

## Comparison of Insulins

—Based on U.S. product information—(Last modified December 2008)

—Information for the non-insulin agents, *Byetta* and *Symlin*, is located at the end of the chart—

### Rapid-acting

	<b>Insulin Lispro Solution</b>	<b>Insulin Aspart Solution</b>	<b>Insulin Glulisine</b>
Brand, Maker	<i>Humalog</i> <sup>19</sup> Eli Lilly	<i>NovoLog</i> , <sup>20</sup> Novo Nordisk	<i>Apidra</i> , <sup>21,30</sup> Aventis
Availability	All are prescription.		
Description	Human insulin analog (rDNA)		
Onset <sup>16</sup>	15 to 30 minutes	10 to 20 minutes	10 to 15 minutes <sup>22</sup>
Peak <sup>16</sup>	30 minutes to 2.5 hours	1 to 3 hours	1 to 1.5 hours <sup>22</sup>
Duration <sup>16</sup>	3 to 6.5 hours	3 to 5 hours	3 to 5 hours <sup>22</sup>
Administration	FDA-labeled for SC injection and SC infusion ( <i>NovoLog</i> approved for IV infusion in clinical settings).		
Meal timing	Give SC injection within 15 minutes before or immediately after meals. <sup>1</sup> Give pump bolus immediately before meal. <sup>6</sup>	Give 5 to 10 minutes before meals.	Give SC injection within 15 minutes before or within 20 min. after starting a meal. <sup>21</sup>
Formulations	100 units/mL. 10 mL vials, 3 mL cartridge and disposable pen.	100 units/mL. 10 mL vials, 3 mL cartridge (latex-free), <sup>24</sup> 3 mL disposable <i>FlexPen</i> .	100 units/mL. 10 mL vials, 3 mL cartridge
Appearance	Clear <sup>1,10</sup>		
Compatibility	<ul style="list-style-type: none"> <li>• Can mix with NPH or ultralente (draw lispro into syringe first and inject immediately).<sup>19</sup></li> <li>• Mixture with NPH (<i>Humulin N</i>) stable in vials for 28 days at room temperature and refrigeration (prefilled syringes stable for 14 days refrigerated).<sup>35</sup></li> <li>• Can mix with Lilly diluent to dilutions of 1:2 (U-50) or 1:10 (U-10). Diluted solutions stable for 28 days at 5° C (41° F) and 14 days at 30° C (86° F).</li> <li>• Do not mix with glargine (see note under <i>Lantus</i>).</li> <li>• Discard pump insulin if exposed to &gt;37° C.</li> </ul>	<ul style="list-style-type: none"> <li>• Can mix with NPH (draw aspart into syringe first and inject immediately after mixing).<sup>16</sup></li> <li>• No data on mixing with regular, lente, or ultralente.<sup>24</sup></li> <li>• Discard pump insulin if exposed to &gt;37° C.</li> <li>• Do not mix with glargine (see note under <i>Lantus</i>).</li> </ul>	<ul style="list-style-type: none"> <li>• Can mix with NPH only (draw glulisine into syringe first and inject immediately).<sup>21</sup></li> </ul>
Stability of in-use products at room temp	Vial, cartridge, pen: 28 days External pump: 48 hours for most parts; 7 days for 3 mL cartridge in D-TRON or D-TRON plus.	Vial, cartridge, pen: 28 days External pump: 48 hours. <sup>24</sup>	Vial, cartridge: 28 days. External pump: 48 hours. <sup>1</sup>
AWP	\$80.35/10 mL vial \$156.18/5 of 3 mL cartridge \$161.69/5 of 3 mL pen	\$83.71/10 mL vial \$155.52/5 of 3 mL cartridge \$161.73/5 of 3 mL <i>FlexPen</i>	\$80.87/10 mL vial \$162.68/5 of 3 mL cartridge

More . . .

