zinc content of 0.017 mg/100 units, and water for injection. The pH is 7.0 to 7.8. Sodium hydroxide and/or hydrochloric acid may be added during manufacture to adjust the pH.

Humulin R U-500 is for subcutaneous injection only. It should not be used intravenously or intramuscularly. **Humulin R U-500 contains 500 units of insulin in each milliliter (5-times more concentrated than Humulin R U-100 [see DOSAGE AND ADMINISTRATION]).** It also contains 16 mg glycerin, 2.5 mg metacresol as a preservative, and zinc-oxide calculated to supplement endogenous zinc to obtain a total zinc content of 0.017 mg/100 units and water for injection. Sodium hydroxide and/or hydrochloric acid may be added during manufacture to adjust the pH.

Adequate insulin dosage permits patients with diabetes to effectively utilize carbohydrates, proteins and fats. Regardless of dose strength, insulin enables carbohydrate metabolism to occur and thus to prevent the production of ketone bodies by the liver. Some patients might develop severe insulin resistance such that daily doses of several hundred units of insulin or more are required.

CLINICAL PHARMACOLOGY

Regulation of glucose metabolism is the primary activity of insulin. Insulin lowers blood glucose by stimulating peripheral glucose uptake by skeletal muscle and fat, 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 Humulin R U-500, 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, Humulin R U-500 restores their ability to metabolize carbohydrates, proteins and fats.

As with all insulin preparations, the duration of action of Humulin R U-500 is dependent on dose, site of injection, blood supply, temperature, and physical activity.

Humulin R U-500 is unmodified by any agent that might prolong its action. Clinical experience has shown that it frequently has time action characteristics reflecting both prandial and basal activity. It takes effect within 30 minutes, has a peak similar to that observed with U-100 regular human insulin and has a relatively long duration of activity following a single dose (up to 24 hours) as compared with U-100 regular insulins. This effect has been credited to the

high concentration of the preparation. The time course of action of any insulin may vary considerably in different individuals or at different times in the same individual.

INDICATIONS AND USAGE

Humulin R U-500 is indicated as an adjunct to diet and exercise to improve glycemic control in adults and children with type 1 and type 2 diabetes mellitus.

Humulin R U-500 is useful for the treatment of insulin-resistant patients with diabetes requiring daily doses of more than 200 units, since a large dose may be administered subcutaneously in a reasonable volume.

CONTRAINDICATIONS

Humulin R U-500 is contraindicated during episodes of hypoglycemia and in patients hypersensitive to Humulin R U-500 or any of its excipients.

WARNINGS

Any change of 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.

Humulin R U-500 contains 500 units of insulin in each milliliter (5-times more concentrated than Humulin R U-100). For Humulin R U-500, extreme caution must be observed in the measurement of dosage because inadvertent overdose may result in serious adverse reaction or life-threatening hypoglycemia.

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 Humulin R U-500, 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.

PRECAUTIONS

Dosing Confusion/Dosing Errors

Medication errors associated with Humulin R U-500 have occurred and resulted in patients experiencing hyperglycemia, hypoglycemia or death. The majority of errors occurred due to errors in dispensing, prescribing or administration. Attention to the following details may prevent:

- Dispensing errors

The Humulin R U-500 vial, which contains 20 mL, versus the Humulin R U-100 vial, which contains 10 mL – is marked with a band of diagonal brown stripes to distinguish it from the U-100 vial, which has no stripes. “U-500” is also highlighted in red on the label.

- Prescribing errors (*see* DOSAGE AND ADMINISTRATION)

The prescribed dose of Humulin R U-500 should always be expressed in actual units of Humulin R U-500 along with corresponding markings on the syringe the patient is using (i.e., a U-100 insulin syringe or tuberculin syringe [*see* DOSAGE AND ADMINISTRATION]).

- Administration errors (*see* DOSAGE AND ADMINISTRATION)

A majority of these errors occurred due to dosing confusion when the Humulin R U-500 dose was prescribed in units or volume corresponding to a U-100 syringe or tuberculin syringe markings, respectively, or the prescribed dose was administered without recognizing that the markings on the syringe used do not directly correspond to U-500 dose. Instructions for use should always be read and followed before use.

