



U-500 Regular Insulin: Who and When?

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U-500 is a concentrated insulin five times as potent as standard U-100 insulin. The use of U-500 is increasing because of the obesity epidemic, tighter A1C goals, and an increase in off-label U-500 use in insulin pumps. There is a high risk of adverse events associated with U-500 use due to its concentration and health care providers' lack of experience with the product. This article is intended to identify patients who may benefit from treatment with U-500 insulin and to enable safe, appropriate administration.

Extreme insulin resistance is defined as requiring greater than 200 units of exogenous insulin per day. Causes of extreme insulin resistance include morbid obesity, Cushing's syndrome, severe infection, acromegaly, insulin receptor abnormalities, pregnancy, steroid use, Werner's syndrome, and high levels of insulin binding antibodies. Some of these conditions are temporary and morbid obesity remains the most common of these causes.

Goals of Therapy

The goals of therapy for patients with extreme insulin resistance are the same as American Diabetes Association (ADA) goals for other forms of diabetes, although these goals are often not met. As insulin resistance increases, the amount of insulin required to meet glycemic goals increases. Patients with insulin-resistant syndromes have less of a dose response to insulin, especially at doses above 100 units. High-dose insulin can help patients reach their glycemic goals, but a limitation of high-dose insulin is that the volume of U-100 needed is often more than can fit in one syringe. When multiple injections are required to administer one dose of insulin, there is frequently less compliance and worse glycemic control.

Pharmacokinetics

U-500 is a regular insulin, but has a kinetic profile very similar to NPH because of its high concentration. U-500 insulin levels rise quickly within 30 minutes and peak in 4-6 hours. One study on the kinetics of U-500 insulin shows significant levels remaining at 8 hours and lasting as long as 24 hours. The volume of the dose of insulin affects its absorption. High doses of insulin can delay the peak and duration of action. U-500 is pregnancy category B, and insulin remains the drug of choice for diabetes control during pregnancy.



Efficacy

There are no large clinical trials assessing the safety and efficacy of U-500, but a number of small studies have assessed use in treating extremely insulin-resistant patients. Three trials evaluating a switch from U-100 insulin to U-500 insulin in a small cohort of patients showed an average decrease in A1C of about 2% with a small associated increase in weight.

Dosing

U-500 insulin is to be used alone and not in combination with other insulin, although

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Objectives:

- ◆ Identify a patient who would be a good candidate for U-500 regular insulin.
- ◆ Discuss the risks and benefits of U-500 use for the treatment of severe insulin resistance.
- ◆ Describe the differences in the half-life, metabolism, and dosing of the DPP-4 inhibitors.

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U-500 Regular Insulin: Who and When?

there is a study evaluating its use with prandial lispro. Oral medications used for increasing insulin sensitivity including metformin and pioglitazone can be continued. Injections are generally given twice daily, but can be divided into three or four injections for patients taking very high doses. One article on U-500 use suggests that doses above 300 units per day should be divided into three doses (or four doses for greater than 750 units), but a study on the kinetics of U-500 showed that twice daily dosing achieved sufficient coverage, even at very high doses. Doses should be injected 30 minutes prior to meals, similar to other regular insulin. Blood glucose should be monitored at least twice daily while on U-500 insulin- just before breakfast and dinner. Target fasting blood glucose levels are 70-120 mg/dL. If morning fasting blood glucose values are less than 70 mg/dL, the evening dose should be decreased. If the fasting glucose readings are consistently high, the previous insulin dose should be increased. The dose of U-500 should be adjusted based on patterns reflected over a number of days of monitoring, not by a single value. Intensive blood glucose monitoring and carbohydrate counting are not commonly used for dosing U-500 insulin. Patients using greater than 2,000 units of U-500 insulin per day should consider the use of an insulin pump. In a

pump you may see a basal rate and boluses given with U-500. It is important that patients on pumps work with a professional who has experience with U-500 as the settings will be very different. Table 1 shows one of several algorithms used to dose U-500 insulin.

