HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use HUMULIN R U-500 safely and effectively. See full prescribing information for HUMULIN R U-500.

HUMULIN R U-500 (insulin human injection), for subcutaneous use
Initial U.S. Approval: 1994

RECENT MAJOR CHANGES

Dosage and Administration:

Delivery of HUMULIN R U-500 from HUMULIN R U-500 KwikPen (2.3) 12/2015

Warnings and Precautions:

Never Share a HUMULIN R U-500 KwikPen or Syringes Between Patients (5.2) 12/2015

INDICATIONS AND USAGE

HUMULIN® R U-500 is a concentrated human insulin indicated to improve glycemic control in adults and children with diabetes mellitus requiring more than 200 units of insulin per day. (1)

Limitation of Use: The safety and efficacy of HUMULIN R U-500 used in combination with other insulins has not been determined. The safety and efficacy of HUMULIN R U-500 delivered by continuous subcutaneous infusion has not been determined. (1.1)

DOSAGE AND ADMINISTRATION

- Adhere to administration instructions to reduce the risk of dosing errors. (2.1, 2.3, 2.4, 5.1)
- Individualize dose of HUMULIN R U-500 based on metabolic needs, blood glucose monitoring results and glycemic control goal. (2.2)
- Administer HUMULIN R U-500 subcutaneously two or three times daily 30 minutes before a meal. Rotate injection sites to reduce the risk of lipodystrophy. (2.1, 2.2)
- Do NOT mix HUMULIN R U-500 with other insulins. (2.1)
- Do NOT administer HUMULIN R U-500 intravenously or intramuscularly.
- Do NOT perform dose conversion when using the HUMULIN R U-500 KwikPen. The dose window of the HUMULIN R U-500 KwikPen shows the number of units of HUMULIN R U-500 to be injected and NO dose conversion is required. Do NOT transfer HUMULIN R U-500 from the HUMULIN R U-500 KwikPen into a syringe. (2.3)
- CONVERT the prescribed dose of HUMULIN R U-500 into a “unit” or “volume” mark when using the vial presentation and a U-100 or a tuberculin syringe device to deliver HUMULIN R U-500. (2.4)

DOSAGE FORMS AND STRENGTHS

HUMULIN R U-500 (500 units per mL) is available in a colorless solution as: (3)

- 3 mL HUMULIN® R U-500 KwikPen® (prefilled, 1,500 units of insulin)
- 20 mL vial (containing 10,000 units of insulin)

CONTRAINDICATIONS

- Do not use during episodes of hypoglycemia. (4)
- Do not use in patients with hypersensitivity to HUMULIN R U-500 or any of its excipients. (4)

WARNINGS AND PRECAUTIONS

- *Hyperglycemia, Hypoglycemia or Death due to Dosing Errors with Vial Presentation:* Can be life-threatening. Overdose has occurred as a result of dispensing, prescribing or administration errors. Attention to details at all levels is required to prevent these errors. (2.1, 2.3, 2.4, 5.1)
- Never share a HUMULIN R U-500 KwikPen or syringe between patients, even if the needle is changed. (5.2)
- *Hyper- or Hypoglycemia with Changes in Insulin Regimen:* Carry out under close medical supervision and increase frequency of blood glucose monitoring. (5.3)
- *Hypoglycemia:* May be life-threatening. Increase monitoring with changes to: insulin dosage, co-administered glucose lowering medications, meal pattern, physical activity; and in patients with renal impairment or hepatic impairment or hypoglycemia unawareness. (5.4)
- *Hypersensitivity Reactions:* Severe, life-threatening, generalized allergy, including anaphylaxis, can occur. Discontinue HUMULIN R U-500, monitor, and treat if indicated. (5.5)
- *Hypokalemia:* May be life-threatening. Monitor potassium levels in patients at risk for hypokalemia and treat if indicated. (5.6)
- *Fluid Retention and Heart Failure with Concomitant Use of Thiazolidinediones (TZDs):* Observe for signs and symptoms of heart failure; consider dosage reduction or discontinuation if heart failure occurs. (5.7)

ADVERSE REACTIONS

Adverse reactions associated with HUMULIN R U-500 include hypoglycemia, allergic reactions, injection site reactions, lipodystrophy, pruritus, and rash. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-LillyRx (1-800-545-5979) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Certain drugs may affect glucose metabolism and may necessitate insulin dose adjustment. (7.1, 7.2, 7.3)
- The signs of hypoglycemia may be reduced or absent in patients taking anti-adrenergic drugs (e.g., beta-blockers, clonidine, guanethidine, and reserpine). (7.3, 7.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 12/2015

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

HUMULIN R U-500 is a concentrated human insulin indicated to improve glycemic control in adult and pediatric patients with diabetes mellitus requiring more than 200 units of insulin per day.

1.1 Limitation of Use

The safety and efficacy of HUMULIN R U-500 used in combination with other insulins has not been determined.

The safety and efficacy of HUMULIN R U-500 delivered by continuous subcutaneous infusion has not been determined.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

- Prescribe HUMULIN R U-500 ONLY to patients who require more than 200 units of insulin per day.
- Train patients on proper use and injection technique before initiating HUMULIN R U-500. Training reduces the risk of administration errors such as needle sticks and dosing errors.
- To avoid serious dosing errors for patients using the vial presentation, determine the type of syringe that the patient will use to deliver the prescribed dose of HUMULIN R U-500, instruct the patient on how to correctly draw the prescribed dose of HUMULIN R U-500 into the particular syringe, and confirm that the patient has understood these instructions and can correctly draw the prescribed dose of HUMULIN R U-500 with their syringe *[see Dosage and Administration (2.4) and Warnings and Precautions (5.1)]*.
- Instruct patients to always check the insulin label before administration to confirm the correct insulin product is being used *[see Warnings and Precautions (5.1)]*.
- Inspect HUMULIN R U-500 visually for particulate matter and discoloration. Only use HUMULIN R U-500 if the solution appears clear and colorless.
- Instruct patients to inject HUMULIN R U-500 subcutaneously into the thigh, upper arm, abdomen, or buttocks.
- Rotate injection sites within the same region from one injection to the next to reduce the risk of lipodystrophy *[see Adverse Reactions (6)]*.
- DO NOT administer HUMULIN R U-500 intravenously or intramuscularly.
- DO NOT dilute or mix HUMULIN R U-500 with any other insulin products or solutions.

2.2 Dosing Instructions

- Instruct patients to inject HUMULIN R U-500 subcutaneously usually two or three times daily approximately 30 minutes before meals.
- Individualize and titrate the dosage of HUMULIN R U-500 based on the patient’s metabolic needs, blood glucose monitoring results, and glycemic control goal.
- Dosage adjustments may be needed with changes in physical activity, changes in meal patterns (i.e., macronutrient content or timing of food intake), changes in renal or hepatic function, changes in medications or during acute illness to minimize the risk of hypoglycemia or hyperglycemia *[see Warnings and Precautions (5.3)]*.

2.3 Delivery of HUMULIN R U-500 using the HUMULIN R U-500 Disposable Prefilled KwikPen Device

- DO NOT perform dose conversion when using the HUMULIN R U-500 KwikPen. **The dose window of the HUMULIN R U-500 KwikPen shows the number of units of HUMULIN R U-500 to be injected and NO dose conversion is required.**

- DO NOT transfer HUMULIN R U-500 from the HUMULIN R U-500 KwikPen into a syringe for administration as overdose and severe hypoglycemia can occur *[see Warnings and Precautions (5.4)]*.
- The HUMULIN R U-500 KwikPen is for single patient use only *[see Warnings and Precautions (5.2)]*.

