

# U-500 Insulin: An Effective Treatment for Patients with Type 2 Diabetes and Severe Insulin Resistance

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## Abstract

Human regular insulin 500 (U-500) is a form of concentrated insulin that allows injection of high insulin doses with 5 times less volume compared with regular insulin. This concentrated insulin is indicated in patients with type 2 diabetes who require more than 200 units of insulin per day. Insulin U-500 displays both prandial and basal actions, and therefore can be injected as monotherapy in a convenient twice-daily regimen. Available data, mainly retrospective, suggest that insulin U-500 is effective, associated with better adherence, and decreased injection pain compared with non-concentrated insulins. Its main limitations are hypoglycemia and weight gain, and possibility of dosing errors. Randomized trials are needed to compare long-term efficacy and safety of insulin U-500 with other forms of insulin regimens.

## Introduction

It is not uncommon that some patients with insulin-resistant type 2 diabetes, particularly morbidly obese, require large doses of insulin for glycemic control. Meanwhile, most insulin preparations are present in concentrations of 100 units/ml. Therefore, a patient who needs one insulin dose of more than 100 units has to use more than one injection. Insulin U-500 is a human regular insulin formulation that is 5 times as concentrated as the commonly used human regular insulin (U-100), i.e. U-500 contains 500 units of insulin per ml as opposed to 100 units/ml in non-concentrated insulins. This concentrated formulation allows the injection of large insulin doses of greater than 100 units to be delivered in the fifth amount of volume of non-concentrated insulin.

Insulin U-500 was approved by the Federal Drug Administration (FDA) in the USA in 1994 for insulin-resistant patients with type 2 diabetes who require more than 200 units of insulin per day [1]. Because of rise in incidence of obesity in the USA, the use of U-500 has been increased approximately 10-fold from 2005 to 2013 [2]. The purpose of this article is to provide a mini-review on the pharmacokinetics, efficacy, safety, advantages and limitations of U-500 based on the available data and author's experience.

## Pharmacokinetics

The time action profile of regular U-500 insulin exhibits both prandial and basal effects [1]. Thus, mean onset and duration of action are 15min and 21 hours, respectively [2]. The peak plasma insulin levels occurred between 4 hours (50-unit dose) and 8hours (100-unit dose).

Concentrated insulins are absorbed slower than non-concentrated insulin [3]. Thus, when compared with traditional human regular insulin (U-100) at doses of 100 units in healthy obese subjects, time to peak concentration and time to maximum effect were significantly longer with U-500 than U100. In addition, maximum plasma concentrations (C<sub>max</sub>) of U-500 were significantly lower than U-100, and its duration of action was longer (21.5 hours versus 18.3 hours for U-100 leading to a flat time-action profile. Mean half-life after a single 100-unit dose is approximately 4.4h for U-500 versus 3.3 h for U-100 [4].

### Available preparations of insulin U-500

U-500 is dispensed in a 3ml pen (1,500 units) or in a 20ml-vial (10,000 units), with maximum insulin doses delivered in a single injection of 300 and 250 units, respectively [1].

### Efficacy of insulin U-500

Available data suggest that U-500 is effective, but the degree of efficacy is variable depending on several factors: doses, patients' characteristics and baseline hemoglobin A1c (HbA1c). Unfortunately, there are no available randomized trials comparing U-500 with other types of insulin regimen. One randomized trial compared U-500 given bid with U500 given tid. After 24 weeks, there was no significant difference in HbA1c reduction, 1.12% and 1.22% in the TID and BID regimen, respectively [5].

### Safety of insulin U-500

Similar to other insulins, the 2 most common adverse effects of U-500 are hypoglycemia and weight gain. Yet, because of lack of head to head comparison between U-500 and other insulins, the specific impact of U-500 on these 2 parameters is not clear. Hood et al. [5] found higher frequency of nocturnal hypoglycemia (blood glucose <50mg/dl) in patients randomized to U-500 given BID compared with TID, 36% and 49%, respectively. Likewise, symptomatic hypoglycemia (blood glucose < 70mg/dl) occurred slightly more frequently among the BID group (92%) compared with TID group (90%),  $P=0.003$ . In the previous study, weight gain was 4.9kg and 5.4kg in the 2 groups of patients randomized to U-500 TID and BID, respectively.

