Study Title: Duration of action and peak effect of high dose U-500 regular insulin in severely insulin resistant subjects with type 2 diabetes

Version: September 23, 2015

- **Introduction**

With the epidemic of obesity and type 2 diabetes, patients today frequently require large doses of insulin to achieve optimal glycemic control because of their severe insulin resistance. Such patients often require multiple injections exceeding 100 units at a time, which can cause discomfort and reduced adherence to therapy. Additionally, a large depot of subcutaneous insulin may delay its absorption (1). Because of the higher concentration of U-500 insulin compared to U100 insulin, patients are able to deliver the same amount of insulin in a much smaller volume, increasing patient satisfaction, adherence and improving glycemic control (2).

Despite the increased use of U-500 insulin, the pharmacokinetics and pharmacodynamics have not been well studied, particularly in subjects with diabetes at clinically meaningful doses. De La Pena et al examined the pharmacokinetics and pharmacodynamics of 50 and 100 unit doses of U-500 and U-100 insulin in healthy, non-diabetic obese volunteers (3). They found that the peaks of the concentration and action profiles for U-500 were blunted, and the effect after the peak was prolonged. A limitation of this study is that the doses used were less than what are typically used in clinical practice and time-action profiles may be different at higher doses of U-500 insulin. Additionally, subjects did not have diabetes, and were excluded if they had a BMI >40 (a group that would be more likely to require high dose insulin).

Davidson et al. measured glucose, insulin and C-peptide levels in 9 severely insulin resistant subjects with type 2 diabetes after administration of 100 units of U-500 insulin subcutaneously (4). Insulin concentrations rose by 30 minutes, peaked at 5 hours and remained elevated for at least 7 hours, although the study ended after only 7 hours, so the full duration of the effect is not known.

This paucity of data makes it difficult for clinicians to dose U-500 safely and effectively. A prospective study lasting 24 hours or more is needed to better understand the duration of action of U-500 insulin. In this study, we propose a double blind, crossover euglycemic clamp study in subjects with type 2 diabetes and severe insulin resistance using clinically relevant dosing to determine duration of action and peaks of U-500 insulin. Such information would be of great benefit to clinicians who wish to prescribe U-500 insulin.

- **Objectives**

Primary Objective: To determine the duration of action of a single injection of 100 vs. 200 units U-500 insulin in severely insulin resistant patients with type 2 diabetes.

Secondary Objective: To determine peak effect of a single injection of 100 vs. 200 units U-500 insulin in severely insulin resistant patients with type 2 diabetes

- **Research design**

What do we intend to do?

This will be a single center double blind, crossover study in which subjects will be randomly assigned to receive 100 or 200 units of U500 insulin on two separate occasions separated by a minimum of two weeks. Following U500 administration, euglycemia will be maintained by the variable infusion of dextrose. Our study design is shown in Figure 1.

How will we do the work?

Following ascertainment of eligibility, potential participants will be sent a letter inviting them to learn more about the study. Individuals who contact the study personnel in response to the letter will be screened on the phone and those who meet the inclusion criteria will be invited to come to the research center to be screened in person. At that time the study will be reviewed in detail and informed consent will be obtained. If an HgbA1c has not been measured in the previous month, a sample will be collected for this measure during the screening visit. Subjects will then be scheduled for their first study day and instructed to avoid exercise 48 hours before the study. Directions for how to manage their diabetes medications will be given to the participant. These will be individualized based on the participant's current regimen with the intention to discontinue all medications so none are present at the start of the study.

Subjects will be admitted to Masonic Clinical Research Unit (MCRU) after dinner on the night (between 8-10 PM) before the study. Two catheters will be placed in the arms to establish intravenous access. One will be used for subsequent blood sampling and the other will be used for infusion. Blood glucose will be measured four hours after their dinner and intravenous insulin will be given as necessary to maintain blood glucose between 100-150 mg/dL. Blood sugars will be obtained every 15-60 minutes overnight to ensure the participant remains at target. At 7 AM (time 0) subjects will be given a blinded dose of either 100 or 200 units of U-500 regular insulin subcutaneously. The randomization to dose and the preparation of the injection will be managed by the investigational pharmacy. Blood glucose will be measured starting at time 0 and every 15-60 minutes and variable infusion of 20% dextrose (D20) will be used to maintain euglycemia (100 mg/dl target) according to pre calibrated algorithm. Samples for subsequent measurement of total insulin and c-peptide by Chemiluminescent immunoassay will be collected at time 0 and every 60 minutes. Measurements will be continued until the subject can maintain euglycemia without a glucose infusion for at least 10 hours or until the subject experiences hyperglycemia (BG > 150 mg/dl) for two hours after discontinuation of the glucose infusion irrespective of total duration of glucose infusion. At that point, the catheters will be removed and the subject will be discharged to home. In case of unusual circumstances including high requirements of glucose beyond 24 hours etc, we will assess for recent insulin dosing (< 15 hours as oppose to > 15 hours required per protocol), sulfonylurea screen etc. Carbohydrate free meals will be provided to the participant starting at noon and continued at traditional mealtimes thereafter for the duration of the glucose infusion. Non-caloric decaffeinated beverages will be available as needed. Subjects will be given their home dose of insulin prior to discharge.

Two to four weeks later, the participant will return to complete the second half of the study in which they are given the dose of U500 they did not get at the time of their previous visit. Between visits, subjects will be instructed to go back on their usual diabetes regimen. They will again be instructed to avoid exercise 48 hours before the study and provided with directions for how to manage their diabetes medications in the days immediately before the second visit. These will again be individualized based on the participant's current regimen with the intention to discontinue all medications so none are present at the start of the study. They will again report to the research center after dinner between 8-10 pm and maintained on an insulin drip as necessary to maintain blood glucose between 100-150 mg/dl. At 7 am on the next day the U500 dose will be given and samples will collected as during the first visit. A glucose infusion will again be given to maintain eyglycemia (100 mg/dl) and discontinued using the same plan as for the first visit.

What is our study population?

We will study adults with type 2 diabetes and insulin resistance. Criteria for participation are listed below.

- **Inclusion Criteria**
  - Type 2 diabetes
  - Ages 30-65 years
  - A1c between 7-9.5% within the past month
  - On ≥100 units of insulin per day.

- Willing to discontinue oral/injectable non-insulin or insulin hypoglycemic agents for minimum of 15 hours prior to the expected U-500 dose administration.
- Willing to avoid exercise 48 hours prior to study
- Willing to be fasting for up to 24 hours
- BMI between 27 and 38 kg/m2

- **Exclusion criteria**

  - On systemic corticosteroids in preceding 3 months
  - Heavy alcohol consumption (>21 drinks/week men, >14 drinks/week women)
  - Unwillingness to stop alcohol consumption for 24 hours before each study visit
  - Pregnant or actively trying to conceive
  - Current diagnosis of active infection, cancer (other than basal cell carcinoma), vascular disease, organ failure
  - Current transplant recipient

How are subjects being selected into the study?

Potential participants will be recruited from the Diabetes Clinics at the University of Minnesota. They will initially be ascertained for eligibility by review of the electronic medical record or on referral by their personal health care provider.

What are your treatment groups?