Instruct the patient to inform hospital or emergency department staff of the dose of Humulin R U-500 prescribed, in the event of a future hospitalization or visit to the Emergency Department.

A conversion chart is provided and should always be used when administering Humulin R U-500 doses with U-100 insulin syringes or tuberculin syringes.

Hypoglycemia

Hypoglycemia is the most common adverse reaction of all insulin therapies, including Humulin R U-500. Severe hypoglycemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or death. Severe hypoglycemia requiring the assistance of another person and/or parenteral glucose infusion or glucagon administration has been observed in clinical trials with insulin, including trials with Humulin R U-500.

As with all insulin preparations, the time course of Humulin R U-500 action may vary in different individuals or at different times in the same individual and is dependent on dose, site of injection, blood supply, temperature, and physical activity.

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 oral antidiabetic treatment may need to be adjusted.

Any patient who requires Humulin R U-500 for control of diabetes should be under close observation until appropriate dosage is established. The response will vary among patients. Most patients will require 2 or 3 injections per day.

Insulin resistance, in some patients is transitory; after several weeks or months during which high dosage is required, responsiveness to the pharmacologic effect of insulin may be regained and dosage can be reduced.

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 (*see* PRECAUTIONS, Drug Interactions).

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 prevent a risk in situations where these abilities are especially important, such as driving or operating other machinery.

Severe hypoglycemia may develop 18 to 24 hours after the original injection of Humulin R U-500.

Hyperglycemia, Diabetic Ketoacidosis, and Hyperosmolar Non-Ketotic Syndrome

Hyperglycemia, diabetic ketoacidosis, or hyperosmolar coma may develop if the patient takes less Humulin R U-500 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. Early signs of diabetic ketoacidosis include glycosuria and ketonuria. Polydipsia, polyuria, loss of appetite, fatigue, dry skin, abdominal pain, nausea and vomiting and compensatory tachypnea come on gradually, usually over a period of some hours or days, in conjunction with hyperglycemia and ketonemia. Severe sustained hyperglycemia may result in hyperosmolar coma or death.

Hypokalemia

Insulin stimulates potassium movement into the cells, possibly leading to hypokalemia, that left untreated may cause respiratory paralysis, ventricular arrhythmia, and death. 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 Humulin R U-500 (*see* ADVERSE REACTIONS).

Localized reactions and generalized myalgias have been reported with the use of metacresol as an injectable excipient.

Renal or Hepatic Impairment

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

Drug Interactions

Some medications may alter insulin requirements and the risk for hypoglycemia and hyperglycemia (*see* ADVERSE REACTIONS, Drug Interactions).

Use in Pregnancy

Pregnancy Category B — All pregnancies have 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 glucose monitoring is essential in these patients. Female patients should be advised to tell their physician if they intend to become, or if they become pregnant.

Studies show that endogenous insulin only crosses the placenta in minimal amounts. While there are no adequate and well-controlled studies in pregnant women, an extensive body of published literature demonstrates the maternal and fetal benefits of insulin treatment in patients with diabetes during pregnancy. Humulin R U-500 is a recombinant human insulin that is identical to the endogenous hormone; therefore, reproduction and fertility studies were not performed in animals.

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. In lactating infants, no adverse reactions have been associated with maternal use of insulin. In a study of eight preterm infants between 26 to 30 weeks gestation, enteral administration of Humulin R did not result in hypoglycemia. Good glucose control supports lactation in patients with diabetes. Patients with diabetes who are lactating may require adjustments in insulin dose and/or diet.

Pediatric Use

There are no well-controlled studies of use of Humulin R U-500 in children.

ADVERSE REACTIONS

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
- 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
- depressed mood
- irritability
- abnormal behavior
- unsteady movement
- personality changes

Signs of severe hypoglycemia can include:

- disorientation
- unconsciousness
- death
- seizures
- coma

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.

