Use of concentrated insulin human regular (U-500) for patients with diabetes

ALISSA R. SEGAL, JACK E. BRUNNER, F. TAYLOR BURCH, AND JEFFREY A. JACKSON

Purpose. The efficacy and safety of and key clinical considerations for using U-500 insulin human regular in the treatment of high-dose insulin-treated patients in a wide variety of settings are examined.

Summary. U-500 regular insulin has been available in the United States since 1952, but only recently has it become more commonly prescribed for patients requiring large amounts of insulin to improve their blood glucose control. This use coincides with the increasing rates of obesity and type 2 diabetes associated with significant insulin resistance, which can necessitate the need for doses of insulin exceeding 200 units/day. However, many health care professionals are relatively unfamiliar with this concentrated insulin formulation. U-500 regular insulin has a pharmacokinetic and pharmacodynamic profile that differs from U-100 human insulins and analogues. Although no randomized clinical trials using U-500 insulin have been performed, eight case series (involving 160 patients) have been published. Rare or infrequent occurrences of hypoglycemia with U-500 insulin have been reported. Of the medication errors associated with U-500 insulin, administration and dispensing errors occurred most frequently. With the increase in prescribing of U-500 insulin, pharmacists must be aware of the complex issues involved with appropriate prescribing, dispensing, and provision of patient education to maximize patient safety and avoid administration errors and dosing confusion.

Conclusion. U-500 insulin is efficacious and safe for patients with type 2 diabetes who require a high dosage of insulin to control hyperglycemia. However, health care professionals should be well educated and vigilant about patient safety issues regarding the drug’s prescription, dosing, and administration.

Index terms: Diabetes mellitus; Dosage; Drug administration; Errors, medication; Hypoglycemia; Insulin human; Insulins; Obesity; Pharmacodynamics; Pharmacokinetics; Toxicity

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extreme insulin resistance, while very rare, can be seen with syndromic diabetes etiologies, such as insulin receptor defects (type A insulin resistance syndrome), congenital or acquired lipodystrophic diabetes, and insulin receptor autoantibodies (type B insulin resistance syndrome). Historically, health care practitioners were reluctant to prescribe higher insulin doses due to concerns that exogenous insulin might be atherogenic. However, the results of several long-term clinical trials have diminished those concerns. Current standards of care support increasing insulin doses to what is necessary to achieve glycemic targets. Careful avoidance of hypoglycemia is an additional goal for patients using insulin, particularly those at high risk for cardiovascular disease.

Treating patients with high daily insulin requirements can be quite challenging. Many of these patients continue to have inadequate glycemic control (glycosylated hemoglobin [HbA1c] values of ≥7%), which predisposes them to long-term complications of diabetes despite receiving high doses of insulin via multiple daily injections or continuous subcutaneous infusion (insulin pump therapy). Providing an appropriate amount of insulin in 100 units/mL (U-100) for these patients may be logistically difficult, and absorption of high-volume doses may be reduced. Their insulin requirements may exceed 100 units in a single injection, thus exceeding the 1-mL maximum volume of U-100 insulin syringes or exceeding the 60–80-unit maximum doses deliverable with insulin pen devices. These high insulin doses may require five to eight separate injections daily or require changing of insulin pump reservoirs more frequently than every 24 hours, which is inconvenient and may reduce adherence to U-100 insulin regimens.

Concentrated (500 units/mL, U-500) insulin beef regular (Iletin, Eli Lilly and Company) entered the U.S. market in 1952 to address high insulin needs in patients with diabetes. Three decades later, in 1980, U-500 insulin pork regular (IletinII, Eli Lilly and Company) received marketing approval. U-500 insulin human regular (Humulin R U-500, Eli Lilly and Company in the United States; Actrapid U-500, Novo Nordisk in the United Kingdom [voluntarily withdrawn in 2008]) became commercially available in 1997. Its use, primarily in obese patients with type 2 diabetes requiring >200 units of insulin daily, increased by 137% from June 2007 to June 2009.

