

# Overview of Insulin and Non-Insulin Delivery Devices In the Treatment of Diabetes

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## INTRODUCTION

Diabetes affects 20.9 million people in the U.S. and 347 million people worldwide.<sup>1,2</sup> It is estimated that one in three American adults will have diabetes by 2050.<sup>1,3</sup> Serious complications, such as blindness, kidney failure, and amputations, have been associated with chronic hyperglycemia.<sup>3</sup> Diabetes is the seventh leading cause of death worldwide.<sup>2,3</sup>

Approximately 5% of diabetes cases in the U.S. are classified as type-1 diabetes mellitus (T1DM), which requires insulin therapy because of  $\beta$ -cell destruction. Of all diabetes cases, 90% to 95% are classified as type-2 diabetes mellitus (T2DM), which results from a progressive insulin secretory defect against a background of insulin resistance.<sup>4,5</sup> T2DM is more common in minority populations, the elderly, obese persons, and those with sedentary lifestyles.<sup>6,7</sup>

In 2011, 17.7 million Americans were being treated with insulin or oral medications.<sup>7,8</sup> Antidiabetic agents were among the top five classes of medications in 2012, accounting for \$22 billion in pharmaceutical sales. These agents included eight insulin products (primarily insulin pen delivery devices) and two non-insulin injectable delivery devices (Byetta and Victoza).<sup>8,9</sup>

A position statement from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), released in 2012, and a comprehensive diabetes management algorithm from the American Association of Clinical Endocrinologists (AACE) have championed a patient-centered approach to selecting appropriate initial therapy for T2DM.<sup>10-12</sup> Both the ADA and the EASD emphasize the use of basal insulin, whereas the AACE consensus statement gives priority to the use of rapid-onset, long-acting insulin analogs and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) because of their positive efficacy and safety profiles and their low risk of hypoglycemia.<sup>11,12</sup>

This article reviews the available insulin and non-insulin delivery devices and their place in current therapy.

## INSULIN

Guidelines from the ADA and the AACE highlight the importance of early and aggressive treatment of diabetes to achieve and maintain glucose levels comparable with those of nondiabetic patients in order to prevent chronic complications.

Insulin preparations (Table 1) are currently the most effective treatments for diabetes and the only therapeutic options for patients with T1DM. They may also be used in patients with T2DM who have failed treatment with oral agents or who have hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) levels greater than 10%.<sup>13</sup>

Health care providers, however, are reluctant to prescribe insulin because of the need for frequent dose adjustments, the

potential for hypoglycemia, and the time required to educate patients regarding insulin administration. Patients, in turn, are often reluctant to use insulin because of their fear of injections, their belief that insulin is difficult to administer, and their perception that insulin preparations have adverse side effects.<sup>14</sup> These barriers to treatment may be overcome by the use of insulin-delivery devices.

For all patients with T1DM and some with T2DM, an ideal insulin regimen mimics the body's own insulin-release pattern (basal-bolus dosing).<sup>13</sup> Intermediate-acting insulin (i.e., neutral protamine Hagedorn [NPH] insulin) and long-acting insulin analogs (i.e., insulin detemir and insulin glargine) provide basal insulin coverage, whereas short-acting regular human insulin and rapid-acting insulin analogs provide prandial coverage.<sup>13</sup>

## Insulin-Delivery Pens

Insulin-delivery pens eliminate the need to draw up insulin, which allows more convenient administration compared with syringes. An insulin pen looks like a large fountain pen. The pen is prefilled with insulin, and the only preparation required is attaching the needle. There are two basic types of pens: disposable and reusable.

### Disposable Insulin Pens

Disposable insulin-delivery pens do not require a cartridge or the installation of an insulin reservoir, and they are discarded when empty or when the use date has expired. Three U.S. companies market disposable insulin pens: Eli Lilly, Sanofi-Aventis, and Novo Nordisk. Eli Lilly manufactures the KwikPen for Humalog, Humalog Mix 50/50, and Humalog Mix 75/25; Sanofi-Aventis manufactures the SoloSTAR for Lantus and Apidra; and Novo Nordisk manufactures the FlexPen for Novolog and Novolog Mix 70/30, as well as the FlexTouch for Levemir. Each of these pens holds 300 units (3 mL) of insulin and delivers 60 to 80 units per dose in 1-unit increments. The FlexPen and the KwikPen deliver up to 60 units per dose, and the SoloSTAR and the FlexTouch deliver up to 80 units per dose.<sup>15</sup>

The following instructions for use are common among devices:<sup>16</sup>

1. Remove the pen cap and attach the pen needle by twisting it onto the rubber stopper of the cartridge.
2. Perform an "air shot" (also called priming the pen or a safety test, depending on the manufacturer of the pen that the patient uses) to remove air bubbles.
  - a. Dial a test dose of 2 units.
  - b. Hold the pen with the needle pointing up and gently tap the cartridge so that air bubbles rise up to the needle.
  - c. Press the injection button all the way to 0 and check to see that insulin comes out of the needle; then...