Each individual will be studied twice, once after the administration of 100 units of U 500 and once after the administration of 200 units of U500. Dosage administration will be in random order.

What is our assignment strategy?

The investigational pharmacy at the University of Minnesota will dispense the doses of U 500 insulin and assign the order of administration based on a randomization scheme developed by Dr. Lynn Eberly, the biostatistician on the project.

How many subjects per treatment group?

We have powered the primary research question using 15 participants, each studied twice as described above. A participant who completes the first dose study but does not return for the second dose study will be replaced.

With 15 subjects (N = 15) completing this cross over study design, we have 85% power using a paired t-test to detect at least a 2 hour difference in the mean duration of action of the 100 vs 200 unit dose of U500 conservatively assuming a within-person correlation of 0.30 (Figure 2). Power will be higher (the detectable difference will be smaller) if the within-person correlation is larger.

What is the schedule of events?

Please see figure 1. In random order subjects will be assigned to receive 100 or 200 units of U-500 insulin on two separate occasions separated by a minimum of two weeks. Following U500 administration, euglycemia will be maintained by the variable infusion of dextrose.

- **Concomitant medications**

Subjects will be continued on their non-diabetic medications. Medications used to treat diabetes will be discontinued before the study day. How medications will be discontinued will be individualized based on the participant's current regimen with the intention to discontinue all medications so none are present at the start of

the study. For example, individuals on metformin, sulfonylureas, DPP4Is, GLP-1 agonists will be instructed to not take this drug on the day they will be admitted to the research center.

- **Outcome measures**

Primary outcome measure: Duration (in hours) of 20 % dextrose infusion requirement.

Secondary outcome measure: 1) Peak 20 % dextrose requirement. 2) Area under the curve (AUC) of 20 % dextrose.

- **Safety measures**

Investigator related measures: Our research group has had extensive experience in subject recruitment of patients with diabetes in research studies including GRADE, ACCORD and REWIND. We have performed hundreds of precise clamp studies including euglycemic, hypoglycemic and hyperglycemic. We have a dedicated staff and are well equipped to handle these experiments.

Subject related measures: Subjects will be under constant supervision by staff of MCRU overnight during insulin infusion to keep blood glucose within target. U-500 insulin will be handled by Investigational Drug Service (IDS) pharmacy according to institutional policies regarding U-500 regular insulin (attached document: U 500 Insulin Safety Plan, U 500 insulin formulary committee meeting). Pre specified dose of U 500 regular insulin will be calculated, drawn and verified in U-100 insulin syringe at IDS pharmacy according to a conversion chart (attached document: U-500 regular insulin conversion chart). After the administration of insulin, the D20 infusion will be titrated by an experienced member of the group. Subject will remain in the research unit until the subject can maintain euglycemia without a glucose infusion for at least 10 hours or until the subject experiences hyperglycemia (BG > 150 mg/dl) for two hours after discontinuation of the glucose infusion.

- **Sample size computation and power analysis**

We have powered the primary research question using 15 participants, each studied twice as described above. A participant who completes the first dose study but does not return for the second dose study will be replaced. With 15 subjects (N = 15) completing this cross over study design, we have 85% power using a paired t-test to detect at least a 2 hour difference in the mean duration of action of the 100 vs 200 unit dose of U500 conservatively assuming a within-person correlation of 0.30 (Figure 2).

- **Statistical analysis plan**

The duration (in hours) of 20 % dextrose infusion requirement, peak 20 % dextrose requirement , and the AUC of 20 % dextrose will be calculated for each subject after the administration of each of the 100 unit and 200 unit doses of U-500 regular insulin. These measures will then each be compared between doses by paired t-test.

- **Publication strategy**

We intend to submit a report of this work to Diabetes Care and submit an abstract to American Diabetes Association Scientific Sessions in 2015.

- **References**

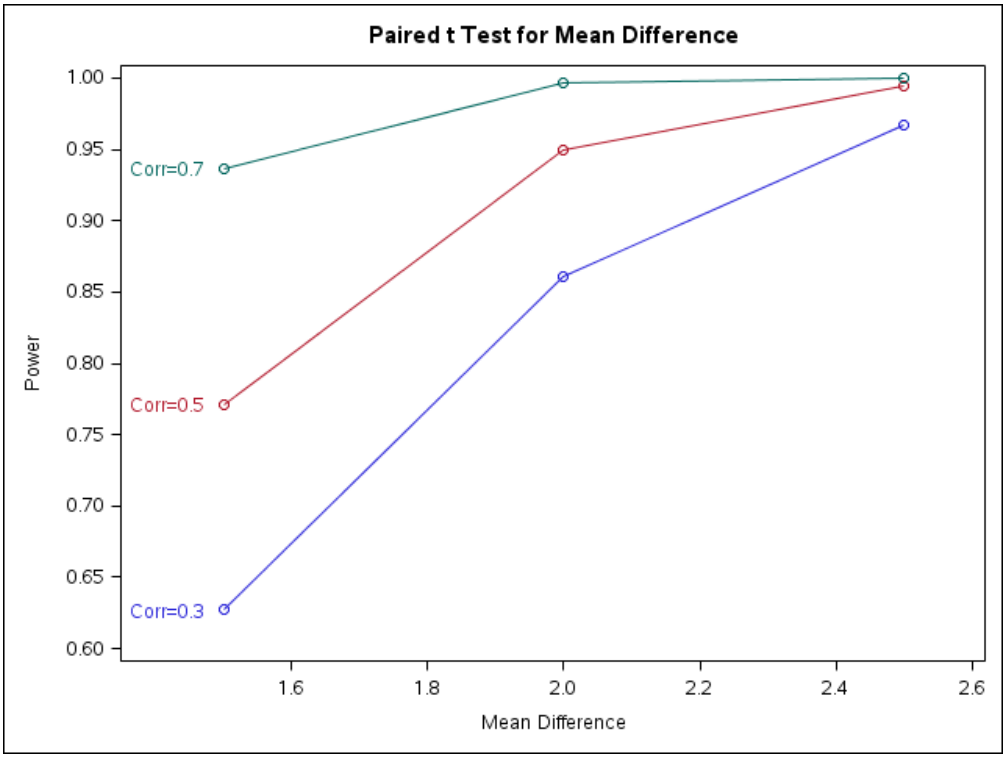
1. Gagnon-Auger M, du Souich P, Baillargeon JP, Martin E, Brassard P, Menard J, Ardilouze JL. Dose-dependent delay of the hypoglycemic effect of short-acting insulin analogs in obese subjects with type 2 diabetes: a pharmacokinetic and pharmacodynamics study. Diabetes Care. 2010 Dec;33(12):2502-7.
2. Dailey AM, Williams S, Taneja D, Tannock LR. Clinical efficacy and patient satisfaction with U-500 insulin

use. Diabetes Res Clin Pract. 2010 Jun;88(3):259-64.
3. de la Pena A, Riddle M, Morrow LA, Jiang HH, Linnebjerg H, Scott A, Win KM, Hompesch M, Mace KF, Jacobson JG, Jackson JA. Pharmacokinetics and pharmacodynamics of high-dose human regular U-500 insulin versus human regular U-100 insulin in healthy obese subjects. Diabetes Care. 2011 Dec;34(12):2496-501.
4. Davidson MB, Navar MD, Echeverry D, Duran P. U-500 regular insulin: clinical experience and pharmacokinetics in obese, severely insulin-resistant type 2 diabetic patients. Diabetes Care. 2010 Feb;33(2):281-3.

