

# Type 2 Diabetes Mellitus: Outpatient Insulin Management

Amanda Howard-Thompson, PharmD, Veterans Affairs Medical Center, Memphis, Tennessee

Muneeza Khan, MD, University of Tennessee Health Science Center, Memphis, Tennessee

Morgan Jones, PharmD, MS, Cleveland Clinic Independence Family Health Center, Independence, Ohio

Christa M. George, PharmD, University of Tennessee Health Science Center, Memphis, Tennessee

In patients with type 2 diabetes mellitus, insulin may be used to augment therapy with oral glycemic medications or as insulin replacement therapy. The American Diabetes Association suggests the use of long-acting (basal) insulin to augment therapy with one or two oral agents or one oral agent plus a glucagon-like peptide 1 receptor agonist when the A1C level is 9% or more, especially if the patient has symptoms of hyperglycemia or catabolism. Insulin regimens should be adjusted every three or four days until targets of self-monitored blood glucose levels are reached. A fasting and premeal blood glucose goal of 80 to 130 mg per dL and a two-hour postprandial goal of less than 180 mg per dL are recommended. Insulin use is associated with hypoglycemia and weight gain. Insulin analogues are as effective as human insulin at lowering A1C levels with lower risk of hypoglycemia, but they have significantly higher cost. Patients with one or more episodes of severe hypoglycemia (i.e., requiring assistance from others for treatment) may benefit from a short-term relaxation of glycemic targets. Several new insulin formulations have been approved recently that are associated with less risk of hypoglycemia compared with older formulations. The goals of therapy should be individualized based on many factors, including age, life expectancy, comorbid conditions, duration of diabetes, risk of hypoglycemia, cost, patient motivation, and quality of life. (*Am Fam Physician*. 2018;97(1):29-37. Copyright © 2018 American Academy of Family Physicians.)

**Type 2 diabetes mellitus** is a chronic, progressive disease characterized by multiple defects in glucose metabolism, the core of which is insulin resistance in muscle, liver, and adipocytes and progressive beta cell failure.<sup>1</sup> Beta cell failure progresses at a rate of approximately 4% per year, requiring the use of multiple medications, often including insulin, to attain and maintain glycemic control.<sup>2</sup>

Data from the National Health and Nutrition Examination Survey show that the percentage of U.S. adults with diabetes and an A1C level of more than 9% decreased slightly between 2003 to 2006 and 2007 to 2010, from 13% to 12.6% (relative risk reduction = 3.1%; 95% confidence interval, -3.8% to -3.0%).<sup>3</sup> According to the Centers for Disease Control and Prevention, from 2010 to 2012, 57% of patients with type 2 diabetes used only oral diabetes medications.<sup>4</sup> Thus, it is likely that many patients who should be

receiving insulin therapy are not. *American Family Physician* recently published a review of noninsulin therapies for type 2 diabetes.<sup>5</sup> Our article reviews insulin management in the outpatient setting.

## Concerns About Insulin Therapy

Insulin use, particularly in high doses, is associated with weight gain.<sup>6-8</sup> American Diabetes Association (ADA) guidelines and American Association of Clinical Endocrinologists/American College of Endocrinology (AAACE/ACE) guidelines suggest minimizing the use of concomitant medications that may cause weight gain when treating patients with type 2 diabetes.<sup>9,10</sup> Based on expert opinion, long-acting (basal) insulin combined with metformin, pramlintide (Symlin), or a glucagon-like peptide 1 (GLP-1) receptor agonist may be preferable to mitigate weight gain in obese patients compared with basal insulin alone or combined with a sulfonyleurea.<sup>11</sup>

Hypoglycemia may result from a mismatch between insulin and carbohydrate intake, exercise, or alcohol consumption. Concerns about the risk of hypoglycemia can prevent or delay the initiation or intensification of insulin therapy.<sup>12</sup> Of patients taking insulin, 7% to 15% experience at least one episode of hypoglycemia per year, and 1% to 2% have severe hypoglycemia (i.e., requiring assistance

**Additional content** at <http://www.aafp.org/afp/2018/0101/p29.html>.

**CME** This clinical content conforms to AAFP criteria for continuing medical education (CME). See CME Quiz on page 12.

**Author disclosure:** No relevant financial affiliations.

TABLE 1

### Considerations for Individualizing A1C Goals in Older Adults with Type 2 Diabetes Mellitus

Patient health status	Rationale	Reasonable A1C goals*	Fasting or premeal glucose level	Bedtime glucose level
Healthy (few coexisting chronic illnesses, intact cognitive and functional status)	Longer remaining life expectancy	< 7.5%	90 to 130 mg per dL (5.0 to 7.2 mmol per L)	90 to 150 mg per dL (5.0 to 8.3 mmol per L)
Complex/intermediate (multiple coexisting chronic illnesses,† 2 or more instrumental ADL impairments, or mild to moderate cognitive impairment)	Intermediate remaining life expectancy, high treatment burden, hypoglycemia vulnerability, fall risk	< 8.0%	90 to 150 mg per dL	100 to 180 mg per dL (5.6 to 10.0 mmol per L)
Very complex/poor health (long-term care, end-stage chronic illnesses,‡ moderate to severe cognitive impairment, or 2 or more ADL impairments)	Limited remaining life expectancy makes benefit uncertain	< 8.5%	100 to 180 mg per dL	110 to 200 mg per dL (6.1 to 11.1 mmol per L)