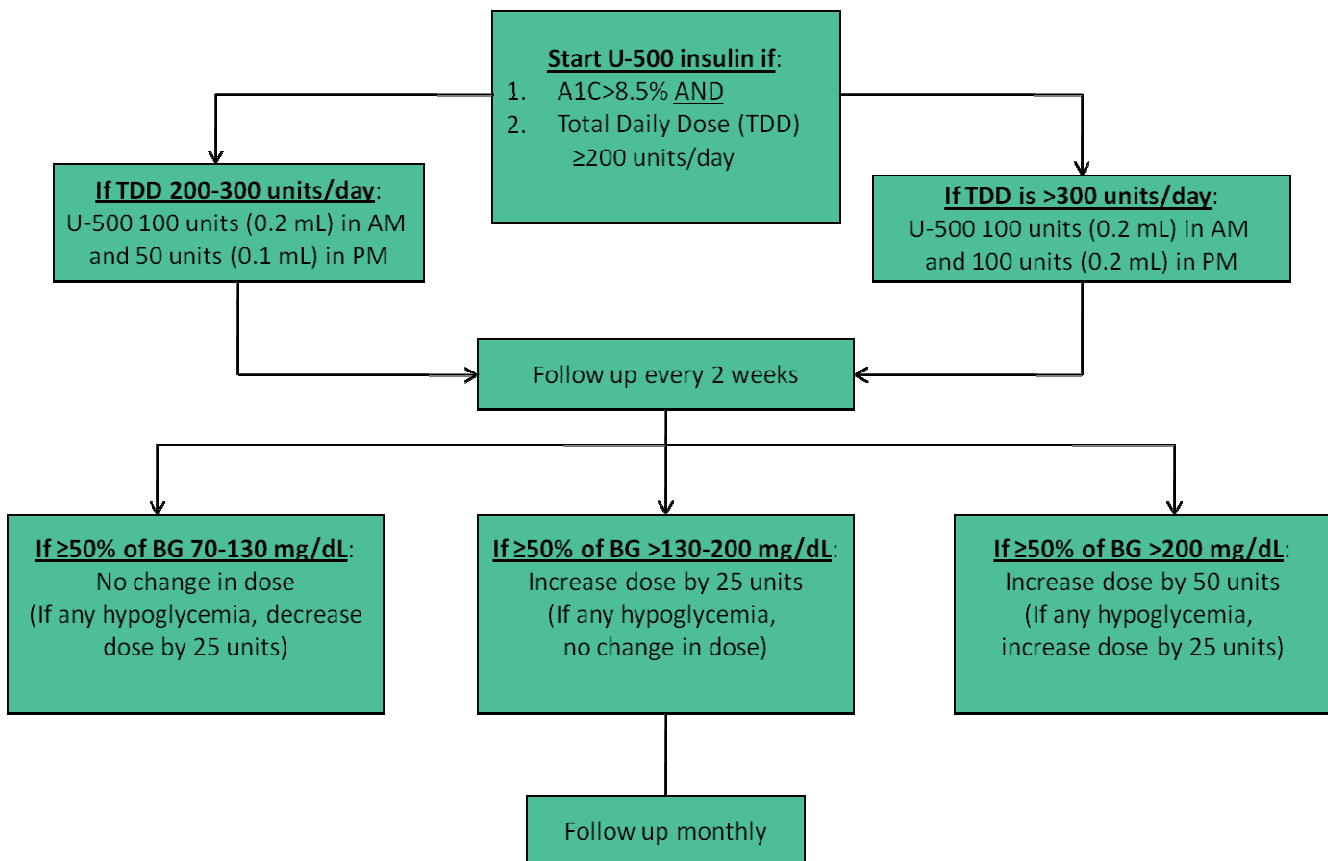
Who Should be Treated With U-500?

U-500 insulin can be considered in patients who require greater than 200 units of insulin per day and have an A1C greater than 8.5%. Patients on U-500 insulin should be able to understand the differences between U-500 and U-100 insulin, including how to draw up the appropriate number of units, when to dose the insulin, and not to self-adjust insulin doses based upon carbohydrate consumption. Patients who are used to a basal-bolus insulin regimen may have difficulties with transitioning to only two injections a day and not using a rapid-acting insulin to treat episodes of hyperglycemia.

