HIGHLIGHTS OF PRESCRIBING INFORMATION

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

HUMULIN R (insulin human) injection, for subcutaneous or intravenous use

Initial U.S. Approval: 1982

----------INDICATIONS AND USAGE----------

HUMULIN® R is a short-acting human insulin indicated to improve glycemic control in adult and pediatric patients with diabetes mellitus. (1)

----------DOSAGE AND ADMINISTRATION----------

- See Full Prescribing Information for important administration instructions. (2.1)
- *Subcutaneous injection:* inject subcutaneously 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. (2.2)
- *Intravenous infusion:* administer intravenously ONLY under medical supervision at concentrations from 0.1 unit/mL to 1 unit/mL in infusion systems containing 0.9% Sodium Chloride Injection. (2.2)
- Individualize dose based on route of administration, metabolic needs, blood glucose monitoring results and glycemic control goal. (2.3)
- HUMULIN R given by subcutaneous injection should generally be used in regimens with an intermediate- or long-acting insulin. (2.3)
- Do not mix with insulin preparations other than HUMULIN® N. (2.5)

----------DOSAGE FORMS AND STRENGTHS----------

Injection: 100 units/mL (U-100) is available as:
- 10 mL multiple-dose vial (3)
- 3 mL multiple-dose vial (3)

----------CONTRAINDICATIONS----------

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

----------WARNINGS AND PRECAUTIONS----------

- Never share needles or syringes with another person. (5.1)
- *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. (5.2)
- *Hypoglycemia:* May be life-threatening. Increase frequency of blood glucose monitoring with changes to: insulin dosage, co-administered glucose lowering medications, meal pattern, physical activity; in patients with renal or hepatic impairment or with hypoglycemia unawareness. (5.3)
- *Hypoglycemia Due to Medication Errors:* Accidental mix-ups between insulin products can occur. Instruct patients to check insulin labels before injection. (5.4)
- *Hypersensitivity Reactions*: Severe, life-threatening, generalized allergy, including anaphylaxis, can occur. Discontinue HUMULIN R, 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 observed with HUMULIN R include hypoglycemia, allergic reactions, injection site reactions, lipodystrophy, weight gain, edema, 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: 06/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

HUMULIN R is indicated to improve glycemic control in adult and pediatric patients with diabetes mellitus.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

- Always check the insulin label before administration to confirm the correct insulin product is being used *[see Warnings and Precautions (5.4)]*.
- Inspect HUMULIN R visually before use. It should appear clear and colorless. Do not use HUMULIN R if particulate matter or coloration is seen.

2.2 Route of Administration

Subcutaneous Injection

- Inject HUMULIN R subcutaneously approximately 30 minutes before meals 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 (5.2) and Adverse Reactions (6)]*.
- HUMULIN R may be diluted with Sterile Diluent for HUMULIN R for subcutaneous injection ONLY under medical supervision.
    - Dilute one part HUMULIN R to nine parts diluent to yield a concentration one-tenth that of HUMULIN R (equivalent to U-10).
    - Dilute one part HUMULIN R to one part diluent to yield a concentration one-half that of HUMULIN R (equivalent to U-50).
    - Diluted HUMULIN R may be used for 28 days when stored at 41°F (5°C) or for 14 days when stored at 86°F (30°C).

Intravenous Administration

- Administer HUMULIN R intravenously ONLY under medical supervision with close monitoring of blood glucose and potassium levels to reduce the risk of hypoglycemia and hypokalemia *[see Warnings and Precautions (5.3, 5.6)]*.
- For intravenous use, HUMULIN R should be used at concentrations from 0.1 unit/mL to 1 unit/mL in infusion systems containing 0.9% Sodium Chloride Injection.
- Intravenous infusion bags prepared with HUMULIN R are stable when stored in a refrigerator (36° to 46°F [2° to 8°C]) for 48 hours and then may be used at room temperature for up to an additional 48 hours.

2.3 Dosing Instructions

- Individualize and adjust the dosage of HUMULIN R based on the route of administration, the patient's metabolic needs, blood glucose monitoring results, and glycemic control goal.
- HUMULIN R given by subcutaneous injection should generally be used in regimens with an intermediate- or long-acting insulin.
- During changes to a patient's insulin regimen, increase the frequency of blood glucose monitoring *[see Warnings and Precautions (5.2)]*.
- Dosage adjustments may be needed with changes in physical activity, changes in meal patterns (e.g., macronutrient content or timing of food intake), changes in renal or hepatic function, or during acute illness *[see Warnings and Precautions (5.2, 5.3), Use in Specific Populations (8.6, 8.7)]*.
- Dosage adjustment may be needed when changing from another insulin to HUMULIN R *[see Warnings and Precautions (5.2)]*.