Figure 1: Study Design

8 – 10 pm	10 pm – 7 am	7 am – 7 pm	7 pm – 7 am
Subjects will arrive at MCRU Placement of 2 IV catheters in each arm	IV insulin infusion Target blood glucose of 100-150 mg/dL	Administration of 100 or 200 U of U-500 regular Insulin subcutaneously 20% Dextrose infusion Target blood glucose ~100 mg/dL	When no longer requiring 20% dextrose for 10 hours, IV catheter will removed and subjects will be discharged.

Figure 2: Power to detect a within-person difference in mean duration of action (hours) for dose 100 units vs. dose 200 units of U500 insulin. Type I error 5% assumed.



November 2012

U-500 Insulin Safety Plan

Situation: Non-standard insulin concentrations (eg. U-500) are high risk medications that require additional safety measures to prevent errors.

Background: Insulin products are typically prescribed using a concentration of U-100 (100 units/mL). Increasingly we are seeing requests for non-standard concentrations, particularly for the commercially available U-500 (500 units/mL) regular insulin. This product can be difficult to order, prepare and administer. An error with this high risk medication could have significant adverse events associated with the administration and result in severe, prolonged hypoglycemia.

U-500 regular insulin is typically used in patients that have a high resistance to insulin, most often in patient that require >100 units/dose. This insulin is usually administered on a q8h schedule (NOT PRN).

In the outpatient setting, patients are thought to use an insulin syringe to draw doses. Because of this, the nomenclature patients learn are usually both the actual dose of insulin they are to administer in actual units of insulin, as well as what mark on an insulin syringe to drawn the dose up to. Example: 100 units of U-500 insulin = 20 units on an insulin syringe. This can be very confusing not only to patients, but to others providing care.

Our current safety practices for U-500 insulin:

Specific entry in Epic for U-500. Currently this requires both the actual Units of U-500 to be administered as well as the volume in mL to which it is to be drawn.

Storage in central pharmacy is in the C-II safe, away from all other insulin products
Pharmacy must draw up individual doses

Assessment: Several aspects of our safety plan could be improved in addition to our currect practices. These include:

Formulary

- Restrict to use only when each dose is >100 units
- Implement pharmacy consult for **all** U-500 patients
  - Double check patient's home dose and make sure ordered correctly
  - Autosub any doses </= 100 units to regular U-100 insulin

Ordering

- BPA to fire for providers if dose is <101 units not allowing them to process order
- Revise Epic ordering so that mLs is not part of the order as it leads to confusion because insulin syringe is not in mL
- Attach a document to the order with a crosswalk of actual dose to units on an insulin syringe

Storage/Preparation

- All sites to draw to dose and store product in central pharmacy C-II safe
- Require a pharmacy double check (best with 2 pharmacist, but if not available pharmacist/technician)

Education

- Reminder to Pharmacy and nursing staff

Plan: Approve above plan at 10/31/12 meeting. Get formulary approval for restrictions. Roll-out/educate other recommendations by 12/1/12.

May 2008 Formulary
Committee Meeting

U-500 Regular Insulin

Situation:
On occasion, a patient requiring very high doses of regular insulin will be prescribed U-500 regular insulin.

Background:
Regular insulin comes in two concentrations U-100 (100 units/mL) and U-500 (500 units/mL). Historically, Fairview has elected to not use the U-500 insulin because of potential errors that could result if this insulin was administered the U-500 in place of U-100 insulin, but in recent months we have had a few patients that warranted the use of U-500 due to doses in excess of 100 units..

To prevent accidental selection of this medication in both FCIS and WORx, the U-500 insulin was not included in the programming. Because of this a miscellaneous medication entry is required into the electronic system. When this feature is used, no alerts and safety features are built into the programming.

Assessment:
Because of the need to use this concentration on rare occasion, safety plans should be put into place to prevent errors.

Recommendation:

0. • Restrict prescribing of U-500 insulin to endocrinology
0. • Require the medication be stored in a separate location in central pharmacy (Whenever possible in the C-II safe fridge)
0. • Require all doses be drawn-to-dose (in an insulin syringe, with no overfill) in central pharmacy
1. • Add an alert in WORx stating the above
0. • On the insulin product page in FCIS, add this U-500 insulin to the non-formulary section with a note that it is restricted to endocrinology. If possible to create an MLM if U-500 insulin is ordered and the dose is <100 units/dose prohibiting use of U-500.
0. • Add teaching aid for nursing to FCIS in background

Regular Insulin U-500 Dosing Guidelines, Acute Care Diabetes Advisory Committee

Indication: U-500 insulin shall be considered when a patient is on a total daily dose (TDD)

of insulin ≥ 250 units.
Dosing: Prescribe in ml and insulin unit equivalents on a U-100 Lo Dose ½ CC insulin syringe

U-500: 1ml = 500 units
0.1ml of U-500 = 50 units of U-100
Start at 0.1ml every 8 hours, which provides 150 units/ 24 hours Increase in increments of 0.05 ml in hospitalized patient every 1-2 days.

Write as:
U-500 Regular Insulin 0.1ml = 50 insulin unit equivalents
To draw this up in a U-100 insulin syringe, draw to 10 units on the insulin syringe. Frequency: Every 8 hours 0800-1600-0000 or 0700-1500-2300
Do Not Order Prandial Bolus Doses with this insulin.
You may utilize U-100 Regular Insulin High Resistance Correction scale if necessary. We typically do not.

1

Conversion Information for Humulin® R U-500 (Concentrated) Insulin Dose

Humulin R U-500 dose (units)	U-100 insulin syringe (unit markings)	Volumetric (tuberculin or allergy) syringe volume (mL)
25	5	0.05
50	10	0.1
75	15	0.15
100	20	0.2
125	25	0.25
150	30	0.3
175	35	0.35
200	40	0.4
225	45	0.45
250	50	0.5
275	55	0.55
300	60	0.6
325	65	0.65
350	70	0.7
375	75	0.75
400	80	0.8
425	85	0.85
450	90	0.9
475	95	0.95
500	100	1.0

Dosing Formulas U-100 insulin syringe
Divide prescribed dose (actual units of Humulin R U-500) by 5 = unit markings in a U-100 insulin syringe

Volumetric (tuberculin or allergy) syringe
Divide prescribed dose (actual units of Humulin R U-500) by 500 = volume (mL) in a volumetric syringe

Indication for Humulin R U-500

0. • Humulin R U-500 is indicated as an adjunct to diet and exercise to improve glycemic control in adults and children with type 1 and type 2 diabetes mellitus.

0. • Humulin R U-500 is useful for the treatment of insulin-resistant patients with diabetes requiring daily doses of more than 200 units, since a large dose may be administered subcutaneously in a reasonable volume.