2.4 Delivery of HUMULIN R U-500 using a U-100 Insulin Syringe or a Tuberculin Syringe

- U-100 insulin and tuberculin syringes are not scaled to measure HUMULIN R U-500 insulin. When using a U-100 insulin syringe or a tuberculin syringe to deliver HUMULIN U-500, **a conversion step is REQUIRED to ensure the correct amount of HUMULIN R U-500 is drawn up in the syringe.** Failure to follow this conversion step will result in failure to draw up the correct amount of HUMULIN R U-500 in the syringe and will result in serious dosing errors *[see Warnings and Precautions (5.1)]*.
- Markings on the U-100 syringe refer to units of less concentrated insulin products (i.e., U-100 insulin products) **and NOT units of HUMULIN R U-500**. If U-100 insulin syringes are used, prescribers or healthcare workers **MUST CONVERT** the prescribed dose of HUMULIN R U-500 into a U-100 insulin syringe "unit marking" to determine the correct amount of HUMULIN R U-500 to draw up in the syringe. Prescribers or healthcare workers **MUST DETERMINE** that patients can draw up the correct amount of HUMULIN R U-500 in the syringe before prescribing and dispensing.
  - **To convert from the HUMULIN R U-500 prescribed dose to a U-100 insulin syringe "unit marking"**, divide the prescribed dose of HUMULIN R U-500 by 5. The resulting number is the "unit marking" on a U-100 insulin syringe to which the patient should draw up HUMULIN R U-500. For example, if a patient is prescribed 100 units of HUMULIN R U-500, then the patient should draw up HUMULIN R U-500 to the 20 "unit mark" on a U-100 insulin syringe (i.e., 100 divided by 5).
- Markings on the tuberculin syringe refer to volume (mL) and **NOT units of HUMULIN R U-500.** If tuberculin syringes are used, prescribers or healthcare workers **MUST CONVERT** the prescribed dose of HUMULIN R U-500 into a tuberculin syringe "volume marking" in mL to determine the correct amount of HUMULIN R U-500 to draw up in the syringe. Prescribers or healthcare workers **MUST DETERMINE** that patients can draw up the correct amount of HUMULIN R U-500 in the syringe before prescribing and dispensing.
- **To convert from the HUMULIN R U-500 prescribed dose to a tuberculin syringe "volume marking" in mL**, divide the prescribed dose of HUMULIN R U-500 by 500. The resulting number is the "volume (mL) marking" on a tuberculin syringe to which the patient should draw up HUMULIN R U-500. For example, if a patient is prescribed 100 units of HUMULIN R U-500, then the patient should draw up HUMULIN R U-500 to the 0.2 mL "volume mark" on a tuberculin syringe (i.e., 100 divided by 500).

Table 1: Examples of prescribed doses of HUMULIN R U-500 converted to amount of HUMULIN R U-500 to draw up in a U-100 insulin syringe or a tuberculin syringe for delivery of HUMULIN R U-500 using these devices

HUMULIN R U-500 dose prescribed (units of insulin)	**Delivery Using a U-100 insulin syringe** **Amount of HUMULIN R U-500 to draw up in the syringe in "unit marking"**	**Delivery Using a Tuberculin syringe** **Amount of HUMULIN R U-500 to draw up in the syringe in "volume marking"**
	Conversion: Divide prescribed dose by 5	Conversion: Divide prescribed dose by 500
25 Units	Draw to the 5 unit mark on syringe	Draw to the 0.05 mL mark on syringe
50 Units	Draw to the 10 unit mark on syringe	Draw to the 0.1 mL mark on syringe
75 Units	Draw to the 15 unit mark on syringe	Draw to the 0.15 mL mark on syringe
100 Units	Draw to the 20 unit mark on syringe	Draw to the 0.2 mL mark on syringe
125 Units	Draw to the 25 unit mark on syringe	Draw to the 0.25 mL mark on syringe
150 Units	Draw to the 30 unit mark on syringe	Draw to the 0.3 mL mark on syringe
175 Units	Draw to the 35 unit mark on syringe	Draw to the 0.35 mL mark on syringe
200 Units	Draw to the 40 unit mark on syringe	Draw to the 0.4 mL mark on syringe
225 Units	Draw to the 45 unit mark on syringe	Draw to the 0.45 mL mark on syringe
250 Units	Draw to the 50 unit mark on syringe	Draw to the 0.5 mL mark on syringe
…	…	…
500 Units	Draw to the 100 unit mark on syringe	Draw to the 1.0 mL mark on syringe

3 DOSAGE FORMS AND STRENGTHS

HUMULIN R U-500 (500 units per mL) is available in a colorless solution as:

- 3 mL HUMULIN R U-500 KwikPen (prefilled, 1,500 units of insulin)
- 20 mL vial (containing 10,000 units of insulin)

4 CONTRAINDICATIONS

HUMULIN R U-500 is contraindicated:

- During episodes of hypoglycemia
- In patients who are hypersensitive to HUMULIN R U-500 or any of its excipients.

5 WARNINGS AND PRECAUTIONS

5.1 Hyperglycemia, Hypoglycemia or Death due to Dosing Errors with the Vial Presentation

Medication errors associated with the HUMULIN R U-500 vial presentation 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 details at all levels may prevent these errors.

Dispensing Errors

Instruct patients to always inspect insulin vials to confirm that the correct insulin is dispensed including the correct insulin brand and concentration.

The HUMULIN R U-500 vial, which contains 20 mL, has a band of diagonal brown stripes. “U-500” is also highlighted in red on the HUMULIN R U-500 vial label.

Prescribing Errors

When using a U-100 insulin syringe or tuberculin syringe, express the prescribed dose of HUMULIN R U-500 in units of insulin along with the appropriate corresponding markings on the syringe the patient is using *[see Dosage and Administration (2.4)]*.

Administration Errors

Instruct patients to always check the insulin label before each injection.

A majority of the medication errors with HUMULIN R U-500 vial presentation 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. Adhere to administration and conversion instructions *[see Dosage and Administration (2.1, 2.4)]*.

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.

Conversion instructions are provided and should always be used when administering HUMULIN R U-500 doses with U-100 insulin syringes or 1 mL tuberculin syringes *[see Dosage and Administration (2.4)]*.

5.2 Never Share a HUMULIN R U-500 KwikPen or Syringe Between Patients

HUMULIN R U-500 KwikPens should never be shared between patients, even if the needle is changed. Patients using HUMULIN R U-500 vials should never share needles or syringes with another person. Sharing poses a risk for transmission of blood-borne pathogens.

5.3 Hyperglycemia or Hypoglycemia with Changes in Insulin Regimen

Changes in insulin, manufacturer, type, or method of administration may affect glycemic control and predispose to hypoglycemia or hyperglycemia. These changes should be made cautiously and only under medical supervision and the frequency of blood glucose monitoring should be increased. For patients with type 2 diabetes, adjustments in concomitant oral anti-diabetic treatment may be needed.

5.4 Hypoglycemia

Hypoglycemia is the most common adverse reaction associated with insulin, including HUMULIN R U-500. Severe hypoglycemia can cause seizures, may be life-threatening or cause death. Severe hypoglycemia may develop as long as 18 to 24 hours after an injection of HUMULIN R U-500. Hypoglycemia can impair concentration ability and reaction time; this may place an individual and others at risk in situations where these abilities are important (e.g., driving, or operating other machinery). Hypoglycemia can happen suddenly and symptoms may differ in each individual and change over time in the same individual.

Symptomatic awareness of hypoglycemia may be less pronounced in patients with longstanding diabetes, in patients with diabetic nerve disease, in patients using medications that block the sympathetic nervous system (e.g., beta-blockers) *[see Drug Interactions (7.3, 7.4)]*, or in patients who experience recurrent hypoglycemia.