2.4 Dosage Adjustment due to Drug Interactions

- Dosage adjustment may be needed when HUMULIN R is co-administered with certain drugs *[see Drug Interactions (7)]*.

2.5 Instructions for Mixing with Other Insulins for Subcutaneous Injection

- Do not mix HUMULIN R with insulin preparations other than HUMULIN N.
- To mix HUMULIN R and HUMULIN N, draw HUMULIN R into the syringe first. Inject immediately after mixing.

3 DOSAGE FORMS AND STRENGTHS

Injection: 100 units/mL (U-100), clear and colorless solution available as:

- 10 mL multiple-dose vial
- 3 mL multiple-dose vial

4 CONTRAINDICATIONS

HUMULIN R is contraindicated:

- during episodes of hypoglycemia *[see Warnings and Precautions (5.3)]*
- in patients with hypersensitivity to HUMULIN R or any of its excipients *[see Warnings and Precautions (5.5)]*

5 WARNINGS AND PRECAUTIONS

5.1 Never Share Needles or Syringes between Patients

Patients using HUMULIN R vials must never share needles or syringes with another person. Sharing poses a risk for transmission of blood-borne pathogens.

5.2 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 (5.3)]* 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 anti-diabetic medications may be needed.

5.3 Hypoglycemia

Hypoglycemia is the most common adverse reaction of all insulins, including HUMULIN R. Severe hypoglycemia can cause seizures, may lead to unconsciousness, may be life threatening or cause death. 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)]*, or in patients who experience recurrent hypoglycemia.

Risk Factors for Hypoglycemia

The risk of hypoglycemia after an injection is related to the duration of action of the insulin and, in general, is highest when the glucose lowering effect of the insulin is maximal. As with all insulins, the glucose lowering effect time course of HUMULIN R 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 *[see Clinical Pharmacology (12.2)]*.

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)]*. 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 who have reduced symptomatic awareness of hypoglycemia, increased frequency of blood glucose monitoring is recommended.

5.4 Hypoglycemia Due to Medication Errors

Accidental mix-ups between insulin products have been reported. To avoid medication errors between HUMULIN R and other insulins, instruct patients to always check the insulin label before each injection.

5.5 Hypersensitivity Reactions

Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with HUMULIN R *[see Adverse Reactions (6)]*. If hypersensitivity reactions occur, discontinue HUMULIN R; treat per standard of care and monitor until symptoms and signs resolve. HUMULIN R is contraindicated in patients who have had a hypersensitivity reaction to HUMULIN R or its excipients.

5.6 Hypokalemia

All insulins, including HUMULIN R, 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. Monitor potassium levels in patients at risk for hypokalemia if indicated (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, 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 also discussed elsewhere in the labeling:

- Hypoglycemia *[see Warnings and Precautions (5.3)]*
- Hypoglycemia Due to Medication Errors *[see Warnings and Precautions (5.4)]*
- Hypersensitivity *[see Warnings and Precautions (5.5)]*
- Hypokalemia *[see Warnings and Precautions (5.6)]*

Adverse Reactions from Clinical Studies or Postmarketing Reports

The following additional adverse reactions have been identified during clinical studies or from postmarketing reports with use of HUMULIN R. Because some of 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.

Adverse reactions associated with insulin initiation and glucose control intensification

Intensification or rapid improvement in glucose control has been associated with a transitory, reversible ophthalmologic refraction disorder, worsening of diabetic retinopathy, and acute painful peripheral neuropathy. Over the long-term, improved glycemic control decreases the risk of diabetic retinopathy and neuropathy.

Hypersensitivity Reactions

Severe allergic reactions may include anaphylaxis, generalized skin reactions, rash, angioedema, bronchospasm, hypotension, and shock.

Hypoglycemia

Hypoglycemia is the most commonly observed adverse reaction in HUMULIN R.

Hypokalemia

HUMULIN R can cause a shift in potassium from the extracellular to intracellular space, possibly leading to hypokalemia.