Select Safety Information for Humulin R U-500

0. • Humulin R U-500 is contraindicated during episodes of hypoglycemia and in patients hypersensitive to Humulin R U-500 or any of its excipients.
0. • **Starting or changing insulin therapy should be done cautiously and only under medical supervision.**
0. • **Humulin R U-500 contains 500 units of insulin in each milliliter (5 times more concentrated than Humulin R U-100). For Humulin R U-500, extreme caution must be observed in the measurement of dosage because inadvertent overdose may result in serious adverse reaction or life-threatening hypoglycemia.**

- Fluid retention and heart failure can occur with concomitant use of TZDs and Humulin R U-500.

Please see Important Safety Information starting on page 2 and accompanying Patient Information and Full Prescribing Information.

Important Safety Information for Humulin R U-500 (regular U-500 [Concentrated] insulin human injection, USP [rDNA origin])

Contraindications

0. • 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

0. • **Starting or changing insulin therapy should be done cautiously and only under medical supervision.**
0. • **Humulin R U-500 contains 500 units of insulin in each milliliter (5 times more concentrated than Humulin R U-100). For Humulin R U-500, extreme caution must be observed in the measurement of dosage because inadvertent overdose may result in serious adverse reaction or life-threatening hypoglycemia.**
0. • **Fluid Retention and Heart Failure with Concomitant Use of PPAR-gamma Agonists:** Thiazolidinediones (TZDs), which are PPAR-gamma agonists, can cause dose-related fluid retention, particularly when used in combination with insulin, including Humulin R U-500. Fluid retention may lead to or exacerbate heart failure. Observe patients for signs and symptoms of heart failure and consider discontinuation or dose reduction of the PPAR-gamma agonist.

Precautions

- • **Dosing Confusion/Dosing Errors**: Medication errors associated with Humulin R U-500 have occurred and resulted in hyperglycemia, hypoglycemia, or death. The majority of errors occurred due to errors in dispensing, prescribing, or administration.
  - − The Humulin R U-500 vial, which contains 20 mL, versus the Humulin R U-100 vial, which contains 10 mL, is marked with a band of diagonal brown stripes to distinguish it from the U-100 vial, which has no stripes. “U-500” is also highlighted in red on the label.
  - − The prescribed dose of Humulin R U-500 should always be expressed in actual units of Humulin R U-500 along with corresponding markings on the syringe the patient is using (ie, a U-100 insulin syringe or volumetric [tuberculin or allergy] syringe).
  - − A majority of administration errors occurred due to dosing confusion when the Humulin R U-500 dose was prescribed in units or volume corresponding to a U-100 insulin syringe or volumetric syringe markings, respectively, or the prescribed dose was administered without recognizing that the markings on the syringe used do not directly correspond to U-500 dose. 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 Humulin R U-500 doses with U-100 insulin syringes or volumetric syringes.

- **Hypoglycemia**: Hypoglycemia is the most common adverse reaction of all insulin therapies, including Humulin R U-500. Hypoglycemia may occur suddenly. Severe hypoglycemia may lead to unconsciousness, convulsions, temporary or permanent impairment of brain function, or death. As with all insulin preparations, the time course of Humulin R U-500 action may vary in different individuals or at different times in the same individual and is dependent on dose, site of injection, blood supply, temperature, and physical activity.
  - − Adjustment of dosage of any insulin may be necessary in patients with renal or hepatic impairment or if patients change their physical activity or their usual meal plan, or during times of illness, emotional disturbances, or other stresses. Concomitant oral antidiabetic treatment may need to be adjusted; however concomitant use is not recommended.
  - − Any patient who requires Humulin R U-500 for control of diabetes should be under close observation until appropriate dosage is established. Insulin resistance may be transitory, and dosage requirements may change over time. Use caution in patients with hypoglycemia unawareness and in patients who may be predisposed to hypoglycemia. The patient's ability to concentrate and react may be impaired as a result of hypoglycemia. These abilities are especially important in driving or operating other machinery.

Pease see Important Safety Information continued on page 3 and accompanying Patient Information and Full Prescribing Information.

Continued on next page >

Important Safety Information for Humulin R U-500, continued

Precautions, continued

0. **Hyperglycemia, Diabetic Ketoacidosis, and Hyperosmolar Non-Ketotic Syndrome**: Hyperglycemia, diabetic ketoacidosis, or hyperosmolar coma may develop if the patient takes less Humulin R U-500 than needed to control blood glucose levels. Severe sustained hyperglycemia may result in hyperosmolar coma or death.
0. **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 (eg, patients using potassium-lowering medications, patients taking medications sensitive to serum potassium concentrations).
0. **Hypersensitivity and Allergic Reactions**: Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products, including Humulin R U-500. Localized reactions and generalized myalgias have been reported.
0. **Renal or Hepatic Impairment**: Frequent glucose monitoring and insulin dose reduction may be required.
0. **Drug Interactions**: Some medications may alter insulin requirements and the risk for hypoglycemia and hyperglycemia. Some medications may mask the signs of hypoglycemia in some patients. Therefore, insulin dose adjustment and particularly close monitoring may be required.
0. **Pregnancy Category B**: There are no adequate and well-controlled clinical studies of the use of Humulin R U-500 in pregnant or nursing women or during labor and delivery.
1. **Pediatric Use**: There are no well-controlled studies of use of Humulin R U-500 in children.

Adverse Reactions

- **Hypoglycemia**: Hypoglycemia is one of the most frequent adverse events experienced by insulin users.
  - − Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as long duration of diabetes, autonomic diabetic neuropathy, use of medications such as beta-adrenergic blockers, changing insulin preparations, or intensified control (3 or more insulin injections per day) of diabetes.
  - − Hypoglycemia when using Humulin R U-500 can be prolonged and severe.
- **Additional adverse reactions include hypokalemia, lipodystrophy, local and systemic**

allergy, weight gain, and peripheral edema.

Dosage and Administration

- The injection of Humulin R U-500 should be followed by a meal within approximately 30 minutes of administration.
- Humulin R U-500 should only be administered subcutaneously. Do not administer Humulin R U-500 intravenously or intramuscularly.
- **Do not mix Humulin R U-500 with other insulins in the same syringe**.

For more safety information, please see accompanying Patient Information and Full Prescribing Information.

HI U500 HCP ISI 29MAR2013

INFORMATION FOR THE PHYSICIAN

HUMULIN® R

REGULAR
U-500 (CONCENTRATED)
INSULIN HUMAN INJECTION, USP
(rDNA ORIGIN)

DESCRIPTION

Humulin R® U-500 is a polypeptide hormone structurally identical to human insulin synthesized through rDNA technology in a special non-disease-producing laboratory strain of Escherichia coli bacteria.

Humulin R U-500 has the empirical formula $C_{257}H_{383}N_{65}O_{77}S_6$ and a molecular weight of 5808.

Humulin R U-500 is a sterile, clear, aqueous and colorless solution that contains human insulin (rDNA origin) 500 units/mL, glycerin 16 mg/mL, metacresol 2.5 mg/mL and zinc oxide to supplement the endogenous zinc to obtain a total zinc content of 0.017 mg/100 units, and water for injection. The pH is 7.0 to 7.8. Sodium hydroxide and/or hydrochloric acid may be added during manufacture to adjust the pH.

Humulin R U-500 is for subcutaneous injection only. It should not be used intravenously or intramuscularly.