Risk Factors for Hypoglycemia

The timing of hypoglycemia usually reflects the time-action profile of the administered insulin formulation. As with all insulin preparations, the glucose lowering effect time course of HUMULIN R U-500 may vary in different individuals or at different times in the same individual and depends on many conditions, including the area of injection as well as the injection site blood supply and temperature. Other factors which may increase the risk of hypoglycemia include changes in meal pattern (e.g., macronutrient content or timing of meals), changes in level of physical activity, or changes to co-administered medication *[see Drug Interactions (7.1, 7.2, 7.3, 7.4)]*. Patients with renal or hepatic impairment may be at higher risk of hypoglycemia *[see Use in Specific Populations (8.6, 8.7)]*.

Risk Mitigation Strategies for Hypoglycemia

Patients and caregivers must be educated to recognize and manage hypoglycemia. Self-monitoring of blood glucose plays an essential role in the prevention and management of hypoglycemia. In patients at higher risk for hypoglycemia and patients who have reduced symptomatic awareness of hypoglycemia, increased frequency of blood glucose monitoring is recommended. To minimize the risk of hypoglycemia do not administer HUMULIN R U-500 intravenously, intramuscularly or in an insulin pump or dilute or mix HUMULIN R U-500 with any other insulin products or solutions *[see Dosage and Administration (2.1)]*.

5.5 Hypersensitivity and Allergic Reactions

Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products, including HUMULIN R U-500 *[see Adverse Reactions (6)]*. If hypersensitivity reactions occur, discontinue HUMULIN R U-500; treat per standard of care and monitor until symptoms and signs resolve *[See Adverse Reactions (6)]*.

5.6 Hypokalemia

All insulin products, including HUMULIN R U-500, cause a shift in potassium from the extracellular to intracellular space, possibly leading to hypokalemia. Untreated hypokalemia 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).

5.7 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.

6 ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere:

- Hypoglycemia *[see Warnings and Precautions (5.4)]*.
- Hypokalemia *[see Warnings and Precautions (5.6)]*.

The following additional adverse reactions have been identified during post-approval use of HUMULIN R U-500. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or to establish a causal relationship to drug exposure.

Hypoglycemia

Hypoglycemia is the most commonly observed adverse reaction in patients using insulin, including HUMULIN R U-500 [*see Warnings and Precautions (5.4)*].

Allergic Reactions

Severe, life-threatening, generalized allergy, including anaphylaxis, generalized skin reactions, rash, angioedema, bronchospasm, hypotension, and shock may occur with any insulin, including HUMULIN R U-500 and may be life threatening [*see Warnings and Precautions (5.5)]*.

Lipodystrophy

Long-term use of insulin, including HUMULIN R U-500, can cause lipodystrophy at the site of repeated insulin injections. Lipodystrophy includes lipohypertrophy (thickening of adipose tissue) and lipoatrophy (thinning of adipose tissue) and may affect

insulin absorption. Rotate insulin injections sites within the same region to reduce the risk of lipodystrophy *[see Dosage and Administration (2.1)]*.

Injection Site Reactions

Patients taking HUMULIN R U-500 may experience injection site reactions, including injection site hematoma, pain, hemorrhage, erythema, nodules, swelling, discoloration, pruritus, warmth, and injection site mass.

Weight Gain

Weight gain can occur with insulin therapy, including HUMULIN R U-500, and has been attributed to the anabolic effects of insulin.

Peripheral Edema

Insulin, including HUMULIN R U-500, may cause sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

Immunogenicity

As with all therapeutic proteins, insulin administration may cause anti-insulin antibodies to form. The presence of antibodies that affect clinical efficacy may necessitate dose adjustments to correct for tendencies toward hyper- or hypoglycemia.

The incidence of antibody formation with HUMULIN R U-500 is unknown.

7 DRUG INTERACTIONS

7.1 Drugs That May Increase the Risk of Hypoglycemia

The risk of hypoglycemia associated with HUMULIN R U-500 use may be increased with antidiabetic agents, ACE inhibitors, angiotensin II receptor blocking agents, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, pentoxifylline, pramlintide, propoxyphene, salicylates, somatostatin analogs (e.g., octreotide), and sulfonamide antibiotics. Dose adjustment and increased frequency of glucose monitoring may be required when HUMULIN R U-500 is co-administered with these drugs.

7.2 Drugs That May Decrease the Blood Glucose Lowering Effect of HUMULIN R U-500

The glucose lowering effect of HUMULIN R U-500 may be decreased when co-administered with atypical antipsychotics (e.g., olanzapine and clozapine), corticosteroids, danazol, diuretics, estrogens, glucagon, isoniazid, niacin, oral contraceptives, phenothiazines, progestogens (e.g., in oral contraceptives), protease inhibitors, somatropin, sympathomimetic agents (e.g., albuterol, epinephrine, terbutaline) and thyroid hormones. Dose adjustment and increased frequency of glucose monitoring may be required when HUMULIN R U-500 is co-administered with these drugs.

7.3 Drugs That May Increase or Decrease the Blood Glucose Lowering Effect of HUMULIN R U-500

The glucose lowering effect of HUMULIN R U-500 may be increased or decreased when co-administered with alcohol, beta-blockers, clonidine, and lithium salts. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia. Dose adjustment and increased frequency of glucose monitoring may be required when HUMULIN R U-500 is co-administered with these drugs.

7.4 Drugs That May Affect Signs and Symptoms of Hypoglycemia

The signs and symptoms of hypoglycemia *[see Warnings and Precautions (5.4)]* may be blunted when beta-blockers, clonidine, guanethidine, and reserpine are co-administered with HUMULIN R U-500.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

Risk Summary

All pregnancies have a background risk of birth defects, loss, or other adverse outcome regardless of drug exposure. This background risk is increased in pregnancies complicated by hyperglycemia and may be decreased with good metabolic control. It is essential for patients with diabetes or history of gestational diabetes to maintain good metabolic control before conception and throughout pregnancy. In patients with diabetes or gestational diabetes, insulin requirements may decrease during the first trimester, generally increase during the second and third trimesters, and rapidly decline after delivery. Careful monitoring of glucose control is

essential in these patients. Therefore, female patients should be advised to tell their physicians if they intend to become, or if they become pregnant while taking HUMULIN R U-500.

Human Data

While there are no adequate and well-controlled studies in pregnant women, evidence from published literature suggests that good glycemic control in patients with diabetes during pregnancy provides significant maternal and fetal benefits.

Animal Data

Reproduction and fertility studies were not performed in animals.

8.3 Nursing Mothers

Endogenous insulin is present in human milk. Insulin orally ingested is degraded in the gastrointestinal tract. No adverse reactions associated with infant exposure to insulin through the consumption of human milk have been reported. In a study of eight preterm infants between 26 to 30 weeks gestation, enteral administration of biosynthetic human insulin did not result in hypoglycemia. Good glucose control supports lactation in patients with diabetes. Women with diabetes who are lactating may require adjustments in their insulin dose.

8.4 Pediatric Use

There are no well-controlled studies of use of HUMULIN R U-500 in children. Standard precautions as applied to use of HUMULIN R U-500 in adults are appropriate for use in children. As in adults, the dosage of HUMULIN R U-500 in pediatric patients must be individualized based on metabolic needs and results of frequent monitoring of blood glucose.

8.5 Geriatric Use

The effect of age on the pharmacokinetics and pharmacodynamics of HUMULIN R U-500 has not been studied. Caution should be exercised when HUMULIN R U-500 is administered to geriatric patients. In elderly patients with diabetes, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemia.

8.6 Renal Impairment

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

8.7 Hepatic Impairment

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

10 OVERDOSAGE

Excess insulin administration may cause hypoglycemia and hypokalemia. 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.

