Basal Insulin Therapy in the Treatment of Insulin Resistant Type 2 Diabetes:

The Role of the Pharmacist in Ensuring Their Safe and Effective Use in Patients

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Objectives

1. Describe the reasons for the use of high concentration insulin formulations in the treatment of type 2 diabetes

2. Discuss the clinical, pharmacokinetic and pharmacodynamic profiles for current and emerging basal insulins

3. Implement strategies for safely converting between U-100 and concentrated insulin formulations using different syringes and pen devices in patients with type 2 diabetes

4. Review currently available insulin pens and syringes used for the administration of insulin

5. Explain and apply strategies to overcome the barriers to insulin-mediated glucose control
Joshua J. Neumiller, PharmD, CDE, FASCP has received research grant support from Johnson & Johnson, AstraZeneca, Merck and Novo Nordisk. He has served on a speaker bureau for Novo Nordisk and Janssen, and has served on an advisory board for Sanofi and Janssen.
The Diabetes Epidemic
Diabetes in the United States

- 29.1 million people (9.3% of the population) have diabetes
- 8.1 million are undiagnosed
- CDC estimates that 1 in 3 adult Americans will have diabetes by 2050
- Type 2 Diabetes (T2DM)
  - Associated with obesity, older age, decreased physical activity, and race/ethnicity
  - Incidence in children and adolescents is increasing
- Estimated total costs in 2012: $245 billion

Type 2 Diabetes

- Characterized by chronic hyperglycemia
- Associated with microvascular and macrovascular complications
- Generally arises from a combination of insulin resistance and β-cell dysfunction

By the time a person is diagnosed with type 2 diabetes, approximately how much β-cell function has been lost?

1. <10%
2. 10–30%
3. 30–50%
4. 50–80%
5. 100%
Progressive Deterioration in β-Cell Function Over Time

HOMA = homeostasis model assessment.
Pathophysiologic Defects in Type 2 Diabetes: The Ominous Octet

Decreased Incretin Effect

Neurotransmitter Dysfunction

Islet $\beta$-cell

Impaired Insulin Secretion

Increased Glucagon Secretion

Islet $\alpha$-cell

Increased Glucose Secretion

Hyperglycemia

Increased Lipolysis

Increased Glucose Reabsorption

Increased HGP

Decreased Glucose Uptake

Neurotransmitter Dysfunction

Insulin Resistance
~90% of People with Type 2 Diabetes are Overweight or Obese

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…

More than 80% of Patients Progressing to Type 2 Diabetes are Insulin Resistant

- Insulin sensitive; low insulin secretion (16%)
- Insulin sensitive; good insulin secretion (1%)
- Insulin resistant; good insulin secretion (29%)
- Insulin resistant; low insulin secretion (54%)

Insulin Resistance Reduces Response to Circulating Insulin

- **Glucose output** increases in the Liver.
- **Glucose uptake** decreases in Muscle and Adipose tissue.
- Insulin/medication requirements needed to maintain glycemic control increases, leading to **Hyperglycemia**.
Treatment Options for Type 2 Diabetes
12 Pharmacotherapy Options

**Insulin**
- **Bolus insulin**
  - Insulin lispro (Humalog)
  - Insulin aspart (NovoLog)
  - Insulin glulisine (Apidra)
  - Insulin human inhaled (Afrezza)
  - Regular human insulin
    - (Humulin R)
    - (Novolin R)
- **Basal insulin**
  - Insulin NPH
    - (Humulin N)
    - (Novolin N)
  - Insulin detemir (Levemir)
  - Insulin glargine U-100 (Lantus)
  - Insulin glargine U-300 (Toujeo)

**Oral Medications**
- \(\alpha\)-glucosidase inhibitors (AGI)
- Biguanides
- Bile acid sequestrants (BAS)
- Dipeptidyl peptidase-4 (DPP-4) inhibitors (gliptins)
- Dopamine agonists
- Glitinides
- Sulfonylureas
- Sodium glucose co-transporter-2 inhibitors
- Thiazolidinediones (TZDs or glitazones)