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**Table 1 Pharmacokinetics of Available Insulin Preparations<sup>13</sup>**

Insulin, Generic Name (Brand, Manufacturer)	Onset	Peak	Effective Duration
<b>Rapid-acting</b>			
Insulin aspart injection (Novolog, Novo Nordisk)	5–15 minutes	30–90 minutes	< 5 hours
Insulin lispro injection (Humalog, Lilly)	5–15 minutes	30–90 minutes	< 5 hours
Insulin glulisine injection (Apidra, Sanofi-Aventis)	5–15 minutes	30–90 minutes	< 5 hours
<b>Short-acting</b>			
Regular	30–60 minutes	2–3 hours	5–8 hours
<b>Intermediate, basal</b>			
Neutral protamine Hagedorn insulin	2–4 hours	4–10 hours	10–16 hours
<b>Long-acting, basal</b>			
Insulin glargine injection (Lantus, Sanofi-Aventis)	2–4 hours	No peak	20–24 hours
Insulin detemir injection (Levemir, Novo Nordisk)	3–8 hours	No peak	6–23 hours
<b>Premixed</b>			
75% insulin lispro protamine suspension/25% insulin lispro injection (Humalog Mix 75/25)	5–15 minutes	Dual	10–16 hours
50% insulin lispro protamine suspension/50% insulin lispro injection (Humalog Mix 50/50)	5–15 minutes	Dual	10–16 hours
70% insulin aspart protamine suspension/30% insulin aspart injection (Novolog Mix 70/30)	5–15 minutes	Dual	10–16 hours
70% neutral protamine Hagedorn insulin/30% regular	30–60 minutes	Dual	10–16 hours

3. Dial your dose and, while keeping the pen straight down or at a 90-degree angle, insert the needle into the skin.
4. Press the injection button all the way down with your thumb.
5. Hold for five to 10 seconds to ensure full-dose delivery.
6. Release the button; remove the needle from the skin; twist off the pen needle to discard it; and recap the pen.

### Reusable Insulin Pens

Reusable insulin-delivery pens require the patient to load insulin cartridges into the pen. The pen requires only the replacement of cartridges and needles, and can be used safely for several years. Reusable pens are available from Owen Mumford, Eli Lilly, and Novo Nordisk. They are used only with rapid-acting insulin preparations.

The following instructions for use are typical:<sup>17</sup>

1. Remove the pen cap and insert the cartridge. To insert the cartridge, unscrew the cartridge holder and insert the small end of the cartridge into the holder.
2. Make sure the dose knob is pushed back before pushing the cartridge and pen body together. Screw the pen body onto the cartridge holder until the pen is secure.<sup>17</sup>
3. Once that is complete, follow the instructions given above for prefilled insulin pens. All of the insulin-delivery devices differ slightly, and it is important to refer to the manufacturer's user guide.

### Features of Insulin-Delivery Pens

Insulin-delivery pen devices have special features that may influence a patient's preference. For example, Humalog insulin 3-mL cartridges are available for use with the HumaPen Memoir and the Luxura HD.

The HumaPen Memoir is an electronic pen with a dose memory that allows patients to set the date and time and to record the last 16 doses administered. The device can deliver insulin in doses from 1 to 60 units. It was discontinued by Eli Lilly in March 2011; however, if a patient has this pen, it can still be used with the Humalog cartridges.

The Luxura HD can deliver from 1 to 30 units in half-unit increments, allowing more precise measurement. This can be an advantage for children or for a patient trying to cover the amount of carbohydrates consumed per meal.<sup>17</sup>

The NovoPen Junior is available in two bright colors. This pen features a dosing window and a dial dosing mechanism. It can deliver from 1 to 35 units of insulin in half-unit increments, making it an attractive option for children. The NovoPen 3 also features a dosing window and a dial dosing mechanism. This device delivers 2 to 70 units of insulin in 1-unit increments. Both pens were discontinued in March 2014 but are still available for use with Novolog Penfill 3-mL cartridges.<sup>16</sup>

Patients may find disposable pens more convenient than reusable pens because the user does not have to be trained on how to install and replace cartridges. Moreover, the low injection force of disposable pens requires less thumb button pressure to effectively deliver a complete dose. Less thumb pressure makes disposable pens easier to use, especially for older adults and those with dexterity problems.

