


**pln** PHARMACY LEARNING NETWORK™ **1-DAY REGIONAL MEETINGS**

## Examining the Necessity of Newer Insulins for In-Hospital Diabetes Management



**ICHHP**

Presented in partnership with the ICHP Annual Meeting

## Faculty

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## Disclosures

- **Susan Cornell, PharmD, CDE, FAPhA, FADE:**  
Speakers' Bureau—Sanofi

## Learning Objectives


- Describe the reasons for use of concentrated insulin formulations in the treatment of diabetes
- Discuss the clinical, pharmacokinetic, and pharmacodynamic profiles for current and emerging basal insulins
- Describe the pharmacist's role in counseling patients from inpatient to outpatient settings to minimize the risk of insulin administration errors and hospital readmissions

## Technician Learning Objectives

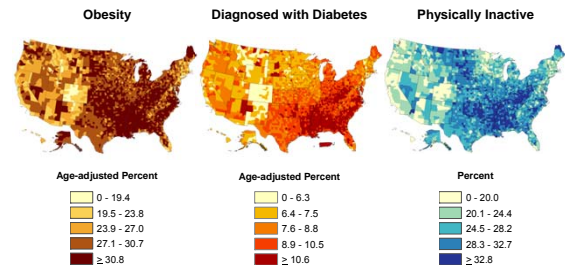
- Describe the reasons for use of concentrated insulin formulations in the treatment of diabetes
- List the available formulations of newer insulins
- Explain how to use an insulin pen

## Concentrated Insulin:

### The Diabetes Epidemic



## Type 2 Diabetes with Severe Insulin Resistance Due to Obesity and Physical Inactivity



Centers for Disease Control and Prevention, National Diabetes Surveillance System. [www.cdc.gov/diabetes/data/index.html](http://www.cdc.gov/diabetes/data/index.html). Accessed on October 23, 2015.

## Insulin Resistance

- Major defect in individuals with type 2 diabetes
- Reduced biological response to insulin
- Closely associated with obesity
- Associated with cardiovascular risk
- Type 1 diabetes patients can be insulin resistant as well

American Diabetes Association. *Diabetes Care*. 1998;21(2):310-314. Beck-Nielsen H, et al. *J Clin Invest*. 1994;94(5):1714-1721. Bloomgarden ZT. *Clin Ther*. 1998;20(2):216-231. Boden G. *Diabetes*. 1997;46(1):3-10.

## Glucose-Lowering Comparison

Monotherapy	Route of Administration	Targets Insulin Resistance	Target Glucose: FPG or PPG	A1C Reduction (%)
Sulfonylurea	Oral	No	Both	1.5-2.0
Metformin	Oral	Yes	FPG	1.5
Glitazones	Oral	Yes	Both	1.0-1.5
Meglitinides	Oral	No	PPG	0.5-2.0
AGIs	Oral	No	PPG	0.5-1.0
DPP-4 inhibitors	Oral	No	PPG	0.5-0.7
Bile acid sequestrant	Oral	No	PPG	0.4
Dopamine agonists	Oral	No	PPG	0.4
SGLT-2 inhibitors	Oral	Maybe	FPG	0.7 - 1.1
GLP-1 agonists	Injectable	No	Short-acting - PPG Long-acting - Both	0.8-1.5
Amylin analogs	Injectable	No	PPG	0.6
Insulin	Injectable	Yes (to a degree)	Basal - FPG Bolus - PPG	↓ as much as needed

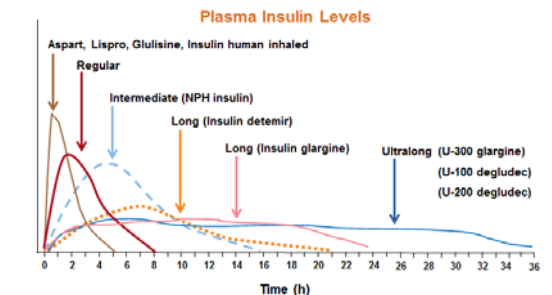
AGIs = alpha-glucosidase inhibitors; DPP-4 = dipeptidyl peptidase 4; GLP-1 = glucagon-like peptide-1; FPG = fasting plasma glucose; PPG = postprandial glucose; SGLT-2 = sodium-glucose cotransporter 2.  
Unger J, et al. *Postgrad Med*. 2010;122(3):145-157. Cornell S, et al. *Postgrad Med*. 2012;124(4):84-94.

## Insulin Therapy for Insulin Resistance

- Insulin, insulin, and yet more insulin!
  - Causes weight gain and fluid retention
  - Increased risk of hypoglycemia
  - Expensive at high volumes (especially the pens)
  - Multiple injections per day often needed
- Pumps not practical with high-volume insulin usage

American Diabetes Association. *Diabetes Care*. 2016;39(Suppl 1):S6-S12.

## Pharmacokinetic Profile of Currently Available Insulins



NPH = neutral protamine Hagedorn.  
Hirsh IB. *N Engl J Med*. 2005;352(2):174-183. Flood TM. *J Fam Pract*. 2007;56(1 Suppl):S1-S12. Becker RH, et al. *Diabetes Care*. 2015;38(4):637-643.