**Note:** The patient characteristic categories are general concepts. Not every patient will clearly fall into a particular category.

ADL = activities of daily living.

\*—A lower A1C goal may be set for an individual if achievable without recurrent or severe hypoglycemia or undue treatment burden.

†—Coexisting chronic illnesses may include arthritis, cancer, congestive heart failure, depression, emphysema, falls, hypertension, incontinence, stage 3 or worse chronic kidney disease, myocardial infarction, and stroke. A total of at least 3 conditions is considered multiple, but many patients may have 5 or more.

‡—The presence of a single end-stage chronic illness, such as stage 3 or 4 congestive heart failure or oxygen-dependent lung disease, chronic kidney disease requiring dialysis, or uncontrolled metastatic cancer, may cause significant symptoms or impairment of functional status and significantly reduce life expectancy.

Adapted with permission from American Diabetes Association. *Standards of medical care in diabetes—2017*. *Diabetes Care*. 2017;40(suppl 1):S101.

from others for treatment). Hypoglycemia has been associated with poor outcomes and higher rates of death, especially in older patients.<sup>13-17</sup> Patients with type 2 diabetes and a history of at least one severe hypoglycemic event have an approximately two- to fourfold higher death rate than those who have not had a severe event.<sup>18-21</sup> Hypoglycemia has also been associated with an increased risk of dementia and cardiac arrhythmias.<sup>22-24</sup>

All patients should be educated about the symptoms and self-treatment of hypoglycemia. The ADA recommends the following: (1) check the blood glucose level if signs or symptoms of hypoglycemia are present; (2) if the blood glucose level is less than 70 mg per dL (3.9 mmol per L), treat with 15 g of fast-acting carbohydrate, such as 4 oz of fruit juice or three or four glucose tablets; and (3) recheck the blood glucose level after 15 minutes to ensure that it has normalized.<sup>9</sup>

Table 1 lists several patient characteristics that should be considered when individualizing A1C goals in older patients.<sup>9</sup> In addition, the ADA suggests that all patients with one or more episodes of severe hypoglycemia may benefit from a short-term relaxation of glycemic targets.<sup>9</sup>

### Initiation of Insulin

Insulin may be used as augmentation or replacement therapy. ADA and AACE/ACE guidelines

for starting insulin therapy are summarized in Figure 1<sup>25</sup> and Table 2.<sup>10</sup> Table 3 lists terms commonly used in insulin therapy.<sup>26</sup>

### AUGMENTATION

Augmentation therapy with basal insulin may be initiated at 10 units once daily, or by using weight-based dose calculations.<sup>9,10</sup> The ADA suggests the use of basal insulin to augment therapy with one or two oral agents or one oral agent plus a GLP-1 receptor agonist when the A1C is 9%

## BEST PRACTICES IN ENDOCRINOLOGY

### Recommendations from the Choosing Wisely Campaign

Recommendation	Sponsoring organization
Do not medicate to achieve tight glycemic control in older adults. Moderate control is generally better.	American Geriatrics Society
Do not use sliding scale insulin for long-term diabetes management for individuals residing in the nursing home.	American Medical Directors Association

**Source:** For more information on the Choosing Wisely Campaign, see <http://www.choosingwisely.org>. For supporting citations and to search Choosing Wisely recommendations relevant to primary care, see <http://www.aafp.org/afp/recommendations/search.htm>.