Hypoglycemia when using Humulin R U-500 can be prolonged and severe.

Hypokalemia

See Precautions

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.

Drug Interactions

The concurrent use of oral antihyperglycemic diabetes agents with Humulin R U-500 is not recommended since there are limited data to support such use.

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 Humulin R U-500 and susceptibility to hypoglycemia:

- Oral antihyperglycemic diabetes 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.

OVERDOSAGE

Excess insulin may cause hypoglycemia and hypokalemia. 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.

DOSAGE AND ADMINISTRATION

Humulin R U-500 is usually given two or three times daily before meals. The dosage and time of Humulin R U-500 should be individualized and determined, based on the physician's advice, in accordance with the needs of the patient. The injection of Humulin R U-500 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 1.0 unit/kg/day. However, in pre-pubertal children it usually varies from 0.7 to 1.0 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. Initial dosages for type 2 diabetes patients are often lower, e.g., 0.2 to 0.4 units/kg/day.

Humulin R U-500 is useful for the treatment of insulin resistant patients with diabetes requiring daily doses of more than 200 units, since a large dose may be administered subcutaneously in a reasonable volume.

Humulin R U-500 may be administered by subcutaneous injection in the abdominal wall, the thigh, the gluteal region or in the upper arm. Subcutaneous 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.

Humulin R U-500 should only be administered subcutaneously. Do not administer Humulin R U-500 intravenously or intramuscularly.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Never use Humulin R U-500 if it has become viscous (thickened) or cloudy; use it only if it is clear and colorless. **Humulin R U-500 should not be used after the printed expiration date.**

Do not mix Humulin R U-500 with other insulins, as there are no data to support such use.

When administering Humulin R U-500

If U-100 insulin syringes are used, since their markings are in units and are designed and intended for use with the less concentrated U-100 insulin products, it is extremely important to explain the amount of Humulin R U-500 insulin to be administered in both actual dose and with specification of "unit markings" on the U-100 syringe.

If tuberculin syringes are used, since their markings are in volume (mL), the actual amount of Humulin R U-500 should be explained in both actual dose and with specification of volume

(mL). Table 1 contains conversion information using both U-100 insulin and tuberculin syringes to help avoid dose confusion.

Table 1: Conversion Information for Humulin R U-500 Insulin Dose When Using a U-100 Insulin Syringe or a Tuberculin Syringe

Humulin R U-500 dose (units)	U-100 insulin syringe (unit markings)	Tuberculin syringe (volume in mL)
25	5	0.05
50	10	0.1
75	15	0.15
100	20	0.2
125	25	0.25
150	30	0.3
175	35	0.35
200	40	0.4
225	45	0.45
250	50	0.5
275	55	0.55
300	60	0.6
325	65	0.65
350	70	0.7
375	75	0.75
400	80	0.8
425	85	0.85
450	90	0.9
475	95	0.95
500	100	1.0
Dose (actual Humulin R U-500 units)	Divide dose (actual Humulin R U-500 units) by 5	Divide dose (actual Humulin R U-500 units) by 500

For doses other than those listed above refer to the following formulas:

U-100 insulin syringe

Divide prescribed Dose (actual units) by 5 = Unit markings in a U-100 insulin syringe.

Tuberculin syringe

Divide prescribed Dose (actual units) by 500 = Volume (mL) in a tuberculin syringe

Storage

Not in-use (unopened): Humulin R U-500 vials not in-use should be stored in a refrigerator, (2° to 8°C [36° to 46°F]), but not in the freezer.

In-use (opened): The Humulin R U-500 vial currently in-use can be kept unrefrigerated as long as it is kept as cool as possible (below 30°C [86°F]) away from heat and light. In-use vials must be used within 31 days or be discarded, even if they still contain Humulin R U-500.

Do not use Humulin R U-500 after the expiration date stamped on the label or if it has been frozen.