**Non-insulin injectable agents**
- Glucagon-like peptide-1 (GLP-1) agonists
- Amylinomimetics

## Glucose-Lowering Comparison

<table>
<thead>
<tr>
<th>Monotherapy</th>
<th>Route of Administration</th>
<th>Targets Insulin Resistance</th>
<th>Target Glucose: FPG or PPG</th>
<th>A1C Reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylurea</td>
<td>Oral</td>
<td>No</td>
<td>Both</td>
<td>1.5–2.0</td>
</tr>
<tr>
<td>Metformin</td>
<td>Oral</td>
<td>Yes</td>
<td>FPG</td>
<td>1.5</td>
</tr>
<tr>
<td>Glitazones</td>
<td>Oral</td>
<td>Yes</td>
<td>Both</td>
<td>1.0–1.5</td>
</tr>
<tr>
<td>Meglitinides</td>
<td>Oral</td>
<td>No</td>
<td>PPG</td>
<td>0.5–2.0</td>
</tr>
<tr>
<td>AGIs</td>
<td>Oral</td>
<td>No</td>
<td>PPG</td>
<td>0.5–1.0</td>
</tr>
<tr>
<td>DDP-4 inhibitors</td>
<td>Oral</td>
<td>No</td>
<td>PPG</td>
<td>0.5–0.7</td>
</tr>
<tr>
<td>Bile acid sequestrant</td>
<td>Oral</td>
<td>No</td>
<td>PPG</td>
<td>0.4</td>
</tr>
<tr>
<td>Dopamine agonists</td>
<td>Oral</td>
<td>No</td>
<td>PPG</td>
<td>0.4</td>
</tr>
<tr>
<td>SGLT-2 inhibitors</td>
<td>Oral</td>
<td>↓ glucose toxicity</td>
<td>FPG</td>
<td>0.7–1.1</td>
</tr>
<tr>
<td>GLP-1 agonists</td>
<td>Injectable</td>
<td>No</td>
<td>Short-acting – PPG</td>
<td>0.8–1.5</td>
</tr>
<tr>
<td>Amylin analogs</td>
<td>Injectable</td>
<td>No</td>
<td>Long-acting – Both</td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>Injectable</td>
<td>↓ glucose toxicity</td>
<td>Basal – FPG Solar – FPG</td>
<td>↓ as much as needed</td>
</tr>
</tbody>
</table>

FPG = fasting plasma glucose; PPG = postprandial glucose.

Basal Insulin Therapy: Concept and Physiology
UKPDS: Progressive Deterioration in Glycemic Control Over Time

<table>
<thead>
<tr>
<th>Time from Randomization (y)</th>
<th>Median A1C (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>6.9</td>
</tr>
<tr>
<td>3</td>
<td>7.6</td>
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<td>6</td>
<td>8.6</td>
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<tr>
<td>9</td>
<td>9.6</td>
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<tr>
<td>12</td>
<td>10.6</td>
</tr>
<tr>
<td>15</td>
<td>11.6</td>
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</table>

HbA1C Level

### Currently Available Insulins

<table>
<thead>
<tr>
<th>Insulin Type</th>
<th>Onset</th>
<th>Peak, h</th>
<th>Duration of Action, h</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rapid-acting analogs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin lispro, aspart,</td>
<td>15 min</td>
<td>0.5–1.5</td>
<td>3–5</td>
</tr>
<tr>
<td>glulisine</td>
<td>12–15 min</td>
<td>~1.0</td>
<td></td>
</tr>
<tr>
<td>Insulin human inhaled</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Short-acting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular human (U-100)</td>
<td>30–60 min</td>
<td>2–4</td>
<td>5–8</td>
</tr>
<tr>
<td><strong>Regular human (U-500)</strong></td>
<td>30–60 min</td>
<td>4–8</td>
<td>14–15</td>
</tr>
<tr>
<td><strong>Intermediate-acting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human NPH insulin</td>
<td>1–3 h</td>
<td>6–12</td>
<td>12–24</td>
</tr>
<tr>
<td><strong>Long-acting (basal)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin glargine</td>
<td>2–4 h</td>
<td>No pronounced peak</td>
<td>20–24</td>
</tr>
<tr>
<td>Insulin detemir</td>
<td>1–3 h</td>
<td></td>
<td>18–20</td>
</tr>
<tr>
<td><strong>Ultralong-acting (basal)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin glargine U-300</td>
<td>6 h</td>
<td>No pronounced peak</td>
<td>≤36</td>
</tr>
</tbody>
</table>

Thinking Like a Pancreas

- **No food**
- **Meals**
- **Less overnight**
- **More for “waking up”**

Time:
- 8 AM
- 12 NOON
- 3 PM
- 6 PM
- 9 PM
- 3 AM
- 7 AM
PK Profile of Currently Available Insulins

PK = pharmacokinetic; NPH = neutral protamine Hagedorn.