### Patient satisfaction

Patients who switched from multiple insulin injections (median 5 injections/day) to U-500 reported improvement in treatment burden, daily life and compliance, particularly with the BID regimen compared with the TID regimen. Moreover, there was significant improvement in injection site pain from baseline to end of trial at week 24 whether U-500 was given BID or TID [6].

### Indications and initiation of insulin U-500

Candidates for U-500 are insulin-resistant patients with type 2 diabetes requiring more than 200 units of insulin/day. These patients are commonly morbidly obese and already receiving high number (5-7) of insulin injections/day. Before the conversion of prior insulin regimen to U-500, it is crucial to confirm the actual insulin doses because incomplete adherence to insulin therapy is frequent as result of increase injection burden. It is a common practice to reduce insulin daily doses by~20% or more when converting to U-500 to avoid hypoglycemia and to account for possible prior non-adherence [7]. Then, the U-500 total daily dose may be divided into 2 doses: 60% of the dose 30 min before breakfast and 40% 30min before dinner to decrease incidence of nocturnal hypoglycemia.

### Use of U-500 in hospitals

The use of U-500 is not indicated in hospitalized patients to avoid dosing errors. When a patient taking U-500 is admitted to the

hospital, it is safer to switch to a non-concentrated insulin regimen. Because food intake in hospitals is much less compared with home, it is recommended to decrease the initial total daily dose of insulin by 50% or more after hospital admission [8,9].

### Cost of insulin U-500

The whole price sale of 20ml vial (10,000 units) of U-500 and the 3ml Kwik-pen (1,500 units) is approximately \$1,200 and \$303, respectively [10]. Although these prices are higher than regular insulin U-100, using a large healthcare claims database in the USA, Eby et al. [11] showed that treatment with insulin U-500 was associated with significant decreases in pharmacy and overall costs, and better adherence compared with treatment with high-dose (>200 units/day) of insulin U-100. Moreover, there was no significance difference between the 2 insulin regimens in hypoglycemia-specific costs and in resource utilization [11].

### Limitations of U-500

Dosing errors may occur if patient is not properly informed about the concept of U-500, and if U-500 is injected by syringes of non-concentrated insulin. Propensity of dosing errors has greatly diminished after the introduction of a dedicated syringe, specifically graduated for U-500 injection. This U-500 specific syringe was approved by the FDA and is commercially available since 2016. It is a 0.5ml green-capped syringe with bold markings in 5-unit increments allowing a maximum dose of 250 units at one injection [12]. In addition, in 2016, the FDA approved the U-500 R Kwik-pen by Eli Lilly [1]. This pen can provide up to 300 units per dose but is more expensive than the dedicated syringe. Advantages and disadvantages of U-500 are summarized in Table 1.

**Table 1:** Advantages and disadvantages of insulin U-500.

Advantages	Disadvantages
Lesser number of injections per day, usually only 2 injections.	No head to head trials comparing U-500 with other insulin regimens.
Works as basal/bolus insulin so can be used as monotherapy.	Requires comprehensive patient education to avoid dosing errors.
Can be delivered by a dedicated syringe or a pen.	High cost, especially with the Kwik-pen U-500.
High patient satisfaction and adherence	

### Conclusion

Insulin U-500 is the most concentrated available form of insulin allowing the reduction of injected volume of insulin by one-fifth. This insulin is a convenient treatment of patients with type 2 diabetes who are insulin-resistant and require high number of daily insulin injections. Compliance with this form of insulin is higher than non-concentrated insulin because of reduction in injection frequency to only 2 injections per day, its use a monotherapy, and decreased injection pain. Randomized trials should better define the efficacy, safety, and overall cost of U-500 compared with other insulin modalities.

## Conflict of Interest

The author has no conflict of interest in any product mentioned in the article

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