The Humulin® R U-500 Initiation Trial Algorithms

**STEP 1: Determine Starting Dose**

- **Patient A1C ≤8% OR patient's mean SMPG <183 mg/dL within the past 7 days**
  - **YES**
    - Start at 80% of final U-100 total daily dose
  - **NO**
    - Start at 100% of final U-100 total daily dose

**NOTE:** After calculating total daily dose, round down to the nearest increment of 5.

**STEP 2: Determine Dose Proportions**

**TID Dose Proportions**

- **BEFORE BREAKFAST:** 40%
- **BEFORE LUNCH:** 30%
- **BEFORE DINNER:** 30%

**BID Dose Proportions**

- **BEFORE BREAKFAST:** 60%
- **BEFORE DINNER:** 40%

See study design information on next page.

An Effective Treat-to-Target Dosing Algorithm With 2 or 3 Injections of U-500 per Day

- Both doses of the BID regimen were titrated; only 2 of 3 TID doses were titrated (those most needing adjustment)
- Dose reductions for hypoglycemia prioritized over dose increases for hyperglycemia

**TID Initial Dose Proportions: 40:30:30**

<table>
<thead>
<tr>
<th>INSULIN DOSE TO ADJUST</th>
<th>PLASMA-EQUIVALENT GLUCOSE VALUE*</th>
<th>SMPG (mg/dL)</th>
<th>DOSE TITRATION†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PRE-BREAKFAST</strong></td>
<td>MEDIAN** PRE-LUNCH SMPG</td>
<td>≤70</td>
<td>-10%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>71-130</td>
<td>No change in dose</td>
</tr>
<tr>
<td><strong>PRE-LUNCH</strong></td>
<td>MEDIAN** PRE-DINNER SMPG</td>
<td>131-180</td>
<td>-5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>181-220</td>
<td>+10%</td>
</tr>
<tr>
<td><strong>PRE-DINNER</strong></td>
<td>MEDIAN** PRE-BREAKFAST SMPG</td>
<td>&gt;220</td>
<td>+15%</td>
</tr>
</tbody>
</table>

**BID Initial Dose Proportions: 60:40**

<table>
<thead>
<tr>
<th>INSULIN DOSE TO ADJUST</th>
<th>PLASMA-EQUIVALENT GLUCOSE VALUE*</th>
<th>SMPG (mg/dL)</th>
<th>DOSE TITRATION†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PRE-Breakfast</strong></td>
<td>MEDIAN** PRE-DINNER SMPG</td>
<td>≤70</td>
<td>-10%</td>
</tr>
<tr>
<td></td>
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<tr>
<td><strong>PRE-DINNER</strong></td>
<td>MEDIAN** PRE-BREAKFAST SMPG</td>
<td>131-180</td>
<td>-5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>181-220</td>
<td>+10%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;220</td>
<td>+15%</td>
</tr>
</tbody>
</table>

*Patients should check their blood glucose before each meal and at bedtime daily, and at 3 am if they have increased their dose in the last 48 hours.

†Used conventional rounding to nearest 5-unit increment.

‡10% dose reduction if any pre-mealtime median, bedtime median, or single 3 am SMPG ≤70 mg/dL.

§Median of 3 most recent daily self-monitored plasma glucose (SMPG) readings.

To learn more about initiation and titration in the Humulin R U-500 Initiation Trial, visit humulinhcp.com

Indication for Humulin R U-500

- 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.
- 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.

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.
- Dosing Errors: Extreme caution must be observed in measuring the dose of Humulin R U-500 because inadvertent overdose may result in serious adverse reaction or life-threatening hypoglycemia.

Please see Important Safety Information on next page and accompanying Full Prescribing Information.
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 and Precautions
• Dosing Errors: Extreme caution must be observed in measuring the dose of Humulin R U-500 because inadvertent overdose or underdose may result in serious adverse reactions.
• Hypoglycemia, Hypoglycemia, or Death Due to Dosing Errors in the Vial Presentation: Medication errors associated with the Humulin R U-500 vial resulting in patients experiencing hypoglycemia, hypoglycemia, or death have been reported.