Often, insulin-resistant conditions will resolve and a patient can be transitioned back to U-100 insulin. One study showed that this was most successful once a patient required less than 175 units per day. The algorithm used to initiate U-500 in a patient can be used in reverse order to transition a patient back to U-100 insulin.

Table 1. Dosing Algorithm for U-500 Insulin

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FDA Approves Linagliptin (Tradjenta™) For Type 2 Diabetes

Linagliptin (Tradjenta™) was approved by the FDA in May 2011 for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes.

Mechanism of Action

Linagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor. The DPP-4 enzyme is responsible for inactivating GLP-1, incretins that stimulate insulin release and inhibit glucagon release. DPP-4 inhibitors also delay gastric emptying and decrease blood glucose levels.

Dosing

The dose of linagliptin is 5 mg once daily. It can be taken with or without food. When used in combination with a sulfonylurea, the dose of the sulfonylurea should be decreased to avoid episodes of hypoglycemia. Unlike the other DPP-4 inhibitors, no dosing adjustment is required for renal impairment.

Drug Interactions

Rifampin decreases the concentration of linagliptin when co-administered. Linagliptin should not be administered with a P-glycoprotein inducer (e.g., rifampin) or CYP3A4 inducer (e.g., phenytoin) when possible.

Table 2. Comparison of DPP-4 Inhibitors

DPP-4 Inhibitor	Recommended Daily Dose	Dosing Adjustments Required?	Half-life	Therapeutic Notes
Linagliptin (Tradjenta™)	5 mg	No	12 hours	Not studied for use with insulin, not for use in Type 1 diabetes or patients with DKA, lower dose of sulfonylurea when used together to avoid hypoglycemia, majority is excreted unchanged.
Saxagliptin (Onglyza™)	5 mg	Yes 2.5 mg for patients with CrCl<50mL/min or concomitant strong CYP450 3A4 inhibitor	3 hours	Substrate of CYP3A4, eliminated via renal and hepatic pathways, not for use in Type 1 diabetes or patients with DKA, can increase peripheral edema when used with a TZD, can increase hypoglycemia when used with a sulfonylurea.
Sitagliptin (Januvia®)	100 mg	Yes CrCl 30-50 mL/min: 50 mg CrCl<30 mL/min: 25 mg OR concomitant insulin	12.4 hours	Can be used with insulin. Not studied in patients with a history of pancreatitis, not for use in Type 1 diabetes or patients with DKA, can increase hypoglycemia when used with a sulfonylurea or insulin, 87% excretion by kidneys, must be dose modified for renal impairment

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- ♦ Dicker D. DPP-4 Inhibitors: Impact on glycemic control and cardiovascular risk factors. *Diabetes Care*. 2011;34:S276-78.
- ♦ Tradjenta package insert. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; 2011.

Efficacy

Linagliptin lowers A1C about 0.5% when used as monotherapy. Two randomized controlled trials found significant improvements in A1C, fasting plasma glucose, and 2-hour post-prandial glucose when compared with placebo.

Safety and Adverse Events

Adverse events associated with DPP-4 use include nasopharyngitis, headaches, hypersensitivity reactions, Stevens-Johnson syndrome, and pancreatitis.

Limitations of Use

Linagliptin should not be used in patients with Type 1 diabetes or for the treatment of diabetic ketoacidosis. Linagliptin has not been studied for use in combination with insulin.



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Potential Errors

The type of syringe used to administer U-500 insulin should be carefully considered. Standard insulin syringes unit markings will not represent the number of units being injected with U-500 insulin. This may be confusing to some patients and is a potential source of error and overdose. Tuberculin syringes can be used with U-500 as the markings represent volume only (not units). The drawbacks to tuberculin syringes are that they are often difficult to obtain, the needle is much larger than standard insulin syringes, and some insurers may not recognize them as diabetes supplies. Patients should be thoroughly educated on how to properly draw up a dose of U-500 and that the volume will not match the number of units being injected. All family members and caregivers should be counseled that U-500 insulin is highly concentrated.

