IMPORTANT PRESCRIBING INFORMATION

Subject: Humulin® R U-500 KwikPen® is now available as a dedicated dosing device

Dear Healthcare Professional:

Eli Lilly and Company (Lilly) is writing to inform you of important safety information about prescribing and administration of Humulin® R U-500 insulin. Dosing and administration errors have been reported in patients using U-100 insulin syringes or volumetric (tuberculin) syringes with the Humulin R U-500 insulin vial. To reduce the potential for these errors, a Humulin R U-500 KwikPen (prefilled pen) is now available for use as a dedicated dosing device for Humulin R U-500. Humulin R U-500 is indicated to improve glycemic control in adult and pediatric patients with diabetes mellitus requiring more than 200 units of insulin per day. The safety and efficacy of Humulin R U-500 when used in combination with other insulins or when delivered by continuous subcutaneous infusion has not been determined.

Prescriber Actions

• Consider prescribing Humulin R U-500 KwikPen to those patients with diabetes mellitus who require high daily doses of insulin (that is, more than 200 units of insulin per day)

• Write prescriptions for Humulin R U-500 KwikPen in units of insulin and inform patients of their dose in units of insulin. Prescribe the dose in 5-unit increments to match the dose dial increments on the Humulin R U-500 KwikPen. No dose or volume conversion is required
  - For example, for a patient receiving 125 units of Humulin R U-500 insulin twice per day, write the prescription as “Humulin R U-500 KwikPen 125 units subcutaneously (SC) twice daily 30 minutes before breakfast and dinner”

Recommendations for Patient Counseling with the Humulin R U-500 KwikPen

• Advise your patients NOT to withdraw Humulin R U-500 insulin from the KwikPen with a syringe. This may result in incorrect dosing due to differences in syringe markings and potentially result in overdose causing severe hypoglycemia. Instruct your patients to maintain backup U-500 KwikPens. In the event of a malfunction, they should use their backup pen or contact a pharmacist, healthcare professional, or The Lilly Answers Center for more information at 1-800-545-5979

• Instruct your patients NOT to count clicks to determine their dose because they could dial the wrong dose since the Humulin R U-500 KwikPen dials in 5-unit increments

Please see Instructions for Use included with the pen.
Features of Humulin R U-500 KwikPen

• The Humulin R U-500 KwikPen is aqua in color and has an aqua dose knob with raised ridges on the end. The pen label states “Humulin® R U-500” at the top and includes “500 units/mL” in a green highlighted box.

• The Humulin R U-500 KwikPen can deliver from 5 to 300 units of insulin in a single injection.

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

• The Humulin R U-500 KwikPen is designed to dose up to a total of 1500 units per pen.

• The Humulin R U-500 KwikPen cartridge holder and carton both contain the following yellow warning box:

Reporting Adverse Events and Product Complaints

Healthcare professionals and patients are encouraged to report adverse events in patients taking Humulin R U-500 KwikPen to The Lilly Answers Center at 1-800-545-5979. You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

This letter is not intended as a complete description of the benefits and risks related to the use of Humulin R U-500 KwikPen. Please refer to the Full Prescribing Information available at http://pi.lilly.com/us/humulin-r-u500-pi.pdf.

Please contact Lilly at 1-800-545-5979 if you have any questions about the information in this letter or the safe and effective use of Humulin R U-500 KwikPen.

Sincerely,

Robert W. Baker, MD
Vice President, Global Patient Safety

Please see Instructions for Use included with the pen.
Important Safety Information for Humulin R U-500

Contraindications
- Humulin R U-500 is contraindicated during episodes of hypoglycemia and in patients hypersensitive to Humulin R U-500 or any of its excipients.

Warnings and Precautions
- Dosing Errors: Extreme caution must be observed in measuring the dose of Humulin R U-500 because inadvertent overdose may result in serious adverse reaction or life-threatening hypoglycemia.
  - Medication errors associated with the Humulin R U-500 vial have occurred and resulted in patients experiencing hyperglycemia, hypoglycemia, or death.

Dispensing
- Instruct patients to always inspect insulin vials to confirm that the correct insulin is dispensed including the correct brand and concentration.
- The Humulin R U-500 vial, which contains 20 mL, has a band of diagonal brown stripes. “U-500” is also highlighted in red on the Humulin R U-500 vial label.

Prescribing
- When using a U-100 insulin syringe or tuberculin syringe, express the prescribed dose of Humulin R U-500 in units of insulin along with the appropriate corresponding markings on the syringe the patient is using.