**Short-acting (ie, Regular insulin)**

Brand, maker	<i>Humulin R</i> , Eli Lilly	<i>Novolin R</i> , Novo Nordisk	<i>Iletin II Regular</i> , <sup>25</sup> Eli Lilly*
Species	Human (rDNA)	Human (rDNA)	Pork
Availability	Non-prescription (except 500 units/mL <i>Humulin R</i> ). <b>As of July 2005, Lilly will discontinue <i>Iletin II Regular</i>; stock depletion expected by end of 2005.</b>		
Onset <sup>16</sup>	30 to 60 minutes; onset more rapid with human than pork.		
Peak <sup>16</sup>	1 to 5 hours; peak may be more rapid with human than pork.		
Duration <sup>16</sup>	6 to 10 hours; longer with pork than human. May be longer with U-500.		4 to 12 hours
Administration	SC, IM, IV (unlabeled). 500 units/mL SC only.	SC, IM, IV. <sup>39</sup>	SC, IV (unlabeled), but not IM.
Meal timing	SC injection: 30 minutes before meals. <sup>1</sup> Pump bolus: 20 to 30 minutes before a meal. <sup>6</sup>		
Formulations	100 units/mL: 10 mL vial. 500 units/mL: 20 mL vial.	100 units/mL: 10 mL vial, 3 mL cartridge, 3 mL <i>Innolet</i> .	100 units/mL. 10 mL vial.
Appearance	Clear and colorless. <sup>1</sup>		
Compatibility	<ul style="list-style-type: none"> <li>• Can mix with NPH; use immediately or store for future use.<sup>1</sup> Mixture in vials stable at room temperature for 1 month, refrigerator for 3 months, but must consider possibility of microbial contamination.<sup>16,36</sup></li> <li>• Mixing with lente/ultralente can delay onset of regular; may not reach binding equilibrium for 24 hours. Per ADA, mix with lente only if patient already stabilized on regimen. Standardize interval between mixing &amp; injecting (either immediately or <math>\geq 24</math> hours after mixing).<sup>1, 5, 6</sup></li> <li>• <i>Humulin R</i> stable for 1 month at room temp after dilution with Lilly insulin diluent.<sup>18</sup></li> <li>• Do not mix with glargine.</li> <li>• Can mix with Water for Injection or 0.9% Sodium Chloride for Injection for use in SC infusion pump. Use within 24 hours.<sup>16</sup></li> </ul>		<ul style="list-style-type: none"> <li>• Can mix with <i>Iletin II Lente</i> if administered immediately.<sup>6</sup></li> <li>• Can mix with NPH.<sup>5</sup></li> <li>• Can mix with ultralente.<sup>5</sup></li> <li>• Do not mix with glargine.</li> <li>• Diluent no longer available for <i>Iletin II Regular</i>.<sup>18</sup></li> </ul>
Stability of in-use products at room temperature	Vial: 28 days <sup>42</sup>	Vial: 30 days <sup>43</sup> 3 mL cartridge & <i>Innolet</i> : 28 days	Vial: 28 days <sup>42</sup>
AWP	\$36.19/10 mL vial (U-100) \$219.46/20 mL vial (U-500)	\$37.71/10 mL vial \$119.34/5 of 3 mL cartridge \$80.28/5 of 3 mL <i>Innolet</i>	\$47.98/10 mL vial Discontinued

**Intermediate-acting**

	<b>Lente</b> (Insulin zinc suspension; contains zinc and acetate buffers) <sup>5</sup>	<b>NPH</b> (Isophane insulin suspension; contains zinc and protamine) <sup>5</sup>		
Brand, maker	<i>Humulin L</i> , Lilly	<i>Novolin N</i> , Novo Nordisk	<i>Humulin N</i> , <sup>25</sup> Lilly	<i>Iletin II NPH</i> , <sup>25</sup> Lilly
Species	Human	Human	Human	Pork
Availability	Non-prescription. <b>As of July 2005, Lilly will discontinue <i>Humulin L</i> and <i>Iletin II NPH</i>; stock depletion expected by end of 2005.</b>			
Onset <sup>16</sup>	1 to 3 hours	1 to 2 hours; onset more rapid with human than pork		
Peak <sup>16</sup>	6 to 14 hours	6 to 14 hours		
Duration <sup>16</sup>	16 to 24 hours	16 to 24+ hours; duration of human < pork		
Administration	SC only. <sup>16</sup> Re-suspend before injection. <sup>6</sup>	SC only. <sup>16</sup> Re-suspend before injection. <sup>6</sup>		
Meal timing	<ul style="list-style-type: none"> <li>Inject within 15 minutes before meals when NPH mixed with rapid-acting insulin.<sup>1</sup></li> <li>Usually injected 30 minutes before meals when mixed with regular.<sup>1</sup></li> <li>Individualize based on blood glucose.<sup>8</sup></li> </ul>			
Formulations	100 units/mL. 10 mL vial.	100 units/mL. 10 mL vial, 3 mL cart, 3 mL <i>Innolet</i> .	100 units/mL. 10 mL vial, 3 mL cartridge.	100 units/mL. 10 mL vial.
Appearance	Cloudy <sup>1</sup>			
Compatibility	<ul style="list-style-type: none"> <li>Do not mix with regular insulin unless patient stabilized on regimen (delays onset of regular insulin). Standardize interval between mixing and injecting (either immediately or at least 24 hours after mixing).<sup>1,5</sup> Mix with <i>Iletin II</i> regular immediately before injecting.<sup>6</sup></li> <li>Can mix with ultralente.<sup>5</sup></li> <li>Do not mix with NPH or glargine.<sup>1</sup></li> <li>Diluent no longer available for <i>Humulin L</i>.<sup>18</sup></li> </ul>	<ul style="list-style-type: none"> <li>Can mix with aspart or lispro.<sup>5</sup> Draw up rapid-acting insulin first and inject immediately.<sup>24</sup> (See additional stability information in lispro section).</li> <li>Can mix with regular. Draw up regular insulin first; can be used immediately or stored for future use.<sup>1</sup> Mixture in vials stable at room temperature for 1 month and in refrigerator for 3 months.<sup>5</sup></li> <li>Lilly NPH products stable for 1 month at room temperature after dilution with Lilly insulin diluent.<sup>6,18</sup></li> <li>Do not mix with lente, ultralente, or glargine.<sup>1,5</sup></li> </ul>		
Room temp stability, in-use products	Vial: 28 days <sup>42</sup>	Vial: 30 days <sup>43</sup> 3 mL cart, <i>Innolet</i> : 14 days	Vial: 28 days <sup>42</sup> 3 mL pen: 14 days	Vial: 28 days <sup>42</sup>
AWP	\$29.85/10 mL vial Discontinued	\$37.71/10 mL vial \$119.44/5 of 3 mL cart \$80.28/5 of 3 mL <i>Innolet</i>	\$36.19/10 mL vial \$119.43/5 of 3 mL pens	\$47.98/10 mL vial Discontinued