## The Basal-Bolus Concept

- Basal insulin: 50% of daily needs
  - Controls nighttime and between-meal glucose at a nearly constant level
- Bolus insulin: 50% of daily needs
  - Controls mealtime glucose
  - 10% to 20% of total daily insulin requirement at each meal
- Correction dose (sensitivity factor)
  - Correct hyperglycemia reactively

## Concentrated Insulin:

The Pharmacokinetic, Pharmacodynamic, and Clinical Properties of Concentrated Insulin Products

## U-100 Insulin vs U-500 Insulin

- Human Regular U-500 is highly concentrated and contains 5 × as much insulin in 1 mL as standard U-100 insulin
  - Truly used for patients on high doses of insulin (usually >200 units daily)
- Both have onset of action at 30 minutes
  - U-500 insulin exhibits a delayed and lower peak effect relative to U-100
  - U-500 insulin typically has a longer duration of action compared with U-100 (up to 24 hours following a single dose)
- Clinical experience has shown that U-500 insulin frequently has time-action characteristics reflecting both prandial and basal activity

de la Peña A, et al. *Diabetes Care*. 2011;34(12):2496-2501.

## PK and PD profiles for U-500 vs U-100 Human Insulin

IRI = immunoreactive insulin; PK = pharmacokinetic; PD = pharmacodynamic.  
de la Peña A, et al. *Diabetes Care*. 2011;34(12):2496-2501.

## Human Regular U-500 Pen

- Can deliver up to 300 units in a single injection
  - No dose conversion for pen
    - Vials/syringes will need dose conversion
  - Dials in 5-unit increments
  - Holds 1500 units of insulin in every pen
  - For severely insulin-resistant patients
    - When daily insulin requirements are in excess of 200 units/day

US Food and Drug Administration. [www.accessdata.fda.gov/scripts/cder/drugsatfda/](http://www.accessdata.fda.gov/scripts/cder/drugsatfda/).

## High-Concentration Glargine (U-300)

- Available only in a pen
  - U-300: 450 units/pen, max 80 units/injection
  - Can be used for patients on small and large volumes of insulin
- Offers a smaller depot surface area, leading to a reduced rate of absorption
- Provides flatter and prolonged PK and PD profiles and more consistency
  - Half-life is ~23 hours
  - Steady state in 4 days
  - Duration of action ≤36 hours

Garber AJ. *Diabetes Obes Metab*. 2014;16(6):483-491. Owens DR, et al. *Diabetes Metab Res Rev*. 2014;30(2):104-119. Steinstaesser A, et al. *Diabetes Obes Metab*. 2014;16(9):873-876. US Food and Drug Administration. [www.accessdata.fda.gov/scripts/cder/drugsatfda/](http://www.accessdata.fda.gov/scripts/cder/drugsatfda/).

## PK and PD of U-300 Insulin Glargine vs U-100 Insulin Glargine

U-300 glargine displays a more even and prolonged PK/PD profile compared with U-100 glargine, offering blood glucose control beyond 24 hours

LLOQ = lower limit of quantification; GIR = glucose infusion rate.  
Becker RH, et al. *Diabetes Care*. 2015;38(4):637-643.

## U-100 and U-200 Insulin Degludec

- Available only in a pen
  - U-200: 600 units/pen, max 160 units/injection
  - U-100: 300 units/pen, max 80 units/injection
- Can be used for patients on small and larger volumes of insulin
- Provides flatter and prolonged PK and PD profiles and more consistency
  - Duration of action >42 hours
  - Half-life ~25 hours
    - Detectable for at least 5 days
  - Steady state in 3 to 4 days

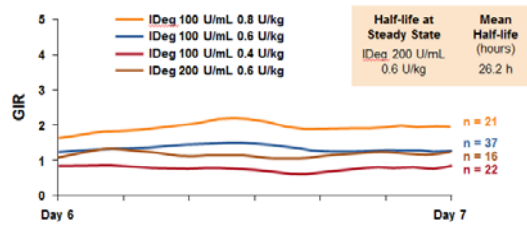


Garber AJ. *Diabetes Obes Metab.* 2014;16(6):483-491. Owens DR, et al. *Diabetes Metab Res Rev.* 2014; 30(2):104-119. US Food and Drug Administration. [www.accessdata.fda.gov/scripts/cder/drugsatfda/](http://www.accessdata.fda.gov/scripts/cder/drugsatfda/).

## Basal Insulin Degludec

Flat, stable profile of both 100 unit/mL and 200 unit/mL formulations

Mean 24-Hour GIR Profile of the Two Insulin Degludec Formulations at Steady State



GIR = glucose infusion rate. Heise T, et al. *Diabetes.* 2012;61(suppl 1):A91 [abstract 349-OR]. Heise T, et al. *Diabetes Obes Metab.* 2012;14(10):944-950.