This article discusses the efficacy and safety of and best practices and processes for the clinical use of U-500 insulin.

Time–action profile studies

Figure 1 shows the comparative pharmacokinetic profiles of U-500 and U-100 pork regular insulins at doses of 0.15 unit/kg. U-500 insulin human regular and insulin lispro at doses of 0.3 unit/kg, and U-100 insulin human regular (Humulin R U-500, Eli Lilly and Company and the United States; Actrapid U-500, Novo Nordisk in the United Kingdom [voluntarily withdrawn in 2008]) became commercially available in 1997. Its use, primarily in obese patients with type 2 diabetes requiring >200 units of insulin daily, increased by 137% from June 2007 to June 2009.

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Figure 1. Comparative pharmacokinetic profiles of (A) U-100 regular insulin pork and U-500 regular insulin pork, (B) U-100 regular insulin human and insulin lispro, and (C) U-100 isophane insulin human (neutral protamine hagedorn [NPH]).

(A) Serum Insulin (microunits/mL) vs. Time (hr)
- Neutral regular insulin pork U-100 0.25 unit/kg (n = 6)
- Acid regular insulin pork U-500 0.25 unit/kg (n = 6)

(B) Serum Insulin (ng/mL) vs. Time (hr)
- Regular insulin human U-100 0.3 unit/kg (n = 9)
- Insulin lispro U-100 0.3 unit/kg (n = 3)

(C) Plasma Insulin (microunits/mL) vs. Time (hr)
- NPH insulin U-100 0.3 unit/kg (n = 20)
- Insulin glargine U-100 0.3 unit/kg (n = 21)
Efficacy

Although no randomized clinical trials of U-500 insulin have been conducted, eight case series (seven retrospective\textsuperscript{25,29,32,33} and one prospective\textsuperscript{2}; 160 total patients with primarily type 2 diabetes given U-500 insulin for up to 98 months) have been published. These were summarized in a recent clinical review by Lane et al.\textsuperscript{3} Approximately one third of the patients treated with U-500 insulin were also receiving concomitant oral antihyperglycemic medications, predominantly metformin, consistent with current treatment guidelines.\textsuperscript{13}

It is important to note that such combination therapy is not approved by the Food and Drug Administration (FDA) due to insufficient study. The combined improvement in HbA\textsubscript{lc} values was 1.6\%, from a weighted mean of 10.0\% at baseline to 8.4\% at endpoint (\(p < 0.001\)), with mean study durations of 3–30 months.\textsuperscript{3}

Some case series reported dramatic HbA\textsubscript{lc} reductions of \(\geq 2\%\),\textsuperscript{24,25,27,30,31} resulting in individual HbA\textsubscript{lc} values as low as 6.9\% at endpoint.\textsuperscript{30} The weighted mean total daily dose (TDD) increased from 286 units of U-100 insulin to 316.9 units of U-500 insulin (TDD) increased from 286 units of U-100 insulin instead of the 100 units ordered, but the patient recovered uneventfully.\textsuperscript{26} Only one report of severe hypoglycemia requiring management in an emergency room has been published; this patient also recovered without major sequelae.\textsuperscript{22}

The manufacturer of U-500 insulin conducted a comprehensive evaluation of its database to search for potential dosing errors associated with U-500 insulin in October 2008 in response to the FDA Adverse Event Reporting System report published a few months earlier.\textsuperscript{40} Serious and nonserious adverse events reported spontaneously from postmarketing experience and clinical studies were included in the database. Twenty-two cases of medication errors associated with U-500 insulin were identified in the database (Table 1). Administration and dispensing errors were the most common (82\% of cases), with hypoglycemia occurring in 36.3\% of cases. Hyperglycemia was documented in 2 of the 4 patients who were given U-100 insulin vials instead of the prescribed U-500 concentration. There were two spontaneously reported cases involving U-500 insulin associated with fatal outcomes, including a patient who received a U-500 insulin vial instead of a U-100 insulin vial, overdosed, experienced a hypoglycemic coma, and died. The calculated reporting rate (based on assumptions from the number of vials prescribed from August 2003 to October 2008) for medication errors associated with U-500 insulin was 0.06\%, considered to be a rarely reported event.\textsuperscript{41} The limitation of the analysis of these reported cases is that the database relies on voluntary reporting systems, which traditionally underreport postmarketing events. Although this analysis suggests that medication errors associated with U-500 insulin are infrequent in a naturalistic setting, practitioners and patients must be diligent with U-500 dose adjustments and frequent self-monitoring of blood glucose (SMBG) to minimize adverse events.

