

# Clinical Challenges With Concentrated Insulins: Setting the Record Straight

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The availability of insulins with concentrations greater than the standard 100 units/mL (U-100) concentration (adopted in the United States in 1973) provides additional options for managing diabetes, but these agents may be a source of confusion for many clinicians. Our awareness of such confusion has come about after a number of inquiries from health care providers (HCPs) to Lilly Diabetes, U.S. Medical Affairs, and inaccuracies in recent articles and published guidance. The purpose of this editorial is to bring attention to some of the more common and crucial issues and provide relevant background and clinical evidence to address and clarify misunderstandings and instruct HCPs on the safe and appropriate use of these agents.

## 1. What concentrated insulins are available, and why were they developed?

Four concentrated insulins are available in the United States. Three are analog insulins, which have been approved in the past 2–3 years: insulin glargine 300 units/mL (IGlar300) (1), insulin degludec 200 units/mL (IDeg200) (2), and insulin lispro 200 units/mL (ILis200) (3). The fourth, human regular insulin 500 units/mL (U-500R) (4), has been commercially available since 1997.

These agents have diverse pharmacokinetic/pharmacodynamic (PK/PD) profiles and were developed to address different challenges of insulin therapy (5). Designing a

basal insulin with stable, prolonged action was the rationale for IGlar300 (6). Insulin degludec was also developed as a longer-acting basal agent; the concentrated formulation (IDeg200) may benefit patients with higher insulin requirements (7). The more stable and protracted time-action profile for IGlar300 and insulin degludec (both 100 and 200 units/mL) supports once-daily dosing and may result in reduced hypoglycemia compared to insulin glargine 100 units/mL (IGlar100) (6–18). Rapid-acting prandial ILis200 is delivered in half the volume of the corresponding U-100 formulation, allowing a twofold increase in device capacity (19) and resulting in a longer-lasting pen. U-500R is a prandial/basal agent intended specifically for patients with severe insulin resistance (i.e., total daily dose [TDD] >200 units) as insulin monotherapy (4,20).

## 2. What is the difference between concentrated and U-100 formulations?

Insulin concentration is defined by the number of insulin units per milliliter. The standard concentration, U-100, contains 100 units/mL. Likewise, U-200, U-300, and U-500 contain 200, 300, and 500 units/mL, respectively, thereby reducing the administered volume by two- to five-fold. Injection of lower volumes is a potential benefit of these agents and has been shown to reduce injection site discomfort for U-500R (21). Differences in concentration/volume

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can have both direct and indirect effects, such as PK/PD effects. These and other distinctions are discussed below.

### 3. How is bioequivalence defined, which concentrated insulins are bioequivalent, and what are the clinical implications?

Bioequivalence is defined by PK parameters per regulatory guidance. To establish bioequivalence, 90% confidence intervals (CIs) for area under the curve (AUC) and maximum concentration ( $C_{\max}$ ) ratios of comparators must fall within 0.80–1.25 (22,23). The bioequivalent concentrated insulins with respect to their U-100 counterparts are IDeg200 and ILis200. Bioequivalence of these agents was demonstrated in euglycemic clamp studies, including a steady-state study for IDeg200 versus insulin degludec 100 units/mL (IDeg100) (8) and a single-dose study for ILis200 versus insulin lispro 100 units/mL (ILis100) (19). When changing from U-100 to U-200 bioequivalent insulins, that is, from IDeg100 to IDeg200 or from ILis100 to ILis200, the dose remains the same (i.e., unit-for-unit). Likewise, safety and efficacy are expected to be similar.

In contrast, IGlar300 and U-500R are not bioequivalent to their U-100 counterparts. Pharmacokinetic studies comparing IGlar300 to IGlar100 did not support bioequivalence in terms of either AUC or  $C_{\max}$  (6,11,14). Although PK results for U-500R versus human regular insulin 100 units/mL (U-100R) met the above criterion for AUC, confidence intervals for  $C_{\max}$  treatment ratios were outside the acceptable range for bioequivalence (24).