Insulin Regimens Used in T2DM

- **Basal only**
  - 1 injection
  - Added to oral agents

- **Basal plus**
  - 2 injections or 1 injection + 1 inhalation
  - Adding one rapid-acting analog sequentially starting with largest meal

- **Basal bolus**
  - 4 injections or 1 injection + 3 inhalations
  - Rapid-acting analog before each meal

- **Pre-mixed**
  - 2 injections

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
  – 10–20 % of total daily insulin requirement at each meal

• Correction dose (sensitivity factor)
  – Correct hyperglycemia reactivity

Insulin Therapy in Patients with 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
High Doses of Insulin

• **Concerns:**
  - Hypoglycemia
  - Medication errors in dosing
  - Absorption issues

• **Problems:**
  - Over-basalization
  - Failure to treat the physiological defects
    - Insulin resistance
    - Decrease satiety
Concentrated Insulin
Why Concentrated Insulin?

• When daily insulin requirements are in excess of 200 units/day, the volume of U-100 injected insulin becomes a challenge:
  – Physically too large for a single SC administration
  – Multiple injections are required to deliver a single dose
  – Increased injections may lead to adherence issues and poor glycemic control
  – Discomfort
  – Unpredictable absorption (rate-limiting step in insulin activity)

Patients Who May Require Concentrated Insulin

• Patients with insulin resistance
  – Patients with inherited insulin receptor abnormalities or presence of autoantibodies to insulin receptor
  – Diabetes patients with insulin antibodies
  – Type 2 diabetes patients
  – Overweight/obese Type 1 diabetes patients

• Other patients
  – Obstetrics patients
  – Patients receiving high-dose glucocorticoid therapy

Currently Available Concentrated Insulins

Regular human insulin U-500
(Humulin R U-500)

Insulin glargine U-300
(Toujeo)

U-500 Regular Human Insulin

• U-500 is highly concentrated and contains five times as much insulin in 1 mL as standard U-100 insulin

• U-500 vial
  - U-500: contains 20 mL
  - U-100: contains 10 mL

• U-500 vial
  - Marked with a band of diagonal brown stripes to distinguish it from the U-100 vial, which has no stripes
  - “U-500” is also highlighted in red on the label

U-100 Insulin vs U-500 Insulin

- Both have onset of action of 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 to 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

PK and PD Profiles for U-500 vs U-100 Human Insulin

IRI = immunoreactive insulin.

Safety Concerns with Concentrated Insulin
Medication Errors Associated with U-500 Insulin

• Some health care professionals may not be aware of U-500 insulin, increasing the chance of dispensing errors
  – From the shelf during dispensing
  – From the computer screen when prescribing
  – Communication errors during medication reconciliation

• Dosing errors
  – No insulin syringe designed to measure U-500 insulin

• Due to increasing medication errors with U-500 insulin and the lack of a U-500 specific syringe, The Institute for Safe Medication Practices suggests “It’s time to rethink safe use of strengths above U-100”

