

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

INDICATIONS AND USAGE

HUMULIN® R U-500 is a concentrated human insulin indicated to improve glycemic control in adults and pediatric patients 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 single-patient-use 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 into the thigh, upper arm, abdomen, or buttocks. Rotate injection sites to reduce risk of lipodystrophy and localized cutaneous amyloidosis. (2.1, 2.2)
- Do NOT mix HUMULIN R U-500 with other insulins. (2.1)
- Do NOT administer HUMULIN R U-500 intravenously (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

Injection: 500 units/mL (U-500) available as: (3)

- 3 mL single-patient-use 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)
- *Hyperglycemia or Hypoglycemia with Changes in Insulin Regimen:* Make changes to a patient's insulin regimen (e.g., insulin strength, manufacturer, type, injection site or method of administration) under close medical supervision with increased 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

- *Drugs that Affect Glucose Metabolism:* Adjustment of insulin dosage may be needed. (7)
- *Antiadrenergic Drugs (e.g., beta-blockers, clonidine, guanethidine, and reserpine):* Signs and symptoms of hypoglycemia may be reduced or absent. (5.3, 7)

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

Revised: 02/2024

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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.
- HUMULIN R U-500 is available as a single-patient-use 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)*].
- 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 and localized cutaneous amyloidosis. Do not inject into areas of lipodystrophy or localized cutaneous amyloidosis [see *Warnings and Precautions (5.3)* and *Adverse Reactions (6)*].
- During changes to a patient's insulin regimen, increase the frequency of blood glucose monitoring [see *Warnings and Precautions (5.3)*].
- Use HUMULIN R U-500 KwikPen with caution in patients with visual impairment that may rely on audible clicks to dial their dose.
- DO NOT administer HUMULIN R U-500 intravenously.
- 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

- The HUMULIN R U-500 KwikPen dials in 5 unit increments and delivers a maximum dose of 300 units per injection.
- 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)].

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

Injection: 500 units/mL (U-500) clear, colorless solution available as:

- 3 mL single-patient-use HUMULIN R U-500 KwikPen prefilled pen (containing 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 [see *Warnings and Precautions* (5.4)]
- In patients who are hypersensitive to HUMULIN R U-500 or any of its excipients [see *Warnings and Precautions* (5.5)]

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 an insulin regimen (e.g., insulin strength, manufacturer, type, injection site or method of administration) may affect glycemic control and predispose to hypoglycemia [see *Warnings and Precautions* (5.4)] or hyperglycemia. Repeated insulin injections into areas of lipodystrophy or localized cutaneous amyloidosis have been reported to result in hyperglycemia; and a sudden change in the injection site (to an unaffected area) has been reported to result in hypoglycemia [see *Adverse Reactions* (6)].

Make any changes to a patient's insulin regimen under close medical supervision with increased frequency of blood glucose monitoring. Advise patients who have repeatedly injected into areas of lipodystrophy or localized cutaneous amyloidosis to change the injection site to unaffected areas and closely monitor for hypoglycemia. 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 insulins, 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 the patient 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 patient and change over time in the same patient. Symptomatic awareness of hypoglycemia may be less pronounced in patients with longstanding diabetes, in patients with diabetic neuropathy, 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 concomitant drugs [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 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 Reactions

Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulins, including HUMULIN R U-500. 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 insulins, 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, 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)].
- Hypersensitivity Reactions [see *Warnings and Precautions* (5.5)].
- 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.

Allergic Reactions

Severe, life-threatening, generalized allergy, including anaphylaxis, generalized skin reactions, rash, angioedema, bronchospasm, hypotension, and shock may occur with insulins, including HUMULIN R U-500 and may be life threatening.

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

Localized Cutaneous Amyloidosis

Localized cutaneous amyloidosis at the injection site has occurred. Hyperglycemia has been reported with repeated insulin injections into areas of localized cutaneous amyloidosis; hypoglycemia has been reported with a sudden change to an unaffected injection site.

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 insulins, including HUMULIN R U-500, and has been attributed to the anabolic effects of insulin.