## OUTPATIENT INSULIN MANAGEMENT

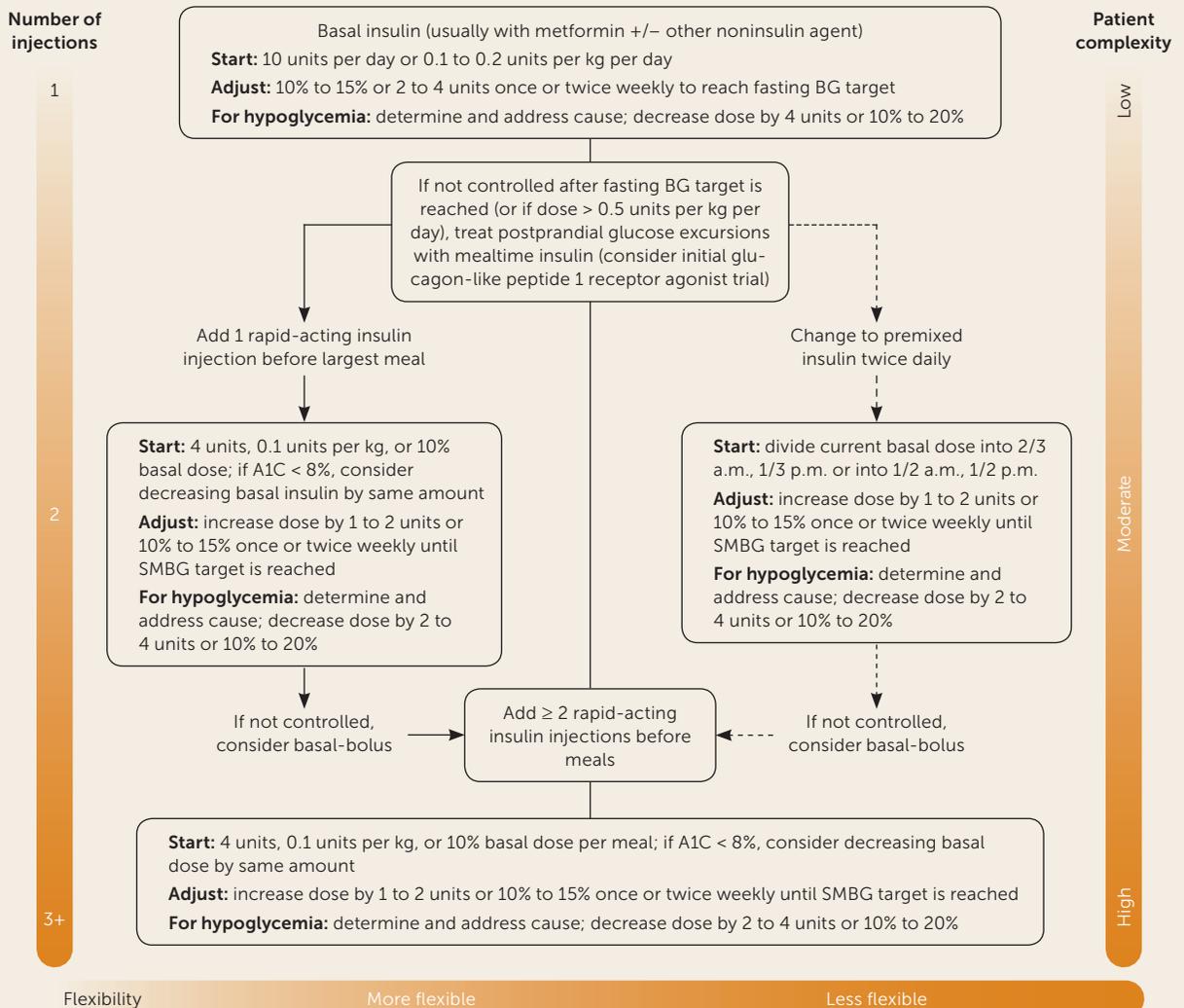
or more, especially if the patient has symptoms of hyperglycemia or catabolism.<sup>9</sup> The AACE/ACE guidelines recommend the addition of basal insulin to augment therapy with two oral agents with or without GLP-1 receptor agonists when the A1C is more than 8%.<sup>10</sup> The ADA also recommends basal insulin combined with other agents when

the A1C is more than 9% at diagnosis and the patient has symptoms of hyperglycemia.<sup>10</sup>

### REPLACEMENT

The ADA suggests insulin replacement therapy with basal and rapid-acting prandial (basal-bolus) insulin when the

**FIGURE 1**



### An approach to starting insulin in patients with type 2 diabetes mellitus based on American Diabetes Association guidelines.

BG = blood glucose; SMBG = self-monitoring of blood glucose.

Adapted with permission from Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2015;38(1):146.

TABLE 2

**AACE/ACE Approach to Starting Insulin****Augmentation therapy with long-acting (basal) insulin**

A1C < 8%: total daily dosage 0.1 to 0.2 units per kg

A1C > 8%: total daily dosage 0.2 to 0.3 units per kg

**Replacement therapy with basal and rapid-acting prandial (basal-bolus) insulin**

Add prandial insulin 1 meal at a time\*: start at 10% of long-acting dose or 5 units

Add prandial insulin before each meal: total daily dosage 0.3 to 0.5 units per kg and divide 50% basal and 50% prandial†

AACE = American Association of Clinical Endocrinologists; ACE = American College of Endocrinology.

\*—Begin prandial insulin with largest meal and add on to other meals as clinically needed.