Injection Site Reactions

Injection site reactions may include injection site hematoma, pain, hemorrhage, erythema, nodules, swelling, discoloration, pruritus, warmth, and injection site mass.

Lipodystrophy

Administration of insulin subcutaneously, including HUMULIN R, has resulted in lipoatrophy (depression in the skin) or lipohypertrophy (enlargement or thickening of tissue) in some patients *[see Dosage and Administration (2.2)]*.

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.

Medication Errors

Medication errors in which other insulins have been accidentally substituted for HUMULIN R have been identified during postapproval use.

Peripheral Edema

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

Weight Gain

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

Immunogenicity

As with all therapeutic proteins, insulin administration may cause anti-insulin antibodies to form. The incidence of antibody formation with HUMULIN R is unknown.

7 DRUG INTERACTIONS

Table 1: Clinically Significant Drug Interactions with HUMULIN R

Drugs that May Increase the Risk of Hypoglycemia	
Drugs:	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
Intervention:	Dose adjustment and increased frequency of glucose monitoring may be required when HUMULIN R is co-administered with these drugs.
Drugs that May Decrease the Blood Glucose Lowering Effect of HUMULIN R	
Drugs:	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.
Intervention:	Dose adjustment and increased frequency of glucose monitoring may be required when HUMULIN R is co-administered with these drugs.
Drugs that May Increase or Decrease the Blood Glucose Lowering Effect of HUMULIN R	
Drugs:	Alcohol, beta-blockers, clonidine, and lithium salts. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.
Intervention:	Dose adjustment and increased frequency of glucose monitoring may be required when HUMULIN R is co-administered with these drugs.
Drugs that May Blunt Signs and Symptoms of Hypoglycemia	
Drugs:	Beta-blockers, clonidine, guanethidine, and reserpine
Intervention:	Increased frequency of glucose monitoring may be required when HUMULIN R 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, 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 on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for HUMULIN R and any potential adverse effects on the breastfed child from HUMULIN R or from the underlying maternal condition.

8.4 Pediatric Use

HUMULIN R is indicated to improve glycemic control in pediatric patients with diabetes mellitus.

The dosage of HUMULIN R must be individualized in pediatric patients based on metabolic needs and frequent monitoring of blood glucose to reduce the risk of hypoglycemia *[see Dosage and Administration (2.3), Warnings and Precautions (5.3)]*.

8.5 Geriatric Use

The effect of age on the pharmacokinetics and pharmacodynamics of HUMULIN R has not been studied. Elderly patients using HUMULIN R may be at increased risk of hypoglycemia due to co-morbid disease *[see Warnings and Precautions (5.3)]*.

8.6 Renal Impairment

The effect of renal impairment on the pharmacokinetics and pharmacodynamics of HUMULIN R has not been studied. Patients with renal impairment are at increased risk of hypoglycemia and may require more frequent HUMULIN R dose adjustment and more frequent blood glucose monitoring *[see Warnings and Precautions (5.3)]*.

8.7 Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics and pharmacodynamics of HUMULIN R has not been studied. Patients with hepatic impairment are at increased risk of hypoglycemia and may require more frequent HUMULIN R dose adjustment and more frequent blood glucose monitoring *[see Warnings and Precautions (5.3)]*.

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 intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycemia may recur after apparent clinical recovery. Hypokalemia must be corrected appropriately *[see Warnings and Precautions (5.3, 5.6)]*.

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 (insulin human) injection is a short-acting human insulin for subcutaneous or intravenous use.

HUMULIN R is a sterile, aqueous, clear, and colorless solution. HUMULIN R contains 100 units of insulin human in each milliliter. Each milliliter of HUMULIN R also contains glycerin (16 mg), metacresol (2.5 mg), endogenous zinc (approximately 0.015 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

The primary activity of insulin, including HUMULIN R, is the regulation of glucose metabolism. Insulin lowers blood glucose by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin inhibits lipolysis and proteolysis, and enhances protein synthesis.

12.2 Pharmacodynamics

The time course of insulin action (i.e., glucose lowering) may vary considerably in different individuals or within the same individual. With subcutaneous use, the pharmacologic effect of HUMULIN R begins approximately 30 minutes (range: 10 to 75 minutes) after administration of doses in the 0.05 to 0.4 units/kg range (Figure 1). The effect is maximal at approximately 3 hours (range: 20 minutes to 7 hours) and terminates after approximately 8 hours (range: 3 to 14 hours). In a study that administered 50 and 100 units doses subcutaneously to obese subjects, mean time of termination of effect was prolonged to approximately 18 hours (range approximately 12-24 hours).

