Latest Trends in Insulin

Jasmine D. Gonzalvo, PharmD, BCPS, BC-ADM, CDE, LDE
Clinical Associate Professor | College of Pharmacy | Purdue University
Clinical Pharmacy Specialist | Primary Care | Eskenazi Health
(317) 880-5406 | jgonzalv@purdue.edu
Twitter: @JasGonzalvo
Objectives

- List the newly approved insulin products since 2015
- Compare and contrast older U-100 insulin products to newer insulins
- Know how to transition from older U-100 insulin regimens to newer insulin regimens
- Convert U-100 insulin regimens to regimens with newer insulins in a variety of patient scenarios
- List insulin products on the horizon
Disclosure

• Board Member/Advisory Panel: Lilly; Novo Nordisk, Inc.; Merck
List the newly approved insulin products since 2015
### Newly Approved Products since 2015

<table>
<thead>
<tr>
<th>U-100</th>
<th>U-200</th>
<th>U-300</th>
<th>U-500</th>
<th>Combination products</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Faster-acting</strong></td>
<td><strong>insulin lispro</strong></td>
<td><strong>insulin glargine</strong></td>
<td><strong>Pen</strong></td>
<td><strong>insulin degludec</strong></td>
</tr>
<tr>
<td><strong>insulin degludec</strong></td>
<td><strong>insulin degludec</strong></td>
<td></td>
<td><strong>Syringe</strong></td>
<td><strong>/ insulin aspart 70/30</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>insulin glargine</strong></td>
<td></td>
<td><strong>/ liraglutide</strong></td>
</tr>
<tr>
<td><strong>Follow-on</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>insulin glargine</strong></td>
</tr>
<tr>
<td><strong>insulin glargine</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>/ lixisenatide</strong></td>
</tr>
</tbody>
</table>
Compare and contrast older U-100 insulin products to newer insulins

Know how to transition from U-100 insulins to newer insulins
Faster acting insulin aspart
Faster-acting insulin aspart (FA aspart)

100 units/ml

Bolus insulin – can take after meal

Available as 10 ml multidose vial or 3 ml pen

1:1 conversion if converting from another mealtime insulin

0.1 units/kg takes about 20 minutes for first effect and about 90 minutes to peak
### Type 1 Diabetes

<table>
<thead>
<tr>
<th></th>
<th>Mealtime FA insulin aspart + insulin detemir</th>
<th>Postmeal FA insulin aspart + insulin detemir</th>
<th>Mealtime insulin aspart + insulin detemir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>381</td>
<td>382</td>
<td>380</td>
</tr>
<tr>
<td><strong>A1c</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>7.6</td>
<td>7.6</td>
<td>7.6</td>
</tr>
<tr>
<td>Adjusted mean change from baseline</td>
<td>-0.32</td>
<td>-0.13</td>
<td>-0.17</td>
</tr>
<tr>
<td>Estimated treatment difference vs insulin aspart (95% CI)</td>
<td>-0.15 [-0.23;0.07]</td>
<td>0.04 [-0.04;0.12]</td>
<td></td>
</tr>
<tr>
<td>Change in 2 hour post-prandial glucose</td>
<td>-5.2 mg/dL; p= 0.0375</td>
<td>5.32 mg/dL</td>
<td>6.6 mg/dL</td>
</tr>
</tbody>
</table>

### Type 2 Diabetes

<table>
<thead>
<tr>
<th></th>
<th>Mealtime FA insulin aspart + insulin glargine + metformin</th>
<th>Mealtime insulin aspart + insulin glargine + metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>345</td>
<td>344</td>
</tr>
<tr>
<td><strong>A1c</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>8.0</td>
<td>7.9</td>
</tr>
<tr>
<td>Adjusted mean change from baseline</td>
<td>-1.38</td>
<td>-1.36</td>
</tr>
<tr>
<td>Estimated treatment difference vs insulin aspart (95% CI)</td>
<td>-0.02 [-0.15;0.1]</td>
<td></td>
</tr>
<tr>
<td>Change in 1 hour post-prandial glucose</td>
<td>-2.1 mg/dL</td>
<td>-1.6 mg/dL</td>
</tr>
</tbody>
</table>
Insulin lispro U-200
Insulin lispro U-100 vs. insulin lispro U-200