## U-500 Insulin Dosing Conversion

<table>
<thead>
<tr>
<th>U-500 Insulin Dose (Actual units)</th>
<th>U-100 Syringe (Unit markings)</th>
<th>Volume for Tuberculin Syringe (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>5</td>
<td>0.05</td>
</tr>
<tr>
<td>50</td>
<td>10</td>
<td>0.10</td>
</tr>
<tr>
<td>75</td>
<td>15</td>
<td>0.15</td>
</tr>
<tr>
<td>100</td>
<td>20</td>
<td>0.20</td>
</tr>
<tr>
<td>125</td>
<td>25</td>
<td>0.25</td>
</tr>
<tr>
<td>150</td>
<td>30</td>
<td>0.30</td>
</tr>
<tr>
<td>175</td>
<td>35</td>
<td>0.35</td>
</tr>
<tr>
<td>200</td>
<td>40</td>
<td>0.40</td>
</tr>
<tr>
<td>225</td>
<td>45</td>
<td>0.45</td>
</tr>
<tr>
<td>250</td>
<td>50</td>
<td>0.50</td>
</tr>
<tr>
<td>275</td>
<td>55</td>
<td>0.55</td>
</tr>
<tr>
<td>300</td>
<td>60</td>
<td>0.60</td>
</tr>
<tr>
<td>325</td>
<td>65</td>
<td>0.65</td>
</tr>
<tr>
<td>350</td>
<td>70</td>
<td>0.70</td>
</tr>
<tr>
<td>375</td>
<td>75</td>
<td>0.75</td>
</tr>
<tr>
<td>400</td>
<td>80</td>
<td>0.80</td>
</tr>
<tr>
<td>425</td>
<td>85</td>
<td>0.85</td>
</tr>
<tr>
<td>450</td>
<td>90</td>
<td>0.90</td>
</tr>
<tr>
<td>475</td>
<td>95</td>
<td>0.95</td>
</tr>
<tr>
<td>500</td>
<td>100</td>
<td>1.00</td>
</tr>
</tbody>
</table>

*The following dosing formulas may also be used: dose (actual units) x 0.2 = unit markings in a U-100 insulin syringe, dose (actual units) x 0.002 = volume (mL) in a tuberculin syringe.

Food and Drug Administration. Humulin R-U-500 (concentrated) Insulin Human Injection. Drugs@FDA.gov.
New and Emerging Basal Insulins
Quest for Better Insulin Products

1. Efficacy
   - Reductions in A1C
   - Reductions in FBG and PPG

2. Convenience
   - Pen dosing
   - Flexible dosing (any time of day)
   - Different concentrations
   - Ability to mix with other insulin and non-insulin agents

3. Safety
   - Low incidence of hypoglycemia
   - Low incidence of nocturnal hypoglycemia
   - Less individual variability
   - Less weight gain
Newly Approved U-300 Insulin Glargine

- U-300 insulin glargine offers a smaller depot surface area leading to a reduced rate of absorption

- Provides a flatter and prolonged pharmacokinetic and pharmacodynamic profiles and more consistency

- Half-life is ~23 hours

- Steady state in 4 days

- Duration of action ≤36 hours

- Associated with less hypoglycemia especially nocturnal hypoglycemia

- FDA approved February 25, 2015

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; PK = pharmacokinetic; PD = pharmacodynamic.

### U-300 Glargine vs U-100 Glargine in T2DM: Meta-Analysis of Phase III Trials EDITION 1, 2, & 3

<table>
<thead>
<tr>
<th></th>
<th>Glar U-300 (N=1247)</th>
<th>Glar U-100 (N=1249)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A1C (%)</strong>, LS mean</td>
<td>–1.02</td>
<td>–1.02</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Weight (kg), LS mean</strong></td>
<td>0.49</td>
<td>0.75</td>
<td><em>P = 0.058</em></td>
</tr>
<tr>
<td><strong>Any hypo in 24 hr</strong></td>
<td>67.8</td>
<td>73.8</td>
<td>0.92 (0.87–0.96)</td>
</tr>
<tr>
<td><strong>Any nocturnal hypo</strong></td>
<td>31.7</td>
<td>41.3</td>
<td>0.77 (0.69–0.85)</td>
</tr>
<tr>
<td><strong>Confirmed BG &lt;54 mg/dl or severe hypo</strong></td>
<td>26.9</td>
<td>33.3</td>
<td>0.81 (0.72–0.90)</td>
</tr>
<tr>
<td><strong>Confirmed nocturnal BG &lt;54 mg/dl or severe hypo</strong></td>
<td>9.7</td>
<td>13.2</td>
<td>0.73 (0.59–0.91)</td>
</tr>
</tbody>
</table>

*% people ≥1 event.
LS = least squares; RR = relative risk; BG = blood glucose; CI = confidence interval.
Flexible vs Fixed Dosing U-300 Glargine: Sub-Studies of Phase III Trials