†—Further divide prandial dose between number of meals per day.

Information from reference 10.

blood glucose level is 300 to 350 mg per dL (16.7 to 19.4 mmol per L) or more or the A1C is more than 10% to 12%. Insulin replacement therapy may also be considered in patients with newly diagnosed type 2 diabetes and elevated blood glucose or A1C and hyperglycemic symptoms.<sup>9,25</sup> In patients already receiving insulin augmentation therapy who are not meeting A1C goals, the AACE/ACE guidelines suggest adding rapid-acting prandial insulin.<sup>10</sup>

Insulin analogues are as effective as human insulin at lowering A1C levels with lower risk of hypoglycemia, but they have significantly higher cost.<sup>10,27</sup> The long-acting

insulin analogues detemir (Levemir) and glargine (Lantus) cause significantly fewer nocturnal hypoglycemic events compared with isophane (NPH; Humulin N) human insulin.<sup>28</sup> The rapid-acting insulin analogues aspart (Novolog), glulisine (Apidra), and lispro (Humalog) are associated with small but statistically significant reductions in hypoglycemic events compared with regular human insulin.<sup>29</sup>

**Titration, Monitoring, and Goals of Therapy**

The ADA recommends that an insulin regimen be adjusted once or twice weekly (or every three or four days) until self-monitoring of blood glucose (SMBG) targets are reached.<sup>9,25</sup> AACE/ACE guidelines differ slightly, recommending adjustment every two or three days.<sup>10</sup> Table 4<sup>30</sup> and Figure 1<sup>25</sup> show different approaches to insulin titration depending on the type of insulin used and the resulting SMBG readings. It should be noted that these recommendations were developed before the U.S. Food and Drug Administration (FDA) approved new, highly concentrated insulins.

The ADA suggests that patients taking multiple daily insulin injections consider performing SMBG before meals and snacks, occasionally after meals, at bedtime, before exercise, when hypoglycemia is suspected and after it is treated, and before critical tasks such as driving.<sup>9</sup> Reduced A1C levels have also been demonstrated in patients taking only basal insulin who perform fasting blood glucose testing and achieve their fasting blood glucose goal.<sup>31</sup> Performing more frequent SMBG may be helpful; one study showed that increased frequency is associated with better glycemic control.<sup>32</sup> The ADA recommends a fasting and premeal SMBG goal of 80 to 130 mg per dL (4.4 to 7.2 mmol per L) and a two-hour postprandial goal of less than 180 mg per dL (10.0 mmol per L).<sup>9</sup> The AACE/ACE guidelines recommend a fasting and premeal SMBG goal of 70 to 110 mg per dL (3.9 to 6.1 mmol per L) and a two-hour postprandial goal of less than 140 mg per dL (7.8 mmol per L).<sup>10</sup> The A1C should be tested every three months in patients with unstable or uncontrolled type 2 diabetes. Twice yearly measurements are reasonable for patients with stable diabetes and an A1C level that is within the goal.<sup>9</sup>

TABLE 3

**Terms Commonly Used in Insulin Therapy**

Term	Definition	Calculation
Augmentation	Use of basal or bolus insulin to help improve glucose control in patients with partial beta cell failure	0.3 units per kg
Replacement	Use of basal and bolus insulin to control blood glucose when endogenous insulin production is minimal or absent	0.6 to 1.0 unit per kg
Carbohydrate ratio	The number of units of insulin needed to cover for a certain number of grams of carbohydrates ingested	500 divided by total daily insulin dosage (usually about 1 unit per 10 g)
Correction (sensitivity)	How much 1 unit of insulin is expected to decrease the patient's blood glucose level; when the blood glucose level is above predefined targets, short-acting insulin may be added to the bolus dose or given separately between meals	1,500 divided by total daily insulin dosage (usually about 1 unit per 25 g)

Adapted with permission from Petznick A. Insulin management of type 2 diabetes mellitus. *Am Fam Physician*. 2011;84(2):186.