11 DESCRIPTION

HUMULIN R U-500 (insulin human injection, USP) is a human insulin solution used to lower blood glucose. Human insulin is produced by recombinant DNA technology utilizing a non-pathogenic laboratory strain of *Escherichia coli*. HUMULIN R has the empirical formula $C_{257}H_{383}N_{65}O_{77}S_6$ with a molecular weight of 5808.

HUMULIN R U-500 is a sterile, aqueous, and colorless solution. HUMULIN R U-500 contains 500 units of insulin in each milliliter. Each milliliter of HUMULIN R U-500 also contains glycerin 16 mg, metacresol 2.5 mg, zinc oxide to supplement the endogenous zinc to obtain a total zinc content of 0.017 mg/100 units, and Water for Injection. Sodium hydroxide and hydrochloric acid may be added during manufacture to adjust the pH.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Regulation of glucose metabolism is the primary activity of insulins, including HUMULIN R U-500. Insulins lower blood glucose by stimulating peripheral glucose uptake by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulins inhibit lipolysis and proteolysis, and enhance protein synthesis.

12.2 Pharmacodynamics

In a euglycemic clamp study of 24 healthy obese subjects (BMI=30-39 kg/m^2), single doses of HUMULIN R U-500 at 50 units (0.4-0.6 unit/kg) and 100 units (0.8-1.3 unit/kg) resulted in a mean time of onset of action of less than 15 minutes at both doses and a mean duration of action of 21 hours (range 13-24 hours). The time action characteristics reflect both prandial and basal activity, consistent with clinical experience. This effect has been attributed to the high concentration of the preparation.

Figure 1 should be considered a representative example since the time course of action of insulin may vary in different individuals or within the same individual. The rate of insulin absorption and consequently the onset of activity is known to be affected by the site of injection, exercise, and other variables *[see Warnings and Precautions (5.3)]*.

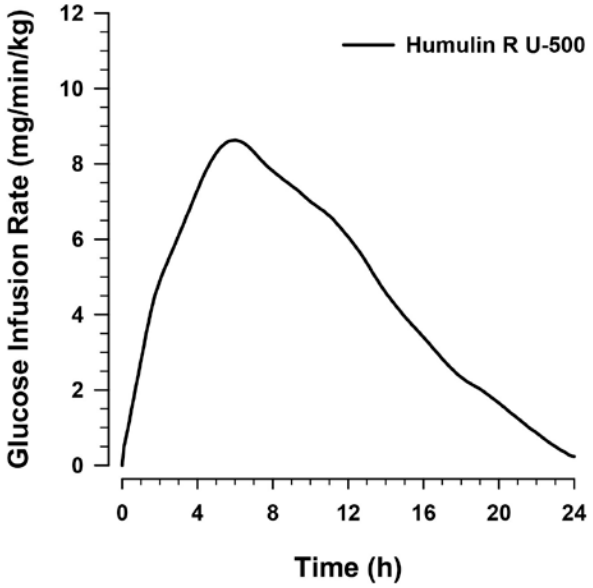

Figure 1: Mean Insulin Activity Versus Time Profiles After Subcutaneous Injection of a 100 U Dose of HUMULIN R U-500 in Healthy Obese Subjects

12.3 Pharmacokinetics

Absorption — In a euglycemic clamp study of 24 healthy obese subjects, the median peak insulin level occurred between 4 hours (50 unit dose) and 8 hours (100 unit dose) with a range of 0.5-8 hours.

Metabolism — The uptake and degradation of insulin occurs predominantly in liver, kidney, muscle, and adipocytes, with the liver being the major organ involved in the clearance of insulin.

Elimination — Mean apparent half-life after subcutaneous administration of single doses of 50 units and 100 units to healthy obese subjects (N≥21) was approximately 4.5 hours (range=1.9-10 hours) for HUMULIN R U-500.

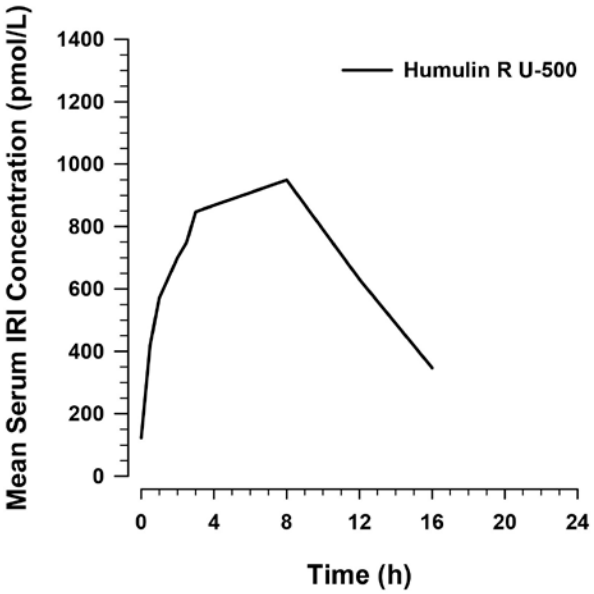

Figure 2: Mean Serum Insulin Concentrations Versus Time After Subcutaneous Injection of a 100 U Dose of HUMULIN R U-500 Healthy Obese Subjects

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity and fertility studies were not performed with HUMULIN R U-500 in animals. Biosynthetic human insulin was not genotoxic in the *in vivo* sister chromatid exchange assay and the *in vitro* gradient plate and unscheduled DNA synthesis assays.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

HUMULIN R U-500 (500 units per mL) is available as:

2 x 3 mL HUMULIN R U-500 KwikPen (prefilled)	NDC 0002-8824-27
20 mL vials	NDC 0002-8501-01

16.2 Storage and Handling

Protect from heat and light. Do not freeze. Do not use HUMULIN R U-500 after the expiration date printed on the label or if it has been frozen. Do not shake the vial.

<u>Not In Use (Unopened) HUMULIN R U-500 KwikPen</u>

Refrigerated

Store in a refrigerator (36° to 46°F [2° to 8°C]), but not in the freezer. Do not use if it has been frozen.

Room Temperature

If stored at room temperature, below 86°F (30°C) the pen must be discarded after 28 days.

<u>In-Use (Opened) HUMULIN R U-500 KwikPen</u>

Refrigerated

Do NOT store in a refrigerator.

Room Temperature

Store at room temperature, below 86°F (30°C) and the pen must be discarded after 28 days, even if the pen still contains HUMULIN R U-500. See storage table below:

<u>Not In Use (Unopened) HUMULIN R U-500 Vials</u>

Refrigerated

Store in a refrigerator (36° to 46°F [2° to 8°C]), but not in the freezer. Do not use if it has been frozen.

Room Temperature

If stored at room temperature, below 86°F (30°C) the vial must be discarded after 40 days.

In-Use (Opened) HUMULIN R U-500 Vials

Refrigerated

Store in a refrigerator (36° to 46°F [2° to 8°C]), but not in the freezer. Do not use if it has been frozen. Vials must be used within 40 days or be discarded, even if they still contain HUMULIN R U-500.

Room Temperature

If stored at room temperature, below 86°F (30°C) the vial must be discarded after 40 days, even if the vial still contains HUMULIN R U-500. See storage table below:

	Not In-Use (Unopened) Refrigerated	**In-Use (Opened)**
3 mL HUMULIN R U-500 KwikPen (prefilled)	Until expiration date	28 days, room temperature. **Do not refrigerate.**
20 mL vial	Until expiration date	40 days, refrigerated or room temperature

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling.