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One study found that the SoloSTAR and FlexPen were preferable in terms of usability (i.e., the ability to prepare the pen and to inject insulin into a receptacle) compared with Humulin and Humalog.<sup>18</sup>

The FlexTouch is a new prefilled insulin pen without a push-button extension at any dose setting. It is currently available only with insulin detemir (Levemir). It only requires a light touch to deliver the insulin dose and has an audible click confirmation when the dose is delivered.<sup>16</sup> In a study, the insulin mechanism of the FlexTouch pen resulted in a significantly lower injection force when compared with that of both the Solostar and the KwikPen at all injection speeds.<sup>19</sup>

### Storage

All insulin pens and insulin cartridges are stable until the expiration date on the label if they are stored unopened in a refrigerator. Once the package has been opened, the length of days that the pens and cartridges remain stable varies based on the insulin preparation.

**Table 2 Stability of Insulin-Delivery Pens<sup>21</sup>**

Pen Device	Stability Once Opened (Days)*
Rapid-acting insulin	
Novolog Flexpen (aspart)	28
Novolog Penfill	28
Humalog KwikPen (lispro)	28
Humalog Cartridge	28
Apidra Solostar (glulisine)	28
Intermediate-acting insulin (neutral protamine Hagedorn insulin)	
Novolin N Pen	14
Humulin N Pen	14
Premixed insulin	
Humalog Mix KwikPen 50/50	10
Humalog Mix KwikPen 75/25	10
Humulin 70/30 Pen	10
Novolog Mix 70/30 FlexPen	14
Long-acting insulin	
Lantus Solostar	28
Levemir FlexTouch	42
GLP-1 receptor agonists	
Exenatide (Byetta)	30
Exenatide ER (Bydureon)	28
Liraglutide (Victoza)	30
Amylin analogue	
Pramlintide (Symlin)	30

\* Once in use, all insulin pens are kept at room temperature. If a pen is kept in a refrigerator unopened, it is usable until the expiration date on the label. ER = extended release; GLP-1 = glucagon-like peptide 1

### Stability of Insulin Pens

Table 2 describes the stability of the various insulin pens.

### Safety

Diabetic patients may use several types of insulin per day. Most pens are color-coded; however, they still look very similar, and patients need to ensure that they do not accidentally use the incorrect insulin.

### Place in Therapy

Insulin-delivery pens offer enhanced convenience and controlled dosing. Many diabetic patients find that these devices are more convenient than syringes because they eliminate the need for drawing up a dose.<sup>20</sup> The traditional vial-and-syringe method of insulin administration involves several steps, including drawing up the correct amount of air into the syringe; injecting the air into the vial; drawing the correct dose of insulin from the vial into the syringe; and injecting.

Studies have shown that patients using the traditional vial-and-syringe method of delivery have a higher risk of drawing up an incorrect insulin dose, with a relative error of approximately 19% in the accuracy of dosing.<sup>20</sup> Pen devices have a dial that must be turned to select the correct dose, as opposed to reading the syringe. Moreover, these devices click as the patient selects each unit, which may be helpful for patients with impaired vision. Pen devices are also more accurate than syringes in measuring insulin at very low doses (i.e., 1 or 2 units).<sup>20</sup>

Another advantage of insulin pens is that they are more portable than syringes. They are considered to be more discreet and may reduce embarrassment when injecting insulin in public.<sup>21,22</sup>

A randomized, open-label, crossover study comparing a prefilled, disposable pen with the vial-and-syringe method found that 73% of the patients using the pen were confident in the accuracy of insulin doses compared with 19% of those using syringes.<sup>23</sup> Furthermore, 85% of the pen group considered the devices to be more discreet for use in public than syringes. These patients also showed statistically significant improvements in glycosylated hemoglobin values during the study. Overall, 74% of patients found that the pen device was easier to use than the vial-and-syringe method of insulin delivery.

Another study evaluated patients' satisfaction with the method by which insulin was administered before hospital discharge.<sup>24</sup> Significantly more patients using pen devices than those using syringes reported that they would continue administering insulin at home by the same method. The study concluded that if patients are comfortable and confident with their insulin-delivery device, they are more likely to adhere to their insulin therapy, resulting in fewer hypoglycemic episodes and reduced associated health care costs.

Nurses also prefer insulin-pen devices over syringes for use in hospitalized patients. A satisfaction survey was conducted among 54 registered nurses in a community hospital after the implementation of pen-device use on two medical-surgical floors.<sup>25</sup> Most of the nurses (70% to 80%) felt that insulin pens were more convenient and easier to use than syringes.

Children with diabetes often have more-positive feelings about using the pens as well. Syringes can be associated with pain and with illicit drug use, which is a concern for young people. Pen devices are easy to use and provide accurate dosing

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for young patients who are busy with sports and social activities. Moreover, the lower insulin doses that are commonly used in children are easier to measure with pen devices.<sup>26</sup>

### Cost and Formulary Considerations

Insulin pens are generally more expensive than syringes and insulin vials (Table 3).<sup>19</sup> However, coverage for pens by private health plans and Medicare Part D plans has improved in recent years. Some plans may require higher copays from patients for a pen, while other plans may ask physicians to submit a prior authorization, in which they must document the need for the pen device rather than the syringe/vial method.