TABLE 4

### Rational Approach to Titration of Insulin

Fasting blood glucose levels for 3 consecutive days	Adjustment of basal insulin dose (units)	Premeal or bedtime blood glucose levels for 3 consecutive days	Adjustment of rapid-acting insulin dose (units)
<b>Titration schedule for basal insulin*</b>		<b>Titration schedule for rapid-acting insulin†</b>	
> 180 mg per dL (10.0 mmol per L)	8	> 180 mg per dL	3
160 to 180 mg per dL (8.9 to 10.0 mmol per L)	6	140 to 180 mg per dL	2
140 to 159 mg per dL (7.8 to 8.8 mmol per L)	4	120 to 139 mg per dL	1
120 to 139 mg per dL (6.7 to 7.7 mmol per L)	2	100 to 119 mg per dL	Maintain dose
100 to 119 mg per dL (5.6 to 6.6 mmol per L)	1	80 to 99 mg per dL	-1
80 to 99 mg per dL (4.4 to 5.5 mmol per L)	Maintain dose	60 to 79 mg per dL	-2
60 to 79 mg per dL (3.3 to 4.4 mmol per L)	-2	< 60 mg per dL	-4
< 60 mg per dL (3.3 mmol per L)	-4		
Fasting blood glucose levels for 3 consecutive days	Adjustment of pre-dinner dose (units)	Predinner blood glucose levels for 3 consecutive days	Adjustment of pre-breakfast insulin dose (units)
<b>Titration schedule for premixed insulins</b>			
> 180 mg per dL	6	> 180 mg per dL	6
141 to 180 mg per dL (7.8 to 10.0 mmol per L)	4	141 to 180 mg per dL	4
111 to 140 mg per dL (6.2 to 7.8 mmol per L)	2	111 to 140 mg per dL	2
80 to 110 mg per dL (4.4 to 6.1 mmol per L)	Maintain dose	80 to 110 mg per dL	Maintain dose
60 to 79 mg per dL	-2	60 to 79 mg per dL	-2
< 60 mg per dL	-4	< 60 mg per dL	-4

\*—Efficacy and safety of this regimen have been shown in clinical trials.

†—Recommendation based on expert opinion. If the patient has an elevated glucose level at lunchtime, the breakfast rapid-acting dose should be adjusted; if the patient has an elevated premeal glucose level at dinnertime, the lunchtime rapid-acting dose should be adjusted; if the patient has an elevated bedtime glucose level, the dinnertime rapid-acting dose should be adjusted.

Adapted with permission from Mooradian AD, Bernbaum M, Albert SG. Narrative review: a rational approach to starting insulin therapy. *Ann Intern Med.* 2006;145(2):130-131.

A1C goals should be individualized according to patient characteristics.<sup>9,10</sup> The U.K. Prospective Diabetes Study showed that patients with newly diagnosed type 2 diabetes who received intensive therapy (median A1C of 7% achieved) with sulfonylureas, insulin, or metformin had a significantly lower risk of microvascular complications compared with patients who received conventional therapy (median A1C of 7.9% achieved).<sup>33,34</sup> However, most of the benefits in this study were due to a reduced need for photocoagulation treatment of diabetic retinopathy. Several recent trials of intensive therapy in older patients with long duration of diabetes and a high risk of atherosclerotic cardiovascular disease have shown no effect on the incidence of macrovascular complications or an increased incidence of hypoglycemic events and increased mortality.<sup>13,35-37</sup>

The ADA suggests a target A1C of less than 7% for most nonpregnant patients with type 2 diabetes. An A1C goal of less than 6.5% may be appropriate for patients with short duration of type 2 diabetes that is treated with lifestyle changes or metformin only, a long life expectancy, and

no significant cardiovascular disease, as long as significant hypoglycemia or other adverse effects do not occur. For patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbidities, or long duration of type 2 diabetes, an A1C goal of less than 8% or more may be appropriate (*Table 1*).<sup>9</sup>

### New Insulin Products

*Table 5* summarizes FDA-approved insulin products; see *eTables A and B* for information about pharmacokinetics and shelf life. Before 2015, the standard concentration for all insulin formulations was U-100, with the exception of the U-500 regular human insulin Humulin R. Since then, the FDA has approved several higher-concentration insulin products that are associated with less risk of hypoglycemia compared with older formulations.

### RAPID- AND SHORT-ACTING INSULINS

The only available highly concentrated rapid-acting insulin is the U-200 lispro pen. It is bioequivalent to the U-100