Humulin R U-500 contains 500 units of insulin in each milliliter (5-times more concentrated than Humulin R U-100 [see DOSAGE AND ADMINISTRATION]). It also contains 16 mg glycerin, 2.5 mg metacresol as a preservative, and zinc-oxide calculated to supplement endogenous zinc to obtain a total zinc content of 0.017 mg/100 units and water for injection. Sodium hydroxide and/or hydrochloric acid may be added during manufacture to adjust the pH.

Adequate insulin dosage permits patients with diabetes to effectively utilize carbohydrates, proteins and fats. Regardless of dose strength, insulin enables carbohydrate metabolism to occur and thus to prevent the production of ketone bodies by the liver. Some patients might develop severe insulin resistance such that daily doses of several hundred units of insulin or more are required.

CLINICAL PHARMACOLOGY

Regulation of glucose metabolism is the primary activity of insulin. Insulin lowers blood glucose by stimulating peripheral glucose uptake by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulins inhibit lipolysis, proteolysis, and gluconeogenesis, and enhance protein synthesis and conversion of excess glucose into fat.

Administered insulin, including Humulin R U-500, substitutes for inadequate endogenous insulin secretion and partially corrects the disordered metabolism and inappropriate hyperglycemia of diabetes mellitus, which are caused by either a deficiency or a reduction in the biologic effectiveness of insulin. When administered in appropriate doses at prescribed intervals to patients with diabetes mellitus, Humulin R U-500 restores their ability to metabolize carbohydrates, proteins and fats.

As with all insulin preparations, the duration of action of Humulin R U-500 is dependent on dose, site of injection, blood supply, temperature, and physical activity.

Humulin R U-500 is unmodified by any agent that might prolong its action. Clinical experience has shown that it frequently has time action characteristics reflecting both prandial and basal activity. It takes effect within 30 minutes, has a peak similar to that observed with U-100 regular human insulin and has a relatively long duration of activity following a single dose (up to 24 hours) as compared with U-100 regular insulins. This effect has been credited to the high concentration of the preparation. The time course of action of any insulin may vary considerably in different individuals or at different times in the same individual.

INDICATIONS AND USAGE

Humulin R U-500 is indicated as an adjunct to diet and exercise to improve glycemic control in adults and children with type 1 and type 2

diabetes mellitus.

Humulin R U-500 is useful for the treatment of insulin-resistant patients with diabetes requiring daily doses of more than 200 units, since a large dose may be administered subcutaneously in a reasonable volume.

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

Any change of insulin should be made cautiously and only under medical supervision. Changes in insulin strength, manufacturer, type (e.g., regular, NPH, analog, etc.), species, or method of administration may result in the need for a change in dosage.

Humulin R U-500 contains 500 units of insulin in each milliliter (5-times more concentrated than Humulin R U-100). For Humulin R U-500, extreme caution must be observed in the measurement of dosage because inadvertent overdose may result in serious adverse reaction or life-threatening hypoglycemia.

Fluid retention and heart failure with concomitant use of PPAR-gamma agonists: Thiazolidinediones (TZDs), which are peroxisome proliferator-activated receptor (PPAR)-gamma agonists, can cause dose-related fluid retention, particularly when used in combination with insulin. Fluid retention may lead to or exacerbate heart failure. Patients treated with insulin, including Humulin R U-500, and a PPAR-gamma agonist should be observed for signs and symptoms of heart failure. If heart failure develops, it should be managed according to current standards of care, and discontinuation or dose reduction of the PPAR-gamma agonist must be considered.

PRECAUTIONS

Dosing Confusion/Dosing Errors

Medication errors associated with Humulin R U-500 have occurred and resulted in patients experiencing hyperglycemia, hypoglycemia or death. The majority of errors occurred due to errors in dispensing, prescribing or administration. Attention to the following details may prevent:

• Dispensing errors

The Humulin R U-500 vial, which contains 20 mL, versus the Humulin R U-100 vial, which contains 10 mL – is marked with a band of diagonal brown stripes to distinguish it from the U-100 vial, which has no stripes. “U-500” is also highlighted in red on the label.

• Prescribing errors (see DOSAGE AND ADMINISTRATION)

The prescribed dose of Humulin R U-500 should always be expressed in actual units of Humulin R U-500 along with corresponding markings on the syringe the patient is using (i.e., a U-100 insulin syringe or tuberculin syringe [see DOSAGE AND ADMINISTRATION]).

• Administration errors (see DOSAGE AND ADMINISTRATION)

A majority of these errors occurred due to dosing confusion when the Humulin R U-500 dose was prescribed in units or volume corresponding to a U-100 syringe or tuberculin syringe markings, respectively, or the prescribed dose was administered without recognizing that the markings on the syringe used do not directly correspond to U-500 dose. 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, in the event of a future hospitalization or visit to the Emergency Department.

A conversion chart is provided and should always be used when administering Humulin R U-500 doses with U-100 insulin syringes or tuberculin syringes.

Hypoglycemia

Hypoglycemia is the most common adverse reaction of all insulin therapies, including Humulin R U-500. Severe hypoglycemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or death. Severe hypoglycemia requiring the assistance of another person and/or parenteral glucose infusion or glucagon administration has been observed in clinical trials with insulin, including trials with Humulin R U-500.

As with all insulin preparations, the time course of Humulin R U-500 action may vary in different individuals or at different times in the same individual and is dependent on dose, site of injection, blood supply, temperature, and physical activity.

Adjustment of dosage of any insulin may be necessary if patients change their physical activity or their usual meal plan. Insulin requirements may be altered during illness, emotional disturbances, or other stresses. Concomitant oral antidiabetic treatment may need to be adjusted.

Any patient who requires Humulin R U-500 for control of diabetes should be under close observation until appropriate dosage is established. The response will vary among patients. Most patients will require 2 or 3 injections per day.

Insulin resistance, in some patients is transitory; after several weeks or months during which high dosage is required, responsiveness to the pharmacologic effect of insulin may be regained and dosage can be reduced.

The timing of hypoglycemia usually reflects the time-action profile of the administered insulin formulations. Other factors such as changes in food intake (e.g., amount of food or timing of meals), injection site, exercise, and concomitant medications may also alter the risk of hypoglycemia (see PRECAUTIONS, Drug Interactions).

As with all insulins, use caution in patients with hypoglycemia unawareness and in patients who may be predisposed to hypoglycemia (e.g., the pediatric population and patients who fast or have erratic food intake). The patient’s ability to concentrate and react may be impaired as a result of hypoglycemia. This may prevent a risk in situations where these abilities are especially important, such as driving or operating other machinery.

Severe hypoglycemia may develop 18 to 24 hours after the original injection of Humulin R U-500.

Hyperglycemia, Diabetic Ketoacidosis, and Hyperosmolar Non-Ketotic Syndrome

Hyperglycemia, diabetic ketoacidosis, or hyperosmolar coma may develop if the patient takes less Humulin R U-500 than needed to control blood glucose levels. This could be due to increases in insulin demand during illness or infection, neglect of diet, omission or improper administration of prescribed insulin doses or use of drugs that affect glucose metabolism or insulin sensitivity. Early signs of diabetic ketoacidosis include glycosuria and ketonuria. Polydipsia, polyuria, loss of appetite, fatigue, dry skin, abdominal pain, nausea and vomiting and compensatory tachypnea come on gradually, usually over a period of some hours or days, in conjunction with hyperglycemia and ketonemia. Severe sustained hyperglycemia may result in hyperosmolar coma or death.