### 4. Are concentrated insulins better absorbed?

A common misconception is that concentrated insulins are better absorbed than the corresponding U-100 agents. This is not supported by PK results. Euglycemic clamp studies comparing IDeg200, ILis200, and U-500R

with the corresponding U-100 counterparts demonstrated similar overall exposure levels (AUCs) between comparators (8,19,24), which correlate with insulin absorption. These studies involved subjects with type 1 diabetes (IDeg200/IDeg100, steady-state dosing), healthy volunteers (ILis200/ILis100, single-dose method), or healthy obese subjects (U-500R/U-100R, single-dose method). On the other hand, for IGlar300 versus IGlar100, results from single-dose PK/PD studies in subjects with type 1 diabetes showed lower exposure for the concentrated product (i.e., lower AUC,  $P < 0.05$ ) (14), which was consistent with 24-hour results at steady state (treatment ratio [IGlar300/IGlar100], 0.83 [90% CI, 0.69–1.00]) (11).

### 5. When is “a unit a unit?”

Unit equivalence, or equipotency, of two insulin preparations can potentially be affected by changes in concentration as a consequence of altered exposure/absorption. The insulin unit has been defined by various international standards, which historically were quantified according to glucose reduction in a fasting rabbit (25). Presently, euglycemic clamp studies characterizing PD time-action profiles are used to assess relative potency, which can be confirmed in Phase 3 efficacy studies. The three concentrated products demonstrating similar exposure between comparators (IDeg200/IDeg100, ILis200/ILis100, and U-500R/U-100R) also showed similar potency (overall glucose infusion) (8,19,24), thus supporting unit equivalence. Alternatively, lower potency for IGlar300 versus IGlar100 was demonstrated in single-dose ( $P < 0.05$ ) and steady-state comparisons (24-hour ratio IGlar300/IGlar100, 0.73 [90% CI 0.56–0.94]) and in randomized clinical trials (RCTs) (9–16). Importantly, it is incorrect to state that any of the concentrated insulins are more potent by virtue of their higher concentration. For example, U-500R is not a more potent

form of regular human insulin; it is five times more concentrated (i.e., it delivers the same number of units in one-fifth the volume).

### 6. How do clinicians initiate/switch to concentrated insulin therapy and titrate doses?

Treatment with concentrated insulins should be individualized, considering overall patient needs and circumstances, as is generally recommended. Basal insulins IGlar300 and IDeg200 are initiated at a TDD of 0.2 units/kg and 10 units/day, respectively, in insulin-naïve patients with type 2 diabetes (1,2,7,12). When switching to concentrated insulins in insulin-experienced patients, which may be the more common clinical scenario, the starting dose for IGlar300 and IDeg200 should be the same as the previous total daily basal insulin dose; exceptions include a 20% reduction for patients on twice-daily NPH insulin (when switching to IGlar300) and for pediatric patients >1 year of age (when switching to IDeg200) (1,2,9,10,13,15,16,18,26). It should be anticipated that upward titration may be needed when switching from IGlar100 to IGlar300 to maintain the same level of glucose control (1). Initiation of ILis200 follows the same guidance as that for ILis100, and switching between formulations uses a one-to-one conversion (3). Recommended dose transitions to prandial/basal insulin U-500R are based on U-100 insulin TDDs: one-to-one dosing for patients with an A1C >8% and a 20% dose reduction for those with an A1C ≤8% (20,27). U-500R is usually administered as insulin monotherapy either two or three times daily, approximately 30 minutes before meals (20,27).

Weekly dose titration of the concentrated basal agents (IGlar300 and IDeg200) is recommended with a minimum of 3- to 4-day intervals (1,2,7,9,10,12,13,26). ILis200 is titrated identically to ILis100 (3). Titration of U-500R may be performed progressively from weekly

to biweekly to triweekly and then extended according to clinical judgment (20).