Patients should be counseled that HUMULIN R U-500 is a 5-times concentrated insulin product. Extreme caution must be observed in the measurement of dosage because inadvertent overdose may result in serious adverse reaction or life-threatening hypoglycemia. Accidental mix-ups between HUMULIN R U-500 and other insulins have been reported. To avoid medication errors between HUMULIN R U-500 and other insulins, patients should be instructed to always check the insulin label before each injection *[see Warnings and Precautions (5.1)]*.

If using the HUMULIN R U-500 KwikPen, patients should be counseled to dial and dose the prescribed number of units of insulin (no dose conversion is required) *[see Dosage and Administration (2.3)]*.

When using HUMULIN R U-500 from a vial, patients should be counseled to calculate the conversion and measure the amount of delivered insulin using the unit of measurement that corresponds to the type of syringe being used *[see Dosage and Administration (2.4)]*.

Patients should be instructed on self-management procedures including glucose monitoring, proper injection technique, and management of hypoglycemia and hyperglycemia, especially at initiation of HUMULIN R U-500 therapy. Patients must be instructed on handling of special situations such as intercurrent conditions (illness, stress, or emotional disturbances), an inadequate or skipped insulin dose, inadvertent administration of an increased insulin dose, inadequate food intake, and skipped meals. Refer patients to the HUMULIN R U-500 Patient Information Leaflet for additional information *[see Warnings and Precautions (5)]*.

Women with diabetes should be advised to inform their doctor if they are pregnant or are contemplating pregnancy.

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 dilute or mix HUMULIN R U-500 with any other insulin products or solutions *[see Dosage and Administration (2.1)]*.

Literature Revised: December 2015

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

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Patient Information
Humulin® (HU-mu-lin) R U-500
insulin human injection
(500 units per mL)

Do not share your Humulin R U-500 KwikPen or syringes with other people, even if the needle has been changed. You may give other people a serious infection or get a serious infection from them.

What is Humulin R U-500?

- Humulin R U-500 is a man-made insulin that is used to control high blood sugar in adults and children with diabetes mellitus who need more than 200 units of insulin in a day.
- Humulin R U-500 contains **5** times as much insulin (500 units/mL) in 1 mL as standard insulin (100 units/mL).
- 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 you:

- are having an episode of low blood sugar (hypoglycemia).
- have an allergy to human insulin or any of the ingredients in Humulin R U-500. See the end of this Patient Information leaflet for a complete list of ingredients in Humulin R U-500.

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

Before using Humulin R U-500, tell your healthcare provider about all your medical conditions including, if you:

- have liver or kidney problems.
- take other medicines, especially ones 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, planning to become pregnant, or breast-feeding. It is not known if Humulin R U-500 will harm your unborn or breastfeeding baby.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, or herbal supplements.

Before you start using Humulin R U-500, talk to your healthcare provider about low blood sugar and how to manage it.

How should I use Humulin R U-500?

- Read the detailed **Instructions for Use** that come with your Humulin R U-500.
- Use Humulin R U-500 exactly as your healthcare provider tells you to. Your healthcare provider should tell you how much Humulin R U-500 to use and when to use it.
- Know the amount of Humulin R U-500 you use. **Do not** change the amount of Humulin R U-500 you use unless your healthcare provider tells you to.
- Check your insulin label each time you give your injection to make sure you are using the correct insulin.
- **When using the Humulin R U-500 KwikPen:** The Humulin R U-500 KwikPen is specially made to dial and deliver doses of Humulin R U-500 insulin. **Do not** use a syringe to remove Humulin R U-500 from your Humulin R U-500 KwikPen. The markings on a syringe will not measure your dose correctly. A severe overdose can happen, causing low blood sugar, which may put your life in danger.
- **When using the Humulin R U-500 vial:** There are no special syringes to measure Humulin R U-500. Use a U-100 insulin syringe or tuberculin syringe as instructed by your healthcare provider. It is important that you use only the syringes that your healthcare provider tells you to use. 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). 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 drawn up into the syringe.
  - For 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.
  - For tuberculin syringes, your healthcare provider should explain how to use this syringe to give the prescribed dose with volume markings on the syringe.
- Use Humulin R U-500 **30 minutes** before eating a meal.
- Inject Humulin R U-500 under your skin (subcutaneously). **Do not** use Humulin R U-500 in an insulin pump or inject Humulin R U-500 into your vein (intravenously) or your muscle (intramuscularly).
- **Do not** mix Humulin R U-500 in the KwikPen or vial with any other type of insulin or liquid medicine.
- Change (rotate) your injection site with each dose.

- **Check your blood sugar levels.** Ask your healthcare provider what your blood sugars should be and when you should check your blood sugar levels.

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

Your dose of Humulin R U-500 may need to change because of:

- change in level of physical activity or exercise, weight gain or loss, increased stress, illness, change in diet, or because of other medicines you take.

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

While using Humulin R U-500 do not:

- drive or operate heavy machinery, until you know how Humulin R U-500 affects you.
- drink alcohol or use over-the-counter medicines that contain alcohol.

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

Humulin R U-500 may cause serious side effects that can lead to death, including:

- **low blood sugar (hypoglycemia).** Signs and symptoms of low blood sugar may include:
  - dizziness or lightheadedness, sweating, confusion, headache, blurred vision, slurred speech, shakiness, fast heartbeat, anxiety, irritability or mood changes, hunger.
  - 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.
- **severe allergic reaction (whole body reaction). Get medical help right away if you have any of these signs or symptoms of a severe allergic reaction:**
  - a rash over your whole body, have trouble breathing, a fast heartbeat, or sweating.
- **low potassium in your blood (hypokalemia)**.
- **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.

Get emergency medical help if you have:

- severe hypoglycemia needing hospitalization or emergency room care, and be sure to tell the hospital staff the units of Humulin R U-500 that your healthcare provider has prescribed for you.
- trouble breathing, shortness of breath, fast heartbeat, swelling of your face, tongue, or throat, sweating, extreme drowsiness, dizziness, confusion.

The most common side effects of Humulin R U-500 include:

- low blood sugar (hypoglycemia), allergic reactions including reactions at your injection site, skin thickening or pits at the injection site (lipodystrophy), itching, and rash.

These are not all of the possible side effects of Humulin R U-500. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General Information about the safe and effective use of Humulin R U-500

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. **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 Patient Information 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 pharmacist or healthcare provider for information about Humulin R U-500 that is written for healthcare professionals. For more information go to www.humulin.com or call 1-800-545-5979.

What are the ingredients in Humulin R U-500?

Active ingredient: human insulin

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

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

For more information about Humulin R U-500 go to www.humulin.com.

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This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: December 2015

Instructions for Use

HUMULIN® R U-500 KwikPen®

insulin human injection U-500 (500 units/mL, 3 mL pen)

Important:

- **Know your dose of HUMULIN R U-500 insulin.** The Pen delivers your dose in **insulin units**. Insulin units may **not be the same** as syringe markings. **Ask your health care provider what your dose should be for your Pen.**
- Your HUMULIN® R U-500 KwikPen® (Pen) works differently from other pens. It dials 5 insulin units with each click. **Do not count clicks of the dose knob to select your dose.** You may not get enough insulin or you may get too much insulin.
- **HUMULIN R U-500 is a concentrated insulin. Do not transfer HUMULIN R U-500 insulin from your Pen into a syringe. A severe overdose can happen, causing very low blood sugar, which may put your life in danger.**

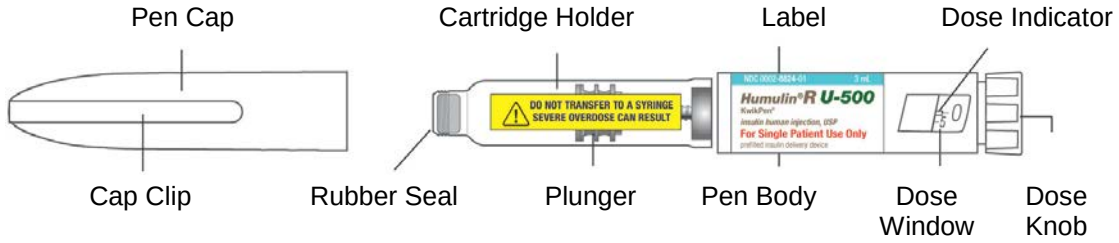
Read the Instructions for Use before you start taking HUMULIN R U-500 and each time you get another Pen. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

Do not share your HUMULIN R U-500 Pen with other people, even if the needle has been changed. You may give other people a serious infection or get a serious infection from them.

