



New Insulin Preparations: Potential Benefits and Risk Assessments

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Abstract

Concentrated insulins have been especially problematic high alert medications. On February 25, 2015 Federal Drug Administration (FDA) approval made available insulin glargine, Toujeo U-300 (300 units/ml) in a SoloSTAR pen. On May 27, 2015 the FDA approved insulin lispro, Humalog U-200 (200 units/ml) KwikPen. Increased incidence of insulin resistant type 2 diabetes has escalated the need for concentrated insulin. This paper discusses each insulin, appropriate patient selection, benefits of the new insulins for people with diabetes and providers, and suggestions for prevention of potential off-label use of insulin pens. Counseling and assessment are essential to avoid unintended harm.

New Insulin Preparations: Potential Benefits and Risk Assessments

Insulin in any form is a high-alert medication. Two new products address safety concerns related to insulin pharmacology and administration. On February 25, 2015, the Federal Drug Administration approved insulin glargine (Toujeo U-300 [300 U/mL], Sanofi-Aventis, Bridgewater, NJ) delivered subcutaneously with a SoloSTAR insulin pen.¹ Then, on May 27, 2015, the Food and Drug Administration approved insulin lispro (Humalog U-200 [200 U/mL] KwikPen, Eli Lilly and Company, Indianapolis, IN).² Factors motivating the development of these products include 1) the growing number of people using more than 200 units of insulin per day because of insulin-resistant type 2 diabetes (T2DM) and 2) safety issues associated with concentrated insulin dosing and administration. In response, manufacturers released these insulins in pen form only^{1,3} (Toujeo and Humalog U-200) and modified the insulin pharmacokinetics and pharmacodynamics (Toujeo).¹

The increased incidence of insulin-resistant T2DM has created a need for concentrated, long-acting, insulin with a stable action over time.^{4,5} Insulin with steady bioavailability over time is characterized as having a flat time action curve. Insulin without a peak action (flat time action curve) is desired clinically in order to meet the body's ongoing physiologic

need for basal (background) insulin while preventing hypoglycemia. In contrast, a steep time action curve is appropriate for bolus (meal time) insulin. Clinically, this peak of insulin action is beneficial, paralleling the increased glycemic load of a meal.

Particularly during care transitions and/or in hospital settings, patients using concentrated U-500 insulin were at increased risk for medication errors.^{6,7} Reports of insulin administration errors related to the use of U-500 insulin in hospital settings are well documented.⁵⁻⁸ Errors have multiple contributing factors. One factor is that U-500 insulin syringes are not available.^{5,6} Instead, the person administering the insulin must convert the concentrated insulin dose for administration in a U-100 or tuberculin syringe. U-500 dosage errors occur when calculating this volume-based dose without an equivalent unit-based syringe.^{6,7} Insulin dosing and administration errors created a need for a safer means of administering concentrated insulin. Adults with type 1 diabetes (T1DM) or T2DM and providers benefit from the approval of both new concentrated formulations of insulin in multiple ways.

INSULIN GLARGINE: TOUJEO U-300

Toujeo U-300 (glargine U-300) has been approved for use in adults with T1DM and T2DM.¹ Insulin

glargine substitutes Gly for 21A-Asn in its amino acid sequence,⁹ creating an acid soluble solution that precipitates at physiologic pH forming a depot that slowly releases insulin glargine.^{10,11} Glargine U-300 has a flatter and longer pharmacokinetic and pharmacodynamics profile than glargine U-100.^{9,12} Clinically, these characteristics prevent basal insulin gaps and hypoglycemia. Glargine U-300 users experienced fewer hypoglycemic episodes (14% reduction overall and 31% reduction in nocturnal hypoglycemia)^{13,14} and less weight gain.⁹ Adults with T1DM using glargine U-300 had fewer glycemic fluctuations as measured with continuous glucose monitoring than those using glargine U-100.¹⁵ This finding demonstrates benefit for all basal insulin users. Once daily subcutaneous injections of glargine U-300 may take up to 5 days to reach a steady state.¹ This longer time to a steady state is one reason Toujeo is not indicated for use in diabetic ketoacidosis.¹ Currently, the cash price of Toujeo (glargine U-300) is approximately \$0.27 per unit.¹⁶ This cost is about \$0.53 more per 1,000 units than glargine U-100.^{16,17} Coupons and copay discounts are available and were not considered in this calculation. Price information varies widely and is available at sites such as www.drugs.com. Full prescribing information is available at <https://www.toujeopro.com/dosing-and-administration>.

