



# What You Need to Know

## Individualization of Insulin Therapy for Type 2 Diabetes Mellitus

### New Concentrated Insulins in Pen Devices

The year 2015 might be considered the “modern golden age” of insulins because of new insulin options that became available, including longer acting insulin products like insulin degludec and concentrated forms of this and several established insulins (insulin glargine, regular insulin, and insulin lispro) in pen devices (see table).

The smaller injection volume of concentrated insulins is a potential advantage over conventional U-100 (100 units/mL) insulin for obese or other severely insulin-resistant patients with large insulin dosing requirements. Many of these patients require multiple injections of U-100 insulin to deliver a single dose or divided daily doses if they use a 1-mL syringe (which accommodates only 100 units) or a U-100 insulin pen (the maximum dose delivered using U-100 pens is 60-80 units).

Injection of a smaller volume of a concentrated insulin creates a smaller SC depot for absorption that may be

less painful and provides more reliable absorption than a large volume. Use of single injections of concentrated insulin instead of multiple injections of U-100 insulin to deliver a dose may improve adherence. It also may reduce the frequency of prescription refills, which improves convenience. All of the new concentrated insulin products are available only as insulin pens, except for U-500 (500 units/mL) regular insulin, which still is also available in vials.

Insulin pens are an alternative to the use of vials and syringes for administration. Potential advantages of insulin pens over vials and syringes include improved dose accuracy, convenience, ease of use, and adherence. However, the use of insulin pens has been associated with problems, including the [risk for transmission of blood-borne pathogens](#) if insulin pens are used for multiple patients, even if the needle is changed. Errors in insulin pen administration technique by patients and healthcare professionals have been reported.

#### Recently Introduced Insulin Products Available as Pens

Characteristic	Degludec U-100	Degludec U-200	Glargine U-300	Regular U-500 <sup>a</sup>	Lispro U-200 <sup>b</sup>
Type of insulin	Basal with slow onset and ultra-long duration	Basal with slow onset and ultra-long duration	Basal with slow onset and ultra-long duration	Mixed basal/bolus with short onset and intermediate duration	Bolus with rapid onset and short duration
Concentration (units/mL)	100	200	300	500	200
Volume (mL)/pen	3	3	1.5	3	3
Units/pen	300	600	450	1500	600
Dial increments (units/click)	1	2	1	5	1
Maximum units/injection	80	160	80	300	60

<sup>a</sup>Regular U-500 insulin also is available as multiple-dose vials.

<sup>b</sup>Insulin lispro also is available as U-100 pens, multiple-dose vials, and cartridges.

Another potential problem can occur if patients or healthcare professionals attempt to draw up doses out of the insulin pen using a syringe. This practice should be avoided. It can result in under dosing because of the introduction of air into the cartridge or reservoir or overdosing if a U-100 syringe is used to withdraw the wrong volume of a concentrated insulin from a pen. Problems with the use of concentrated insulin pens can be averted or minimized through staff and patient education.

#### More information

- » Garber AJ. Will the next generation of basal insulins offer clinical advantages? *Diabetes Obes Metab.* 2014; 16:483-91.
- » Bzowycykj AS. Embracing the insulin revolution in the ambulatory care setting. *Diabetes Spectr.* 2016; 29:140-5.
- » Meece J. Effect of insulin pen devices on the management of diabetes mellitus. *Am J Health-Syst Pharm.* 2008; 65:1076-82.

## U-500 Insulin Syringes Coming Soon

In the past, U-500 regular insulin was available only in 20-mL multiple-dose vials, and the only syringes available for administration were 1-mL U-100 syringes and 1-mL tuberculin syringes. The use of these syringes required dose conversion, which introduces the potential for error. The Food and Drug Administration (FDA) recently approved [U-500 syringes](#) for use only with U-500 insulin in vials. The number of units of U-500 insulin is displayed on the syringe barrel.

It is expected that the U-500 syringes will be available in November by prescription only and should be dispensed

with U-500 regular insulin vials. The U-100 and tuberculin syringes should not be used with U-500 insulin once U-500 syringes become available. The [prescribing information](#) for U-500 regular insulin no longer provides a conversion table for using U-100 or tuberculin syringes.

At the current time, no safety guard is provided on the U-500 syringes to prevent needlestick injuries. According to the [Institute for Safe Medication Practices](#), the lack of this safety feature may preclude the use of U-500 syringes in hospitals.