Administration
- Instruct patients to always check the insulin label before each injection.
- A Majority of the medication errors with Humulin R U-500 vial occurred due to dosing confusion when the dose was prescribed in units or volume corresponding to a U-100 syringe or tuberculin syringe markings, respectively, or the prescribed dose was administered without recognizing that the markings on the syringe used do not directly correspond to the U-500 dose. Instructions for use should always be read and followed before use.
- Instruct the patient to inform hospital or emergency department staff of the dose of Humulin R U-500 prescribed.
- A conversion chart should always be used when administering doses from the Humulin R U-500 vial with U-100 insulin syringes or 1 mL tuberculin syringes.
  - If using the Humulin R U-500 KwikPen, patients should be counseled to dial and dose the prescribed number of units of insulin (NO dose conversion is required). DO NOT transfer Humulin R U-500 from the Humulin R U-500 KwikPen into a syringe for administration. Overdose and severe hypoglycemia can occur.
  - Patients Should Never Share KwikPens, Needles, or Syringes with Other People, even if the needle is changed. Sharing poses a risk for transmission of blood-borne pathogens.
  - Hyperglycemia or Hypoglycemia with Changes in Insulin Regimen: Changes in insulin, manufacturer, type, or method of administration should be made cautiously and only under medical supervision and the frequency of blood glucose monitoring should be increased.
  - Hyperglycemia: Hyperglycemia is the most common adverse reaction associated with insulin, including Humulin R U-500. Severe hyperglycemia can cause seizures, may be life-threatening, or cause death. Severe hyperglycemia may develop as long as 18 to 24 hours after an injection of Humulin R U-500. Hypoglycemia can impair concentration ability and reaction time; this may place an individual and others at risk in situations where these abilities are important, such as driving or operating other machinery.
  - Hypoglycemia can happen suddenly and symptoms may differ in each individual and change over time in the same individual.
  - Early warning symptoms of hypoglycemia may be less pronounced in patients with longstanding diabetes, in patients with diabetic nerve disease, in patients using medications that block the sympathetic nervous system, or in patients who experience recurrent 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.
  - 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.

Warnings and Precautions, continued
- Hypersensitivity and Allergic Reactions: Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products, 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.
  - Hypokalemia: Insulin use can lead to hypokalemia that left untreated may cause respiratory paralysis, ventricular arrhythmia, and death. Use caution in patients who may be at risk for hypokalemia (e.g., patients using potassium-lowering medications, patients taking medications sensitive to serum potassium concentrations).
  - Fluid Retention and Heart Failure Associated with Changes in Insulin Regimen: Thiazolidinediones (TZDs), which are PPAR-gamma agonists, can cause dose-related fluid retention, particularly when used in combination with insulin. Fluid retention may lead to or exacerbate heart failure. Observe patients 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.

Adverse Reactions
- Adverse reactions include hypoglycemia, allergic reactions, lipodystrophy, injection site reactions, weight gain, peripheral edema, and immunogenicity.

Drug Interactions
- Some medications may alter glucose metabolism and may necessitate insulin dose adjustment. Signs of hypoglycemia may be reduced or absent in patients taking antiadrenergic drugs. Particularly close monitoring may be required.

Use in Specific Populations
- Pregnancy Category B: While there are no adequate and well-controlled studies in pregnant women, evidence from published literature suggests that good glycemic control in patients with diabetes during pregnancy provides significant maternal and fetal benefits.
- Pediatric Use: There are no well-controlled studies of use of Humulin R U-500 in children. Standard precautions as applied to use of Humulin R U-500 in adults are appropriate for use in children.
- Geriatric Use: There are no well-controlled studies of use of Humulin R U-500 in geriatric patients. In elderly patients with diabetes, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemia.
- Renal or Hepatic Impairment: Frequent glucose monitoring and insulin dose reduction may be required in patients with renal or hepatic impairment.

Dosage and Administration
- Prescribe Humulin R U-500 ONLY to patients who require more than 200 units of insulin per day.
- Adhere to administration instructions to reduce the risk of dosing errors.
  - Individualize dose of Humulin R U-500 based on metabolic needs, blood glucose monitoring results, and glycemic control goal.
  - Administer Humulin R U-500 subcutaneously two or three times daily approximately 30 minutes before a meal. Rotate injection sites to reduce the risk of lipodystrophy.
  - Do NOT mix Humulin R U-500 with other insulins.
  - Do NOT administer Humulin R U-500 intravenously or intramuscularly.
  - Do NOT perform dose conversion when using the Humulin R U-500 KwikPen. The dose window of the 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 KwikPen into a syringe.
  - CONVERT the prescribed dose of Humulin R U-500 into a “unit” or “volume” mark when using the vial and a U-100 or a tuberculin syringe device to deliver Humulin R U-500.

Storage
- Protect from heat and light. Do not freeze. Do not use Humulin R U-500 after the expiration date stamped on the label.
  - Humulin R U-500 Vials: Unopened vials of Humulin R U-500 should be kept in a refrigerator. Opened (in-use) vials of Humulin R U-500 should be kept in the refrigerator or at room temperature and used within 40 days of opening. Throw away any opened vial after 40 days of use, even if there is insulin left in the vial.
  - Humulin R U-500 KwikPen: Unopened Humulin R U-500 KwikPens should be kept in a refrigerator. Opened (in-use) Humulin R U-500 KwikPens should be kept at room temperature and used within 28 days of opening. Do not refrigerate opened KwikPens. Throw away any opened KwikPen after 28 days of use, even if there is insulin left in the pen.


HI US05 HCP ISS 04JAN2016
Humulin® and KwikPen® are registered trademarks owned or licensed by Eli Lilly and Company, its subsidiaries, or affiliates. Humulin® R U-500 is available by prescription only.