Peripheral Edema

Insulins, 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

Table 1: Clinically Significant Drug Interactions with HUMULIN R U-500

| Drugs That May Increase the Risk of Hypoglycemia | |
|---|--|
| <i>Drugs:</i> | Antidiabetic agents, ACE inhibitors, angiotensin II receptor blocking agents, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, pentoxifylline, pramlintide, salicylates, somatostatin analog (e.g., octreotide), and sulfonamide antibiotics. |

| | |
|---|---|
| <i>Intervention:</i> | Dose adjustment and increased frequency of glucose monitoring may be required when HUMULIN R U-500 is co-administered with these drugs. |
| Drugs That May Decrease the Blood Glucose Lowering Effect of HUMULIN R U 500 | |
| <i>Drugs:</i> | 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. |
| <i>Intervention:</i> | Dose adjustment and increased frequency of glucose monitoring may be required when HUMULIN R U-500 is co-administered with these drugs. |
| Drugs That May Increase or Decrease the Blood Glucose Lowering Effect of HUMULIN R U 500 | |
| <i>Drugs:</i> | Alcohol, beta-blockers, clonidine, and lithium salts. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia. |
| <i>Intervention:</i> | Dose adjustment and increased frequency of glucose monitoring may be required when HUMULIN R U-500 is co-administered with these drugs. |
| Drugs That May Blunt Signs and Symptoms of Hypoglycemia | |
| <i>Drugs:</i> | Beta-blockers, clonidine, guanethidine and reserpine |
| <i>Intervention:</i> | Increased frequency of glucose monitoring may be required when HUMULIN R U-500 is co-administered with these drugs. |

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from published studies over decades have not established an association with human insulin use during pregnancy and major birth defects, miscarriage, or adverse maternal or fetal outcomes (see Data). There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy (see Clinical Considerations). Animal reproduction studies were not performed.

The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with a HbA1c >7% and has been reported to be as high as 20-25% in women with a HbA1c >10%. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia-related morbidity.

Data

Human Data

While available studies cannot definitively establish the absence of risk, published data from retrospective studies, open-label, randomized, parallel studies and meta-analyses over decades have not established an association with human insulin use during pregnancy and major birth defects, miscarriage, or adverse maternal or fetal outcomes. All available studies have methodological limitations, including lack of blinding, unclear methods or randomization, and small sample size.

8.2 Lactation

Risk Summary

Available data from published literature suggests that exogenous human insulin products, including HUMULIN R U-500, are transferred into human milk. There are no adverse reactions reported in breastfed infants in the literature. There are no data on the effects of exogenous human insulin products, including HUMULIN R U-500 on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for HUMULIN R U-500 and any potential adverse effects on the breastfed child from HUMULIN R U-500 or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of HUMULIN R U-500 in pediatric patients with diabetes mellitus requiring more than 200 units of insulin per day to improve glycemic control have been established. Use of HUMULIN R U-500 for this indication is supported by evidence from studies with other insulin human in pediatric patients with type 1 diabetes mellitus and from studies in adults with diabetes mellitus. Standard precautions as applied to use of HUMULIN R U-500 in adults are appropriate for use in pediatric patients.

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 a glucagon product for emergency use 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

Insulin human is produced by recombinant DNA technology utilizing a non-pathogenic laboratory strain of *Escherichia coli* and has the empirical formula $C_{257}H_{383}N_{65}O_{77}S_6$ with a molecular weight of 5.808 kDa.

HUMULIN R U-500 (insulin human) injection is a sterile, aqueous, and colorless solution for subcutaneous use. HUMULIN R U-500 contains 500 units of insulin human 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. The pH is 7.0 to 7.8.

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)].