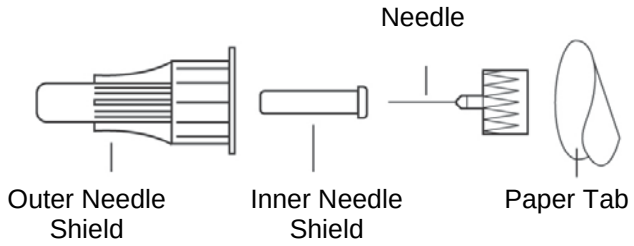
HUMULIN R U-500 KwikPen ("Pen") is a disposable prefilled pen containing 1500 units of HUMULIN R. You can give yourself more than 1 dose from the Pen. Each turn (click) of the Dose Knob dials 5 units of insulin. You can give from 5 to 300 units in a single injection. The plunger only moves a little with each injection, and you may not notice that it moves. The plunger will only reach the end of the cartridge when you have used all 1500 units in the Pen.

This Pen is not recommended for use by the blind or visually impaired without the help of someone trained to use the Pen.

KwikPen Parts



Pen Needle Parts (Needles Not Included)



Dose Knob Raised ridges on end

How to recognize your HUMULIN R U 500 KwikPen

- Pen color: Aqua
- Dose Knob: Aqua with raised ridges on the end
- Label: HUMULIN R U-500 and 500 units/mL in a green box

500 units/mL

Supplies needed to give your injection

- HUMULIN R U-500 KwikPen
- KwikPen compatible Needle (Becton, Dickinson and Company Pen Needles recommended)
- Alcohol swab

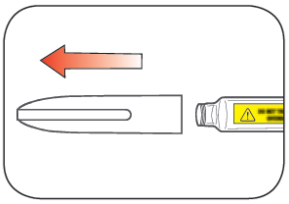
Preparing your Pen

- Wash your hands with soap and water.
- Check the Pen to make sure you are taking the right type of insulin. This is especially important if you use more than 1 type of insulin.
- **Do not** use your Pen past the expiration date printed on the Label or for more than 28 days after you first start using the Pen.
- **Always use a new Needle for each injection to help prevent infections and blocked Needles. Do not reuse or share your needles with other people. You may give other people a serious infection or get a serious infection from them.**

Step 1:

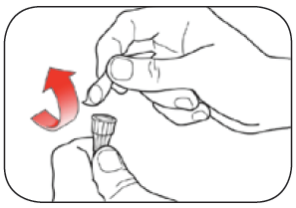
- Pull the Pen Cap straight off.
  - **Do not** remove the KwikPen Label.
- Wipe the Rubber Seal with an alcohol swab.

HUMULIN R U-500 should look clear and colorless. **Do not** use if it is cloudy, colored, or has particles or clumps in it.



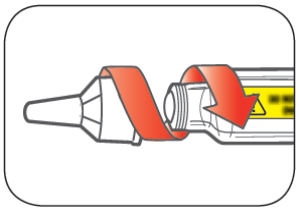
Step 2:

- Select a new Needle.
- Pull off the Paper Tab from the Outer Needle Shield.



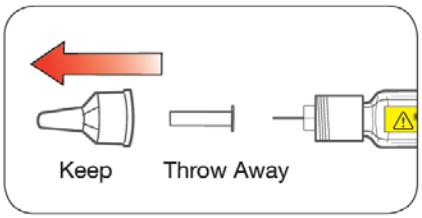
Step 3:

- Push the capped Needle straight onto the Pen and twist the Needle on until it is tight.



Step 4:

- Pull off the Outer Needle Shield. **Do not** throw it away.
- Pull off the Inner Needle Shield and throw it away.



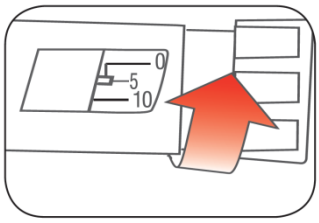
Priming your Pen

Prime before each injection.

- Priming your Pen means removing the air from the Needle and Cartridge that may collect during normal use and ensures that the Pen is working correctly.
- If you **do not** prime before each injection, you may get too much or too little insulin.

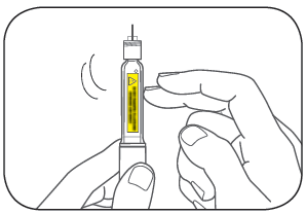
Step 5:

- To prime your pen, turn the Dose Knob to **select 5 units**.



Step 6:

- Hold your Pen with the Needle pointing up. Tap the Cartridge Holder gently to collect air bubbles at the top.



Step 7:

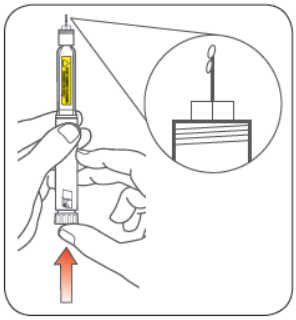
- Continue holding your Pen with Needle pointing up. Push the Dose Knob in until it stops, and "**0**" is seen in the Dose Window. Hold the Dose Knob in and **count to 5 slowly**.

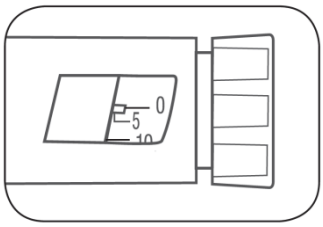
  You should see insulin at the tip of the Needle.

  – If you **do not** see insulin, repeat priming steps 5 to 7, no more than 8 times.

  – If you **still do not** see insulin, change the Needle and repeat priming steps 5 to 7.

Small air bubbles are normal and will not affect your dose.





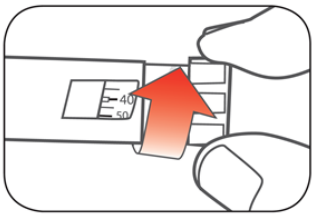
Selecting your dose

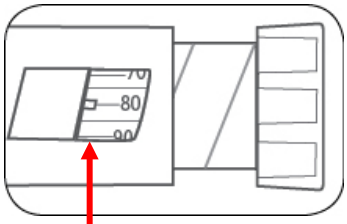
This Pen has been made to deliver the dose **in insulin units** that is shown in the Dose Window. Ask your healthcare provider what your dose should be for this Pen.

- You can give from 5 to 300 units in a single injection.
- If your dose is more than 300 units, you will need to give more than 1 injection.
  - If you need help with dividing up your dose the right way, ask your healthcare provider.
  - You must use a new Needle for each injection and repeat the priming step.