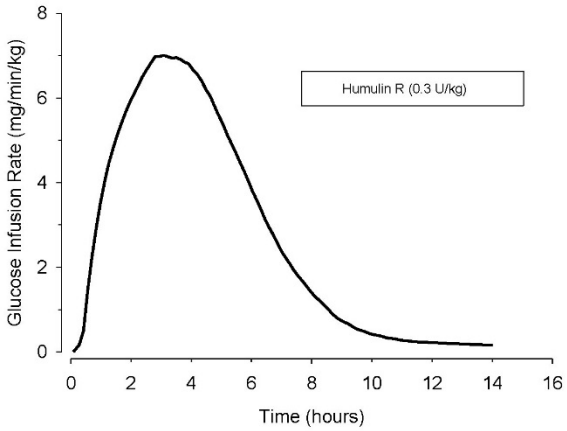


Figure 1: Mean Insulin Activity Versus Time Profile After Subcutaneous Injection of HUMULIN R (0.3 unit/kg) in Healthy Subjects.

With intravenous use, the pharmacologic effect of HUMULIN R begins at approximately 10 to 15 minutes and terminates at a median time of approximately 4 hours (range: 2 to 6 hours) after administration of doses in the range of 0.1 to 0.2 units/kg.

The intravenous administration of HUMULIN R was tested in 21 people with type 1 diabetes. During the 6-hour assessment phase patients received intravenous HUMULIN R at an initial dose of 0.5 units/hour, adjusted to maintain blood glucose concentrations near normoglycemia (100 to 160 mg/dL).

The mean blood glucose levels during the assessment phase for patients on HUMULIN R therapy are summarized below in Table 2. All patients achieved near normoglycemia during the 6-hour assessment phase. The average time (± SE) required to attain near normoglycemia was 161 ± 14 minutes for HUMULIN R.

Table 2: Mean Blood Glucose Concentrations (mg/dL) during Intravenous Infusions of HUMULIN R

Time from Start of Infusion (minutes)	Mean Blood Glucose (mg/dL) Intravenous[a]
0	220 ± 11
30	204 ± 17
60	193 ± 18

120	172 ± 28
180	153 ± 30
240	139 ± 24
300	131 ± 22
360	128 ± 18

[a] Results shown as mean ± Standard Deviation.

12.3 Pharmacokinetics

Absorption — In healthy subjects given subcutaneous doses of HUMULIN R ranging from 0.05 to 0.4 unit/kg, mean peak serum levels occurred between 36 to 150 minutes after dosing. After subcutaneous administration of a single 12 unit dose (approximately 0.15 units/kg) to patients with type 1 diabetes, the median peak serum level occurred at approximately 2 hours (range: 20 minutes-6 hours). In a study that administered 50 units (0.4-0.6 unit/kg) and 100 units (0.8-1.3 unit/kg) doses subcutaneously to healthy obese subjects, median peak serum levels were prolonged to approximately 3 hours (range 1 to 8 hours). The absolute bioavailability after a single subcutaneous injection of HUMULIN R ranges from 48% to 89% in the 0.1 to 0.3 unit/kg dose range.

Distribution — When HUMULIN R is administered intravenously at doses of 0.1 or 0.2 unit/kg, the mean volume of distribution ranges between 0.32 to 0.67 L/kg.

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.

Excretion — After subcutaneous administration of HUMULIN R doses in the 0.05-0.4 unit/kg dose range, the median apparent half-life is approximately 1.5 hours (range: 40 minutes-7 hours). Mean apparent half-life of HUMULIN R after subcutaneous administration of higher doses (50 and 100 units) to healthy obese subjects was approximately 3.6 hours (range= 1.6-8.6 hours).

When administered intravenously, HUMULIN R had a mean half-life of approximately 20 minutes at a 0.1 unit/kg dose and 1 hour at a 0.2 unit/kg dose.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity and fertility studies were not performed in animals.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

HUMULIN R injection is 100 units/mL (U-100), a clear and colorless solution available as:

10 mL multiple-dose vial	NDC 0002-8215-01
3 mL multiple-dose vial	NDC 0002-8215-17

Patients using HUMULIN R vials must never share needles or syringes with another person.