INSULIN LISPRO: HUMALOG U-200

Humalog U-200 (lispro U-200) is bioequivalent to Humalog U-100 (lispro U-100) and approved for adults with T1DM and T2DM.³ The pharmacokinetics and pharmacodynamics of Humalog U-200 are unchanged from those of Humalog U-100.³ Both concentrations are administered 15 minutes before or immediately after a meal. A patient education sheet is available at <http://pi.lilly.com/us/humalog-u200-ppi.pdf>. Although Humalog U-100 is available in vial or KwikPen, the Humalog U-200 formulation is available only in the KwikPen.³ The cash price of the Humalog U-100 KwikPen is around \$0.31 per unit.¹⁸ The cash price of Humalog U-200 with a discount coupon ranges from \$0.26 per unit to \$0.37 per unit.¹⁹ The Humalog U-200 KwikPen averaged around \$9.95 more for 1,000 units than the Humalog U-100 KwikPen. However, prices vary widely, and erroneous online pharmacy information was

common (eg, Humalog U-200 KwikPen is packaged with 2 pens not 5¹⁹).

INSULIN PEN

Thin pen needles create challenges for high-volume insulin administration by increasing the time it takes to deliver the insulin dose.²⁰ Removing the pen too soon during insulin administration reduces the insulin delivered by the pen.²⁰ A more concentrated (lower volume) insulin delivered by the pen decreases insulin administration time and may decrease the incidence of insulin underdelivery caused by early needle removal. One injection with the SoloSTAR pen delivers up to 80 units of glargine U-300. The glargine U-300 dose is equivalent to a glargine U-100 dose with a third of the insulin volume.⁹ The KwikPen delivers up to 60 units of lispro U-200 with half the insulin volume of the U-100 pen.³ Both pens are calibrated by 1-unit increments.¹⁻³

DOSING

Concentrated insulin (eg, U-500) has been available since the 1950s.⁸ Understanding insulin concentrations is key when prescribing and counseling patients. U-100, U-200, and U-300 describe the number of units in 1 mL insulin. It is a ratio used to convey concentration. For example, 1 mL U-200 insulin contains 200 units, whereas 1 mL U-300 insulin contains 300 units. The subcutaneous delivery of U-200 and U-300 insulins with an insulin pen is an innovation designed to prevent dosing errors. Manufacturers^{1,3} have engineered the pens' mechanism to control the volume that each unit marking on the pen delivers to the person with diabetes. Fifty units of a U-100 insulin equals 0.5 mL insulin. However, 50 units of a U-200 insulin administered with a pen delivers half that volume (0.25 mL) of insulin, with a similar efficacy to the 50-unit U-100 insulin dosage. Previously prescribing a concentrated insulin required translation of the dose for delivery with a U-100 or tuberculin syringe. For current U-100 insulin users, the prescriber simply orders the same number of U-200 or U-300 units, and the pen mechanism converts the volume.

A basal insulin, glargine U-300, is dosed subcutaneously at a consistent time once daily. First calculate the total daily insulin dose for an insulin-naïve client as 0.2 to 0.4 units of insulin/kg. Then, prescribe one

half to one third of this calculated total daily insulin dose to initiate the glargine U-300.¹ This initial glargine U-300 basal dose is titrated 1 to 2 units every 3 to 4 days until the fasting glycemic goal is achieved.¹ Glargine U-300 may take 5 days to reach a steady state.¹ Therefore, dosage adjustments should not be more frequent than every 3 to 4 days. The remainder of the total daily insulin requirements are met with a rapid-acting mealtime bolus insulin. In the basal insulin—using adult, initiate glargine U-300 with the same basal insulin units as the U-100 basal. People required slightly more glargine U-300 units than those using glargine U-100 to reach their blood glucose goals.¹ Each glargine Toujeo U-300 SoloSTAR pen contains 450 units and expires after 28 days from the first use.¹ Individuals requiring as little as 15 units a day would consume 1 pen before expiration. See full Toujeo prescribing information at <https://www.toujeopro.com/dosing-and-administration>.

Lispro U-200 is a rapid-acting insulin and is administered subcutaneously 15 minutes before or immediately after a meal.³ Peak action is 30 to 90 minutes after dosing.³ Dosing is based on carbohydrate and meal composition with considerations for activity and current blood glucose readings. Dosages are commonly from 0.1 to 0.4 unit/kg.³ Lispro U-200 is not approved for use in an insulin pump or intravenously.³ Each Humalog U-200 KwikPen contains 600 units of insulin that are to be consumed within 28 days of the first use.³ Individuals using at least 20 units a day would empty the pen's contents before the 28-day expiration. See full prescribing information at <http://www.humalog.com/diabetes-information-for-healthcare-providers.aspx>

Adverse Effects

Hypoglycemia is a risk of insulin use. Individuals with diabetes need to be aware of signs/symptoms of hypoglycemia and how to treat it. Lipodystrophy, a loss of fat appearing as a dimple in the skin at insulin injection sites, is a risk for insulin users and may be avoided with careful injection site rotation.