HOW SUPPLIED

Vials, 500 units/mL, 20 mL (HI-500) (1s),

NDC 0002-8501-01

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PATIENT INFORMATION

Humulin[®] (HU-mu-lin) R

Regular

U-500 (Concentrated)

insulin human injection, USP (rDNA origin)

Read the Patient Information that comes with Humulin[®] R U-500 before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your healthcare provider about your diabetes or treatment.

What is the most important information I should know about Humulin R U-500?

Humulin R U-500 (500 units/mL) contains 5 times as much insulin in 1 mL as standard U-100 (100 units/mL) insulin. This means that it is more concentrated than standard U-100 insulin.

Know your insulin. Make sure you know the strength, dose and type of insulin that is prescribed for you. Do not change the strength, dose or type of insulin you use unless told to do so by your healthcare provider.

It is important that you take the right dose of Humulin R U-500. Taking too much Humulin R U-500 can cause life-threatening low blood sugar (hypoglycemia) or death. Taking too little Humulin R U-500 can cause high blood sugar (hyperglycemia).

There are no special syringes to measure Humulin R U-500. It is important that you use only the syringes that your healthcare provider tells you to use. Your healthcare provider should tell you how much Humulin R U-500 to take and when to take it. Your healthcare provider should show you how to draw up Humulin R U-500. The amount of Humulin R U-500 will be less than the amount of standard U-100 insulin which would be drawn up into the syringe. **See the section, “How should I take Humulin R U-500?”**

What is Humulin R U-500?

Humulin R U-500 is a prescription medicine used to treat high blood sugar in people with diabetes mellitus. Humulin R U-500 is a man-made insulin that is similar to the insulin produced by the human pancreas. Humulin R U-500 is used along with diet and exercise to lower blood sugar in people with:

- type 1 diabetes.
- type 2 diabetes whose blood sugars are not controlled well with diabetes medicine taken by mouth.

Humulin R U-500 is useful for the treatment of insulin-**resistant** patients with diabetes who need more than 200 units of insulin a day.

It is not known if Humulin R U-500 is safe and effective in children.

Who should not take Humulin R U-500?

Do not take Humulin R U-500 if:

- your blood sugar is too low (hypoglycemia). See the section, “What are the possible side effects of Humulin R U-500?” for more information on low blood sugar.
- you are allergic to any of the ingredients in Humulin R U-500. See the end of this leaflet for a complete list of ingredients in Humulin R U-500.

What should I tell my healthcare provider before taking Humulin R U-500?

Before you take Humulin R U-500, tell your healthcare provider if you:

- **have liver or kidney problems or any other medical conditions.** Certain medical conditions can affect your insulin needs and your dose of Humulin R U-500.
- take any other medicines, especially ones commonly called TZDs (thiazolidinediones).
- have heart failure or other heart problems. If you have heart failure, it may get worse while you take TZDs with Humulin R U-500.
- **are pregnant, plan to become pregnant, or are breast-feeding.** It is not known if Humulin R U-500 will harm your unborn baby or breast-feeding child. You and your healthcare provider should talk about the best way to manage your diabetes while you are pregnant or breast-feeding. It is especially important to keep good control of your blood sugar during pregnancy.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Many medicines can affect your blood sugar levels and your insulin needs. Your Humulin R U-500 dose may need to change if you take other medicines. Especially tell your healthcare provider if you take other medicines to treat your diabetes.

Know the medicines you take. Keep a list of your medicines with you and show it to your healthcare provider and pharmacist when you get a new medicine.

How should I take Humulin R U-500?

- Take Humulin R U-500 exactly as prescribed.
- **Do not make any changes to your strength, dose or type of insulin unless you are told to do so by your healthcare provider.**
- Check the label carefully to make sure you have the right type and strength of insulin prescribed for you.
- Your healthcare provider should show you how to prepare and inject Humulin R U-500 before you start taking it.
- **Humulin R U-500 should look clear and colorless. Do not use Humulin R U-500 if it does not look clear, colorless or has particles in it. Talk with your pharmacist or healthcare provider if you have any questions.**
- Follow your healthcare provider’s instructions about how often you should check your blood sugar level for hypoglycemia (too low blood sugar) and hyperglycemia (too high blood sugar).
- Humulin R U-500 starts working about 30 minutes after injection. The effects of Humulin R U-500 may last up to 24 hours.
- You should eat a meal within 30 minutes of injecting Humulin R U-500.