**Long-acting**

	<b>Insulin glargine solution</b>	<b>Ultralente</b> (Extended insulin zinc suspension)	<b>Insulin Detemir solution</b>
Brand, maker	<i>Lantus</i> , <sup>12</sup> Aventis	<i>Humulin U</i> , Lilly	<i>Levemir</i> , <sup>34</sup> Novo Nordisk
Availability	Prescription only.	Non-prescription. <b>Will be discontinued; expect stock depletion by end of 2005.</b>	Prescription only.
Species	Human insulin analog (rDNA)	Human (rDNA)	Human insulin analog (rDNA)
Onset <sup>16</sup>	1.1 hours	4 to 6 hours	0.8 to 2 hours (dose-dependent) <sup>39</sup>
Peak <sup>16</sup>	No significant peak	8 to 20 hours	Relatively flat
Duration <sup>16</sup>	24 hours	24 to 28 hours with 0.5 units/kg; somewhat dose-dependent. <sup>6</sup>	Dose-dependent; 12 hours for 0.2 units/kg, 20 hours for 0.4 units/kg, up to 24 hours. Binds to albumin.
Administration	<ul style="list-style-type: none"> <li>Once daily SC at same time each day.</li> <li>Give equivalent dose of <i>Lantus</i> after conversion from once daily human NPH/lente; reduce <i>Lantus</i> dose by 20% after twice daily NPH.</li> <li>No need to shake before administration.</li> <li>Low pH may cause pain at injection site.</li> </ul>	<ul style="list-style-type: none"> <li>Re-suspend before injection.<sup>6</sup></li> <li>SC injection only.</li> </ul>	<ul style="list-style-type: none"> <li>Give SC once or twice daily. Give once-daily dose at evening meal or hs. Give equivalent dose of <i>Levemir</i> after conversion from another basal insulin.<sup>34</sup></li> <li><u>Type 2 diabetes</u>: Some pts may need higher doses of <i>Levemir</i> than <i>NPH</i>. Insulin-naïve pts with poor control on PO drugs: 0.1-0.2 units/kg once daily in evening or 10 units once/ twice daily.<sup>34</sup></li> </ul>
Meal timing	Not applicable.	<ul style="list-style-type: none"> <li>Inject within 15 minutes before meals if mixed with rapid-acting insulin.<sup>1</sup></li> <li>Usually injected 30 minutes before meals if mixed with regular.<sup>1</sup></li> </ul>	<ul style="list-style-type: none"> <li>Evening dose can be given at dinner or hs. In twice-daily regimens, it can also be given 12 h after morning dose.<sup>34</sup></li> </ul>
Formulations	100 units/mL. 10 mL vial, 3 mL cart for <i>Opticlik</i> .	100 units/mL. 10 mL vial.	100 units/mL. 10 mL vial, 3 mL disposable <i>FlexPen</i> .
Appearance	Clear <sup>1</sup>	Cloudy <sup>1</sup>	Clear <sup>14</sup>
Compatibility	<ul style="list-style-type: none"> <li>Do not mix with other insulins; diluent has low pH (4).<sup>1</sup></li> <li>Note: In initial studies, mixing glargine with lispro or aspart did not affect glycemic control. The mixture was cloudy.<sup>13,40</sup></li> </ul>	<ul style="list-style-type: none"> <li>Can mix with insulin lispro (inject within 5 minutes), regular (standardize time from mixing to injecting), or lente.<sup>4,5</sup> Do not mix with NPH.<sup>1</sup></li> <li>Mixture with lente stable at room temp for 1 month, refrigerated for 3 months.<sup>26</sup></li> <li>Diluent no longer available for <i>Humulin U</i>.<sup>18</sup></li> </ul>	<ul style="list-style-type: none"> <li>Do not mix with other insulins or diluent. Mixing with <i>Levemir</i> reduced levels of insulin aspart substantially.<sup>34</sup></li> <li>Has neutral pH (7.4).<sup>2,34</sup></li> </ul>
Room temp stability, in-use products	10 mL vial: 28 days 3 mL cartridge: 28 days	10 mL vial: 28 days <sup>42</sup>	10 mL vial, 3 mL <i>FlexPen</i> : 42 days. In-use vials can be refrigerated; other forms cannot. <sup>43</sup>
AWP	\$80.21/10 mL vial; \$163.44/5 of 3 mL cart	\$29.85/10 mL vial (Discontinued)	\$83.70/10 mL vial; \$161.69/5 <i>FlexPen</i>