TABLE 5

## Summary of FDA-Approved Insulin Products

Insulin	Concentration	Form	Delivery	Cost*
<b>Rapid acting</b>				
Aspart (Novolog)	U-100	Analogue	Pen or vial	\$550 (5 pens) \$300 (1 vial)
Glulisine (Apidra)	U-100	Analogue	Pen or vial	\$400 (5 pens) \$185 (1 vial)
Lispro (Humalog)	U-100	Analogue	Pen or vial	\$325 (5 pens) \$175 (1 vial)
Lispro Human (Afrezza)	U-200 4-, 8-, 12-unit cartridges‡	Analogue Human	Pen Inhaler	\$260 (2 pens†) \$270 (90 cartridges)
<b>Short acting</b>				
Regular (Humulin R)	U-100	Human	Vial	\$100 (1 vial)
<b>Intermediate acting</b>				
Isophane (NPH; Humulin N)	U-100	Human	Pen or vial	\$290 (5 pens) \$50 (1 vial)
<b>Long acting</b>				
Detemir (Levemir)	U-100	Analogue	Pen or vial	\$485 (5 pens) \$300 (1 vial)
Glargine (Lantus, Basaglar)	U-100	Analogue	Pen or vial	\$330 (5 pens, Lantus or Basaglar) \$260 (1 vial, Lantus)
Glargine (Toujeo Solostar)	U-300	Analogue	Pen	\$400 to \$600 (3 or 5 pens§)
<b>Ultra-long acting</b>				
Regular	U-500	Human	Pen or vial	\$600 (3 pens  ) \$1,500 (1 vial)
Degludec (Tresiba Flextouch)	U-100	Analogue	Pen	\$450 (5 pens)
Degludec	U-200	Analogue	Pen	\$575 (3 pens†)
<b>Premixed</b>				
70% isophane/30% regular (Humulin 70/30)	U-100	Human	Pen or vial	\$300 (3 pens) \$50 (1 vial)
70% isophane/30% regular (Novolin 70/30)	U-100	Human	Vial	\$165 (1 vial)
70% aspart protamine/30% aspart (Novolog Mix 70/30)	U-100	Analogue	Pen or vial	\$550 (5 pens) \$300 (1 vial)
50% lispro protamine/50% lispro (Humalog Mix 50/50)	U-100	Analogue	Pen or vial	\$535 (5 pens) \$290 (1 vial)
75% lispro protamine/25% lispro (Humalog Mix 75/25)	U-100	Analogue	Pen or vial	\$320 (5 pens) \$330 (1 vial)
70% degludec/30% aspart (Ryzodeg)	U-100	Analogue	Pen	Not yet available to pharmacies

FDA = U.S. Food and Drug Administration.

\*—Estimated retail price based on information obtained at <http://www.goodrx.com> (accessed May 22, 2017). No generics available. 300 units per pen unless otherwise noted.

†—600 units per pen.

‡—4 mg (blue), 8 mg (green), 12 mg (yellow); 1 foil package contains 2 blister cards, and each blister card contains 5 blister strips with 3 cartridges each, for a total of 15 cartridges per blister card.

§—450 units per pen.

||—1,500 units per pen.

version but requires fewer pen changes per month because less volume is injected with each dose.<sup>38,39</sup>

Afrezza, a rapid-acting inhaled human insulin, is delivered through a specially designed inhaler comprised of single-use cartridges.<sup>40</sup> *eTable C* shows dose conversions from rapid-acting U-100 injectable insulin to Afrezza. In January 2016, Sanofi-Aventis announced it would no longer distribute Afrezza because of poor sales, and it is unclear whether Afrezza will remain on the market in the United States.<sup>40,41</sup>

U-500 regular human insulin is now available as a pen. This product is indicated for patients whose total dosage of U-100 insulin is more than 200 units per day. Unlike the vial formulation, the pen does not require a dose conversion when switching from U-100 insulin formulations. Dose adjustments must be made in 5-unit increments because of the dose increments available in the pen. U-500 regular human insulin is the most concentrated formulation of insulin available as a pen and allows for the administration of the largest number of insulin units per injection.<sup>42</sup> U-500 regular human insulin has been shown to improve glycemic control in severely insulin-resistant patients who require large doses of U-100 insulin. It is also associated with increased patient satisfaction and reduced cost.<sup>43</sup>

## SORT: KEY RECOMMENDATIONS FOR PRACTICE

### LONG-ACTING INSULINS

The U-300 glargine pen (Toujeo Solostar) is a long-acting analogue insulin that was developed to reduce injection volume and provide a gradual insulin release to increase its duration of action to more than 24 hours.<sup>44</sup> Toujeo Solostar causes significantly fewer hypoglycemic events at any time of day and nocturnally compared with U-100 glargine (Lantus) in patients with type 2 diabetes.<sup>45</sup> Toujeo Solostar lowers A1C as effectively as Lantus after six months of treatment and marginally better than Lantus after 12 months.<sup>46</sup> Toujeo Solostar reaches steady-state concentration within five days; therefore, the dose should be titrated no more than once every three or four days. Toujeo Solostar allows dosing with 1-unit increments with even numbers visible in the dose counter window.<sup>44</sup>

The insulin glargine pen Basaglar was approved by the FDA in December 2015 as the first “follow-on” insulin. Although its amino acid sequence is identical to Lantus, it is not considered a biosimilar product in the United States because it did not go through the FDA’s biosimilar drug approval process.<sup>47</sup>