Weight gain is commonly observed in patients with type 2 diabetes when initiating insulin therapy. Yki-Järvinen\textsuperscript{42} reported expectation of approximately a 2-kg weight gain for every 1\% decrease in HbA\textsubscript{lc} values over time. A recent clinical trial of intensified U-100 insulin therapy (basal bolus therapy or intensified mixtures therapy) in patients with inadequately controlled type 2 diabetes (baseline weight just under 100 kg; body mass index [BMI] just under 35 kg/m\textsuperscript{2}) reported a weight gain of 4.0–4.5 kg, with HbA\textsubscript{lc} reductions of 1.87–2.09\% with either therapy.\textsuperscript{43} The weight gain associated with insulin therapy increases the risk of patient resistance against and poor adherence to intensified insulin regimens. In comparison, the analysis of U-500 insulin case series by Lane et al.\textsuperscript{3} reported a weight gain of 4.2 kg (from a weighted mean weight of 118.8–123.0 kg, \(p = 0.002\)), which was modest for the degree of HbA\textsubscript{lc} improvement seen (weighted mean change, 1.6\%).

The injection site discomfort associated with administration of large volumes of insulin or insulin analogues with lower pH levels has been reported to be improved with the use of lower-volume U-500.\textsuperscript{28} Development of a large abscess with repeated injections or infusion site infections were reported in one se-
Dosing considerations

Initiating therapy with U-500 insulin may be intimidating to the patient, prescriber, or pharmacist, as it entails the use of large doses of concentrated insulin. However, unlike starting U-100 insulin for the first time, most candidates for U-500 insulin are already taking large doses of U-100 insulin and usually continue to have significant hyperglycemia. Therefore, given an appropriate dosage, these patients may not be easily susceptible to developing hypoglycemia as they start their U-500 regimen.

Dosing advice for U-500 insulin is experience-based, using regimens that have not been subjected to study in randomized clinical trials. The conversion dose for U-500 insulin can be initially derived from the sum of the TDD of U-100 insulin (basal and prandial or premix) after confirmation of the patient’s actual home dosage. Table 2 presents a simplified dosing algorithm that may be used for patients switching from various high-dose U-100 insulin regimens to U-500 insulin. For those patients with HbA1c values of ≥8%, a 1:1 conversion of the TDD of insulin from U-100 to U-500 can be used; for patients with lower initial HbA1c values, a dose reduction of 10–20% has been recommended.3 Frequency of dose administration can be determined in relation to the TDD (Table 2). Three-times-daily administration may take advantage of the apparent basal and prandial action of the U-500 insulin. However, successful glycemic improvement can also be obtained with twice-daily administration in patients resistant to taking more than two injections daily. Like U-100 regular insulin, U-500 is administered preferably 30 minutes before a meal. Although mealtime correction dosing may be applied, use of interprandial corrective dosing is not recommended due to the risk of “stacking;” given the expected longer duration of U-500 (Figure 1), particularly with the high doses typically required in practice. An extensive description of dosing options is available elsewhere.3,38,39 Use of shorter 8-mm versus 12.7-mm needles may be appropriate in patients with a BMI of ≥27 kg/m²,45 though this has not been robustly studied (6-mm syringe needles are not available in the United States).