16.2 Storage and Handling

Protect from heat and light. Do not freeze. Do not use HUMULIN R after the expiration date printed on the label or if it has been frozen. See Table 3 below for storage conditions.

Table 3: Storage Conditions HUMULIN R Vials[a]

	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])**
10 mL multiple-dose vial 3 mL multiple-dose vial	31 days	Until expiration date	31 days	31 days

[a] When stored at room temperature, HUMULIN R can only be used for a total of 31 days including both not in-use (unopened) and in-use (opened) storage time.

Storage of Diluted HUMULIN R and Intravenous Infusion Preparations with HUMULIN R

Diluted HUMULIN R for subcutaneous injection may be stored for 28 days when refrigerated at 36° to 46°F [2° to 8°C] or for 14 days at room temperature up to 86°F (30°C) *[see Dosage and Administration (2.2)]*.

Intravenous infusion bags prepared with HUMULIN R may be stored for 48 hours when refrigerated at 36° to 46°F [2° to 8°C]. The prepared intravenous infusion bags may then be stored at room temperature for up to an additional 48 hours *[see Dosage and Administration (2.2)]*.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Never Share Needles or Syringes between Patients

Advise patients using HUMULIN R vials not to share needles or syringes with another person. Sharing poses a risk for transmission of blood-borne pathogens.

Hyperglycemia or Hypoglycemia

Inform patients that hypoglycemia is the most common adverse reaction with insulin. Instruct patients on self-management procedures including glucose monitoring, proper injection technique, and management of hypoglycemia and hyperglycemia, especially at initiation of HUMULIN R therapy. Instruct patients 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. Instruct patients on the management of hypoglycemia *[see Warnings and Precautions (5.3)]*.

Inform patients that their ability to concentrate and react may be impaired as a result of hypoglycemia. Advise patients who have frequent hypoglycemia or reduced or absent warning signs of hypoglycemia to use caution when driving or operating machinery.

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 *[see Warnings and Precautions (5.2)]*.

Medication Errors

Instruct patients to always check the insulin label before each injection to avoid mix-ups between insulin products *[see Warnings and Precautions (5.4)]*.

Hypersensitivity Reactions

Advise patients that hypersensitivity reactions have occurred with HUMULIN R. Inform patients on the symptoms of hypersensitivity reactions and to seek medical attention if they occur *[see Warnings and Precautions (5.5)]*.

Literature Revised: June 2022

Manufactured by:
Eli Lilly and Company
Indianapolis, IN 46285, USA
US License Number 1891

A8.0-LINR100-0003-USPI-YYYYMMDD

Patient Information
Humulin® (HU-mu-lin) R
(insulin human)
injection, for subcutaneous or intravenous use
U-100 (100 units/mL)

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.

What is Humulin R?

- Humulin R is a man-made insulin that is used to control high blood sugar in adults and children with diabetes mellitus.

Who should not use Humulin R?

Do not use Humulin R 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. See the end of this Patient Information leaflet for a complete list of ingredients in Humulin R.

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

Before using Humulin R, 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.
- are pregnant, planning to become pregnant. Talk with your healthcare provider about the best way to control your blood sugar if you plan to become pregnant or while you are pregnant.
- are breast-feeding or plan to breastfeed. HUMULIN R may pass into your breast milk. Talk with your healthcare provider about the best way to feed your baby while using HUMULIN R.

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, talk to your healthcare provider about low blood sugar and how to manage it.

How should I use Humulin R?

- Read the detailed **Instructions for Use** that comes with your Humulin R.
- Use Humulin R exactly as your healthcare provider tells you to. Your healthcare provider should tell you how much Humulin R to use and when to use it.
- Use Humulin R **30 minutes** before eating a meal.
- Know the type, strength, and amount of insulin you use. **Do not** change the type, or amount of insulin you use unless your healthcare provider tells you to. The amount of insulin and the best time for you to take your insulin may need to change if you use different types of insulin.
- Check your insulin label each time you give your injection to make sure you are using the correct insulin.
- Inject Humulin R under the skin (subcutaneously) of your upper legs (thighs), upper arms, buttocks or stomach area (abdomen). **Do not** inject Humulin R into your vein (intravenously).
  - **Do not** mix Humulin R with any other insulin except Humulin® N. If Humulin R is mixed with Humulin N, Humulin R should be drawn into the syringe first. Inject immediately after mixing.
- **Change (rotate) your injection sites within the area you choose with each dose** to reduce your risk of getting lipodystrophy (pits in skin or thickened skin) and localized cutaneous amyloidosis (skin with lumps) at the injection sites.
  - **Do not** use the exact same spot for each injection.
  - **Do not** inject where the skin has pits, is thickened, or has lumps.
  - **Do not** inject where the skin is tender, bruised, scaly or hard, or into scars or damaged skin.
- **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 and all medicines out of reach of children.