The degludec pen (Tresiba Flextouch) is an ultra-long-acting analogue insulin that is available in two concentrations (U-100 and U-200) with similar safety, effectiveness, and pharmacokinetic profiles. Dose conversion is not required when switching between the two.<sup>48,49</sup> Tresiba Flextouch has a longer duration of action than Toujeo Solostar or Lantus. Patients inject Tresiba Flextouch once daily at any time, but there must be at least eight hours between injections.<sup>50</sup> Both concentrations of Tresiba Flextouch lower A1C with a similar effectiveness as U-100 glargine (Lantus) with less overall and nocturnal hypoglycemia.<sup>51-56</sup> U-200 Tresiba Flextouch shows only even numbers in the dose counter window, requiring all doses to be even numbered.<sup>57</sup>

Tresiba Flextouch can be combined in solution with rapid-acting insulin. It is premixed as 70% U-100 degludec

and 30% U-100 aspart (Ryzodeg). This combination has been shown to provide similar reduction in A1C values while significantly lowering the risk of overall confirmed, nocturnal confirmed, and severe hypoglycemia.<sup>58</sup> This product should be injected once daily with the main meal at the same dose as the previously used long-acting insulin. Patients should continue their previously used short- or rapid-acting insulin at the same dose before meals not covered by this product.<sup>59</sup>

**This article** updates previous articles on this topic by Petznick,<sup>26</sup> and by Mayfield and White.<sup>60</sup>

**Data Sources:** We searched PubMed using the following terms: type 2 diabetes treatment, prediabetes treatment, hypoglycemic agents, nutrition and diabetes, diabetes and cardiovascular disease. We also searched Essential Evidence Plus. Search dates: January 2016 and July 2017.

### The Authors

**AMANDA HOWARD-THOMPSON, PharmD**, is a clinical pharmacy specialist at the Veterans Affairs Medical Center, Memphis, Tenn., and an associate professor at the University of Tennessee Health Science Center College of Pharmacy in Memphis.

Clinical recommendation	Evidence rating	References
Clinicians should minimize the use of concomitant medications that may cause weight gain when treating patients with insulin therapy for type 2 diabetes mellitus.	<b>C</b>	6, 9-11, 33
Consider initiating basal insulin to augment therapy with one or two oral agents or one oral agent plus a GLP-1 receptor agonist when the A1C is 9% or more, especially if symptoms of hyperglycemia or catabolism are present. Or, consider the addition of basal insulin to augment therapy with two oral agents with or without GLP-1 receptor agonists when the A1C is more than 8%.	<b>C</b>	9, 10
Consider initiating insulin replacement therapy when the blood glucose level is 300 to 350 mg per dL (16.7 to 19.4 mmol per L) or more or the A1C is more than 10% to 12%. Also consider adding rapid-acting insulin in those patients taking basal insulin who are already on augmentation therapy but not attaining A1C goals.	<b>C</b>	9, 10
Insulin analogues may be used to reduce the risk of hypoglycemia.	<b>A</b>	28, 29
The A1C goal should be individualized based on age, life expectancy, comorbid conditions, duration of diabetes, risk of hypoglycemia, adverse consequences related to hypoglycemia, or patient motivation and adherence.	<b>C</b>	9, 10, 18-25
Intensive control of type 2 diabetes (A1C goal below 7%) significantly decreases the need for photocoagulation treatment of diabetic retinopathy but increases hypoglycemia and mortality risk.	<b>A</b>	13, 33-37

GLP-1 = glucagon-like peptide 1.

**A** = consistent, good-quality patient-oriented evidence; **B** = inconsistent or limited-quality patient-oriented evidence; **C** = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to <http://www.aafp.org/afpsort>.

**MUNEEZA KHAN, MD, FAAFP**, is an assistant professor and program director at the University of Tennessee Health Science Center College of Medicine's Saint Francis Family Medicine Residency.

**MORGAN JONES, PharmD, MS**, is a primary care clinical pharmacy specialist at the Cleveland Clinic Independence (Ohio) Family Health Center. At the time this article was written, she was a second-year resident in ambulatory care pharmacy and academia at the University of Tennessee Health Science Center College of Pharmacy.

**CHRISTA M. GEORGE, PharmD**, is an associate professor of clinical pharmacy and family medicine at the University of Tennessee Health Science Center College of Pharmacy.

Address correspondence to Amanda Howard-Thompson, PharmD, Veterans Affairs Medical Center, 1689 Nonnconnah Blvd., Room 1419, Memphis, TN 38132 (e-mail: amanda.howard-thompson@va.gov). Reprints are not available from the authors.