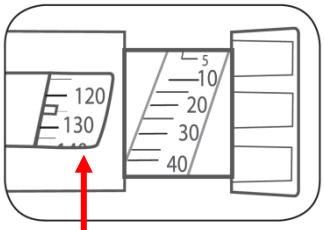
Step 8:

- Turn the Dose Knob to select the number of units you need to inject. The Dose Indicator should line up with your dose.
  - The Dose Knob clicks as you turn it. Each click of the Dose Knob dials **5 insulin units** at a time.
  - **Do not dial your dose by counting the clicks. You may dial the wrong dose. This may lead to you getting too much insulin or not enough insulin.**
  - The dose can be corrected by turning the Dose Knob in either direction until the correct dose lines up with the Dose Indicator.
  - The **even** numbers (for example, 80) are printed on the dial.
  - The **odd** numbers (for example, 125) are shown as lines between the even numbers.
- **Always check the number in the Dose Window to make sure you have dialed the correct dose.**





Example: 80 units shown in Dose Window



Example: 125 units shown in Dose Window

- The Pen will not let you dial more than the number of units left in the Pen.
- If your dose is more than the number of units left in the Pen, you may either:
  - inject the amount left in your Pen and then use a new Pen to give the rest of your dose,

    or
  - get a new Pen and inject your full dose.
- It is normal to see a small amount of insulin left in the Pen that you cannot inject. **Do not transfer this to a syringe. Severe overdose can happen.**

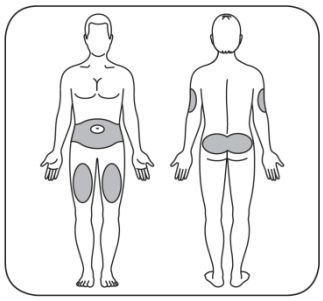
Giving your injection

- Inject your insulin as your healthcare provider has shown you.
- Change (rotate) your injection site for each injection.
- **Do not** try to change your dose while injecting.

Step 9:

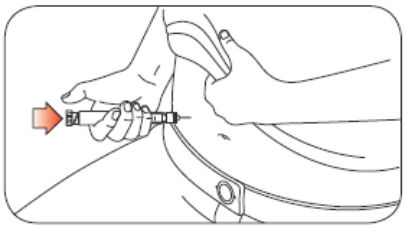
- Choose your injection site.

  HUMULIN is injected under the skin (subcutaneously) of your stomach area, buttocks, upper legs or upper arms.
- Wipe your skin with an alcohol swab, and let your skin dry before you inject your dose.



Step 10:

- Insert the Needle into your skin.
- Push the Dose Knob all the way in.



- Continue to hold the Dose Knob in and **slowly count to 5** before removing the Needle.

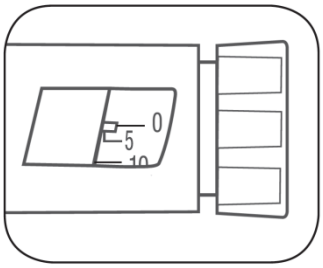
Do not try to inject your insulin by turning the Dose Knob. You will **not** receive your insulin by turning the Dose Knob.

Step 11:

- Pull the Needle out of your skin.
  - A drop of insulin at the Needle tip is normal. It will not affect your dose.
- Check the number in the Dose Window.
  - If you see "**0**" in the Dose Window, you have received the full amount you dialed.
  - If you do not see "**0**" in the Dose Window, **do not** redial. Insert the Needle into your skin and finish your injection.
  - If you **still** do not think you received the full amount you dialed for your injection, **do not start over or repeat your injection**. Monitor your blood glucose as instructed by your healthcare provider.

The Plunger only moves a little with each injection, and you may not notice that it moves.

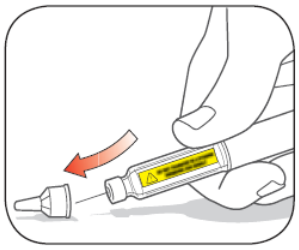
If you see blood after you take the Needle out of your skin, press the injection site lightly with a piece of gauze or an alcohol swab. **Do not** rub the area.



After your injection

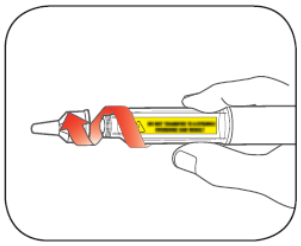
Step 12:

- Carefully replace the Outer Needle Shield.



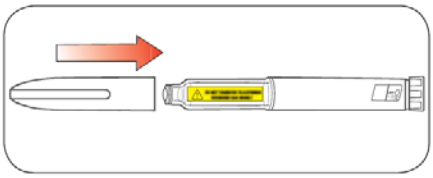
Step 13:

- Unscrew the capped Needle and throw it away (see **Disposing of Pens and Needles** section).
- **Do not** store the Pen with the Needle attached to prevent leaking, blocking the Needle, and air from entering the Pen.



Step 14:

- Replace the Pen Cap by lining up the Cap Clip with the Dose Indicator and pushing straight on.



Disposing of Pens and Needles

- Put your used Needles in a FDA-cleared sharps disposal container right away after use. **Do not** throw away (dispose of) loose Needles in your household trash.

- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
  - made of a heavy-duty plastic,
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
  - upright and stable during use,
  - leak-resistant, and
  - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal
- Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.
- The used Pen may be discarded in your household trash after you have removed the needle.

Storing your Pen

Unused Pens

- Store unused Pens in the refrigerator at 36°F to 46°F (2°C to 8°C).
- **Do not** freeze HUMULIN R U-500. **Do not** use if it has been frozen.
- Unused Pens may be used until the expiration date printed on the Label, if the Pen has been kept in the refrigerator.

In-use Pen

- Store the Pen you are currently using at room temperature up to 86°F (30°C). Keep away from heat and light.
- Throw away the Pen you are using after 28 days, even if it still has insulin left in it.

What you should know if you are switching to HUMULIN R U 500 KwikPen

Ask your healthcare provider what your dose should be for your Pen **in insulin units**. Always follow your healthcare provider's instructions for dosing.

If you are:	**It is important to know:**
Switching from HUMULIN R U-500 vial (and syringe)	Your Pen may measure your dose differently. The markings in the Dose Window may not be the same as the markings on the syringe you used in the past. **Ask your healthcare provider what dose in insulin units you should dial on your Pen.**
Switching from another type of insulin device or pen.	The HUMULIN R U-500 KwikPen is different from other pens. It dials **5 insulin units** with each click of the Dose Knob. **Do not select your dose by counting clicks. You may not get enough insulin or you may get too much insulin.**

General information about the safe and effective use of your Pen

- **Keep your Pen and Needles out of the sight and reach of children.**
- **Do not** use your Pen if any part looks broken or damaged.
- Always carry an extra Pen in case yours is lost or damaged.

Troubleshooting

- If you cannot remove the Pen Cap, gently twist the cap back and forth, and then pull the cap straight off.
- If it is hard to push the Dose Knob:
  - Pushing the Dose Knob more slowly will make it easier to inject.
  - Your Needle may be blocked. Put on a new Needle and prime the Pen.
  - You may have dust, food, or liquid inside the Pen. Throw the Pen away and get a new Pen.

If you have any questions or problems with your HUMULIN R U-500 KwikPen, contact Lilly at 1-800-LillyRx (1-800-545-5979) or call your healthcare provider for help. For more information on HUMULIN R U-500 KwikPen and insulin, go to www.humulin.com.

Scan this code to launch

www.humulin.com

These Instructions for Use have been approved by the U.S. Food and Drug Administration.

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Indianapolis, IN 46285, USA

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HUMULIN R U-500 KwikPen meets the current dose accuracy and functional requirements of ISO 11608-1:2014.

Document revision date: December 29, 2015

Lilly *(red script)*

INSTRUCTIONS FOR INSULIN VIAL USE

HUMULIN® (HU-mu-lin) R U-500

insulin human injection (500 units/mL, 20 mL vial)

Read the Instructions for Use before you start taking HUMULIN R U-500 and each time you get a new HUMULIN R U-500 vial. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

Do not share your syringes with other people, even if the needle has been changed. You may give other people a serious infection or get a serious infection from them.