Prepare by Completing New On-demand CPE Activities

## Upcoming Midday Symposium and Live Webinar

Insulin is the cornerstone of treatment for many patients with type 2 diabetes mellitus. An educational initiative coordinated by ASHP Advantage is under way, with a series of learning opportunities focusing on individualized insulin therapy for type 2 diabetes and an emphasis on new insulin options. The learning opportunities provide both live and on-demand formats, and they are designed to build upon each other to facilitate application of concepts to clinical practice.

An archived version of a live webinar presented on August 31 is now available on demand that provides an overview of the clinical impact of type 2 diabetes mellitus and the use of individualized insulin therapy (1 hour CPE). New types of insulin, concentrated insulin formulations, and insulin delivery systems are described. Optimization of insulin therapy based on glycemic profiles and adverse effects is also discussed. A discussion guide addressing these basic concepts is also available online (1.5 hours CPE). These two activities are considered to be basic level 1 programs that do not require extensive knowledge of or experience with diabetes management.

For a more advanced level 2 program with clinical case vignettes illustrating how insulin therapy can be individualized for patients with type 2 diabetes, plan to attend a Midday Symposium on Monday, December 5, 2016, from 11:30 a.m. – 1:00 p.m. PT (2:30 p.m. – 4:00 p.m. ET) during the 51st ASHP Midyear Clinical Meeting and Exhibition in Las Vegas, Nev. Through the case vignettes, the faculty will highlight strategies for avoiding clinical inertia and initiating or intensifying insulin therapy to optimize outcomes, focusing on the pharmacokinetic and

“Diabetes prevalence, duration of diabetes, and insulin options are all increasing. These offerings are imperative to give clinicians the most up-to-date information on insulin and injectable therapeutic agents for the treatment of type 2 diabetes.”

-- Dr. Curtis L. Triplitt, *Initiative Chair*

pharmacodynamic characteristics of new insulin formulations and delivery methods. The symposium will be broadcast as a live webinar and archived for persons unable to attend the meeting. Attendees at the Midyear symposium and participants in the live webinar will earn 1.5 hours CPE.

The level 1 and level 2 programs in this initiative have been developed and presented by faculty with expertise in endocrinology and the treatment of patients with type 2 diabetes. Participants planning to attend the Midyear symposium with clinical case vignettes are encouraged to complete either the on-demand webinar or discussion guide as preparation for the more advanced level 2 program. The materials are available at [www.ashpadvantage.com/go/type2](http://www.ashpadvantage.com/go/type2). There is no charge for participating in any components of this educational initiative, and ASHP membership is not required.

### Upcoming educational opportunities in 2017 on this topic

- » Engaging the Experts faculty interview hosted by William A. Zellmer
- » Ask the Experts webinar with faculty Curtis Triplitt and Joshua Neumiller (1 hour CPE)
- » Additional e-newsletters
- » On-demand “clinical case vignettes” activity (1.5 hours CPE)

[www.ashpadvantage.com/go/type2](http://www.ashpadvantage.com/go/type2)

## Initiative Faculty



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## Other News

- » In September 2016, a closed-loop system for semi-automatically monitoring blood glucose concentrations and providing an appropriate basal insulin dose—the so-called “artificial pancreas”—was approved by FDA for patients 14 years of age or older with type 1 diabetes.
- » The first follow-on U-100 insulin glargine product (Basaglar) was approved by FDA on December 15, 2015, and is expected to become available in mid December 2016. Basaglar is not approved as a biosimilar because no insulin glargine products currently are licensed under the Public Health Service Act, so there is no

“reference product” for comparison with a proposed biosimilar product. For this reason, most clinicians refer to Basaglar as a “follow-on” insulin. Several biosimilar insulin products are in development.

## News from the EASD Meeting in September

# Combination Products Show Potential

A combination product containing insulin degludec and the glucagon-like peptide (GLP)-1 receptor agonist liraglutide—the first once-daily combination product containing a basal insulin and a GLP-1 agonist to become available in Europe—was recently approved by FDA. Dubbed IDegLira in clinical studies, the product contains insulin degludec 100 units/mL and liraglutide 3.6 mg/mL and is expected to be available in the first half of 2017. It is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes inadequately controlled on less than 50 units of basal insulin daily or less than or equal to 1.8 mg of liraglutide daily. Another once-daily combination basal insulin and GLP-1 receptor agonist product (insulin glargine and lixisenatide, or IGLarLixi) also is under review by FDA with an approval decision expected shortly. This combination is also under review by the European Medicines Agency (the FDA counterpart in Europe) with an approval decision expected in early 2017.