Frequent SMBG by patients is recommended with close telephone or office follow-up. Self-monitored blood glucose patterns are used for progressive dosage adjustment. Consideration of prelunch and predinner readings is typically used for morning dosage adjustments, and bedtime and fasting readings are used for dinner dosage adjustments with the twice-daily regimen; prelunch, predinner, and bedtime readings are primarily used for making adjustments to a three-times-daily regimen. Persistent fasting hyperglycemia can be addressed by the addition of U-500 (approximately 10% of TDD) at bedtime (monitoring some 2:00 a.m. levels for safety) or by adding a basal insulin (NPH isophane, detemir, or glargine).3 The latter approach is more complex, more costly, and potentially confusing, as two insulin concentrations are used.

Use of U-500 insulin by insulin pump is reserved for very experienced, intensive pump practices.3,24,28,30 U-500 insulin pump users usually have a history of requiring approximately 3 units/hr basal rate with U-100 insulin,3 resulting in inconvenient and frequent infusion set, insulin cartridge, and battery changes. Lacking software specific for U-500, programming is done in “pump units” (20% of actual units of U-500), and ratios of basal-to-bolus doses mirror usual pump dosages.47 A single basal rate is usually selected at the beginning, with subsequent fine-tuning according to blood glu-

Table 1.

Summary of U-500 Medication Errors Associated with U-500 Insulin

<table>
<thead>
<tr>
<th>Type of Error</th>
<th>Hypoglycemia</th>
<th>U-100 Insulin Used Instead of U-500 Insulin</th>
<th>U-100 Syringe Used</th>
<th>Occurred in Hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administration errors (n = 11)</td>
<td>3</td>
<td>4</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Dispensing errors (n = 7)</td>
<td>2</td>
<td>4</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Prescription errors (n = 2)</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Product complaint (n = 1)</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Unknown (n = 1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

*Based on Lilly Safety System database analysis.
cose values. Bolus dosing is usually based on carbohydrate counting or per scheduled meal plans. Details of U-500 insulin therapy via insulin pump are available elsewhere.1,24,28,30

Prescribing considerations

With the increase in prescribing of U-500 insulin, pharmacists must assume an active role and be aware of the complex issues involved with appropriate prescribing, dispensing, and provision of patient education to maximize patient safety and avoid administration errors and dosing confusion. Because a dedicated U-500 insulin syringe or pen device is not available, patients have to be clearly instructed by their prescriber on how to use either U-100 insulin or tuberculin syringes to administer U-500 insulin. The dosing instructions are then tailored to the device the patient will use for administration. Being aware of how the patient was taught to inject U-500 insulin will allow pharmacists to ensure that the dosing instructions are clearly understandable to the patient and build on the education the patient has already received. Contacting other institutions for sharing their standard education and educational materials for patients on U-500 is encouraged.

Ambiguity in the notation of dosage and administration instructions could result in a fivefold overdose or underdosage with U-500 insulin. For example, if a prescriber were to write “inject 30 units of U-500 insulin,” is the prescriber meaning to draw up 30 (actual) units of U-500 or does he or she mean to draw U-500 insulin up to the 30-unit mark on a U-100 syringe (corresponding to an actual insulin dose of 150 units)? The risk of these errors may be minimized if the prescriber and pharmacist are diligent about clarifying prescriptions for U-500 insulin. Thus, managed care, long-term-care, and hospital pharmacies must develop a policy for the appropriate and safe handling of U-500 prescriptions (Appendix A).

The communication regarding the use and dosing of U-500 during transitions between care settings, particularly emergency departments and long-term-care facilities, is an important safety concern. Upon admission to these settings, patients are experiencing acute or chronic changes in their health care that affect their ability to communicate accurate information about their treatment and care.