- Choose an injection area (upper arm, abdomen, buttocks, or thigh). Change injection sites within the area you choose for each dose. **Do not inject into the exact same spot for each injection. Never inject Humulin R U-500 into a vein or muscle.**
- Inject Humulin R U-500 under your skin (subcutaneous), as shown to you by your healthcare provider.
- Your healthcare provider should regularly check your diabetes with blood tests, including your blood sugar levels and hemoglobin A_{1C}.
- If you take too much Humulin R U-500, your blood sugar may fall too low (hypoglycemia). You can treat mild low blood sugar (hypoglycemia) by drinking or eating something sugary right away. Always carry a quick source of sugar, such as hard candy, fruit juice or glucose tablets.
- Your healthcare provider may prescribe a glucagon emergency kit so that others can give you an injection if your blood sugar becomes too low (hypoglycemic) and you are unable to take sugar by mouth.

There are no special syringes to measure Humulin R U-500. It is important that you use only the syringes that your healthcare provider tells you to use to give your injections of Humulin R U-500. You should use either a U-100 insulin syringe or tuberculin syringe as instructed by your healthcare provider.

- If you are using **U-100 insulin syringes**, your healthcare provider should explain how to use this syringe to give the prescribed dose with the **unit markings** on the syringe.
- If you are using **tuberculin syringes**, your healthcare provider should explain how to use this syringe to give the prescribed dose with **volume markings** on the syringe.

If you do not use the right syringe type, you may take the wrong dose of Humulin R U-500. This can cause you to have too low blood sugar (hypoglycemia) or too high blood sugar (hyperglycemia).

Make sure you know:

- **your prescribed dose of Humulin R U-500.**
- **which syringe to use and how to draw up your prescribed dose.**

If you do not understand your dose, talk with your healthcare provider about how much insulin to take.

If you are hospitalized or go to an emergency room, make sure to tell the hospital staff the actual dose of Humulin R U-500 that your healthcare provider has prescribed for you.

Your healthcare provider may change your dose of Humulin R U-500 because of:

- illness
- change in diet
- stress
- change in physical activity or exercise
- other medicines you take
- travel

Check your blood sugar and stay on the diet and exercise plan as prescribed by your healthcare provider.

- Do not share needles or syringes with others.
- Place used needles and syringes in a closable, puncture-resistant container. You may use a sharps container (such as a red biohazard container) or a hard plastic container (such as a detergent bottle) or a metal container (such as an empty coffee can). Ask your healthcare provider for instructions on the right way to throw away the container. There may be state and local laws about how you should throw away used needles and syringes.
- Do not throw the container in household trash and do not recycle.

What should I avoid while taking Humulin R U-500?

- **Alcohol.** Drinking alcohol may affect your blood sugar when you take Humulin R U-500.
- **Driving and operating machinery.** You may have trouble paying attention or reacting if you have low blood sugar (hypoglycemia). Be careful when you drive a car or operate machinery. Ask your healthcare provider if it is all right for you to drive if you have:
 - Low blood sugar (hypoglycemia)
 - Decreased or no warning signs of low blood sugar

What are the possible side effects of Humulin R U-500?

Humulin R U-500 can cause serious side effects, including:

- See the section “What is the most important information I should know about Humulin R U-500?”
- **Low blood sugar (hypoglycemia).**

Symptoms of low blood sugar may happen suddenly with Humulin R U-500.