Your dose of Humulin R 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?

While using Humulin R **do not**:

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

What are the possible side effects of Humulin R?

Humulin R 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 product for emergency use 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 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. Your healthcare provider should monitor you closely while you are taking TZDs with Humulin R. 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 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 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 include:

- low blood sugar (hypoglycemia), allergic reactions including reactions at your injection site, skin thickening or pits at the injection site (lipodystrophy), weight gain, swelling (edema) in hands or feet, itching and rash.

These are not all of the possible side effects of Humulin R. 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

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. **Do not** use Humulin R for a condition for which it was not prescribed. **Do not** give Humulin R 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. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about Humulin R that is written for healthcare providers. For more information go to www.humulin.com or call 1-800-LillyRx (1-800-545-5979).

What are the ingredients in Humulin R?

Active Ingredient: insulin human

Inactive ingredients: glycerin, metacresol, and Water for Injection as inactive ingredients. Sodium hydroxide and hydrochloric acid may be added to adjust the pH.

Manufactured by: Eli Lilly and Company, Indianapolis, IN 46285, USA

US License Number 1891

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

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: June 2022

A3.0-LINR100-0003-PPI-YYYYMMDD

Instructions for Use

Humulin® (HU-mu-lin) R
(insulin human)
injection, for subcutaneous or intravenous use
3 mL or 10 mL multiple-dose vial (100 units/mL)

Read the Instructions for Use before you start taking HUMULIN R and each time you get a new 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.

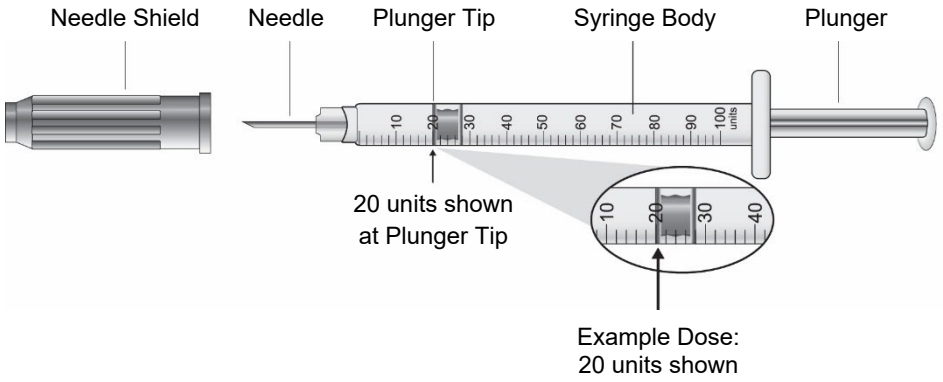
Do not share your syringes with other people, even if the needle has been changed. You may give other people a serious infection or get a serious infection from them.

Supplies needed to give your injection

- a 3 mL or 10 mL multiple-dose HUMULIN® R vial
- a U-100 insulin syringe and needle
- 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.

Vial

Syringe



Preparing the Dose

- Wash your hands with soap and water.
- Check the HUMULIN R 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 past the expiration date printed on the label or 31 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 solution should look clear and colorless. **Do not** use HUMULIN R if it looks cloudy, thick, slightly colored, or if you see particles in the solution.

Step 2:

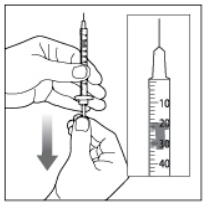
If you are using a new HUMULIN R vial, flip off the plastic protective Cap, but **do not** remove the Rubber Stopper.

Step 3:

Wipe the Rubber Stopper 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 units for your prescribed dose.



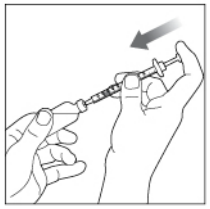
(Example Dose: 20 units shown)

Step 5:

Push the needle through the Rubber Stopper of the vial.