- Bioequivalent
- Patients may prefer smaller injection volume of insulin lispro U-200
- Each 3 ml pen: 600 units total
- Maximum dose per injection is 60 units
- 1:1 conversion from other bolus insulins
- Initiation: 0.1 units/kg or 10% of basal dose

https://www.humalog.com/hcp/
Follow-on Insulin glargine
<table>
<thead>
<tr>
<th>Available as a 100 unit/mL pen device</th>
<th>Maximum injection of 80 units</th>
<th>1 unit increments</th>
</tr>
</thead>
<tbody>
<tr>
<td>300 total units per 3 mL pen</td>
<td>Store at room temperature after first use and dispose after 28 days</td>
<td>Prime with 2 units before each use</td>
</tr>
</tbody>
</table>

http://uspl.lilly.com/basaglar/basaglar.html#ug
Follow-on insulin glargine vs. insulin glargine
Insulin glargine to follow-on insulin glargine

Initiation in Type 2 Diabetes

0.2 units/kg

Initiation in Type 1 Diabetes

1/3 of total daily insulin requirement

Switching from other basal insulins

1:1

https://www.basaglar.com/hcp/dosing
Insulin degludec
U-100 and U-200
Insulin degludec U-100 vs. Insulin degludec U-200

Basal insulin

Both formulations available as pen devices

Bioequivalent with very similar PK/PD profiles

<p>| Differences between insulin degludec U-100 and insulin degludec U-200 |
|-------------------------------------------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Max Dose</th>
<th>Total Units per Pen</th>
<th>Adjustable Dose Setting</th>
<th>Expiration Once Opened</th>
</tr>
</thead>
<tbody>
<tr>
<td>U-100 degludec</td>
<td>80 units</td>
<td>300</td>
<td>1 unit increments</td>
</tr>
<tr>
<td>U-200 degludec</td>
<td>160 units</td>
<td>600</td>
<td>2 unit increments</td>
</tr>
</tbody>
</table>

U-200 insulin degludec

1:1 from other long-acting insulins

Initiation in T1DM: ⅓ to ⅔ total daily dose of insulin

Initiation in T2DM: 10 units

Insulin glargine U-300
Insulin glargine U-300

- Each 1.5 mL pen contains 450 units
- Once opened, can be stored at room temperature for up to 42 days
- Maximum injection: 80 units
- Pen markings in 1 unit increments
- May experience temporary rise in FPG when switching from U-100 insulin glargine to U-300 insulin glargine
- Less incidence of hypoglycemia compared to other basal insulins
## Insulin glargine U-300 vs insulin glargine U-100

<table>
<thead>
<tr>
<th></th>
<th>EDITION 1 6-Month Data</th>
<th>EDITION 1 12-Month Data</th>
<th>EDITION 2 6-Month Data</th>
<th>EDITION 2 12-Month Data</th>
<th>EDITION 3 6-Month Data</th>
<th>EDITION 4 6-Month Data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>U-300</td>
<td>U-100</td>
<td>U-300</td>
<td>U-100</td>
<td>U-300</td>
<td>U-100</td>
</tr>
<tr>
<td>n</td>
<td>404</td>
<td>403</td>
<td>404</td>
<td>403</td>
<td>403</td>
<td>405</td>
</tr>
<tr>
<td>Baseline A1c (%)</td>
<td>8.15</td>
<td>8.16</td>
<td>8.15</td>
<td>8.16</td>
<td>8.26</td>
<td>8.22</td>
</tr>
<tr>
<td>Change in A1c (%)</td>
<td>-0.83</td>
<td>-0.83</td>
<td>-0.86</td>
<td>-0.69</td>
<td>-0.57</td>
<td>-0.56</td>
</tr>
<tr>
<td>A1c &lt;7 (%)</td>
<td>39.6</td>
<td>40.9</td>
<td>-</td>
<td>-</td>
<td>30.6</td>
<td>30.4</td>
</tr>
<tr>
<td>Confirmed Nocturnal Hypoglycemia (%)</td>
<td>44.6</td>
<td>57.5</td>
<td>54.5</td>
<td>64.7</td>
<td>28.3</td>
<td>39.9</td>
</tr>
</tbody>
</table>
U-300 insulin glargine