A retrospective analysis involving 486 adults with a diagnosis of T2DM found a significant decrease in hypoglycemia associated with emergency department and physician visits among patients who switched from syringes to insulin-pen delivery devices.<sup>27</sup> Similarly, Lee et al reported significant reductions in annual hypoglycemia-attributable costs with pen devices, and this cost savings represented 57% of the total savings in the use of diabetes-related health care resources.<sup>20</sup>

A study by Ward et al evaluated the switch from vial/syringe insulin administration to insulin injector pens among more than 4,000 patients with T2DM in a specialty clinic and hospital. The total insulin costs for the pre-implementation and post-implementation periods were \$124,181 and \$60,655, respectively.<sup>28</sup>

There is ongoing concern, however, regarding the safety of insulin pens for routine inpatient use. The Institute for Safe Medication Practices (ISMP) issued a statement in February 2013 advising hospitals to re-examine the use of pen devices, with a strong recommendation to move away from insulin pens.<sup>29</sup> According to the ISMP, more than 700 patients at a New York hospital might have been exposed to human immunodeficiency virus and hepatitis B or C because of the reuse of insulin pens in multiple patients. Another New York hospital reported that 1,915 insulin-dependent patients were exposed to bloodborne pathogens because of improper sharing of insulin pens between November 2009 and January 2013.<sup>29</sup>

**Table 3 Comparative Costs of Insulin Pens and Syringe Vials (AWP)<sup>21</sup>**

Insulin	One Box of Five Pens (3 mL Each; 1,500 Units/Box)	One Vial (10 mL, 1,000 Units/Vial)
Lantus	\$331	\$200
Levemir	\$331	\$200
Novolog	\$341	\$184
Humulin N	\$314	\$22

AWP = average wholesale price (rounded to the nearest dollar)

### Insulin Pump Therapy

The main purposes of insulin-pump therapy are to maintain long-term glycemic control and to minimize hypoglycemia compared with multiple daily insulin injections. It has been suggested that fluctuations in blood glucose levels are the cause of various diabetic complications, including neuropathy and retinopathy.<sup>9</sup>

Insulin pumps provide a constant subcutaneous infusion of rapid-acting insulin analogues or regular insulin to mimic

normal pancreatic insulin release. Doses can be adjusted to provide a basal level of insulin between meals as well as to allow bolus delivery with food. The insulin is infused from a reservoir into the body through a catheter that has been inserted into the tissue via a needle. The catheter does not need to be disconnected from the needle unless the patient is bathing or swimming. The needle should be changed once every three days, and the patient should rotate the needle's injection sites.<sup>22</sup>

Insulin delivery from a pump is more exact than delivery from either a syringe or a pen. With a pump, basal insulin can be adjusted in 0.25-unit increments and bolus insulin can be adjusted in 0.05-unit increments, depending on the individual device. This more-exact dosing can help prevent fluctuations in blood glucose.<sup>30</sup>

All available insulin pumps have similar modes of operation; however, specific features may influence patient preference. Varying features include the size of the reservoir; the type and size of the screen; basal and bolus delivery increments; the device's compatibility with blood glucose meters; the specificity of bolus calculations; the ease of programming; data downloading and uploading options; and history reports.<sup>23</sup>

The Medtronic Paradigm Revel, for example, provides high and low blood glucose alerts. The Tandem Diabetes T-Slim is the only touch-screen insulin pump available in the U.S. The Animas Ping stores up to 500 foods from the CalorieKing database on its meter, making carbohydrate counting easy.

Many pumps allow patients to administer a bolus dose from the meter based on the blood glucose reading.<sup>31</sup> All insulin pumps except the OmniPod require the use of a separate infusion set, which consists of thin plastic tubing connected to a stainless steel or flexible Teflon cannula, with a plastic connector that joins the tubing to the cannula. The cannula is inserted subcutaneously at a 30- to 90-degree angle and at a depth of 6 to 8 mm.<sup>30</sup>

The OmniPod is a wireless insulin pump that delivers insulin without shots or tubing. It is waterproof, so the patient can wear it while bathing or swimming. The OmniPod inserts automatically with the push of a button and uses a Personal Diabetes Manager (PDM) for dosing. The PDM has a built-in FreeStyle blood glucose meter, which eliminates the need to carry a meter or to transfer results. This device also contains a bolus calculator, which recommends doses based on the patient's settings and on his or her blood glucose values.<sup>32</sup>

### Safety

Insulin pumps require more patient education than is needed with other forms of insulin delivery. Extensive training is required to ensure that patients understand how to use the pump to manage their diabetes. Patients starting to use an insulin pump must be motivated to improve their glucose control and must be prepared to work closely with their health care team.