## Importance of Patient Education



## Overcoming Barriers to Insulin Therapy

- Avoid using insulin as a "threat," but as a solution; discuss it as an option early
- Use insulin pens and regimens that offer maximum flexibility
- Give a "limited" trial of insulin
- Tell patient that injection is less painful than a finger stick; give an injection in the office/hospital/pharmacy
- Teach patient to recognize and treat hypoglycemia
  - Use basal analog insulin to minimize hypoglycemia

Kruger DF, et al. *Diabetes Educ.* 2010;36 Suppl 3:44S-72S. Funnell MM. *Clinical Diabetes.* 2007;25(1):36-38. Derr RL, et al. *Diabetes Spectrum.* 2007;20(3):177-185.

## Patient Education: From Inpatient to Outpatient Setting

- Equipment and supplies needed to effectively manage insulin therapy at home
  - Insulin
    - Compare at home vs hospital (formulary) insulin
  - Syringes or pen needles
  - Blood glucose meter and strips
  - Lancets and lancing device
  - Glucagon emergency kit
  - Contact information of diabetes care provider(s)

## What Patients Need to Know about Insulin AND Delivery Devices

- Storage and expiration
  - When it should be refrigerated
  - When it can be at room temperature
  - Time medication expires after first use
- How to prepare product for first use
- How to properly use the device
- How to dispose of the device

## Product Expiration

Products/Device	Refrigerated	Unrefrigerated	Once used (opened)
<b>Viats</b>			
Insulin lispro U-100 Insulin aspart Insulin glulisine Insulin glargine	Expiration Date	28 days	28 days
<b>Viats</b>			
Insulin human N Insulin human R	Expiration Date	31 days	31 days
<b>Pens</b>			
Insulin lispro U-100, U-200 Insulin aspart Insulin glulisine Insulin glargine U-100 Insulin glargine U-300	Expiration Date	28 days Glargine U-300: 42 days	<b>Do not refrigerate</b> Lispro, glargine, glulisine: 28 days Aspart: 14 days
<b>Viats &amp; pens:</b> Insulin detemir	Expiration Date	42 days	42 days (pens should not be refrigerated)
<b>Pens:</b> Insulin degludec U-100, U-200	Expiration Date	56 days	56 days (pens should not be refrigerated)
<b>Inhaled:</b> Insulin human	—	Expiration Date	15 days for device

Physicians Desk Reference. [www.pdr.net/browse-by-drug-name](http://www.pdr.net/browse-by-drug-name). Accessed on February 12, 2016.

## Basal Insulin Delivery Options

Insulin	Concentration	Vial	Pen
<b>NPH</b>	U-100	X	X
<b>Glargine</b>	U-100	X	X
<b>Glargine</b>	U-300		X
<b>Detemir</b>	U-100	X	X
<b>Degludec</b>	U-100 U-200		X
<b>Regular Human</b>	U-500	X	X

US Food and Drug Administration. [www.accessdata.fda.gov/scripts/cder/drugsatfda/](http://www.accessdata.fda.gov/scripts/cder/drugsatfda/).

## First-Time Preparation

- **Check the pen**
  - Make sure liquid is clear, colorless, and particle-free (N insulin and mixed insulin will be cloudy)
  - Wipe the rubber stopper with alcohol
- **Attach the needle**
- **Prime the needle**
  - Dial 2 to 3 units; hold up, depress the button
    - Repeat process until a drop of insulin appears at tip of the needle
- **Dial up the dose**
- **Inject straight into the skin**
  - Depress button to release insulin into subcutaneous tissue
- **Hold for 5 to 10 seconds** before removing needle from skin
- **Remove needle and dispose** into sharps container



## Concentrated Basal Insulin Dosing Conversion Comparison

	Glargine U-300	Degludec U-200	Human R U-500
	True basal insulin	True basal insulin	Pseudo-basal insulin
1 daily injection	1 to 1	1 daily injection	1 to 1
2 daily injections	80% of total daily basal dose	2 daily injections	80% of total daily basal dose
Maximum single-dose injection	80 units	Maximum single-dose injection	160 units
Dialed in 1-unit increments	450 units of insulin per pen	Dialed in 2-unit increments	600 units of insulin per pen
Expect higher daily dose of Glargine U-300 to maintain glycemic control		Dialed in 5-unit increments	1500 units of insulin per pen
			Monitor for hypoglycemia

## Clinical Pearls

- Watch for over basalization
  - High basal dose with no or little bolus insulin
- Continually increasing insulin doses does not reduce insulin resistance
- Humulin R U-500 is useful for patients on very high total daily insulin doses (eg, >200 TDD/day)
- Ultra long-acting basal insulins (Glargine U-300 and Degludec U-200) provide longer duration of action for better basal coverage with low nocturnal hypoglycemia

## Take Aways

- **Insulin resistance is a MAJOR problem**
  - Some concentrated insulin may help people on large doses of insulin
  - However, need to use combination drug therapy to improve insulin sensitivity
- **Novel, long-acting basal insulin analogs in development may provide benefit compared with current agents**
  - Flatter time-action profiles with less variability
  - Less hypoglycemia, particularly nocturnal hypoglycemia
- **Patients need to know how to properly use insulin devices**
  - Hospital pharmacists should review technique at discharge
  - Community pharmacists should review technique at initial fill and periodically thereafter

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# Questions?