Switching from once daily basal U-100 insulin: 1:1

Switching from twice daily NPH: 80% of total daily NPH dose

Initiation for T1DM: ⅓ to ½ of total daily dose

Initiation for T2DM: 0.2 units/kg

For patients who have a total daily dose of more than 200 units

Replaces all other insulins

Available as a vial or a pen

Markings in increments of 5 units on pen device

BID or TID dosing

5 unit increments marked on 0.5 mL U-500 syringe

https://www.humulin.com/clinical-considerations.aspx#delivery-methods
U-500 Dosing

Determining initial dose:

A1c <8% or mean SMBG <183 mg/dL within the past 7 days?

Yes: Start at 80% of the U-100 total daily dose

No: Start at 100% of final U-100 total daily dose

TID Dosing:

- 40% of daily dose before breakfast
- 30% of daily dose before lunch
- 30% of daily dose before dinner

BID Dosing:

- 60% of daily dose before breakfast
- 40% of daily dose before dinner

Combination Products
Insulin degludec/liraglutide (iDegLira)

Consider use in patients with a total basal insulin dose <50 units/day or liraglutide <1.8mg daily

Initial dose: 16 units (16 units degludec and 0.58 mg liraglutide)

Titrate dose every 3-4 days by 2 units

Maximum dose of iDegLira is 50 units

One box has five 3 ml pens

After initial dose, the pen can be used for 21 days

Insulin glargine/lixisenatide (iGlarLixi)

- For patients with a daily insulin dose of 15-29 units:
  - initiate iGlarLixi 15 units
  - (15 units of insulin glargine, 5 mcg of lixisenatide)

- For patients with a daily insulin dose of 30-60 units:
  - initiate iGlarLixi at 30 units
  - (10 units of insulin glargine, 10 mcg of lixisenatide)

- Maximum dose of iGlarLixi:
  - 60 units
  - (60 units of insulin glargine, 20 mcg of lixisenatide)

- Not recommended for patients who take
  - <15 units or
  - >60 units of insulin per day

https://www.soliqua100-33.com/hcp/soliqua-100-33-dosing
Insulin degludec/aspart

Switching from a daily or BID basal insulin:
1:1 to insulin degludec/aspart

Switching from basal and bolus insulin:
start insulin degludec/aspart once daily with the main meal at the same unit dose as the basal insulin
Continue the bolus insulin at the same dose for the meals that are not covered by this combination product

Available in prefilled pens

Once open, should not be refrigerated, but kept at room temperature

Open pens can be used up to 28 days, at room temperature

https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/203313lbl.pdf
Convert U-100 insulin regimens to newer insulins in a variety of patient scenarios.
LJ is a 59 YOWF who comes to clinic today to help address Type 2 Diabetes. She denies any severe s/sxs of hypo or hyperglycemia.

**Labs**
- A1C: 8.4% (taken today)
- SMBG: 190-220
- eAG: 194 mg/dL
- Wt: 215 lbs
- BP: 134/82

**Medications**
- metformin 1000 mg PO BID
- insulin detemir 45 units SQ QHS
- insulin aspart 15 units SQ TID
Patient 1

Would a switch to faster-acting insulin aspart be appropriate for this patient?

If so, what dose would be appropriate?

Faster-acting insulin aspart 15 units SQ TID before meals
AD is 62 YOAAM who comes to clinic today for Type 2 Diabetes. He denies severe s/sxs of hypo or hyperglycemia.

<table>
<thead>
<tr>
<th>Labs</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C: 9.1% (taken 1 month ago)</td>
<td>metformin 100 mg PO BID</td>
</tr>
<tr>
<td>SMBG: 182, 190, 210, 226, 257</td>
<td>insulin glargine 50 units SQ BID</td>
</tr>
<tr>
<td>eAG: 214 mg/dL</td>
<td>insulin aspart 30 units SQ TID before meals</td>
</tr>
<tr>
<td>Wt: 250 lbs</td>
<td></td>
</tr>
<tr>
<td>BP: 141/92</td>
<td></td>
</tr>
</tbody>
</table>
What would be the equivalent U-200 insulin lispro dose?