**Insulin Mixtures** (Information for **Humalog Mix 50/50** is at the end of this chart)

	<b>30% insulin aspart, 70% insulin aspart protamine</b>	<b>25% insulin lispro, 75% insulin lispro protamine</b>	<b>70% NPH, 30% regular</b>		<b>50% NPH, 50% regular</b>
Brand, Maker	<i>Novolog Mix 70/30</i> <sup>28</sup> Novo Nordisk	<i>Humalog Mix 75/25</i> <sup>27</sup> Eli Lilly	<i>Humulin 70/30</i> <sup>25</sup> Eli Lilly	<i>Novolin 70/30</i> <sup>25</sup> Novo Nordisk	<i>Humulin 50/50</i> Eli Lilly
Availability	Prescription only		Non-prescription		
Species	Human insulin analog (rDNA)		Human (rDNA)		
Onset	10 to 20 minutes <sup>39</sup>	Faster than <i>Humulin 70/30</i>	30 to 60 minutes <sup>7</sup>	30 to 60 minutes <sup>7</sup>	30 to 60 minutes <sup>7</sup>
Peak	Mean 2.4 hours Range 1 to 4 hours	Mean 2.6 hours Range 1 to 6.5 hours	Mean 4.4 hours Range 1.5 to 16 hours	2 to 12 hours	Mean 3.3 hours Range 2 to 5.5 hours
Duration	Effective: 15 to 18 hours Max: Up to 24 hours	Up to 24 hours (similar to <i>Humulin 70/30</i> ).	Effective: 10 to 16 hours <sup>9</sup> Max: Up to 18 to 24 hours <sup>9</sup>	Effective: 10 to 16 hours <sup>9</sup> Max: Up to 18 to 24 hours <sup>9</sup>	Effective: 10 to 16 hours <sup>9</sup> Max: Up to 18 to 24 hours <sup>9</sup>
Administration	SC only. Re-suspend before injection. <sup>6</sup>				
Meal timing	<ul style="list-style-type: none"> <li>• Give within 15 minutes of a meal.</li> <li>• Individualize based on blood glucose.<sup>8</sup></li> </ul>		<ul style="list-style-type: none"> <li>• Give approx. 30 minutes before meals.<sup>1</sup></li> <li>• Individualize based on blood glucose.<sup>8</sup></li> </ul>		
Formulations	100 units/mL. 10 mL vial, 3 mL cart, 3 mL disposable <i>FlexPen</i>	100 units/mL. 10 mL vial, 3 mL disposable pen	100 units/mL. 10 mL vial, 3 mL disposable pen	100 units/mL. 10 mL vial, 3 mL cartridge, 3 mL <i>Innolet</i>	100 units/mL. 10 mL vial
Appearance	Cloudy				
Compatibility	<ul style="list-style-type: none"> <li>• Do not mix with other insulins. • <i>Humalog Mix 75/25</i>, <i>Humulin 70/30</i>, and <i>Humulin 50/50</i> stable for 1 month at room temperature after dilution with Lilly insulin diluent.<sup>18</sup></li> </ul>				
Stability of in- use products at room temp	Vial: 28 days Pen: 14 days 3 mL cart: 14 days	Vial: 28 days Pen: 10 days	Vial: 28 days Pen: 10 days	Vial: 30 days <sup>43</sup> 3 mL cart, <i>Innolet</i> : 10 days	Vial: 28 days
Cost	\$83.71/10 mL vial \$155.52/5 of 3 mL cart \$161.73/5 of 3 mL pen	\$80.35/10 mL vial \$161.69/5 of 3 mL pen	\$36.19/10 mL vial \$119.43/10 of 3 mL pen	\$37.71/10 mL vial \$119.44/5 of 3 mL cart \$80.28/5 of 3 mL <i>Innolet</i>	\$36.19/10 mL vial