Although it is expected that admission orders are clarified, patients treated with U-500 insulin have an increased risk of receiving U-100 insulin by mistake, due to minimal experience with U-500 insulin by the staff or the inability to obtain a supply of U-500 insulin for the patient. Assisting patients in the maintenance of up-to-date medication lists for them to carry and adding the use of U-500 insulin to their medical alert identification are ways to minimize adverse consequences.

In 2001, the Institute for Safe Medication Practices (ISMP) recommended exclusive use of tuberculin syringes to administer U-500 insulin.48 However, in the outpatient setting, the use of U-100 insulin syringes to administer U-500 insulin has become standard practice due to their greater availability, lower cost, and smaller needle size (30–32 gauge versus 27–29 gauge for tuberculin syringes).3 Prescriptions should be clearly labeled as U-500 insulin with actual units and unit markings or volume, depending on the type of syringe the patient is taught about and prescribed. A dosing conversion table with dosage calculation formulas is shown in Table 3. Because of safety concerns, it is imperative for pharmacists to clarify U-500 insulin prescriptions that call for “as-directed” dosing. Pharmacists need to ensure that the patient has been appropriately educated on how to measure and administer doses (Appendix B). For insulin pump therapy, actual units and “pump units” (one

<table>
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<tr>
<th>Required TDDb (Units)</th>
<th>Route and Frequencyc,d</th>
<th>U-500 Insulin Dosagee</th>
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bEmpirically reduce the conversion dose from U-100 by 10–20% if baseline glycosylated hemoglobin (HbA1c) is ≤8%; increase the dose by 10–20% if HbA1c is ≥10%.

cU-500 bolus doses recommended ≤30 minutes before a meal; adjust dosage according to latest SMBG value.

dBasal insulin (glargine, detemir, or isophane [NPH]) may be substituted for bedtime U-500 insulin to adjust fasting blood glucose values according to physician judgment.

eBased on percentage of TDD. May initially use fixed ratios or distribute boluses according to proportion of carbohydrates with meal or carbohydrate-counting according to patient preference and physician judgment.

### Table 2. Simplified Algorithm for Dosage Conversion to U-500 Insulin Therapy Based on a Patient’s Previous TDD of U-100 Insulin

- **Required TDD (Units)**
- **Route and Frequency**
- **U-500 Insulin Dosage**

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- *TDD = total daily dose, CSII = continuous subcutaneous insulin infusion, SMBG = self-monitored blood glucose, 50/50 = 50% of TDD prebreakfast and 50% of TDD predinner, 60/40 = 60% of TDD prebreakfast and 40% of TDD predinner, 33/33/33 = one-third of TDD before each meal.

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fifth of the actual dose) for basal and bolus dosing should be specified on the prescription.

It is also important to note that the U-500 insulin vial and labeling of the vial and box are distinctive. In 2008, the manufacturer obtained FDA approval for color coding of human and analogue insulins: U-500 insulin packaging has black and white lettering with "concentrated" insulin in red, and the vial contains 20 mL (10,000 units) and has a gray flip top (Figure 2).

### Using U-500 insulin in the hospital

Insulin is considered a high-alert medication for use in hospitals; medication errors with insulin can lead to serious adverse events in hospitals, including death. The lead to serious adverse events in medication errors with insulin can result in the hospital can lead to significant confusion and errors at every step of the ordering, dispensing, and administration process. Several questions are raised when U-500 insulin is needed for a hospitalized patient: How should it be ordered? How is it dispensed? Is it available on the floor? Should the patient be allowed to bring his or her own concentrated insulin vial from home to use during the hospital stay? Developing a systematic process consistent with other high-risk medications will assist institutions in avoiding errors and answer these questions for hospital prescribers. The creation of these systematic processes should occur when developing a defined formulary policy to safely provide U-500 insulin. An order sheet or computer order-entry screen specifically designed for U-500 insulin should be utilized. Errors can occur when U-500 insulin is inadvertently selected when U-100 insulin is desired. Ideally, the screen or order sheet for U-500 insulin should have a different appearance or order sheet for U-500 insulin. This would be another preventative measure to ensure that U-500 insulin is not chosen by accident and can also act as a guide for appropriate dosing.