Dispensing
• Instruct patients to always inspect insulin vials to confirm that the correct insulin is dispensed including the correct brand and concentration.
• For the Humulin R U-500 vial, particular attention should be paid to the 20-mL vial size, prominent “U-500” and warning statements on the vial label, and distinctive coloring on the vial and carton.

Prescribing
• Dosing errors have occurred when Humulin R U-500 was administered subcutaneously other than a U-500 insulin syringe. Patients should be prescribed U-500 syringes for use with Humulin R U-500 vials. The dose of Humulin R U-500 should always be expressed in units of insulin.

Administration
• Instruct patients to always check the insulin label before each injection.
• Use only a U-500 insulin syrup with Humulin R U-500 to avoid administration errors. Do not use any other type of syrup to administer Humulin R U-500. Adhere to administration instructions.
• Instruct the patient to inform hospital or emergency department staff of the dose of Humulin R U-500 prescribed.
• 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).
• DO NOT transfer Humulin R U-500 from the Humulin R U-500 KwikPen into any syringe for administration. Overdose and severe hypoglycemia can occur.
• Never Share a KwikPen or U-500 Syringe Between Patients, even if the needle is changed. Sharing poses a risk for transmission of blood-borne pathogens.

Hyperglycemia or Hypoglycemia with Changes in Insulin Regimen: Changes in insulin, manufacturer, type, or method of administration should be made cautiously and only under medical supervision and the frequency of blood glucose monitoring should be increased.

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, such as driving or operating other machinery. Hypoglycemia can happen suddenly and symptoms may differ in each individual and change over time in the same individual. Early warning symptoms of hypoglycemia may be less pronounced in patients with longstanding diabetes, in patients with renal or hepatic impairment, in patients taking medications that block the sympathetic nervous system, or in patients who experience recurrent hypoglycemia.

Important Safety Information for Humulin R U-500

Dosage and Administration
• DO NOT perform dose conversion when using the Humulin R U-500 KwikPen. The dose window of the KwikPen shows the number of units of Humulin R U-500 to be injected and NO dose conversion is required.
• DO NOT perform dose conversion when using a U-500 insulin syringe. The markings on the syringe show the number of units of Humulin R U-500 to be injected. Each marking represents 5 units of insulin.
• Instruct patients using the vial to use only a U-500 insulin syringe and on how to correctly draw the prescribed dose into the syringe. Confirm that the patient has understood these instructions and can correctly draw the prescribed dose with their syringe.
• Advise the patient to read the Patient Information and Instructions for Use.
• Instruct patients to always check the insulin label before administration to confirm the correct insulin product is being used.
• Inspect Humulin R U-500 visually and only use if the solution appears clear and colorless.
• Administer Humulin R U-500 subcutaneously two or three times daily approximately 30 minutes before a meal. Rotate injection sites to reduce the risk of lipodystrophy.
• Individualize the dose of Humulin R U-500 based on metabolic needs, blood glucose monitoring results, and glyemic control goal.
• DO NOT administer Humulin R U-500 intravenously or intramuscularly.
• DO NOT mix Humulin R U-500 with other insulin.

Storage
• Protect from heat and light. Do not freeze. Do not use Humulin R U-500 after the expiration date stamped on the label.

Humulin R U-500 Vials: Unopened vials of Humulin R U-500 should be kept in a refrigerator. Opens (in-use) vials of Humulin R U-500 should be kept in the refrigerator or at room temperature and used within 40 days of opening. Throw away any open vial after 40 days of use, even if there is insulin left in the vial.

Humulin R U-500 KwikPen: Unopened Humulin R U-500 KwikPens should be kept at a refrigerator or at room temperature and used within 28 days of opening. Do not refrigerate opened KwikPens. Throw away any opened KwikPen after 28 days of use, even if there is insulin left in the pen.