### 7. What if a patient needs to switch back to U-100 insulin?

Switching from concentrated insulins to U-100 concentrations has not been broadly studied in phase 3 trials. Switching may be required because of dose reductions, insurance formulary changes, or hospital admissions where formularies may exclude concentrated insulins. In such cases, bioequivalent insulins would be dosed similarly (e.g., 1:1 dosing either between IDeg200 and IDeg100 or between ILis200 and ILis100). When changing from IGLar300 to IGLar100, a dose reduction of approximately 20% is recommended (6,28). However, for inpatients, depending on food intake restrictions, substantial dose reductions may be required for all insulins. For example, with U-500R, expert reviews and case series (29,30) suggest reduction in TDDs from home to hospital by at least 50%, and further reduction may be needed for patients who are NPO (“nothing-by-mouth”) status (30). Guidelines for switching between formulary insulins such as concentrated and U-100 formulations are greatly needed (31).

### 8. What has been done to reduce the risk of dosing errors with concentrated insulins?

All of the concentrated insulin products are available with dedicated pen devices designed to deliver an accurate dose for each insulin concentration without the need for dose conversion (32). For ease of recognition, the devices differ in appearance from their U-100 counterparts, where available, and some have dosing modifications (1–4). The IGLar300 pen is off-white with a green dose knob and “300 units/mL (U-300)” printed on the pen. It dials in 1-unit increments and delivers a maximum dose/injection of 80 units. The IDeg200 pen is blue with a dark green dose knob and “200 units/mL (U-200)” printed on the pen. This pen dials in 2-unit

increments and delivers a maximum dose/injection of 160 units. The ILis200 pen is dark gray with a dark grey dose knob that has a burgundy ring on the end and “200 units per mL (U-200)” printed on the pen. It dials in 1-unit increments and delivers a maximum dose/injection of 60 units. U-500R is available in a pen or 20-mL vial (10,000 units). The U-500R pen is aqua with “U-500” displayed in green. This pen dials in 5-unit increments and delivers a maximum dose/injection of 300 units. A 0.5-mL U-500 insulin syringe with a green needle shield and “U-500” symbol (Becton, Dickinson and Co., Franklin Lakes, N.J.) is available for use with U-500R vials. It delivers 5 units per mark with a maximum dose/injection of 250 units and was approved to replace the use of non-dedicated syringes (U-100 insulin and tuberculin [volumetric] syringes), which are no longer approved by the U.S. Food and Drug Administration for use with U-500R vials.

It is important to note that insulin should not be withdrawn from insulin pen devices by syringe. ILis200 and U-500R have a yellow label on the pen cartridge that states “Do not transfer to a syringe; severe overdose can result.” In addition to the instructions for use, each company has educational materials to help patients use these products as intended.

### 9. Are all concentrated insulins only for severely insulin-resistant diabetes patients taking high insulin doses?

A common misconception is that all new concentrated insulins were developed to assist in the management of patients with severe insulin resistance who are taking high daily doses of insulin (>200 units/day). However, RCTs targeting severely insulin-resistant patients have only been performed with U-500R (20,27,33). Additionally, the only concentrated insulins that may reduce injection burden for such patients are those that allow higher maxi-

mum dosing via the delivery device (IDeg200, 160 units/injection [2], and U-500R pen device, 300 units/injection, or U-500R vial/BD U-500 insulin syringe, 250 units/injection [4,21]).

We hope these comments will provide a better understanding of how available concentrated insulins may be effectively and safely integrated into clinical practice.

### Duality of Interest

C.S.A.B., A.D.T., J.A.J., and M.C.B. are full-time employees of Eli Lilly and Company and/or one of its subsidiaries. C.S.A.B., J.A.J., and M.C.B. are stock shareholders in Eli Lilly and Company. No other potential conflicts of interest relevant to this article were reported.

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