Hypokalemia

Insulin stimulates potassium movement into the cells, possibly leading 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).

Hypersensitivity and Allergic Reactions

Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products, including Humulin R U-500 (see ADVERSE REACTIONS).

Localized reactions and generalized myalgias have been reported with the use of metacresol as an injectable excipient.

Renal or Hepatic Impairment

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

Drug Interactions

Some medications may alter insulin requirements and the risk for hypoglycemia and hyperglycemia (see ADVERSE REACTIONS, Drug Interactions).

Use in Pregnancy

Pregnancy Category B — All pregnancies have background risk of birth defects, miscarriage, or other adverse outcome regardless of drug exposure. This background risk is increased in pregnancies complicated by hyperglycemia and is decreased with good glucose control. It is important for patients to maintain good control of diabetes before conception and during pregnancy. Special attention should be paid to diet, exercise and insulin regimens. Insulin requirements may decrease during the first trimester, usually increase during the second and third trimesters and rapidly decline after delivery. Careful glucose monitoring is essential in these patients. Female patients should be advised to tell their physician if they intend to become, or if they become pregnant.

Studies show that endogenous insulin only crosses the placenta in minimal amounts. While there are no adequate and well-controlled studies in pregnant women, an extensive body of published literature demonstrates the maternal and fetal benefits of insulin treatment in patients with diabetes during pregnancy. Humulin R U-500 is a recombinant human insulin that is identical to the endogenous hormone; therefore, reproduction and fertility studies were not performed in animals.

Labor and Delivery

Careful glucose monitoring and management of patients with diabetes during labor and delivery are required.

Nursing Mothers

Endogenous insulin is present in human milk. Insulin orally ingested is degraded in the gastrointestinal tract. In lactating infants, no adverse reactions have been associated with maternal use of insulin. In a study of eight preterm infants between 26 to 30 weeks gestation, enteral administration of Humulin R did not result in hypoglycemia. Good glucose control supports lactation in patients with diabetes. Patients with diabetes who are lactating may require adjustments in insulin dose and/or diet.

Pediatric Use

There are no well-controlled studies of use of Humulin R U-500 in children.

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ADVERSE REACTIONS

Hypoglycemia

Hypoglycemia is one of the most frequent adverse events experienced by insulin users. Symptoms of mild to moderate hypoglycemia may occur suddenly and can include:

- sweating
- dizziness
- palpitation
- tremor
- hunger
- restlessness
- tingling in the hands, feet, lips, or tongue
- lightheadedness
- inability to concentrate
- headache
- drowsiness
- sleep disturbances
- anxiety
- blurred vision
- slurred speech
- depressed mood
- irritability
- abnormal behavior
- unsteady movement
- personality changes

Signs of severe hypoglycemia can include:

- disorientation
- unconsciousness
- death
- seizures
- coma

Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as long duration of diabetes, autonomic diabetic neuropathy, use of medications such as beta-adrenergic blockers, changing insulin preparations, or intensified control (3 or more insulin injections per day) of diabetes.

Without recognition of early warning symptoms, the patient may not be able to take steps to avoid more serious hypoglycemia. Patients who experience hypoglycemia without early warning symptoms should monitor their blood glucose more frequently, especially prior to activities such as driving. Mild to moderate hypoglycemia may be treated by eating foods or taking drinks that contain sugar. Patients should always carry a quick source of sugar, such as hard candy, non-diet carbohydrate-containing drinks or glucose tablets.

Hypoglycemia when using Humulin R U-500 can be prolonged and severe.

Hypokalemia

See Precautions

Lipodystrophy

Administration of insulin subcutaneously can result in lipoatrophy (depression in the skin) or lipohypertrophy (enlargement or thickening of tissue).

Allergy

Local Allergy — Patients occasionally experience erythema, local edema, and pruritus at the site of injection. This condition usually is self-limiting. In some instances, this condition may be related to factors other than insulin, such as irritants in the skin cleansing agent or poor injection technique.

Systemic Allergy — Less common, but potentially more serious, is generalized allergy to insulin, which may cause rash over the whole body, shortness of breath, wheezing, reduction in blood pressure, fast pulse, or sweating. Severe cases of generalized allergy (anaphylaxis) may be life threatening.

Weight gain

Weight gain can occur with some insulin therapies and has been attributed to the anabolic effects of insulin and the decrease in glycosuria.

Peripheral Edema

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

Drug Interactions

The concurrent use of oral antihyperglycemic diabetes agents with Humulin R U-500 is not recommended since there are limited data to support such use.

A number of substances affect glucose metabolism and may require insulin dose adjustment and particularly close monitoring.

Drugs that may increase the blood-glucose-lowering effect of Humulin R U-500 and susceptibility to hypoglycemia:

0. • Oral antihyperglycemic diabetes agents, salicylates, sulfa antibiotics, certain antidepressants (monoamine oxidase inhibitors, selective serotonin reuptake inhibitors [SSRIs]), pramlintide, disopyramide, fibrates, fluoxetine, propoxyphene, pentoxifylline, ACE inhibitors, angiotensin II receptor blocking agents, beta-adrenergic blockers, inhibitors of pancreatic function (e.g., octreotide), and alcohol.

Drugs that may reduce the blood-glucose-lowering effect:

- Corticosteroids, isoniazid, certain lipid-lowering drugs (e.g., niacin), estrogens, oral contraceptives, phenothiazines, danazol, diuretics, sympathomimetic agents, somatropin, atypical antipsychotics, glucagon, protease inhibitors and thyroid replacement therapy.

Drugs that may increase or decrease blood-glucose-lowering effect:

- Beta-adrenergic blockers, clonidine, lithium salts, and alcohol.
- Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.

Drugs that may mask the signs of hypoglycemia:

- Beta-adrenergic blockers, clonidine, guanethidine, and reserpine.

OVERDOSAGE

Excess insulin may cause hypoglycemia and hypokalemia. Hypoglycemia may occur as a result of an excess of insulin relative to food intake, energy expenditure, or both. Mild episodes of hypoglycemia usually can be treated with oral glucose. Adjustments in drug dosage, meal patterns, or exercise, may be needed. More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycemia may recur after apparent clinical recovery. Hypokalemia must be corrected appropriately.

DOSAGE AND ADMINISTRATION

Humulin R U-500 is usually given two or three times daily before meals. The dosage and time of Humulin R U-500 should be individualized and determined, based on the physician's advice, in accordance with the needs of the patient. The injection of Humulin R U-500 should be followed by a meal within approximately 30 minutes of administration.

The average range of total daily insulin requirement for maintenance therapy in insulin-treated patients without severe insulin resistance lies between 0.5 and 1.0 unit/kg/day. However, in pre-pubertal children it

usually varies from 0.7 to 1.0 unit/kg/day, but can be much lower during the period of partial remission. In situations of insulin resistance, e.g., during puberty or due to obesity, the daily insulin requirement may be substantially higher. Initial dosages for type 2 diabetes patients are often lower, e.g., 0.2 to 0.4 units/kg/day.