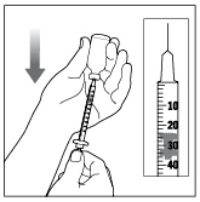
Step 6:

Push the Plunger all the way in. This puts air into the vial.



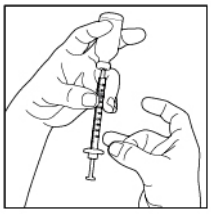
Step 7:

Turn the vial and syringe upside down and slowly pull the plunger down until the tip is a few units past the line for your prescribed dose.



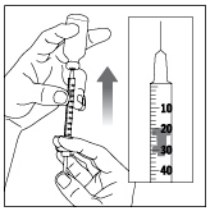
(Example Dose: 20 units
Plunger is shown at 24 units)

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:

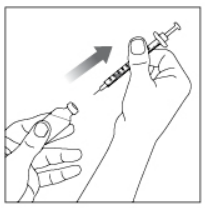
Slowly push the Plunger up until the tip reaches the line for your prescribed dose.
Check to make sure that you have the right dose.



(Example Dose: 20 units
shown)

Step 9:

Pull the syringe out of the vial's Rubber Stopper.



If you use HUMULIN R with HUMULIN N:

- HUMULIN N is the **only** type of insulin that can be mixed with HUMULIN R. Do not mix HUMULIN R with any other type of insulin.
- HUMULIN R should be drawn up into the syringe first, before you draw up Humulin N. Talk to your healthcare provider if you are not sure about the right way to mix HUMULIN R and HUMULIN N.
- Give your injection right away.

Giving your Injection

- Inject your insulin exactly as your healthcare provider has shown you.
- Change (rotate) your injection sites within the area you choose for each dose to reduce your risk of getting lipodystrophy (pits in skin or thickened skin) and localized cutaneous amyloidosis (skin with lumps) at the injection sites.

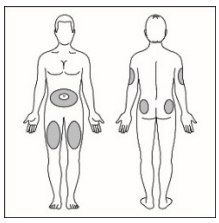
- **Do not** inject where the skin has pits, is thickened, or has lumps.
- **Do not** inject where the skin is tender, bruised, scaly or hard, or into scars or damaged skin.

Step 10:

Choose your injection site.

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

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



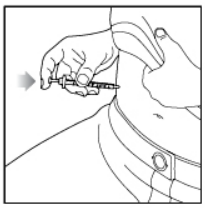
Step 11:

Insert the needle into your skin.

Step 12:

Push down on the Plunger to inject your dose.

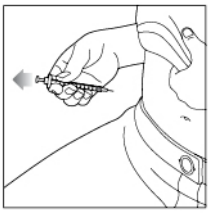
The needle should stay in your skin for at least 5 seconds to make sure you have injected all of your insulin dose.



Step 13:

Pull the needle out of your skin.

- You may see a drop of insulin at the needle tip. This is normal and does not affect the dose you received.
- 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 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?

All unopened vials:

- Store all unopened vials in the refrigerator at 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.
- 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 31 days if they are stored at room temperature

After vials have been opened:

- Store opened vials in the refrigerator or at room temperature up to 86°F (30°C) for up to 31 days.
- Keep away from heat and out of direct light.
- Throw away all opened vials after 31 days, even if there is still insulin left in the vial.

General information about the safe and effective use

- Keep HUMULIN R 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 your HUMULIN, 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

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Humulin® is a trademark of Eli Lilly and Company.

Instructions for Use revised: June 2022

Manufactured by:
Eli Lilly and Company, Indianapolis, IN 46285, USA
US License Number 1891

A3.0-LINR100VL-0003-IFU-YYYYMMDD

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: 06/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

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 injections 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	
Drugs:	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.

Intervention:	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	
Drugs:	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.
Intervention:	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	
Drugs:	Alcohol, beta-blockers, clonidine, and lithium salts. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.
Intervention:	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	
Drugs:	Beta-blockers, clonidine, guanethidine and reserpine
Intervention:	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/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)]*.