- No difference in A1C between flexible- vs fixed-dosing
- No difference in severe or nocturnal hypoglycemia within each sub-study
U-300 Insulin Glargine

• Only available in pens
  – 300 U/mL, 1.5 mL
  – Max dose per shot is 80 units with current pen
  – New pen in development will allow a max dose of 240 units
  – Just dial the prescribed dose; no conversion needed like U-500

• U-300 glargine pen is white and green with the concentration highlighted in orange to distinguish it from U-100 glargine

U-300 Insulin Glargine Dosing

• Insulin-Naive Patients:
  – Type 1 Diabetes – Start with 1/3 to 1/2 of the total daily insulin dose calculated by using 0.2-0.4 U/kg/day; give the remainder of the total daily insulin dose as a short-acting insulin and divide between each daily meal
  – Type 2 Diabetes – Start with 0.2 U/kg/day

• Type 1 or Type 2 Diabetes:
  – Changing from once daily long-acting or intermediate-acting insulin:
    • Initial dose can be the same as the once daily long-acting dose; for patients controlled on U-100 insulin glargine, expect that a higher daily dose of U-300 glargine will be needed to maintain the same level of glycemic control
  – Changing from twice daily NPH insulin:
    • Initial dose is 80% of the total daily NPH dosage

Insulin Degludec*

- Duration of action >42 hours
- Half-life ~25 hours
  - Detectable for at least 5 days
- Steady state in 2–3 days
- FDA denied approval in 2013, research continues
  - Approved in EU

*Not FDA approved.

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.

Pharmacodynamic Variability with Insulin Degludec vs Insulin Glargine

Subjects listed in increasing order of individual coefficient of variation

U-200 Insulin Degludec: Safety and Efficacy

26-week Open-label, Randomized Study of 457 Patients with Type 2 Diabetes

No difference in hypoglycemia between the two treatment groups

PEGylated Insulin Lispro*

- Polyethylene glycol polymer covalently attached to lispro
- Half-life 2–3 days
- Steady state in 7–10 days
- Duration of action >36 hours
- Phase II–III clinical trials

*Not FDA-approved.

PEGylated Insulin Lispro (LY2605541) Pharmacodynamics

Glucose clamp study in 32 patients, 8 per study arm

Pegylated Insulin Lispro

Mean GIR (mg/min/kg) vs Time (hours)

- Purple line: 0.33 U/kg
- Dark blue line: 0.5 U/kg
- Cyan line: 0.67 U/kg
- Salmon line: 1.0 U/kg

GIR = glucose infusion rate.

PEGylated Insulin Lispro (LY2605541) vs Glargine U-100 in T1DM

LY2605541 Treatment at 8 weeks

- Significantly lowered A1C vs glargine
- Significantly reduced weight (1.2 kg)
- Increased overall hypos ($p = 0.04$) but less nocturnal hypos ($p = 0.01$)
- Lowered prandial insulin dose
- Significantly increased liver enzymes

Is there an alternative to concentrated insulin for patients on high doses of insulin?
Combination Basal Insulin and GLP-1 RAs

Lifestyle Changes plus Metformin
(± other agents)

Basal
Add Basal Insulin and Titrate

Basal Plus
Add Prandial Insulin at Main Meal

Basal Bolus
Add Prandial Insulin before Each Meal

Basal plus GLP-1 RAs
Barriers to Insulin-Mediated Glucose Control
Significant Delay in Insulin Initiation


SOLVE: Baseline A1C Distribution at Insulin Initiation

A1C (%)

Patients (%)
The reason for delay in starting insulin in diabetes management is:
a. Provider reluctance (clinical inertia)
b. Patient reluctance
c. Lack of time
d. Fear of hypoglycemia
e. All of the above
# Key Barriers to Insulin Therapy

## Patient Barriers
- Patient reluctance
- Sense of failure
- Loss of independence
- Belief that insulin is ineffective
- Fear of injections
- Fear of hypoglycemia
- Weight gain

## Provider Barriers
- Clinical inertia
- Lack of insulin training, time, and/or support
- Fear of hypoglycemia
- Weight gain