Correct Syringe Type

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. Your healthcare provider should show you how to draw up HUMULIN R U-500 the right way.

- 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.

It is important to remember that the markings on the syringe do not match the HUMULIN R U-500 insulin dose. HUMULIN R U-500 (500 units/mL) is 5 times more concentrated than standard insulin (100 units/mL).

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).

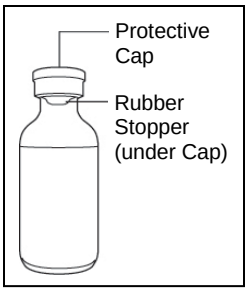
Make sure you know:

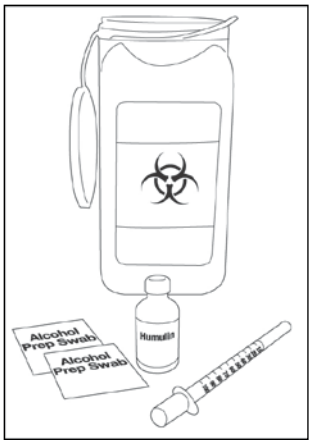
- **your prescribed dose of HUMULIN R U-500.**
- **which syringe to use and how to draw up the insulin to your prescribed dose.**

If you do not understand your dose, talk with your healthcare provider about the right way to measure and take your insulin dose.

Supplies need to give your injection

- a HUMULIN R U-500 vial
- a U-100 insulin syringe or a tuberculin syringe
- 2 alcohol swabs
- 1 sharps container for throwing away used needles and syringes. See “**Disposing of used needles and syringes”** at the end of these instructions.





Preparing the Dose

- Wash your hands with soap and water.
- **Check the HUMULIN R U-500 label to make sure you are taking the right type of insulin. This is especially important if you use more than 1 type of insulin.**• **Do not** use HUMULIN R U-500 past the expiration date printed on the label or 40 days after you first use it.
- **Always use a new syringe or needle for each injection to help make sure the syringe needle is sterile and to prevent blocked needles. Do not reuse or share your syringes or needles with other people. You may give other people a serious infection or get a serious infection from them.**

Step 1:

Check the insulin. HUMULIN R U-500 solution should look clear and colorless. **Do not** use HUMULIN R U-500 if it looks cloudy, thick, slightly colored, or if you see particles in the solution. **Do not** shake.

Step 2:

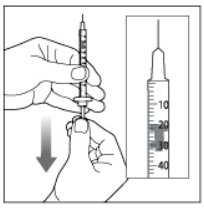
If you are using a new HUMULIN R U-500 vial, flip off the plastic protective cap, but **do not** remove the rubber stopper.

Step 3:

Wipe the rubber stopper of the vial with an alcohol swab.

Step 4:

Hold the syringe with the needle pointing up. Pull down on the plunger until the tip of the plunger reaches the line for the number of unit markings or volume markings (mL) for your prescribed HUMULIN R U-500 dose.



Plunger is shown at the 20 unit marking

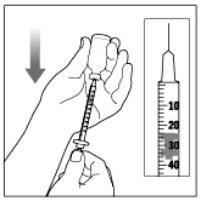
(U-100 insulin syringe)

Step 5:

Push the needle through the rubber stopper of the HUMULIN R U-500 vial and push the plunger all the way in. This puts air into the vial.

Step 6:

Turn the HUMULIN R U-500 vial and syringe upside down. Hold the vial and syringe firmly in one hand. Slowly pull the plunger down until the tip of the plunger is a few markings past the line for the number of unit markings or volume markings (mL)] for your prescribed dose.

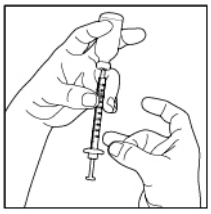


Plunger is shown at the 24 unit marking.

(U-100 insulin syringe)

Step 7:

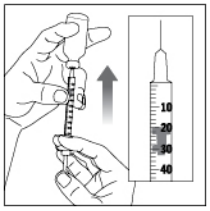
If there are air bubbles in the syringe, tap the syringe gently a few times to let any air bubbles rise to the top.



Step 8:

Slowly push the plunger up until the tip reaches the line for your prescribed dose.

Check to make sure that you have the right dose.

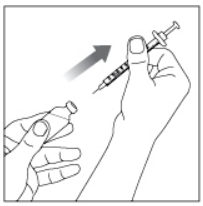


Plunger is shown at the 20 unit marking

(U-100 insulin syringe)

Step 9:

Pull the syringe out of the vial's rubber stopper.



Giving your HUMULIN R U-500 Injection

- Inject your insulin exactly as your healthcare provider has shown you
- Change (rotate) your injection site for each injection

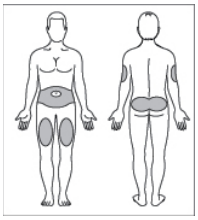
Step 10:

Choose your injection site.

HUMULIN R U-500 is injected under the skin (subcutaneously) of your stomach area (abdomen), buttocks, upper legs, or upper arms.

To avoid tissue damage, choose a site for each injection that is at least 1/2 inch from the previous injection site.

Wipe the skin at the injection site with an alcohol swab. Let the injection site dry before you inject your dose.

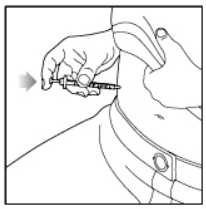


Step 11:

Insert the needle into your skin.

Step 12:

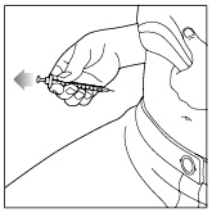
Push down on the plunger to inject your dose. The needle should stay in your skin for at least 5 seconds to make sure you have injected all of your insulin dose.



Step 13:

Pull the needle out of your skin.

- If you see blood after you take the needle out of your skin, press the injection site with a piece of gauze or an alcohol swab. **Do not** rub the area**.**
- **Do not** recap the used needle. Recapping the needle can lead to a needle stick injury.



Disposing of used needles and syringes:

- Put your used needles and syringes in a FDA-cleared sharps disposal container right away after use. **Do not** throw away (dispose of) loose needles and syringes in your household trash.

- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
  - Made of a heavy-duty plastic,
  - Can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
  - Upright and stable during use,
  - Leak resistant, and
  - Properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.
- Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.

How should I store HUMULIN R U-500?

All unopened HUMULIN R U-500 vials:

- Store all unopened vials in the refrigerator between 36° to 46°F (2° to 8°C).
- **Do not** freeze. **Do not** use if it has been frozen.
- Keep away from heat and out of direct light.
- **Do not** shake the vial.
- Unopened vials can be used until the expiration date on the carton and label, if they have been stored in the refrigerator.
- Unopened vials should be thrown away after 40 days if they are stored at room temperature

After HUMULIN R U-500 vials have been opened:

- Store opened vials in a refrigerator or at room temperature below 86°F (30°C) for up to 40 days.
- Keep away from heat and out of direct light.
- **Do not** shake the vial.
- Throw away all opened vials after 40 days, even if there is still insulin left in the vial.

General information about the safe and effective use of HUMULIN R U-500.

- Keep HUMULIN R U-500 vials, syringes, needles, and all medicines out of the reach of children.
- **Always** use a new syringe or needle for each injection.
- **Do not reuse or share your syringes or needles with other people. You may give other people a serious infection or get a serious infection from them.**

If you have any questions or problems with HUMULIN R U-500, contact Lilly at 1-800-Lilly-Rx (1-800-545-5979) or call your healthcare provider for help. For more information on HUMULIN and insulin, go to www.humulin.com.

Scan this code to launch the humulin.com website

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Instructions for Use revised: December 29, 2015

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