Insulin-pump therapy requires frequent monitoring of blood glucose (up to six to eight times a day). Diabetic ketoacidosis (DKA) rarely occurs if patients monitor their blood glucose readings regularly; however, if a pump malfunctions, DKA can develop quickly because of the short half-life of rapid-acting insulin. Patients should always have basal insulin on hand,

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either in a vial or a pen, in the event that the insulin pump cannot be used.<sup>30</sup>

### Place in Therapy

According to the American Association of Diabetes Educators, pump therapy should be considered for patients who are not achieving their treatment goals (e.g., HbA<sub>1c</sub>: 7.0% to 7.5%) on current insulin treatment or in patients with severe hypoglycemia, multiple hypoglycemic events, frequent and unpredictable fluctuations in blood glucose levels, and/or the perception that diabetes management interferes with attaining their personal or professional goals.<sup>30</sup>

### Cost

Cost is a key disadvantage of insulin-pump therapy. Most pumps and supplies, such as tubing, syringes, cartridges, and dressings, can cost more than \$5,000. The infusion set and catheters must be purchased regularly for as long as the pump is used.<sup>31</sup>

Most insurance companies will cover the cost of the pump after prior authorization, especially for T1DM patients. It is more difficult for T2DM patients to receive insurance coverage for the pump. Moreover, if a patient's plan covers the pump, the plan usually pays for up to 80% of the cost, leaving the patient to pay the remaining 20%, which can be costly.<sup>33</sup>

Most patients change their insulin pumps once every five years, which accounts for most of the cost; the maintenance costs for insulin pumps are not much more than those for insulin-pen devices. When equipment costs are added to the cost of supplies, continuous subcutaneous insulin infusion is only slightly more expensive than the use of insulin-pen devices on an annual basis.<sup>33</sup> There is no evidence that insulin-pump therapy improves glycemic control; however, it appears to reduce the risk of hypoglycemia.<sup>33</sup>

### V-Go Device

The V-Go (Valeritas) is a disposable insulin-delivery device designed to control blood glucose in adults with T2DM. Instructions on its use follow:<sup>34</sup>

- Patients fill the device with U-100 rapid-acting insulin using the EZ Fill system. The EZ Fill system transfers insulin from the vial to the V-Go device. An EZ Fill is provided with each 30-day supply of devices. The EZ Fill is used to fill the V-Go on each day of use. The V-Go device should not be filled with insulin and stored for later use.
- The V-Go is applied to a part of the body where the device can be reached and viewed, such as the abdomen.
- The patient pushes the needle button to insert the needle and to begin the flow of insulin at a continuous basal rate.
- For bolus delivery, the patient presses the Bolus Ready button, and then presses the Bolus Delivery button to release the bolus dose of 2 units. Both steps must be repeated until the patient receives the desired bolus dose.
- To remove and dispose of the device, the patient presses the Needle Release button. The needle locks in place and cannot be redeployed. The device is then removed and discarded. (This must be done every 24 hours.)

### Dosing

To determine the insulin dose and basal rate with the V-Go device, the manufacturer recommends starting with either the patient's total daily insulin dose multiplied by 0.7 or 0.75, or with the patient's body weight (in kilograms) multiplied by 0.5. Half of the total daily insulin dose is the basal rate, and the other half is the bolus dosing, divided among meals.

The V-Go device is available as V-Go 20 (20 units/24 hours), V-Go 30 (30 units/24 hours), and V-Go 40 (40 units/24 hours). The bolus dosing can be administered only in 2-unit increments (one push = 2 units) up to 36 units (18 bolus doses per day). Patients have to plan their days so that they have enough insulin for each meal.<sup>34</sup>

### Place in Therapy

The V-Go device does not require extra needles or supplies, and it can work while the patient is showering, sweating, or swimming. In addition, it is more discreet for patients than a pen or a syringe, since patients can give themselves a bolus dose through their clothes. This convenience may improve both adherence and glycemic control.