According to current (2015) [guidelines](#) for the management of hyperglycemia in patients with type 2 diabetes from the American Diabetes Association and European Association for the Study of Diabetes (EASD), basal insulin is an option as part of second-line dual therapy (with metformin) or third-line triple therapy (with metformin and a GLP-1 receptor agonist, thiazolidinedione, dipeptidyl peptidase-4 inhibitor, or sodium glucose cotransporter-2 inhibitor) if glycemic control is not achieved with 3 months of metformin monotherapy or dual therapy, respectively. A once-daily SC injection of a basal insulin plus a GLP-1 receptor agonist would be convenient and could promote adherence.

Data from a 26-week, phase 3, open-label, treat-to-target study of IDegLira known as DUAL V were among the data evaluated by FDA. These data were presented by [John Buse and colleagues](#) at the September 2016 EASD Annual Meeting in Munich, Germany. The efficacy and safety of IDegLira plus metformin were compared with up-titrated insulin glargine (IGlar) plus metformin in 557 adults with uncontrolled type 2 diabetes (A1c 7% to 10%) despite IGLar 20-50 units/day plus metformin. The fasting plasma glucose (FPG) titration target was 4.0-5.0 mmol/L (approximately 72-90 mg/dL) for both treatment groups. Combination therapy with IDegLira plus metformin was significantly more effective than IGLar plus metformin for reducing A1c without hypoglycemia or weight gain. The combination was insulin sparing because significantly lower insulin requirements were associated with its use compared with IGLar.

A post-hoc analysis of the DUAL V study results using a less ambitious target FPG of 7.2 mmol/L (approximately 130 mg/dL) to reflect real world clinical practice was presented

by [Ildiko Lingvay and colleagues](#) at the EASD Annual Meeting. Patients treated with IDegLira plus metformin were significantly more likely to achieve the target FPG without hypoglycemia and weight gain than patients treated with IGLar plus metformin (41.4% vs. 14.3%, respectively,  $p < 0.0001$ ). Significantly more patients in the IDegLira plus metformin group than the IGLar plus metformin group achieved the target A1c of  $<7.0\%$  with no hypoglycemia and no weight gain across all three baseline A1c groups (50.8% vs. 25.0% for A1c  $\leq 7.5\%$ , 39.2% vs. 11.0% for A1c  $>7.5\%$  to  $\leq 8.5\%$ , and 31.9% vs. 5.2% for A1c  $>8.5\%$ ,  $p < 0.005$  for all comparisons).

The results of comparative studies of IGLarLixi also were reported at the recent EASD Annual Meeting. In a 30-week, phase 3, open-label study known as LixiLan-L, [Vinata Aroda and colleagues](#) compared the efficacy and safety of IGLarLixi with IGLar in 736 adults with type 2 diabetes and inadequate glycemic control (A1c  $>7\%$ ) despite the use of a basal insulin alone or with up to two oral antidiabetes drugs. Treatment with metformin was continued in patients who had been receiving the drug before study enrollment, but other oral antidiabetic drugs were discontinued. After a 6-week run-in phase during which IGLar therapy was introduced or optimized, the reduction from baseline in A1c after 30 weeks was significantly greater in patients treated with IGLarLixi than IGLar, with a similar rate of symptomatic hypoglycemia. Patients treated with IGLarLixi were significantly more likely than patients treated with IGLar to achieve the target A1c of  $<7\%$  (55% vs. 30%, respectively,  $p < 0.0001$ ). The mean change from baseline in body weight was a reduction of 0.7 kg in patients in the IGLarLixi group and a gain of 0.7 kg in the IGLar group ( $p < 0.0001$ ).

The findings from these studies suggest that use of a fixed-dose combination basal insulin and GLP-1 receptor agonist product may be useful for the intensification of therapy in adults with type 2 diabetes and inadequate glycemic control despite the use of basal insulin and oral diabetes drug therapy. The combination products are generally well tolerated, and once-daily administration might promote adherence to therapy.



## One Pen One Patient Website Provides Additional Resources



For resources and a tool kit for facilitating the safe and appropriate use of insulin pens in the hospital setting, go to [www.onepenonepatient.org](http://www.onepenonepatient.org). In addition, you will find two related educational activities:

- » *AJHP* supplement, “Best Practices in Ensuring the Safe Use of Insulin Pens in the Hospital” (2.5 hours CPE)
- » On-demand activity focused on the emerging role of newer concentrated insulins in managing diabetes and strategies for ensuring the safe use of concentrated insulins (1 hour CPE)

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