Humulin R U-500 is useful for the treatment of insulin resistant patients with diabetes requiring daily doses of more than 200 units, since a large dose may be administered subcutaneously in a reasonable volume.

Humulin R U-500 may be administered by subcutaneous injection in the abdominal wall, the thigh, the gluteal region or in the upper arm. Subcutaneous injection into the abdominal wall ensures a faster absorption than from other injection sites. Injection into a lifted skin fold minimizes the risk of intramuscular injection. Injection sites should be rotated within the same region. As with all insulin, the duration of action will vary according to the dose, injection site, blood flow, temperature, and level of physical activity.

Humulin R U-500 should only be administered subcutaneously. Do not administer Humulin R U-500 intravenously or intramuscularly.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Never use Humulin R U-500 if it has become viscous (thickened) or cloudy; use it only if it is clear and colorless. Humulin R U-500 should not be used after the printed expiration date.

Do not mix Humulin R U-500 with other insulins, as there are no data to support such use.

When administering Humulin R U-500

If U-100 insulin syringes are used, since their markings are in units and are designed and intended for use with the less concentrated U-100 insulin products, it is extremely important to explain the amount of Humulin R U-500 insulin to be administered in both actual dose and with specification of "unit markings" on the U-100 syringe.

If tuberculin syringes are used, since their markings are in volume (mL), the actual amount of Humulin R U-500 should be explained in both actual dose and with specification of volume (mL). Table 1 contains conversion information using both U-100 insulin and tuberculin syringes to help avoid dose confusion.

Table 1: Conversion Information for Humulin R U-500 Insulin Dose When Using a U-100 Insulin Syringe or a Tuberculin Syringe

Humulin R U-500 dose (units)	U-100 insulin syringe (unit markings)	Tuberculin syringe (volume in mL)
25	5	0.05
50	10	0.1
75	15	0.15
100	20	0.2
125	25	0.25
150	30	0.3
175	35	0.35
200	40	0.4
225	45	0.45
250	50	0.5
275	55	0.55
300	60	0.6
325	65	0.65
350	70	0.7
375	75	0.75
400	80	0.8
425	85	0.85
450	90	0.9
475	95	0.95
500	100	1.0
Dose (actual Humulin R U-500 units)	Divide dose (actual Humulin R U-500 units) by 5	Divide dose (actual Humulin R U-500 units) by 500

For doses other than those listed above refer to the following formulas:

U-100 insulin syringe

Divide prescribed Dose (actual units) by 5 = Unit markings in a U-100 insulin syringe.

Tuberculin syringe

Divide prescribed Dose (actual units) by 500 = Volume (mL) in a tuberculin syringe

Storage

Not in-use (unopened): Humulin R U-500 vials not in-use should be stored in a refrigerator, (2° to 8°C [36° to 46°F]), but not in the freezer.

In-use (opened): The Humulin R U-500 vial currently in-use can be kept unrefrigerated as long as it is kept as cool as possible (below 30°C [86°F]) away from heat and light. In-use vials must be used within 31 days or be discarded, even if they still contain Humulin R U-500.

Do not use Humulin R U-500 after the expiration date stamped on the label or if it has been frozen.

HOW SUPPLIED

Vials, 500 units/mL, 20 mL (HI-500) (1s), NDC 0002-8501-01

Literature revised March 9, 2013		
Marketed by: Lilly USA, LLC,		
Indianapolis, IN 46285, USA		
PA 3055 AMP		
HUMULIN® R REGULAR U-500 (CONCENTRATED)		
INSULIN HUMAN INJECTION, USP (rDNA ORIGIN)	PA 3055 AMP	

PATIENT INFORMATION

Humulin® (HU-mu-lin) R

Regular

U-500 (Concentrated)

insulin human injection, USP (rDNA origin)

Read the Patient Information that comes with Humulin® R U-500 before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your healthcare provider about your diabetes or treatment.

What is the most important information I should know about Humulin R U-500?

Humulin R U-500 (500 units/mL) contains 5 times as much insulin in 1 mL as standard U-100 (100 units/mL) insulin. This means that it is more concentrated than standard U-100 insulin.

Know your insulin. Make sure you know the strength, dose and type of insulin that is prescribed for you. Do not change the strength, dose or type of insulin you use unless told to do so by your healthcare provider.

It is important that you take the right dose of Humulin R U-500. Taking too much Humulin R U-500 can cause life-threatening low blood sugar (hypoglycemia) or death. Taking too little Humulin R U-500 can cause high blood sugar (hyperglycemia).

There are no special syringes to measure Humulin R U-500. It is important that you use only the syringes that your healthcare provider tells you to use. Your healthcare provider should tell you how much Humulin R U-500 to take and when to take it. Your healthcare provider should show you how to draw up Humulin R U-500. The amount of Humulin R U-500 will be less than the amount of standard U-100 insulin which would be drawn up into the syringe. See the section, “How should I take Humulin R U-500?”

What is Humulin R U-500?

Humulin R U-500 is a prescription medicine used to treat high blood sugar in people with diabetes mellitus. Humulin R U-500 is a man-made insulin that is similar to the insulin produced by the human pancreas. Humulin R U-500 is used along with diet and exercise to lower blood sugar in people with:

- type 1 diabetes.
- type 2 diabetes whose blood sugars are not controlled well with diabetes medicine taken by mouth.

Humulin R U-500 is useful for the treatment of insulin-resistant patients with diabetes who need more than 200 units of insulin a day.

It is not known if Humulin R U-500 is safe and effective in children.

Who should not take Humulin R U-500? Do not take Humulin R U-500 if:

- your blood sugar is too low (hypoglycemia). See the section, “What are the possible side effects of Humulin R U-500?” for more information on low blood sugar.
- you are allergic to any of the ingredients in Humulin R U-500. See the end of this leaflet for a complete list of ingredients in Humulin R U-500.

What should I tell my healthcare provider before taking Humulin R U-500? Before you take Humulin R U-500, tell your healthcare provider if you:

- have liver or kidney problems or any other medical conditions. Certain medical conditions can affect your insulin needs and your dose of Humulin R U-500.
- take any other medicines, especially ones commonly 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, plan to become pregnant, or are breast-feeding. It is not known if Humulin R U-500 will harm your unborn baby or breast-feeding child. You and your healthcare provider should talk about the best way to manage your diabetes while you are pregnant or breast-feeding. It is especially important to keep good control of your blood sugar during pregnancy.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Many medicines can affect your blood sugar levels and your insulin needs. Your Humulin R U-500 dose may need to change if you take other medicines. Especially tell your healthcare provider if you take other medicines to treat your diabetes.

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Know the medicines you take. Keep a list of your medicines with you and show it to your healthcare provider and pharmacist when you get a new medicine.

How should I take Humulin R U-500?