Twenty-three patients participated in a 12-week retrospective analysis of glycemic control with a V-Go device. The mean HbA<sub>1c</sub> value decreased significantly from baseline (from 8.8% to 7.6%;  $P = 0.005$ ) during use of the V-Go device, but returned to 8.2% after treatment.<sup>35</sup>

### Cost

The V-Go device is covered by most third-party plans as a pharmacy benefit; however, it may require prior authorization, or the patient may be responsible for a higher co-pay, depending on the plan. For some insurance companies, the device is covered under the medical benefit.<sup>35</sup>

### Inhaled Insulin

Afrezza (MannKind) is a rapid-acting inhaled insulin indicated to improve glycemic control in adults at least 18 years of age with T1DM or T2DM; however, it is not a substitute for long-acting insulin. In patients with T1DM, Afrezza must be used in combination with long-acting insulin. It is considered an ultra-rapid-acting insulin because the onset of action is 12 to 15 minutes, with a peak of about 60 minutes and duration of activity of about 2.5–3 hours.<sup>36</sup>

The cartridges and inhaler should be at room temperature for 10 minutes before use. Patients should use one inhaler for multiple cartridges but should throw away that inhaler after 15 days. The instructions include the following steps:<sup>36</sup>

1. Remove a cartridge from the strip by pressing on the clear side to push the cartridge out. Cartridges left over in an open strip must be used within three days.
2. Open the inhaler by lifting the white mouthpiece to a vertical position.
3. Hold the cartridge with the cup facing down; line up the cartridge with the opening in the inhaler. Place the cartridge into the inhaler, ensuring that the cartridge lies flat.
4. Lower the mouthpiece to close the inhaler; the user should feel a snap when the inhaler is closed.
5. Remove the mouthpiece cover.

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- Keep the inhaler level, hold it away from the mouth, and exhale.
- Keep the head level, place the mouthpiece in the mouth, and tilt the inhaler down toward the head.
- Close the lips around the mouthpiece to form a seal, inhale deeply through the inhaler, and hold the breath for as long as comfortable.
- Place the purple mouthpiece cover onto the inhaler, open the inhaler to remove the cartridge, and throw the cartridge away.

### Storage

Afrezza is available in two strengths: 4 units (blue cartridges) and 8 units (green cartridges), both dispensed in foil packages. Each package contains two blister cards, with 15 cartridges per blister card (for a total of 30 cartridges).<sup>36</sup>

Sealed foil packages can be stored unopened in the refrigerator (36–46°F, 2–8°C) until the expiration date on the package. Opened foil packages (blister cards and strips) kept at room temperature and not refrigerated must be used within 10 days; strips that have been opened must be used within three days.<sup>36</sup>

The inhaler should be kept in a clean, dry place, with the mouthpiece covered until the next dose. It may be stored refrigerated, but must be at room temperature before use. The inhaler should be replaced every 15 days to maintain drug delivery.<sup>36</sup>

### Safety

Afrezza carries a boxed warning for the risk of acute bronchospasms in patients with chronic lung disease. Acute bronchospasms have been seen in patients with asthma and chronic obstructive pulmonary disease, so Afrezza is contraindicated in these patients. Before initiating Afrezza, perform spirometry (measuring forced expiratory volume in one second [FEV<sub>1</sub>]) to identify potential lung disease in all patients. Afrezza causes a decline in lung function over time as measured by FEV<sub>1</sub>. Assess pulmonary function at baseline, after the first six months of therapy, and annually thereafter. If there is a decline of 20% or more in FEV<sub>1</sub> from baseline, consider discontinuation. The use of Afrezza is not recommended in patients who smoke or who have recently stopped smoking because safety and efficacy have not been established.<sup>36</sup>

**Table 4 Converting Insulin Doses to Inhaled Insulin<sup>36</sup>**

Injected Mealtime Insulin Dose	Afrezza Dose
Up to 4 units	One 4-unit cartridge
5–8 units	One 8-unit cartridge
9–12 units	One 4-unit and one 8-unit cartridges
13–16 units	Two 8-unit cartridges
17–20 units	One 4-unit and two 8-unit cartridges
21–24 units	Three 8-unit cartridges
More than 24 units	Combinations of different cartridges can be used

### Dosing

Afrezza is administered via oral inhalation using the provided inhaler once at the beginning of a meal. If a meal is skipped, then the dose is skipped.

Insulin-naïve patients should start with 4 units with each meal. Mealtime insulin patients should convert 1:1, while premixed insulin patients should estimate their mealtime dose by dividing half of their total daily dose of premixed insulin equally among the three meals of the day (Table 4).

### Place in Therapy

Afrezza is ultra-rapid-acting mealtime inhaled insulin. It can be used to decrease the number of injections given per day, but patients must still inject their basal insulin. It can be beneficial for patients who are embarrassed to inject insulin in public. Afrezza is FDA-approved; however, it is not yet available to pharmacies and the cost is unknown.<sup>37</sup>

## NON-INSULIN INJECTABLE DEVICES

Non-insulin medications available in injectable delivery systems include the GLP-1 RAs exenatide, exenatide extended release (ER), and liraglutide, and the amylin analogue pramlintide. All of these agents are administered by subcutaneous injection to avoid degradation in the gut.