**Insulin Administration Devices**

Device Manufacturer	Description	Dosage range and precision	Insulin Used	Storage & stability of in-use pens	AWP	Comments
<i>Autopen Classic</i> AN3810 and AN3800 Owen Mumford 800-421-6936 www.owenmumford.com	Reusable pen	1-21 units in 1-unit increments or 2-42 units in 2-unit increments	3 mL cartridges from Lilly or CP Pharmaceuticals	According to insulin cartridge specifications	\$40	Automatic side injection button. Comes with <i>Unifine Pentip</i> needles (1/2" or 5/16", both 29 G), but can use other needles. Cannot easily correct "over-dialed" dose without losing insulin.
Lilly pens Eli Lilly 800-545-5979 www.lillydiabetes.com <b>(See next pg. for HumaPen Memoir/Luxura)</b>	Prefilled disposable pen	1-60 units in 1-unit increments	3 mL with: <i>Humalog 75/25</i> <i>Humalog 50/50</i> <i>Humalog</i> <i>Humulin N</i> <i>Humulin 70/30</i>	Room temp for: 10 days 10 days 28 days 14 days 10 days	\$161.69 for 5 pens <i>Humalog</i> \$119.43 for 5 pens <i>Humulin</i>	Can use with 28 G <i>BD</i> pen needles or equivalent. Has magnifying dose window. Also additional magnifier that snaps on the pen. <i>Humalog</i> products are prescription only.
<i>Innolet</i> Novo Nordisk www.innolet-us.com	Prefilled disposable device	1-50 units in 1-unit increments	3 mL with: <i>Novolin N</i> <i>Novolin 70/30</i> <i>Novolin R</i>	Room temp for: 14 days 10 days 28 days	\$62.95/5 of 3 mL dosers	Uses <i>NovoFine</i> or <i>BD</i> pen needles. Has large dosage dial and numbers. Audible clicks. <sup>a</sup> Dial dose up/down for dose correction. Resets to zero after shot.
<i>Levemir FlexPen</i> Novo Nordisk www.insulindevice.com	Prefilled disposable pen	1-60 units in 1-unit increments	3 mL with <i>Levemir</i>	42 days at room temperature	\$161.69 for 5 pens	Uses <i>NovoFine</i> or <i>BD</i> pen needles. Large window. Audible clicks. <sup>a</sup> Dial dose up/down for dose correction. Resets to zero after shot.
<i>NovoLog FlexPen</i> Novo Nordisk	Prefilled disposable pen	1-60 units in 1-unit increments	3 mL with <i>NovoLog</i>	28 days at room temperature	\$161.73 for 5 pens	Uses <i>NovoFine</i> or <i>BD</i> pen needles. Large window. Audible clicks. <sup>a</sup> Dial dose up/down for dose correction. Resets to zero after shot.
<i>NovoLog Mix 70/30 FlexPen</i> Novo Nordisk	Prefilled disposable pen	1-60 units in 1-unit increments	3 mL with <i>NovoLog Mix 70/30</i>	14 days at room temperature	\$161.73 for 5 pens	Uses <i>NovoFine</i> or <i>BD</i> pen needles. Large window. Audible clicks. <sup>a</sup> Dial dose up/down for dose correction. Resets to zero after shot.