BENEFITS

Benefits for People With Diabetes

The use of more concentrated insulin benefits adults with type 2 diabetes who are using larger doses of

U-100 insulins.⁵ Larger dosages are described as > 200 units per day or ≥ 2 units of insulin per kilogram of body weight daily.⁵ Often, people with insulin resistance must inject basal insulin in 2 sites to receive a single dose of insulin because of the high volume of their insulin dosage and the limits of the pen. Now, with concentrated insulin, people do not need to divide their dose between 2 injection sites.²¹ Also, the tendency for a person with diabetes to administer less than a full dose is very real when the insulin dosage exceeds the number of units that a pen is capable of administering or when the dose takes longer to administer. Finally, in both T1DM and T2DM, the potential for steady insulin absorption because of changes in the pharmacokinetics and pharmacodynamics of lispro U-300 may reduce the incidence of hypoglycemia.⁹

Provider Benefits

The pen mechanism removes the need for mathematical conversion of dosages when changing to a more concentrated rapid (lispro U-200) or long-acting (glargine U-300) insulin.²⁰ The insulin pen converts the U-200 or U-300 dose to the correct volume.^{1,3} Previously, misunderstandings about the form, type, and dose of insulin during transitions in care and in hospital settings resulted in medication errors.^{5,6} Also, the administration of concentrated insulin in care settings without a calibrated syringe increased the risk for medication errors.^{5,6} Communication of insulin dosage in standard U-100 units prevents provider misunderstandings about the concentration of insulin and alleviates confusion over how to correctly measure and administer the insulin dose. These insulins are only available in an insulin pen, which lessens the potential for dose-related prescribing and administration errors.

CLIENT CONTEXT

Many people starting on concentrated insulin have had a lot of experience with insulin. Potentially, they have also picked up some off-label habits. Some people have proudly used the term “MacGyvering” to describe these off-label improvisations.^{22,23} Bloggers and others describe using a syringe to withdraw insulin from a pen and then using the insulin in a pump or administering it with a

syringe.^{23,24} There are several reasons behind this behavior. Some people do not have access to enough pen needles to meet their needs or they do not want to waste the partial dose of insulin remaining in the pen. Family members with diabetes often share insulin. Consider this case example; grandma has insulin-resistant T2DM and uses U-500 insulin. At times, her 26-year-old grandson with T1DM is unable to obtain enough insulin to cover his needs because of high insurance copays. Occasionally, he borrows grandma's insulin to fill the gap.

Combining these two off-label behaviors (removing insulin from a pen into a syringe and sharing insulin) can be dangerous for the person who does not understand the differences between insulin concentrations. Not accounting for the concentration by transferring the insulin out of its pen into another delivery device could result in severe hypoglycemia.

Counseling Conversations

When prescribing to or working with people using a U-200 and/or U-300 insulin pen, it is important to assess their understanding of the insulin they have been prescribed and to assess their potential for risky behavior related to off-label use of diabetes supplies. Both of these new insulins should not be combined in a syringe with other insulins because of the volume dosing mechanism of the pen.^{1,3} Also, insulin pens should never be shared between people even if the needle is changed.²⁵ The following should be done:

1. Assess the individual for the risk of insulin sharing by asking, "How likely are you to share or loan your insulin?" Do not ask a yes or no question to get the most robust answer. In families and individuals with known sharing or any potential to share, consider providing more education, asking them to sign a "contract" stating they will not share. If the potential for shared use exists, consider not providing the new concentrated insulin as a precaution against severe hypoglycemia.
2. Assess the individual for his or her potential to use an insulin syringe to withdraw insulin from the pen. Ask, "How often do you have difficulty getting pen needles?" Again, asking with the assumption that it may be difficult is a more robust means of getting to the truth.

3. Consider working with insurance companies and pen needle suppliers to obtain enough pen needles to prevent the temptation for extraction of insulin from a pen with a syringe. If possible remove syringes from the home environment. Ask, "Do you or anyone in your family have insulin syringes?"
4. Discuss the importance of only using the pen and needles for the person for whom it is prescribed. Consider calling it "personal insulin."
5. Emphasize that because of its concentration it could be dangerous if given to someone for whom it is not prescribed. Consider using stickers on the pen cartridge to emphasize "no sharing/withdrawing."

Prescribing concentrated insulin is made safer because of the availability of these insulins in pen form only. The pen delivers a unit of U-200 or U-300 insulin clinically equivalent to the action of a unit of U-100 insulin.^{3,26} Previously, only U-100 syringes or tuberculin syringes were available for concentrated insulin administration. This required conversion of the concentrated insulin from units into volume. Each U-200 and U-300 pen contains more insulin units than its U-100 counterparts. Fewer pens per month are necessary compared with the number of U-100 pens per month. Currently, the cash price of the new insulin pens are nearly equivalent to their U-100 counterparts. Both insulins have the potential to be an excellent tool for diabetes management in the insulin-resistant person with diabetes. Others with diabetes can also benefit from the steady availability of glargine U-300 and/or the convenience of a pen that contains a month's supply of insulin. The nurse practitioner who understands potential risks in the everyday management of diabetes is essential for the safe introduction of these new insulin preparations. **JNP**

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