Exenatide, liraglutide, and pramlintide are available as pre-filled, disposable insulin pens. Exenatide ER is an injectable suspension that is available in a single-use tray. The patient must transfer the medication from the vial to the syringe during self-injection. The FDA approved the Bydureon (exenatide ER) pen in March 2014.

Patients take the following steps when using exenatide, liraglutide, or pramlintide disposable pens:<sup>38–41</sup>

- Remove the pen cap and attach the pen needle by twisting it onto the rubber stopper on the cartridge.
- Perform a *one-time-only* pen setup. This is required only the first time a new pen is used.
  - Pull the dose knob out and dial the dose. (Liraglutide must be dialed to the flow check symbol.)
  - Press the injection button all the way to 0 and check to see that insulin comes out of the needle.
- Dial the dose and, while keeping the pen straight down (at a 90-degree angle), insert the needle into the skin.
- Press the injection button all the way down with the thumb.
- Hold the button for five to 10 seconds to ensure full-dose delivery (five seconds for exenatide, six seconds for liraglutide, and 10 seconds for pramlintide).
- Release the button; remove the needle from the skin; twist off the pen needle to discard it; and recap the pen.

To administer an injection of exenatide ER, patients perform the following steps:

- Peel back the tray's paper cover.
- Twist off the needle's blue cap and set it aside. Remove the vial's green cap.
- Peel off the paper cover of the vial connector's package. Hold the vial upside down and, without touching the orange connector, press the top of the vial firmly into the connector.

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4. Pick up the syringe and break off the cap; be careful not to touch the plunger.
5. Twist the orange connector into the syringe until snug.
6. Using a thumb, press down the plunger until it stops.
7. Hold the plunger down and shake hard. Keep shaking until the liquid and powder are mixed well. When mixed well, the liquid should look cloudy.
8. Pull the plunger down beyond the black dashed line; this draws the drug from the vial to the syringe.
9. Twist off the orange connector and twist on the needle.
10. Slowly push in the plunger so that the top of the plunger lines up with the dashed “dose” line.
11. Insert the needle into the skin and press down on the plunger with a thumb until the plunger stops.<sup>40</sup>

### Glucagon-Like Peptide-1 Receptor Agonists

#### Place in Therapy

As noted above, the GLP-1 RAs liraglutide, exenatide, and exenatide ER are available in injectable formulations. These agents are used as adjuncts to diet and exercise to improve glycemic control in adults with T2DM.<sup>38–42</sup> GLP-1 RAs regulate glucose homeostasis by stimulating insulin release in response to the ingested glucose load. This suppresses inappropriately elevated glucagon secretion and slows gastric emptying while causing negligible hypoglycemia.<sup>38–42</sup> Although the GLP-1 RAs are not indicated for weight reduction, significant weight loss can result from the pharmacological effect of delayed gastric emptying.<sup>42</sup>

Since GLP-1 deficiency occurs early in T2DM, the AACE recommends the use of a GLP-1 RA as monotherapy after metformin in patients with HbA<sub>1c</sub> levels of less than 7.5%, and as dual therapy with metformin in those with HbA<sub>1c</sub> levels greater than 7.5%.<sup>11</sup>

Table 5 compares the GLP-1 RAs, and Table 6 compares the dosing regimens with these agents.

### Pramlintide<sup>43</sup>

#### Place in Therapy

Pramlintide acetate injection (Symlin, Amylin Pharmaceuticals) is a synthetic amylin analogue indicated for the adjunctive treatment of patients with T1DM who have failed to achieve desired glucose control despite optimal mealtime insulin therapy. The product is also indicated as adjunctive treatment in patients with T2DM who have failed to achieve desired glucose control despite optimal mealtime insulin therapy, with or without a concurrent sulfonylurea agent and/or metformin.

Pramlintide also increases satiety, which may result in potential weight loss from reduced caloric intake.

Amylin is secreted from pancreatic beta cells along with insulin in response to food. It helps to control post-prandial glucose by slowing gastric emptying and by preventing a post-prandial increase in plasma glucagon.

#### Safety

The labeling for pramlintide acetate injection includes a boxed warning regarding the potential for severe hypoglycemia, especially in patients with T1DM. This effect can be minimized with proper patient selection and with frequent monitoring of pre- and post-meal glucose, as well as with an initial 50% reduction in pre-meal doses of short-acting insulin when initiating therapy. Nausea is the most commonly reported side effect.

#### Dosing

Pramlintide has a subcutaneous starting dose of 15 mcg, which is injected immediately before meals in patients with T2DM. For patients with T1DM, the starting dose is 60 mcg. Pre-prandial, rapid-acting, or short-acting insulin dosages, including fixed-mix insulins (e.g., 70/30), are reduced by 50%. Patients should be instructed to monitor their blood glucose levels frequently, including before and after meals and at bedtime.