Device Manufacturer	Description	Dosage range and precision	Insulin Used	Storage & stability of in-use pens	AWP	Comments
<i>NovoPen 3</i> Novo Nordisk	Reusable pen	2-70 units in 1-unit increments	3 mL Novo Nordisk <i>PenFill</i> cartridges ( <i>Novolin N, R, 70/30, NovoLog, NovoLog Mix 70/30</i> )	Room temperature; duration according to specific cartridge	\$12.50 (pen)	Uses <i>Novofine</i> or <i>BD</i> pen needles. Can add <i>PenMate</i> attachment to hide needle and autoinject.
<i>NovoPen Junior</i> Novo Nordisk	Reusable pen	1-35 units in ½ unit increments	3 mL Novo Nordisk <i>PenFill</i> cartridges ( <i>Novolin N, R, 70/30, NovoLog, NovoLog Mix 70/30</i> )	Room temperature; duration according to specific cartridge	\$37.49 (pen)	Uses <i>NovoFine</i> or <i>BD</i> pen needles. Can add <i>PenMate</i> attachment to hide needle and autoinject.
<i>OptiClik</i> Aventis www.opticlik.com	Reusable pen	1-80 units in 1 unit increments	3 mL <i>Lantus</i> cartridges 3 mL <i>Apidra</i> cartridges	28 days at room temperature. Allow cartridge to reach room temperature (1-2 hours) before using in pen.	Free	Do not store in the refrigerator, as that may damage electronics inside the pen body. If the pen malfunctions, the insulin can be drawn from the cartridge and injected.
<i>HumaPen Memoir</i> Eli Lilly www.humalog.com/patient/humapen_memoir.jsp	Reusable pen with memory	1-60 units in 1-unit increments	3 mL <i>Humalog</i> cartridges only, from Lilly	28 days at room temperature per <i>Humalog</i> cartridge specifications	\$100 (\$45 with coupon)	Do not refrigerate. Battery operated.
<i>HumaPen Luxura HD</i> Eli Lilly	Reusable pen	1-30 units in ½-unit increments (after 1st unit)	3 mL <i>Humalog</i> cartridges only, from Lilly	28 days at room temperature per <i>Humalog</i> cartridge specifications	N/A (product avail April 2007)	Do not refrigerate.

**Chart is based on U.S. product labeling.**

Further information on insulin pens available online at: [http://www.lifeclinic.com/focus/diabetes/supply\\_syringes.asp](http://www.lifeclinic.com/focus/diabetes/supply_syringes.asp);  
[http://www.childrenwithdiabetes.com/d\\_06\\_360.htm](http://www.childrenwithdiabetes.com/d_06_360.htm); [http://www.childrenwithdiabetes.com/d\\_06\\_361.htm](http://www.childrenwithdiabetes.com/d_06_361.htm).

\*Patients should not rely on clicking sound as a means of determining the dose.

—Continue to the next page for information about *Humalog Mix 50/50, Byetta, and Symlin*—

**Inhalation Insulin**

Brand (Generic) Maker	Onset	Peak	Duration	Administration	Meal timing	Formulation	Stability (in-use at room temperature)	AWP
<i>Exubera</i> , <sup>37,38</sup> (Recombinant human insulin), Pfizer. <b>Product Discontinued</b>	10 to 20 minutes	30 to 90 minutes	6 hours	Oral inhalation	Within 10 minutes of meal ingestion	1 mg, 3 mg unit dose blisters	U.D. blister: 3 months after opening foil overwrap	\$140.00 (Combo Pack 12) \$175.00 (Combo Pack 15) \$187.50 (Kit)
<b>Insulin Mixture-Disposable Pen Only</b>								
<i>Humalog Mix 50/50</i> <sup>46</sup> (Insulin lispro 50%, insulin lispro protamine 50%), Human insulin analog (rDNA), Eli Lilly. Prescription only	Faster than <i>Humulin 50/50</i>	Mean-2.3 hrs Range-0.8 to 4.8 hrs	Similar to <i>Humulin 50/50</i>	SC only. Resuspend before injection.	Give within 15 min. of a meal.  Individualize based on blood glucose	100 U/mL, 3 mL disposable pen	Pen: 10 days	\$161.69/5 of 3 mL pen

**Misc. Non-insulin Injectable Agents**

Brand (Generic) Maker	Therapeutic Class	Administration	Meal Timing	Formulation	Stability (in-use)	AWP
<i>Byetta</i> (exenatide) <sup>44</sup> Amylin. Prescription only. www.amylin.com	Incretin mimetic	Subcutaneous injection	Within 60 minute period before morning and evening meals	5 mcg per dose, 60 doses, 1.2 mL prefilled pen  10 mcg per dose, 60 doses, 2.4 mL prefilled pen	Store unused pen in refrigerator. After 1 <sup>st</sup> use, may be kept at room temperature (up to 77°F) for up to 30 days. Discard after 30 days.	\$194.78 (1.2 mL) \$228.59 (2.4 mL)
<i>Symlin</i> (pramlintide) <sup>45</sup> Amylin. Prescription only www.amylin.com	Synthetic amylin analogue	Subcutaneous injection	Immediately before meals containing $\geq 250$ Kcal or $\geq 30$ gm of carbohydrate	0.6 mg per mL, 5 mL vials	Discard 28 days after first use. May be refrigerated or kept at room temperature.	\$107.34

## Insulins

*Lead author: Jill Allen, Pharm.D., BCPS*

Insulins are categorized in the tables above according to their onset and duration of action: rapid-, short-, intermediate-, long-acting, and premixtures of rapid or short-acting insulin combined with intermediate-acting insulin. A second table also provides information about insulin pens and other administration devices.