Overcoming the Barriers to Insulin Therapy

- Avoid using insulin as a “threat,” but a solution and discuss it as an option early
- Use insulin pens and regimens that offer maximum flexibility
- Give a “limited” trial of insulin
- Tell patient injection is less painful than finger stick and give an injection in the office
- Teach patient to recognize and treat hypoglycemia, and use basal analog insulins to minimize hypoglycemia risk
- Meet with dietitian before initiation of insulin

Insulin Administration
Insulin Titration and Education

• First, do no harm
  – Halt the hypoglycemia

• Fix the fastings

• Pare the postprandials
Patient Education

• Equipment and supplies patients need to effectively manage their insulin therapy at home
  – Insulin
  – Syringes or pen needles
  – Blood glucose meter and strips
  – Lancets and lancing device
  – Glucagon emergency kit
  – Contact information of diabetes care provider(s)
## Expiration of Products

<table>
<thead>
<tr>
<th>Products/Device</th>
<th>Refrigerated</th>
<th>Unrefrigerated</th>
<th>Once Used (opened)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vials</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin lispro</td>
<td>Expiration Date</td>
<td>28 days</td>
<td>28 days</td>
</tr>
<tr>
<td>Insulin aspart</td>
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<tr>
<td>Insulin glulisine</td>
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<td>Insulin glargine</td>
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<tr>
<td><strong>Vials</strong></td>
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<td>Insulin human R</td>
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<tr>
<td><strong>Pens</strong></td>
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</tr>
<tr>
<td>Insulin lispro</td>
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<td></td>
</tr>
<tr>
<td>Insulin aspart</td>
<td></td>
<td>28 days</td>
<td></td>
</tr>
<tr>
<td>Insulin glulisine</td>
<td></td>
<td>28 days</td>
<td></td>
</tr>
<tr>
<td>Insulin glargine U-100</td>
<td></td>
<td>28 days</td>
<td></td>
</tr>
<tr>
<td>Insulin glargine U-300</td>
<td></td>
<td>28 days</td>
<td></td>
</tr>
<tr>
<td><strong>Vials and pens</strong></td>
<td>Expiration Date</td>
<td>42 days</td>
<td></td>
</tr>
<tr>
<td>Insulin detemir</td>
<td></td>
<td>42 days</td>
<td></td>
</tr>
<tr>
<td><strong>Inhaled</strong>: Insulin human</td>
<td>—</td>
<td>Expiration Date</td>
<td>15 days for device</td>
</tr>
</tbody>
</table>

Do not refrigerate (lispro, glargine) – 28 days, (aspart) – 14 days

(pens should not be refrigerated)

## Basal Insulin Delivery Options

<table>
<thead>
<tr>
<th>Insulin</th>
<th>Concentration</th>
<th>Vial</th>
<th>Pen</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPH</td>
<td>U-100</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Glargine</td>
<td>U-100</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Glargine</td>
<td>U-300</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Detemir</td>
<td>U-100</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Regular Human</td>
<td>U-500</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

Food and Drug Administration. Drugs@FDA FDA Approved Drug Products. http://www.accessdata.fda.gov
Vial and Syringe

• Some patients still use vials and syringes
  – Wipe the rubber stopper (on vial) with alcohol swab
  – Put equivalent amount of air into the vial before drawing up the insulin (based on insulin dose)

• When mixing insulin:
  – Clear before cloudy
  – Pre-drawn N + R = stable for 30 days refrigerated
Needles and Syringes

- **Outer protective cap**
- **Plunger**
- **Peel foil**
- **Inner protective cap**
- **Needle (cannula)**
- **Needle hub**
- **Barrel**
- **Cap**

Dimensions:
- 12.7 mm (1/2")
- 8 mm (5/16")
- 5 mm (3/16")
Insulin Pens

How to Use an Insulin Pen
Patient Cases
Case 1

- 67-year-old male, retired engineer
  - BMI 45
  - A1c = 8.5%
  - SrCr = 1.2
- Medications:
  - Glargine (pen) 80 units twice per day
  - Aspart (pen) 30–60 units per meal + correction
  - Lisinopril 10 mg daily
  - Atorvastatin 10mg daily
- Total daily dose (TDD) insulin: ~300 units per day
- Largest meal is supper and snacks at night
Case #1 – Question #1

• The physician recently became aware of concentrated insulin and would like to switch the patient to U-500. For a total daily dose of 300 units to be given twice daily, how would you instruct the patient to draw up 150 units of U-500 insulin?