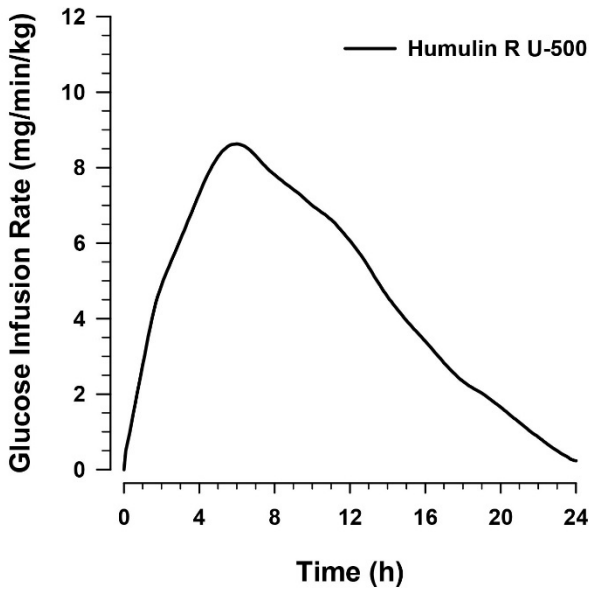


Figure 1: Mean Insulin Activity Versus Time Profiles After Subcutaneous Injection of a 100 U Dose of HUMULIN R U-500 in Healthy Obese Subjects

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.

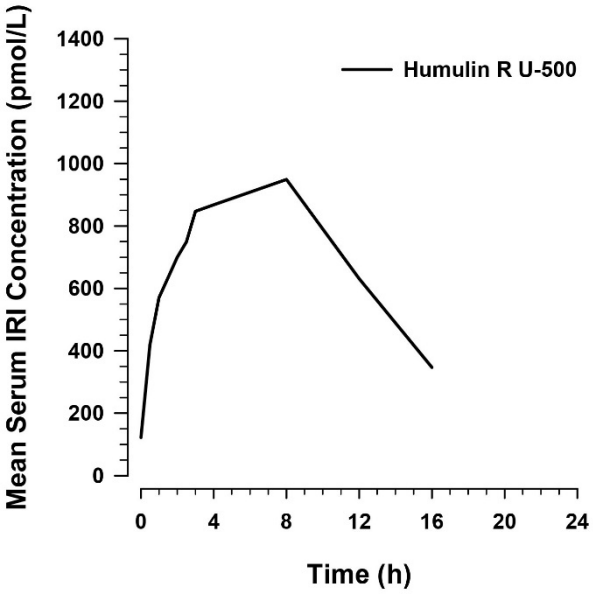


Figure 2: Mean Serum Insulin Concentrations Versus Time After Subcutaneous Injection of a 100 U Dose of HUMULIN R U-500 Healthy Obese Subjects

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/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 HUMILIN 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)]*.

Literature Revised: June 2022

Manufactured by:
Eli Lilly and Company,
Indianapolis, IN 46285, USA
US License Number 1891

A8.0-LINR500-0008-USPI-YYYYMMDD

Patient Information
Humulin® (HU-mu-lin) R U-500
(insulin human)
injection, for subcutaneous use
U-500 (500 units/mL)

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 Humulin R U-100 (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.

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. Talk with your healthcare provider about the best way to control your blood sugar if you plan to become pregnant or while you are pregnant.
- are breast-feeding or plan to breastfeed. Humulin R U-500 may pass into your breast milk. Talk with your healthcare provider about the best way to feed your baby while using HUMULIN R U-500.

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 the skin (subcutaneously) of your upper legs (thighs), upper arms, buttocks or stomach area (abdomen). **Do not** use Humulin R U-500 in an insulin pump or inject Humulin R U-500 into your vein (intravenously).
- **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 sites within the area you choose with each dose** to reduce your risk of getting lipodystrophy (pits in skin or thickened skin) and localized cutaneous amyloidosis (skin with lumps) at the injection sites.
  - **Do not** use the exact same spot for each injection.
  - **Do not** inject where the skin has pits, is thickened, or has lumps.
  - **Do not** inject where the skin is tender, bruised, scaly or hard, or into scars or damaged skin.
- **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 product for emergency use 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: insulin human

Inactive ingredients: glycerin, metacresol, zinc oxide, and Water for Injection as inactive ingredients. Sodium hydroxide and hydrochloric acid may be added to adjust the pH.

Manufactured by: Eli Lilly and Company, Indianapolis, IN 46285, USA

US License Number 1891

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

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: June 2022

A5.0-LINR500-0005-PPI-YYYYMMDD