**Availability.** The new insulin analogs and U-500 insulin are available by prescription only. Other insulins are available OTC, but a prescription may be required for insurance company reimbursement.

**Type.** Species of insulin available in the U.S. will soon be limited to human insulins and human insulin analogs. Years ago, beef insulins were removed from the U.S. market because of a theoretical concern for transmission of bovine spongiform encephalopathy (mad cow disease). For information on obtaining beef insulin from other countries, go to <http://www.fda.gov/cder/drug/beefandporkinsulin/default.htm>. In July 2005, Lilly announced the discontinuation of its pork insulins (*Iletin II regular* and *NPH*), with the expectation that stock will be depleted by the end of the year.<sup>29</sup> Demand for these products has declined in recent years and recombinant human insulin products are easier to manufacture. The dose is usually similar when converting from animal to human insulin. Consider reducing the initial human insulin dose by 10% to 20% in patients receiving more than 100 units per day of animal insulin.<sup>33</sup> Lilly will also discontinue two long-acting human insulins, *Humulin L* (lente) and *Humulin U* (ultralente), with stock depletion also expected by the end of 2005.<sup>29</sup>

A recent statement from the International Diabetes Federation concludes that, in the absence of strong evidence favoring one species of insulin over another, patients should not be converted to a different species unless it has a clear advantage for the patient.<sup>31</sup> Since all insulins have slightly different properties, a particular patient may better tolerate one species of insulin better than another. In the past, anecdotal reports raised concern that human insulins might have a higher risk of hypoglycemia, but this concern has not been supported by further clinical research.<sup>31</sup>

**Onset, peak, duration.** The tables above compare the onset, peak, and duration of action of insulin formulations after subcutaneous injection. These values are approximate since many factors can affect the pharmacokinetics of insulin.<sup>1</sup> Rapid-acting insulin analogs (insulins lispro, aspart, and glulisine) have small modifications to the insulin amino acid sequence that makes them dissociate into monomers more quickly after subcutaneous injection. This allows more rapid absorption into the systemic circulation. There is also less variability in absorption with rapid-acting insulin analogs than regular insulin.<sup>3</sup> Rapid-acting analogs may provide better postprandial glucose control and less nocturnal hypoglycemia than regular insulin, but it is unclear that these benefits translate into long-term improvements in outcome.<sup>31, 32</sup>

After SC injection, intermediate- and long-acting insulin molecules aggregate into hexamers (groups of six molecules) at the injection site. They slowly dissociate into dimers and monomers which are absorbed into the systemic circulation. Insulin detemir is acylated (linked to a fatty acid chain). This promotes hexamer formation and reversible binding to albumin after it reaches the bloodstream.<sup>2</sup> This helps prolong its duration of action. The time-action profile of insulin detemir is less variable than NPH.<sup>2</sup> This may reduce the risk of hypoglycemia and weight gain.<sup>3</sup> Interindividual variability is less with insulin glargine than with NPH and ultralente.<sup>4</sup> Insulin lispro protamine and NPH insulin have similar pharmacokinetic profiles.<sup>5</sup> Newer basal insulins, like insulin glargine, reduce nocturnal hypoglycemia. However, it is unclear whether this benefit improves long-term glycemic control.<sup>31</sup>

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**Administration.** Insulin suspensions should be gently shaken before each injection. Pens and cartridges of insulin suspensions should be rolled and tipped back and forth ten to 20 times to re-suspend the insulin and then primed before each injection.<sup>6, 7</sup> Insulin mixtures or dilutions should not be used in external pumps.

**Meal timing.** The American Diabetes Association (ADA) recommends that rapid-acting insulin analogs (alone or with intermediate- or long-acting insulin) be injected within 15 minutes before or immediately after a meal.<sup>1</sup> It may be helpful to give the dose after a meal in young children who are unreliable eaters.<sup>8</sup> Regular insulin is usually given 30 minutes before meals. Meal-timing for premixed formulations is based on whether the mixture contains rapid-acting or regular insulin. In one algorithm, the interval between injecting insulin and starting a meal depends on blood glucose monitoring. For regular insulin, the interval is 20 to 30 minutes for a blood glucose of 65 to 150 mg/dL, 30 to 45 minutes for >150 to 250 mg/dL, and 50 to 60 minutes for >250 mg/dL. Insulin lispro can be injected immediately before meals when blood glucose is 65 to 150 mg/dL. The interval between injecting and eating is 10 to 20 minutes for >150 to 250 mg/dL, and 20 to 30 minutes for >250 mg/dL.<sup>8</sup> A more detailed algorithm is outlined in the ADA's book, *Intensive Diabetes Management*.<sup>9</sup>