1) Using a U-100 syringe, draw to the 60 units marking

2) Using a U-100 syringe, draw to the 30 units marking

3) Using a tuberculin syringe, draw 0.2 mL

4) Using a tuberculin syringe, draw 0.4 mL
Case 1 Continued

• First assess patient current insulin injection technique
  – If technique is appropriate then…..

• Start U-500 insulin:
  – 300 units divided into two doses = 150 units twice daily
  – 150 units of U-500 insulin is equal to 30 units on a U-100 syringe
    – 30 units x 5 (5 times concentration) = 150 units of actual insulin
    – If using tuberculin syringe, 150 units = 0.3 mL

• U-300 insulin glargine is not a substitute for U-500 insulin because the current U-300 pen delivers only up to 80 units per injection
Case 2

• 56 year old female, high school principal
  – BMI 32
  – A1c = 8.9%
  – SrCr = 1.1

• Patient did report occasional episodes nocturnal hypoglycemia
  – ~ 3–5 per month

• Medications:
  – NPH (pen) 63 units twice per day
    • Morning (7 AM) and 2 hours before bed (9 PM)
  – Metformin 1000 mg daily
  – Sitagliptin 100 mg daily
  – Lisinopril 10 mg daily
  – Simvastatin 20 mg daily

• Total daily dose (TDD) insulin: ~126 units per day
• Patient does not want to start bolus insulin due to erratic meal and work schedules
Case #2 – Question #1

The physician wants to switch the patient to U-300 insulin glargine. What would be your recommendation for switching from 63 units twice daily (126 units/day) NPH to U-300 insulin glargine?

1) Using a U-100 syringe, draw to 21 units marking (63 units) and inject twice daily

2) Using a U-100 syringe, draw to 49 units marking (126 units) and inject once daily

3) Using the U-300 pen, dial to 126 units and inject once daily

4) Using the U-300 pen, dial to 51 units and inject twice daily
Case 2

- Switching to U-300 insulin glargine
  - Determine starting dose:

<table>
<thead>
<tr>
<th>Prior treatment</th>
<th>Start with</th>
</tr>
</thead>
<tbody>
<tr>
<td>Once daily long-acting or intermediate acting insulin</td>
<td>1:1</td>
</tr>
<tr>
<td>Twice-daily NPH</td>
<td>80% total daily basal dose</td>
</tr>
<tr>
<td>No current basal insulin</td>
<td>0.2 U/kg/day</td>
</tr>
</tbody>
</table>

- 126 units x 0.80 = 100.8 units U-300 glargine
  - 101 units/2 = 51 units given twice daily; current U-300 pen has max dose of 80 units per injection

- To minimize hypoglycemia risk, titrate the dose no more frequently than every 3–4 days
Summary

• Type 2 diabetes is a growing epidemic with an ever-growing number of patients requiring high doses of insulin to maintain glycemic control

• Insulin resistance is a MAJOR problem among patients with type 2 diabetes, and combination therapy is often needed to improve insulin sensitivity

• A basal-bolus insulin regimen is best to mimic natural insulin physiology but requires frequent BG monitoring and provider/patient education

• Concentrated insulin is ideal for patients with insulin doses >200 U/day due to the large volume associated with U-100 insulin
Summary Continued

• U-500 regular human insulin is associated with a high incidence of dosing errors due to the lack of a U-500 specific insulin syringe

• Newly approved U-300 insulin glargine is available in a pen, avoiding the need for conversion using U-100 or tuberculin syringes needed with U-500 insulin

• Insulin in T2DM is often delayed, but in order to optimize glycemic control, it is important that clinicians recognize and address the barriers to insulin therapy

• U-300 insulin glargine and emerging basal insulins have improved PK/PD profiles compared to current insulins
  – Flatter time–action profiles with less variability
  – Less hypoglycemia, particularly nocturnal hypoglycemia