

## INFORMATION FOR THE PHYSICIAN

**HUMULIN<sup>®</sup> R**  
**REGULAR**  
**U-500 (CONCENTRATED)**  
**INSULIN HUMAN INJECTION, USP**  
**(rDNA ORIGIN)**

## DESCRIPTION

Humulin R<sup>®</sup> 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<sub>257</sub>H<sub>383</sub>N<sub>65</sub>O<sub>77</sub>S<sub>6</sub> 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**

<b>Humulin R U-500 dose (units)</b>	<b>U-100 insulin syringe (unit markings)</b>	<b>Tuberculin syringe (volume in mL)</b>
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 40 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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