In outpatient practice, the use of U-100 insulin syringes is widespread. Therefore, most patients who use U-500 describe their dose in terms of what they draw into a U-100 syringe. This practice may result in a patient receiving U-100 insulin rather than U-500 insulin. For example, upon admission to the hospital (or arrival to the emergency department), a patient states that his or her insulin dose is "50 units." The patient may inadvertently receive 50 units of U-100 insulin, rather than the 250 units (50-unit markings) of U-500 insulin he or she was taking at home. This error could result in significant hyperglycemia until the error is recognized. A less-common practice is to specify the volume needed per dose if a volumetric (tuberculin) syringe is being used by the patient or if the pharmacy’s policy calls for inclusion of the volume of the dose. The previous example would then be ordered as 0.5 mL to be administered via tuberculin syringe. In institutions where orders for U-500 insulin are a rare occurrence, this particular order may result in the pharmacist being notified of a dose that is too small to measure, mistaken as 0.5 unit rather than milliliters. Therefore, combination of the actual number of units and either the volume needed or "unit markings" on a U-100 insulin syringe should be required. Revised prescribing information for U-500 insulin has recently been submitted to FDA to clarify and reduce the risk of medication errors. However, this suggestion differs from the prior recommendation of ISMP to exclusively use tuberculin syringes for U-500 insulin administration.

Due to the safety concerns and relatively low use of U-500 insulin, many institutions may not have it on the formulary and may ask patients to bring their own vials in to
be used during their hospital stay. In these situations, the patient’s vial should be stored in a different location from any other insulin on the floor. In addition, significant guidance and education should be provided to the nursing staff involved in that patient’s care, and the dose should be double-checked before administration (Appendix A).48,52 Institutions may implement policies requiring the pharmacy to prepare and dispense each individual dose of U-500 insulin. This practice avoids the potential incorrect use of U-500 insulin vials outside of the pharmacy, which is recommended by ISMP.47 Although the U-500 insulin vials are distinctive in their volume and design from U-100 insulin vials (Figure 2), strict compliance with ISMP’s recommendation to never store U-500 insulin on the hospital floors can be an important safety measure to help avoid accidental usage.

Cost considerations
U-500 insulin is supplied in a 20-mL vial (containing 10,000 units) and has a considerably higher cost per vial compared with U-100 insulin (10-mL vials, 1,000 units). However, given the concentrated nature of this insulin, the cost on a per-unit basis is substantially less than other currently available insulin products on the market.39 Knee et al.22 reported potential cost savings of $2,600 for insulin and $3,400 for insulin pump supplies over a one-year period (at 2002 average wholesale prices) with U-500 insulin use via insulin pump. Improving glycemic control over time, potentially reducing long-term diabetes complications10 in this population of difficult-to-manage patients, may lead to the greatest cost savings of U-500 insulin use, though this has not been studied in prospective, randomized clinical trials.

Conclusion
U-500 insulin is efficacious and safe for patients with type 2 diabetes who require a high dosage of insulin to control hyperglycemia. However, health care professionals should be well educated and vigilant about patient safety issues regarding the drug’s prescription, dosing, and administration.

References
Insulin human regular

52. Joint Commission. National Patient Safety Goal: identify and, at a minimum, annually review a list of look-alike/ sound-alike drugs used in the organization, and take action to prevent errors involving the interchange of these drugs. www.jointcommission.org/NR/rdonlyres/C92AA8B3-49BD-431C-8628-11D2D1D53CC0/0/LASA.pdf (accessed 2009 Sep 8).