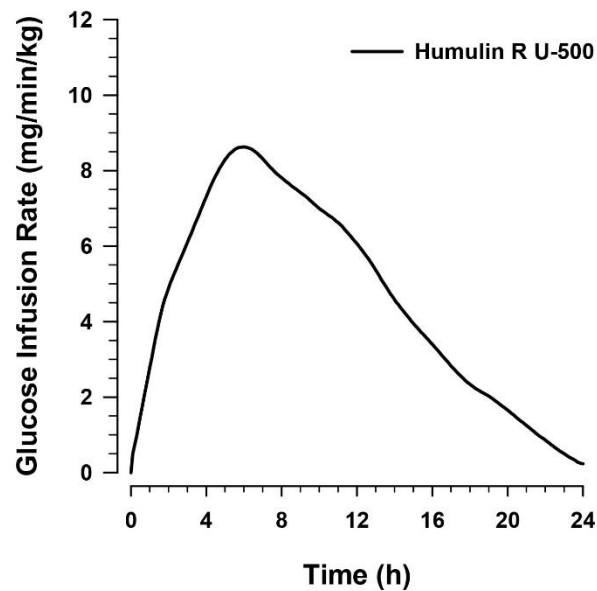


Figure 1: Mean Insulin Activity Versus Time Profiles After Subcutaneous Injection of a 100 U Dose of HUMULIN R U-500 in Healthy Obese Subjects

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 ($N \geq 21$) was approximately 4.5 hours (range=1.9-10 hours) for HUMULIN R U-500.

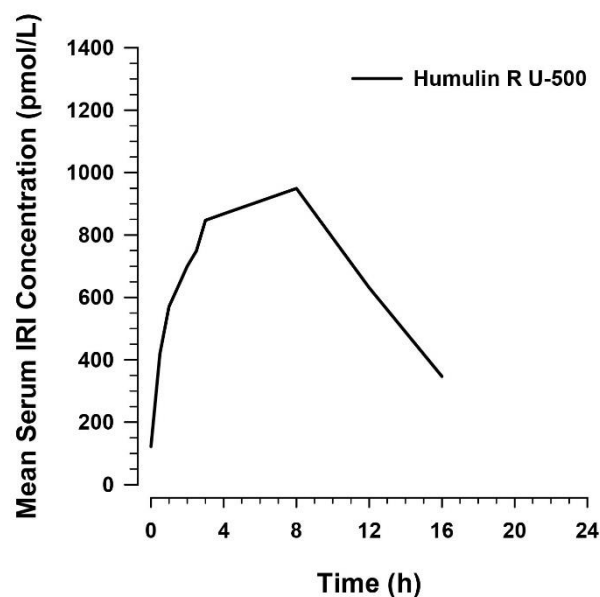


Figure 2: Mean Serum Insulin Concentrations Versus Time After Subcutaneous Injection of a 100 U Dose of HUMULIN R U-500 Healthy Obese Subjects

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/mL) injection is available in a clear, colorless solution as:

2 x 3 mL single-patient-use HUMULIN R U-500 KwikPen NDC 0002-8824-27

20 mL multiple-dose vial NDC 0002-8501-01

The HUMULIN R U-500 KwikPen dials in 5 unit increments.

16.2 Storage and Handling

Dispense in the original sealed carton with the enclosed Instructions for Use.

Protect from heat and light. Do not freeze. Do not use if it has been frozen. Do not shake the vial. See Table 2 below for storage conditions.

Table 2: Storage Conditions for HUMULIN R U-500 Vials and Pens

| | Not In-use (Unopened) | | In-use (Opened) | |
|--|---|---|---|---|
| | Room Temperature (up to 86°F [30°C]) | Refrigerated (36° to 46°F [2° to 8°C]) | Room Temperature (up to 86°F [30°C]) | Refrigerated (36° to 46°F [2° to 8°C]) |
| 20 mL multiple-dose vial ^a | 40 days | Until expiration date | 40 days | 40 days |
| 3 mL single-patient-use HUMULIN R U-500 KwikPen ^b | 28 days | Until expiration date | 28 days | Do not refrigerate. |

^a When stored at room temperature, HUMULIN R U-500 vial can only be used for a total of 40 days, including both not in-use (unopened) and in-use (opened) storage time.

^b When stored at room temperature, HUMULIN R U-500 KwikPen can only be used for a total of 28 days, including both not in-use (unopened) and in-use (opened) storage time.

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 insulin products 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. Advise patients that changes in insulin regimen can predispose to hyperglycemia or hypoglycemia and that changes in insulin regimen should be made under close medical supervision. Refer patients to the HUMULIN R U-500 Patient Information Leaflet for additional information *[see Warnings and Precautions (5)]*.

Do not dilute or mix HUMULIN R U-500 with any other insulin products or solutions *[see Dosage and Administration (2.1)]*.

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