

Conversion Information for Humulin® R U-500 (Concentrated) Insulin Dose

Humulin R U-500 dose (units)	U-100 insulin syringe (unit markings)	Volumetric (tuberculin or allergy) syringe volume (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

Dosing Formulas

U-100 insulin syringe

Divide prescribed dose (actual units of Humulin R U-500) by 5 = unit markings in a U-100 insulin syringe

Volumetric (tuberculin or allergy) syringe

Divide prescribed dose (actual units of Humulin R U-500) by 500 = volume (mL) in a volumetric syringe

Indication for Humulin R U-500

- Humulin R U-500 (regular U-500 [Concentrated] insulin human injection, USP [rDNA origin]) 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.

Select Safety Information for Humulin R U-500

- Humulin R U-500 is contraindicated during episodes of hypoglycemia and in patients hypersensitive to Humulin R U-500 or any of its excipients.
- **Starting or changing insulin therapy should be done cautiously and only under medical supervision.**
- **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 can occur with concomitant use of TZDs and Humulin R U-500.

Please see Important Safety Information starting on page 2 and accompanying Patient Information and Full Prescribing Information.

Humulin® R
REGULAR U-500 (Concentrated)
insulin human injection, USP
(recombinant DNA origin)
500 units/mL



Important Safety Information for Humulin® R U-500

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

- **Starting or changing insulin therapy should be done cautiously and only under medical supervision.**
- 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 PPAR-gamma agonists, can cause dose-related fluid retention, particularly when used in combination with insulin, including Humulin R U-500. Fluid retention may lead to or exacerbate heart failure. Observe patients for signs and symptoms of heart failure and consider discontinuation or dose reduction of the PPAR-gamma agonist.

Precautions

- **Dosing Confusion/Dosing Errors:** Medication errors associated with Humulin R U-500 have occurred and resulted in hyperglycemia, hypoglycemia, or death. The majority of errors occurred due to errors in dispensing, prescribing, or administration.
 - 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.
 - 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 (ie, a U-100 insulin syringe or volumetric [tuberculin or allergy] syringe).
 - A majority of administration errors occurred due to dosing confusion when the Humulin R U-500 dose was prescribed in units or volume corresponding to a U-100 insulin syringe or volumetric 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.
 - A conversion chart should always be used when administering Humulin R U-500 doses with U-100 insulin syringes or volumetric syringes.
- **Hypoglycemia:** Hypoglycemia is the most common adverse reaction of all insulin therapies, including Humulin R U-500. Hypoglycemia may occur suddenly. Severe hypoglycemia may lead to unconsciousness, convulsions, temporary or permanent impairment of brain function, or death. 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 in patients with renal or hepatic impairment or if patients change their physical activity or their usual meal plan, or during times of illness, emotional disturbances, or other stresses. Concomitant oral antidiabetic treatment may need to be adjusted; however concomitant use is not recommended.
 - Any patient who requires Humulin R U-500 for control of diabetes should be under close observation until appropriate dosage is established. Insulin resistance may be transitory, and dosage requirements may change over time. Use caution in patients with hypoglycemia unawareness and in patients who may be predisposed to hypoglycemia. The patient's ability to concentrate and react may be impaired as a result of hypoglycemia. These abilities are especially important in 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. Severe sustained hyperglycemia may result in hyperosmolar coma or death.

(continued on next page)

Please see Important Safety Information continued on page 3 and accompanying Patient Information and Full Prescribing Information.

Important Safety Information for Humulin® R U-500, continued

- **Hypokalemia:** Insulin use can lead to hypokalemia, that left untreated may cause respiratory paralysis, ventricular arrhythmia, and death. Use caution in patients who may be at risk for hypokalemia (eg, 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. Localized reactions and generalized myalgias have been reported.
- **Renal or Hepatic Impairment:** Frequent glucose monitoring and insulin dose reduction may be required.
- **Drug Interactions:** Some medications may alter insulin requirements and the risk for hypoglycemia and hyperglycemia. Some medications may mask the signs of hypoglycemia in some patients. Therefore, insulin dose adjustment and particularly close monitoring may be required.
- **Pregnancy Category B:** There are no adequate and well-controlled clinical studies of the use of Humulin R U-500 in pregnant or nursing women or during labor and delivery.
- **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.
 - 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.
 - Hypoglycemia when using Humulin R U-500 can be prolonged and severe.
- **Additional adverse reactions include hypokalemia, lipodystrophy, local and systemic allergy, weight gain, and peripheral edema.**

Dosage and Administration

- The injection of Humulin R U-500 should be followed by a meal within approximately 30 minutes of administration.
- Humulin R U-500 should only be administered subcutaneously. Do not administer Humulin R U-500 intravenously or intramuscularly.
- **Do not mix Humulin R U-500 with other insulins in the same syringe.**

For more safety information, please see accompanying Patient Information and Full Prescribing Information.

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Humulin® R U-500 is available by prescription only.