U-200 insulin lispro 30 units SQ TID before meals

What would be the equivalent U-200 insulin degludec dose?

U-200 insulin degludec 100 units SQ daily
# Patient 3

JL is a 48 YOWF who comes into the clinic for Type 2 Diabetes. She denies s/sxs of hypo or hyperglycemia.

<table>
<thead>
<tr>
<th>Labs:</th>
<th>Medications:</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1c: 8.1% (taken today)</td>
<td>metformin 1000 mg PO BID</td>
</tr>
<tr>
<td>SMBG: 130-200</td>
<td>insulin lispro 20 units SQ TID</td>
</tr>
<tr>
<td>eAG: 186 mg/dL</td>
<td>insulin detemir 60 units SQ QHS</td>
</tr>
<tr>
<td>Weight: 275 lbs</td>
<td></td>
</tr>
<tr>
<td>BP: 135/72 mmHg</td>
<td></td>
</tr>
</tbody>
</table>
Patient 3

Would this be an appropriate patient for U-200 insulin lispro? At what dose?

U-200 insulin lispro 20 units SQ TID before meals

What would be the appropriate dose of U-300 insulin glargine for this patient?

U-300 insulin glargine 60 units SQ QHS
Patient 4

BA is a 58 YOAAF who comes to the clinic today for Type 2 Diabetes. She denies s/sxs of hypo or hyperglycemia

**Labs:**
A1c: 7.8% (taken 2 months ago)
SMBG: 99, 120, 138, 143, 155, 180, 190
eAG: 177 mg/dL
Wt: 290 lbs
BP: 138/70

**Medications:**
- metformin 1000 mg PO BID
- insulin glulisine 35 units SQ TID
- insulin detemir 75 units SQ BID
Patient 4

What dose of U-500 insulin would you initiate for this patient if they were going to do:

**TID dosing?**
- A1C <8% → start at 80% of TDD (255 units x 80% = 204 units)
- 80 units before breakfast (40%), 60 units before lunch (30%), and 60 units before dinner (30%)

**BID dosing?**
- 120 units before breakfast (60%) and 80 units before dinner (40%)

What would the appropriate U-500 dose be if the A1C was 9.5%?
- A1c >8% → Start at 100% of U-100 total daily dose (255 units)
- TID: 100 units (40%) before breakfast, 75 units (30%) before lunch, and 75 units (30%) before dinner
- BID: 150 units (60%) before breakfast and 100 units (40%) before dinner
MK is a 57 YOAAF who comes to the clinic today for Type 2 diabetes. MK reports frequent symptoms of hypoglycemia. She denies s/sxs of hyperglycemia.

**Labs:**
- A1c: 8% (taken 1 month ago)
- SMBG: 63, 65, 68, 71, 80
- eAG: 183 mg/dL
- Wt: 286 lbs
- BP: 120/72

**Medications:**
- metformin 1000mg PO BID
- insulin detemir 45 units SQ QHS
Patient 5

Would this be an appropriate patient for insulin degludec/liraglutide?

If so, what would the initial dose be?

- Discontinue insulin detemir and initiate insulin degludec/liraglutide 16 units SQ daily

How is it titrated?

- Titrate up or down 2 units every 3-4 days until goal BG are reached with a max dose of 50 units
List insulin products on the horizon
On the horizon (check updated info)

- Several ultra-rapid acting
  - Biosimilars
  - Generic versions
  - Smart insulin: Glucose-responsive insulin which starts and stops working depending on glucose levels
  - Oral and buccal insulin

References

- Yki-Jarvinen H, Bergenstal R, Ziemen M, et al. New Insulin Glargine 300 units/mL versus Glargine 100 units/mL in People with Type 2 Diabetes Using Oral Agents and Basal Insulin: Glucose Control and Hypoglycemia in a 6-Month Randomized Controlled Trial (EDITION 2). *Diabetes Care* 2014; 37: 3235-43.
Latest Trends in Insulin

Jasmine D. Gonzalvo, PharmD, BCPS, BC-ADM, CDE, LDE
Clinical Associate Professor | College of Pharmacy | Purdue University
Clinical Pharmacy Specialist | Primary Care | Eskenazi Health
(317) 880-5406 | jgonzalv@purdue.edu
Twitter: @JasGonzalvo