Symptoms of mild or moderate low blood sugar may include:

- | | |
|---|-----------------------|
| • sweating | • drowsiness |
| • dizziness | • trouble sleeping |
| • fast heart beat | • feeling anxious |
| • tremor | • blurred vision |
| • hunger | • slurred speech |
| • restlessness | • depressed mood |
| • tingling in the hands, feet, lips or tongue | • feeling irritable |
| • lightheadedness | • abnormal behavior |
| • trouble concentrating | • walking unsteady |
| • headache | • personality changes |

Humulin R U-500 can cause low blood sugar (hypoglycemia) that is severe and that can last a long time.

- Severe low blood sugar can cause you to become confused, pass out (become unconscious), have seizures or coma, and could cause death.

Talk to your healthcare provider about how to tell if you have low blood sugar and what to do if this happens while taking Humulin R U-500. Know your symptoms of low blood sugar. Follow your healthcare provider’s instructions for treating your low blood sugar.

Tell your healthcare provider if low blood sugar is a problem for you. Your healthcare provider may need to change the amount of Humulin R U-500 that you take, change your meal plans or your exercise program to help you avoid low blood sugar.

- **Serious allergic reactions. Get medical help right away if you have any of these symptoms of a severe allergic reaction:**
 - rash all over your body
 - shortness of breath
 - trouble breathing (wheezing)
 - fast heart beat
 - sweating
 - feel faint
- **Low potassium (hypokalemia)** in your blood. Your healthcare provider may do blood tests to check you for low potassium.

Common side effects of Humulin R U-500 include:

- Skin thickening or pits at the injection site (lipodystrophy). Change (rotate) where you inject your insulin to help prevent these skin changes from happening. Do not inject insulin into this type of skin. **Do not inject into the exact same spot for each injection.**
- Injection site reactions (local allergic reaction). Symptoms may include: redness, swelling and itching at the injection site. Tell your healthcare provider if you have skin reactions that do not go away.

Humulin R U-500 may cause serious side effects, including:

- **swelling of your hands and feet**
- **heart failure.** Taking certain diabetes pills called thiazolidinediones or “TZDs” with Humulin R U-500 may cause heart failure in some people. This can happen even if you have never had heart failure or heart problems before. If you already have heart failure it may get worse while you take TZDs with Humulin R U-500. Your healthcare provider should monitor you closely while you are taking TZDs with Humulin R U-500. Tell your healthcare provider if you have any new or worse symptoms of heart failure including:
 - shortness of breath
 - swelling of your ankles or feet
 - sudden weight gain

Treatment with TZDs and Humulin R U-500 may need to be adjusted or stopped by your healthcare provider if you have new or worse heart failure.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all of the possible side effect of Humulin R U-500. For more information, ask your healthcare provider or pharmacist.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Humulin R U-500?

Unopened vials of Humulin R U-500:

- Keep unopened vials of Humulin R U-500 in a refrigerator at 36°F to 46°F (2°C to 8°C).
- Do not freeze. Do not use Humulin R U-500 if it has been frozen.
- Do not use Humulin R U-500 after the expiration date stamped on the label.

Opened (in-use) vial of Humulin R U-500:

- Keep opened vial of Humulin R U-500 in the refrigerator or at room temperature below 86°F (30°C).
- Keep Humulin R U-500 away from heat and direct sunlight.
- The opened vial must be used within 31 days of opening. Throw away any opened vial after 31 days of use, even if there is insulin left in the vial.
- Do not use Humulin R U-500 after the expiration date stamped on the label.

Keep Humulin R U-500 and all medicines out of the reach of children.

General Information about Humulin R U-500

Medicines are sometimes prescribed for purposes other than those listed in patient information leaflets. Do not use Humulin R U-500 for a condition for which it was not prescribed. Do not give Humulin R U-500 to other people, even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about Humulin R U-500. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about Humulin R U-500 that is written for healthcare professionals.

For more information about Humulin R U-500 call 1-800-545-5979 or go to www.lilly.com.

What are the ingredients in Humulin R U-500?

Active ingredient: human insulin rDNA origin

Inactive ingredients: glycerin, metacresol, zinc oxide, water for injection, sodium hydroxide or hydrochloric acid.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Marketed by: Lilly USA, LLC, Indianapolis, IN 46285, USA