The pramlintide dose is increased to the next increment (30 mcg, 45 mcg, or 60 mcg) in patients with T2DM when no clinically significant nausea has occurred for at least three days. The dose may be further increased to 120 mcg in these patients

**Table 5 Comparison of GLP-1 Receptor Agonists<sup>38–40</sup>**

	<b>Liraglutide (Victoza, Novo Nordisk)</b>	<b>Exenatide (Byetta, AstraZeneca)</b>	<b>Exenatide ER (Bydureon, AstraZeneca)</b>
Dosing	Once daily	Twice daily	Weekly
Efficacy (monotherapy)	HbA <sub>1c</sub> ↓ 0.8–1.1 FPG: –15 to –26 mg/dL Weight loss: 2.1 to 2.5 kg	HbA <sub>1c</sub> ↓ 0.5 FPG: –12 to –14 mg/dL Weight loss: 1.3 to 1.5 kg	HbA <sub>1c</sub> ↓ 0.7 FPG: –20 mg/dL
Boxed warning	Risk of thyroid C-cell tumors		Risk of thyroid C-cell tumors
Warnings and precautions	Pancreatitis, renal impairment, hypoglycemia	Pancreatitis, renal impairment, hypoglycemia	
Drug interactions		Warfarin ↑ INR	Warfarin ↑ INR
Injection sites	Abdomen, back of upper arms, or thigh	Abdomen, back of upper arms, or thigh	Abdomen, back of upper arms, or thigh
Cost <sup>21</sup> *	18 mg/3 mL (3 mL): \$235	10 mcg/0.04 mL (2.4 mL): \$513 5 mcg/0.02 mL (1.2 mL): \$513	2 mg (1): \$132

ER = extended release; FPG = fasting plasma glucose; INR = international normalized ratio

\* Average wholesale price, rounded to the nearest dollar

# Overview of Insulin and Non-Insulin Delivery Devices in the Treatment of Diabetes

**Table 6 Comparison of GLP-1 Receptor Agonist Dosing and Administration<sup>38–40</sup>**

Initiation of Liraglutide (Victoza) Therapy	Initiation of Exenatide (Byetta) Therapy	Initiation of Exenatide ER (Bydureon) Therapy
<ul style="list-style-type: none"> <li>Initiate at 0.6 mg per day for 1 week to reduce gastrointestinal symptoms during initial titration (not effective for glycemic control).</li> <li>The dose may be increased to 1.2 mg after 1 week.</li> <li>The dose may be increased to 1.8 mg if glycemic control is not achieved with the 1.2-mg dose.</li> <li>Administer once daily at any time of day, independently of meals.</li> <li>Inject subcutaneously in the abdomen, thigh, or upper arm.</li> <li>The injection site and timing can be changed without adjusting the dose.</li> </ul>	<ul style="list-style-type: none"> <li>Inject subcutaneously within 60 minutes prior to morning and evening meals (or before the two main meals of the day, approximately 6 hours or more apart).</li> <li>Initiate at 5 mcg per dose twice daily.</li> <li>Increase to 10 mcg twice daily after 1 month based on clinical response.</li> </ul>	<ul style="list-style-type: none"> <li>Requires reconstitution of the injectable solution.</li> <li>Administer immediately after the powder is suspended.</li> <li>Administer 2 mg by subcutaneous injection once every 7 days (weekly) at any time of day and with or without meals.</li> </ul>

ER = extended release

if no clinically significant nausea has occurred for three to seven days. *Pramlintide dose adjustments should be made only as directed by a health care professional.*

If significant nausea persists at the 45-mcg or 60-mcg dose level, the pramlintide dose should be decreased to 30 mcg. If this dose is not tolerated, the clinician should consider discontinuing pramlintide therapy. If significant nausea persists at the 120-mcg dose, then the dose should be reduced to 60 mcg.

Insulin doses should be adjusted to optimize glycemic control once the target dose of pramlintide is achieved and nausea (if experienced) has subsided. *Insulin dose adjustments should be made only as directed by a health care professional.*

The patient and his or her clinician should review pramlintide and insulin dose adjustments at least once a week until the target dose of pramlintide is achieved.

Pramlintide is well tolerated, and blood glucose concentrations are stable. If recurrent nausea or hypoglycemia occurs, the patient should contact his or her health care professional.

## CONCLUSION

Insulin has been a mainstay of treatment for patients with T1DM and is recommended for aggressive treatment of those with T2DM. Insulin pens offer the advantages of increased adherence, safety, and efficacy compared with other delivery systems. The GLP-1 RAs are injectable non-insulin medications with a unique mechanism of action. They are cited in the 2013 AACE consensus for their efficacy, safety, and low risk of hypoglycemia in the treatment of patients with T2DM.<sup>11</sup> However, costs are an important consideration with many of these agents.

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