See accompanying Full Prescribing Information.
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 (2) 07/2016

Warnings and Precautions (5) 07/2016

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)
• HUMULIN R U-500 is available as a KwikPen or multiple dose vial. Patients using the vial must be prescribed the U-500 insulin syringe to avoid medication errors. (2.1)
• 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. (2.1)
• 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. (2.3)
• Do NOT transfer HUMULIN R U-500 from the HUMULIN R U-500 KwikPen into any syringe. (2.3)
• Do NOT perform dose conversion when using a U-500 insulin syringe. Use only a U-500 insulin syringe with the HUMULIN R U-500 vial. (2.4)

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 pen containing 1,500 units of insulin)
• 20 mL multiple dose 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 U-500 insulin 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-Lilly-Rx (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: 07/2016

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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.
- HUMULIN R U-500 is available as a KwikPen or multiple dose vial. Patients using the vial must be prescribed the U-500 insulin syringe to avoid medication errors.
- Instruct patients using the vial presentation to use only a U-500 insulin syringe and on how to correctly draw the prescribed dose of HUMULIN R U-500 into the U-500 insulin syringe. 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)].
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use). 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.
- 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 any 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 the vial presentation and the U-500 Insulin Syringe

- DO NOT perform dose conversion when using a U-500 insulin syringe. The markings on the U-500 insulin syringe show the number of units of HUMULIN R U-500 to be injected. Each marking on the syringe represents 5 units of insulin.
- Prescribe patients a U-500 insulin syringe to administer HUMULIN R U-500 from the vial to avoid administration errors. DO NOT use any other type of syringe [see Warnings and Precautions (5.1)].

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 multiple dose 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 resulting in patients experiencing hyperglycemia, hypoglycemia or death have been reported. 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 aqua coloring, a 500 units/mL concentration statement consisting of white lettering on a green rectangular background, and a green “U-500” statement prominently displayed next to the trade name. Additionally, the vial has a green flip top and a red warning on the front panel describing the highly concentrated dose and a statement advising use with only U-500 insulin syringes.

Prescribing Errors

Dosing errors have occurred when the HUMULIN R U-500 dose was administered with syringes other than a U-500 insulin syringe. Patients should be prescribed U-500 syringes for use with the HUMULIN R U-500 vials. The prescribed dose of HUMULIN R U-500 should always be expressed in units of insulin [see Dosage and Administration (2.4)].

Administration Errors

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

Use only a U-500 insulin syringe with HUMULIN R U-500 to avoid administration errors. Do not use any other type of syringe to administer Humulin R U-500. Adhere to administration 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.
5.2 Never Share a HUMULIN R U-500 KwikPen or U-500 Insulin 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 U-500 insulin 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 Hepsensitvity 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/m²), 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](image)

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 \textit{in vivo} sister chromatid exchange assay and the \textit{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
- 5 x 3 mL HUMULIN R U-500 KwikPen (prefilled) NDC 0002-8824-59
- 20 mL multiple dose 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.

Not In Use (Unopened) HUMULIN R U-500 KwikPen

\textbf{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.

\textbf{Room Temperature}

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

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

\textbf{Refrigerated}

Do NOT store in a refrigerator.

\textbf{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:

**Not In Use (Unopened) 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.

**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:

<table>
<thead>
<tr>
<th>3 mL HUMULIN R U-500 KwikPen (prefilled)</th>
<th>Not In-Use (Unopened) Refrigerated</th>
<th>In-Use (Opened)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Until expiration date</td>
<td>28 days, room temperature. Do not refrigerate.</td>
</tr>
<tr>
<td>20 mL multiple dose vial</td>
<td>Until expiration date</td>
<td>40 days, refrigerated or room temperature</td>
</tr>
</tbody>
</table>

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 use only a U-500 insulin syringe and be informed that no dose conversion is required [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: July 2016

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

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LINR500-0005-USPI-20160721
Do not share your Humulin R U-500 KwikPen or U-500 insulin 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 when used in combination with other insulins.
- It is not known if Humulin R U-500 is safe and effective when given by continuous subcutaneous infusion.
- 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 dose of Humulin R U-500 you use. Do not change the dose 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 any syringe to remove Humulin R U-500 from your Humulin R U-500 KwikPen. The markings on certain syringes 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 is a special U-500 insulin syringe to measure Humulin R U-500. Use only a U-500 insulin syringe to draw up and inject your Humulin R U-500. 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.
- 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 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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