- Take Humulin R U-500 exactly as prescribed.
- Do not make any changes to your strength, dose or type of insulin unless you are told to do so by your healthcare provider.
- Check the label carefully to make sure you have the right type and strength of insulin prescribed for you.
- Your healthcare provider should show you how to prepare and inject Humulin R U-500 before you start taking it.
- Humulin R U-500 should look clear and colorless. Do not use Humulin R U-500 if it does not look clear, colorless or has particles in it. Talk with your pharmacist or healthcare provider if you have any questions.
- Follow your healthcare provider’s instructions about how often you should check your blood sugar level for hypoglycemia (too low blood sugar) and hyperglycemia (too high blood sugar).
- Humulin R U-500 starts working about 30 minutes after injection. The effects of Humulin R U-500 may last up to 24 hours.
- You should eat a meal within 30 minutes of injecting Humulin R U-500.
- Choose an injection area (upper arm, abdomen, buttocks, or thigh). Change injection sites within the area you choose for each dose. Do not inject into the exact same spot for each injection. Never inject Humulin R U-500 into a vein or muscle.
- Inject Humulin R U-500 under your skin (subcutaneous), as shown to you by your healthcare provider.
- Your healthcare provider should regularly check your diabetes with blood tests, including your blood sugar levels and hemoglobin A_{1C}.
- If you take too much Humulin R U-500, your blood sugar may fall too low (hypoglycemia). You can treat mild low blood sugar (hypoglycemia) by drinking or eating something sugary right away. Always carry a quick source of sugar, such as hard candy, fruit juice or glucose tablets.
- Your healthcare provider may prescribe a glucagon emergency kit so that others can give you an injection if your blood sugar becomes too low (hypoglycemic) and you are unable to take sugar by mouth.

There are no special syringes to measure Humulin R U-500. It is important that you use only the syringes that your healthcare provider tells you to use to give your injections of Humulin R U-500. You should use either a U-100 insulin syringe or tuberculin syringe as instructed by your healthcare provider.

- If you are using U-100 insulin syringes, your healthcare provider should explain how to use this syringe to give the prescribed dose with the unit markings on the syringe.
- If you are using tuberculin syringes, your healthcare provider should explain how to use this syringe to give the prescribed dose with volume markings on the syringe.

If you do not use the right syringe type, you may take the wrong dose of Humulin R U-500. This can cause you to have too low blood sugar (hypoglycemia) or too high blood sugar (hyperglycemia).

Make sure you know:

- your prescribed dose of Humulin R U-500.
- which syringe to use and how to draw up your prescribed dose.

If you do not understand your dose, talk with your healthcare provider about how much insulin to take.

If you are hospitalized or go to an emergency room, make sure to tell the hospital staff the actual dose of Humulin R U-500 that your healthcare provider has prescribed for you.

Your healthcare provider may change your dose of Humulin R U-500 because of:

- illness
- change in diet
- stress
- change in physical activity or exercise
- other medicines you take
- travel

Check your blood sugar and stay on the diet and exercise plan as prescribed by your healthcare provider.

- Do not share needles or syringes with others.
- Place used needles and syringes in a closable, puncture-resistant container. You may use a sharps container (such as a red biohazard container) or a hard plastic container (such as a detergent bottle) or a metal container (such as an empty coffee can). Ask your healthcare provider for instructions on the right way to throw away the container. There may be state and local laws about how you should throw away used needles and syringes.
- Do not throw the container in household trash and do not recycle.

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

- Alcohol. Drinking alcohol may affect your blood sugar when you take Humulin R U-500.
- Driving and operating machinery. You may have trouble paying attention or reacting if you have low blood sugar (hypoglycemia). Be careful when you drive a car or operate machinery. Ask your healthcare provider if it is all right for you to drive if you have:
  - Low blood sugar (hypoglycemia)
  - Decreased or no warning signs of low blood sugar

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

Humulin R U-500 can cause serious side effects, including:

- See the section “What is the most important information I should know about Humulin R U-500?”
- Low blood sugar (hypoglycemia).

Symptoms of low blood sugar may happen suddenly with Humulin R U-500. Symptoms of mild or moderate low blood sugar may include:

- sweating
- dizziness
- fast heart beat
- tremor
- hunger
- restlessness
- tingling in the hands, feet, lips or tongue
- lightheadedness
- trouble concentrating
- headache
- drowsiness
- trouble sleeping
- feeling anxious
- blurred vision
- slurred speech
- depressed mood
- feeling irritable
- abnormal behavior
- walking unsteady
- personality changes

Humulin R U-500 can cause low blood sugar (hypoglycemia) that is severe and that can last a long time.

- Severe low blood sugar can cause you to become confused, pass out (become unconscious), have seizures or coma, and could cause death.

Talk to your healthcare provider about how to tell if you have low blood sugar and what to do if this happens while taking

Humulin R U-500. Know your symptoms of low blood sugar. Follow your healthcare provider's instructions for treating your low blood sugar.

Tell your healthcare provider if low blood sugar is a problem for you. Your healthcare provider may need to change the amount of Humulin R U-500 that you take, change your meal plans or your exercise program to help you avoid low blood sugar.

- • Serious allergic reactions. Get medical help right away if you have any of these symptoms of a severe allergic reaction:
  - • rash all over your body
  - • shortness of breath
  - • trouble breathing (wheezing)
  - • fast heart beat
  - • sweating
  - • feel faint
  - • Low potassium (hypokalemia) in your blood. Your healthcare provider may do blood tests to check you for low potassium.

Common side effects of Humulin R U-500 include:

0. • Skin thickening or pits at the injection site (lipodystrophy). Change (rotate) where you inject your insulin to help prevent these skin changes from happening. Do not inject insulin into this type of skin. Do not inject into the exact same spot for each injection.

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0. • Injection site reactions (local allergic reaction). Symptoms may include: redness, swelling and itching at the injection site. Tell your healthcare provider if you have skin reactions that do not go away.

Humulin R U-500 may cause serious side effects, including:

- • swelling of your hands and feet
- • 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.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all of the possible side effect of Humulin R U-500. For more information, ask your healthcare provider or pharmacist.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Humulin R U-500? Unopened vials of Humulin R U-500:

0. • Keep unopened vials of Humulin R U-500 in a refrigerator at 36°F to 46°F (2°C to 8°C).
0. • Do not freeze. Do not use Humulin R U-500 if it has been frozen.
0. • Do not use Humulin R U-500 after the expiration date stamped on the label.

Opened (in-use) vial of Humulin R U-500:

0. • Keep opened vial of Humulin R U-500 in the refrigerator or at room temperature below 86°F (30°C).
0. • Keep Humulin R U-500 away from heat and direct sunlight.
0. • The opened vial must be used within 31 days of opening. Throw away any opened vial after 31 days of use, even if there is insulin left in the vial.
0. • Do not use Humulin R U-500 after the expiration date stamped on the label.

Keep Humulin R U-500 and all medicines out of the reach of children. General Information about Humulin R U-500

Medicines are sometimes prescribed for purposes other than those listed in patient information leaflets. 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 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 healthcare provider or pharmacist for information about Humulin R U-500 that is written for healthcare professionals.

For more information about Humulin R U-500 call 1-800-545-5979 or go to www.lilly.com.

What are the ingredients in Humulin R U-500? Active ingredient: human insulin rDNA origin

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

This Patient Information has been approved by the U.S. Food and Drug Administration.

Patient Information revised March 9, 2013

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

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HUMULIN® R REGULAR U-500 (CONCENTRATED)
INSULIN HUMAN INJECTION, USP (rDNA ORIGIN) PA 8902 AMP