**Formulations and delivery devices.** All insulins are available in 10 mL vials (U-100; 100 units/mL). The only exception is U-500 (500 units/mL) regular human insulin (20 mL vial), which is available from Lilly by prescription only for patients who require more than 200 units/day.<sup>5</sup> Some formulations are available in prefilled disposable pens or reusable pens with disposable insulin cartridges. These products, reviewed in a table above, are for SC injection. Although they may be more expensive than vials, they can make insulin administration simpler, more convenient, and less error-prone than withdrawing insulin from a vial and injecting with a syringe. Injections with an insulin pen may also be less painful; the needles are small and are not dulled by the withdrawal of insulin from a vial to syringe. Jet injectors (such as *AdvantaJet*, *Medi-Jector*, and *Vitajet*) avoid the use of needles, cost approximately \$250-\$500, weigh about 8 oz, and require frequent cleaning.<sup>10, 11</sup> *Exubera*, approved January 2006, was the first insulin formulation to be administered by oral inhalation. In October 2007, due to poor acceptance by patients and prescribers, Pfizer announced it would be discontinuing sales of *Exubera*.

**Appearance.** Patients and clinicians should check the appearance of an insulin before using it. Rapid- and short-acting insulins and insulin glargine should be clear; the others should be cloudy.<sup>1, 5</sup> Warn patients that insulin glargine can be mistaken for a shorter-acting insulin because it looks clear.

**Compatibility.** Human and pork insulins can probably be mixed, but there is no reason to do so.<sup>6</sup> There is no information on the compatibility between *Novolin* and *Humulin* insulins; incompatibility could result from differences in buffering agents between the two product lines. When mixed with another insulin, a rapid- or short-acting insulin should be drawn up in the syringe first in order to maintain clarity in the vial. The manufacturer recommends against mixing insulin glargine with other insulins. In an animal study, mixing it with regular insulin delayed the onset and peak of regular insulin.<sup>12</sup> A preliminary study in 14 diabetics found no effect on glycemic control when insulin glargine was mixed with lispro or aspart. The mixture did turn cloudy.<sup>13</sup> Pramlintide (*SymLin*), a synthetic amylin analog, is administered by SC injection. The manufacturer recommends against mixing pramlintide with insulin.<sup>14</sup> However, a recent study found that mixing it with short- or long-acting insulin in the same syringe before SC injection did not affect the pharmacokinetics of either agent or change glucose pharmacodynamics.<sup>15</sup> Although some insulin mixtures are chemically stable under refrigeration for up to three months, the possibility of microbial contamination must be considered.<sup>16</sup>

A diluent is not available for Novo Nordisk insulins.<sup>17</sup> In the past, there were three Lilly diluents. Now, a single diluent is available (call 317-276-1610) for use with *Humalog* and *Humalog 75/25* or *70/30*; *Humulin R, N, 70/30* and *50/50*; *Iletin II pork NPH* and U-500.<sup>18</sup> It cannot be used for *Humulin L* or *R*, or

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*Regular Iletin II* pork insulin. Opened vials of diluent and most diluted insulins are stable for one month at room temperature.<sup>6</sup> Diluted *Humalog* is stable at room temperature for 14 days.<sup>19</sup>

**Stability.** Unopened insulin products should be stored in the refrigerator (36 to 46° F; 2 to 8° C) with the exception of packaged *Exubera* unit dose blisters (stored at room temperature, 25°C [77°F]). Once the stopper or seal has been punctured by a needle, the product is considered to be “open” or “in-use.” In-use insulin vials are usually kept at room temperature (59 to 86° F; 15 to 30° C) to make injections less painful. At room temperature, opened vials are stable for about 28 days (*Levemir* is the exception at 42 days). The duration of stability at room temperature varies for other insulin products. In-use insulin pens and cartridges should be stored at room temperature. For *Exubera*, once the foil overwrap is opened (in-use), the unit dose blisters should be stored at room temperature and used within three months. [**Note: *Exubera* has been discontinued.**]

*Users of this document are cautioned to use their own professional judgment and consult any other necessary or appropriate sources prior to making clinical judgments based on the content of this document. Our editors have researched the information with input from experts, government agencies, and national organizations. Information and Internet links in this article were current as of the date of publication.*

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