When providers write a prescription for U-500 insulin, they should include both the volume and the units in the instructions to avoid confusions and errors. Example: "U-500 regular insulin, Inject 0.2 mL (100 units) subcutaneously two times daily 30 minutes before meals." The insulin label should also reflect a warning that the insulin is concentrated and neither the patient nor caregivers should adjust the dose.

All insulin pumps containing U-500 insulin should have a sticker placed on the pump that clearly states this.

Cost

A bottle of U-500 insulin is higher in cost than a bottle of U-100, but U-500 costs less per unit than other insulin. Additionally, a patient on U-500 will use significantly less syringes or pump cartridges than a patient on U-100, adding to cost savings.

U-500 is an effective therapy for a subset of extremely insulin-resistant patients. With a kinetic profile similar to NPH, it can be considered for twice daily use in patients on more than 200 units of insulin per day who have not reached their glycemic goals. Because it is five times as potent and U-100 insulin, patients should be educated about calculating and drawing up the proper dose, not self-adjusting doses, and informing all caregivers that they are on a concentrated insulin. U-500 costs less per unit than other insulin. Caution should be used in the storage and administration of U-500 insulin. U-500 insulin is recommended and can be used safely in patients requiring high doses of insulin to achieve their glycemic goals.

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Goal-The goal of the Diabetes Dispatch is to increase the reader's knowledge of diabetes treatments and technologies and to provide the most current information on new drugs, therapies, and devices.

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Continuing Education Quiz

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1) U-500 insulin doses should be adjusted based on which of the following?

- Intense blood glucose monitoring
- Carbohydrate counting
- Trends in prebreakfast and predinner glucose values
- Fasting blood glucose value on day 7 of therapy

2) True or False: Patients using U-500 insulin should check their blood glucose a minimum of four times daily.

3) Which of the following is not an important counseling point for a patient using U-500 insulin?

- Educate family member and caregivers about concentrated insulin
- Insurance may not cover high cost of U-500
- Syringe markings do not reflect units of U-500 given
- Do not self-adjust insulin doses

4) Which of the following can be co-administered with U-500?

- Glyburide
- Metformin
- Exenatide
- Insulin aspart

5) The pharmacokinetic profile of U-500 regular insulin is most similar to which of the following?

- Glargine
- U-100 regular insulin
- NPH
- Insulin aspart

6) True or False: U-500 should be used with prandial insulin for optimal glycemic control.

7) LS is a 67-year old male with Type 2 diabetes with extreme insulin resistance. LS is using 150 units of glargine every night with 50 units of aspart with each meal during the day. His current A1C is 6.7%. Is LS a candidate for U-500 insulin?

- Yes
- No

8) Which of the following blood glucose levels would be within the appropriate range for pre-breakfast and pre-dinner testing in a patient using U-500?

- 65 mg/dL
- 109 mg/dL
- 133 mg/dL
- 140 mg/dL

9) AL is a 48 year old female currently being treated for Type 2 diabetes with metformin, glargine, and aspart. His total daily dose of insulin is around 300 units. His diabetes team has decided to use U-500 insulin to help better control his blood glucose. Which of these medications should be discontinued with the addition of U-500?

- Metformin
- Glargine
- Aspart
- B and C

10) Linagliptin can reduce a patient's A1C by about:

- 0.2-0.4%
- 0.5%
- 1-2%

Pharmacists and Technicians:

To obtain CPE credit for this lesson you must answer the questions on the quiz (70% correct required) return the quiz and evaluation tool. Should you score less than 70%, you will be asked to repeat the quiz. In May and November of each year we will mail a statement of credit, unless otherwise arranged with the AkPhA office. This program furnishes 1.0 hour CPE (0.1 CEU) credit per lesson.

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3) Increased my knowledge of topic	1	2 3 4 5	6) Overall, I was satisfied with the activity	1	2 3 4 5

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