**Appendix A—U-500 insulin hospital formulary policy template**

- Patients may be considered for U-500 insulin therapy if they are currently on a dosage of ≥200 units per day or coming into the hospital already on a U-500 regimen.
- The U-500 insulin home dosage should be verified by a nurse through patient interview and patient demonstration using the type of syringe the patient uses at home.
- Orders for U-500 insulin should be written as the dosage in actual units and the volume of that dosage in milliliters (e.g., 80 units [0.16...
At discharge, U-500 insulin prescriptions should be entered on the discharge orders in the same manner (actual dosage and volume with specification of volume [milliliters]). Because of this onset of action and duration, U-500 may be the only insulin that the patient is prescribed.

Correct syringe type (two recommended options)
- If U-100 syringes are used, explain the amount of U-500 insulin in the actual dose and with specification of unit markings on the U-100 syringe, since U-100 insulin syringes are designed and intended for use with less concentrated U-100 insulins.
- If tuberculin syringes are used, the amount of U-500 insulin should be explained in both actual dose and with specification of volume (milliliters).

Onset of action
The U-500 insulin onset of action is typically within 30 minutes and may have a duration of up to 24 hours (i.e., both bolus and basal effects). Because of this onset of action and duration, U-500 may be the only insulin that the patient is prescribed.

Patient type
- Most patients on U-500 insulin will take more than 200 units per day.
- These patients typically have not met glycemic targets on oral medications or conventional U-100 basal bolus insulin regimens.

Hypoglycemia
Hypoglycemia when using U-500 insulin can be prolonged and severe. Teach patients the signs and symptoms of hypoglycemia and the importance of testing their blood glucose. Hypoglycemia can occur suddenly and symptoms include sweating, dizziness, tremors, hunger, slurred speech, anxiety, and headache.

Deep secondary hypoglycemia reactions may develop 18–24 hours after the original injection. Consequently, patients should be carefully observed, and prompt treatment of recurrent reactions should be initiated with 15–30 g of carbohydrates orally (e.g., as 4–8 oz of fruit juice, 6–12 oz of regular soft drink, 1–2 T of sugar, four to eight Life Savers, or three to six glucose tablets) if the patient is sufficiently alert; otherwise, intra-muscular glucagon injection or i.v. glucose should be administered.

Patients on insulin therapy should keep an in-date glucagon emergency kit in case of severe hypoglycemia episodes. Before treating a patient, the signs and symptoms of severe hypoglycemia should be confirmed by a blood glucose meter if possible (expected self-monitored blood glucose concentration of <70 mg/dL). Family members or other individuals close to the patient should be instructed on the appropriate use of glucagon.

Other safety issues
- It is imperative that hospitalized U-500-treated patients communicate with their hospital caregivers, visually confirming with use of the applicable syringe to ensure the appropriate insulin type and doses the patient requires are given.

General comments
- Remind patients that switching to U-500 insulin will only manage hyperglycemia; underlying reasons leading to obesity and insulin resistance must still be assessed and addressed appropriately with lifestyle changes—caloric reduction and exercise program or be referred for bariatric surgery according to the National Institutes of Health's guidelines.
- It is important for patients with diabetes to carry medical alert identification.
- The best places to give insulin are the abdomen, upper arms, and thighs. It is important to remember to rotate the injections between these injection sites.

Sick day therapy
- The patient should always take the usual dose of U-500 insulin. The patient should not skip insulin for the day just because of being sick or vomiting. The patient should call the diabetes care provider if unsure about how much insulin to take.
- Patients will need to check their blood glucose more frequently on sick days: at least four times per day for mild illnesses and every 4–6 hours for more severe illnesses. In addition, patients should check for the presence of ketones if blood sugar is >250 mg/dL. Ketones are present when the body starts to break down fat for energy. To help prevent the presence of ketones, patients must continue to take in adequate calories on sick days. Patients should contact their health care provider if urine ketones are moderate or large or blood ketones are >1.0 mmol/L.
- Patients should drink plenty of caffeine-free, sugar-free fluids (about 6–8 oz every hour while awake to prevent dehydration). The patient may need to alternate sugar-free fluids with fluids containing sugar if unable to eat solid food.
- Patients should get plenty of rest to allow the body to heal.

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