References

1. DeFronzo RA. Banting Lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. *Diabetes*. 2009;58(4):773-795.
2. U.K. Prospective Diabetes Study Group. U.K. prospective diabetes study 16. Overview of 6 years' therapy of type II diabetes: a progressive disease. [published correction appears in *Diabetes*. 1996;45(11):1655]. *Diabetes*. 1995;44(11):1249-1258.
3. Ali MK, Bullard KM, Saaddine JB, Cowie CC, Imperatore G, Gregg EW. Achievement of goals in U.S. diabetes care, 1999-2010 [published correction appears in *N Engl J Med*. 2013;369(6):587]. *N Engl J Med*. 2013;368(17):1613-1624.
4. Centers for Disease Control and Prevention. Diabetes report card 2014. <https://www.cdc.gov/diabetes/pdfs/library/diabetesreportcard2014.pdf>. Accessed May 21, 2017.
5. George CM, Brujin LL, Will K, Howard-Thompson A. Management of blood glucose with noninsulin therapies in type 2 diabetes. *Am Fam Physician*. 2015;92(1):27-34.
6. Holman RR, Thorne KI, Farmer AJ, et al.; 4-T Study Group. Addition of biphasic, prandial, or basal insulin to oral therapy in type 2 diabetes. *N Engl J Med*. 2007;357(17):1716-1730.
7. Holman RR, Farmer AJ, Davies MJ, et al.; 4-T Study Group. Three-year efficacy of complex insulin regimens in type 2 diabetes [published correction appears in *N Engl J Med*. 2010;363(21):2078]. *N Engl J Med*. 2009;361(18):1736-1747.
8. Jansen HJ, Vervoort GM, de Haan AF, Netten PM, de Grauw WJ, Tack CJ. Diabetes-related distress, insulin dose, and age contribute to insulin-associated weight gain in patients with type 2 diabetes: results of a prospective study. *Diabetes Care*. 2014;37(10):2710-2717.
9. American Diabetes Association. Standards of medical care in diabetes—2017. *Diabetes Care*. 2017;40(suppl 1):S1-S135.
10. Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm—2016 executive summary. *Endocr Pract*. 2016;22(1):84-113.
11. Apovian CM, Aronne LJ, Bessesen DH, et al. Pharmacological management of obesity: an Endocrine Society clinical practice guideline [published correction appears in *J Clin Endocrinol Metab*. 2015;100(5):2135-2136]. *J Clin Endocrinol Metab*. 2015;100(2):342-362.

12. Peyrot M, Barnett AH, Meneghini LF, Schumm-Draeger PM. Insulin adherence behaviours and barriers in the multinational Global Attitudes of Patients and Physicians in Insulin Therapy study. *Diabet Med*. 2012;29(5):682-689.
13. Gerstein HC, Miller ME, Byington RP, et al.; Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med*. 2008;358(24):2545-2559.
14. Huang ES, Laiteerapong N, Liu JY, John PM, Moffet HH, Karter AJ. Rates of complications and mortality in older patients with diabetes mellitus: the diabetes and aging study. *JAMA Intern Med*. 2014;174(2):251-258.
15. Geller AI, Shehab N, Lovegrove MC, et al. National estimates of insulin-related hypoglycemia and errors leading to emergency department visits and hospitalizations. *JAMA Intern Med*. 2014;174(5):678-686.
16. Budnitz DS, Lovegrove MC, Shehab N, Richards CL. Emergency hospitalizations for adverse drug events in older Americans. *N Engl J Med*. 2011;365(21):2002-2012.
17. Lipska KJ, Ross JS, Wang Y, et al. National trends in US hospital admissions for hyperglycemia and hypoglycemia among Medicare beneficiaries, 1999 to 2011. *JAMA Intern Med*. 2014;174(7):1116-1124.
18. DeWitt DE, Hirsch IB. Outpatient insulin therapy in type 1 and type 2 diabetes mellitus: scientific review. *JAMA*. 2003;289(17):2254-2264.
19. UK Hypoglycaemia Study Group. Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. *Diabetologia*. 2007;50(6):1140-1147.
20. Zoungas S, Patel A, Chalmers J, et al.; ADVANCE Collaborative Group. Severe hypoglycemia and risks of vascular events and death. *N Engl J Med*. 2010;363(15):1410-1418.
21. Moghissi E, Ismail-Beigi F, Devine RC. Hypoglycemia: minimizing its impact in type 2 diabetes. *Endocr Pract*. 2013;19(3):526-535.
22. Biessels GJ, Staekenborg S, Brunner E, Brayne C, Scheltens P. Risk of dementia in diabetes mellitus: a systematic review [published correction appears in *Lancet Neurol*. 2006;5(2):113]. *Lancet Neurol*. 2006;5(1):64-74.
23. Robinson RT, Harris ND, Ireland RH, Lindholm A, Heller SR. Comparative effect of human soluble insulin and insulin aspart upon hypoglycaemia-induced alterations in cardiac repolarization. *Br J Clin Pharmacol*. 2003;55(3):246-251.
24. Mellbin LG, Rydén L, Riddle MC, et al.; ORIGIN Trial Investigators. Does hypoglycaemia increase the risk of cardiovascular events? A report from the ORIGIN trial. *Eur Heart J*. 2013;34(40):3137-3144.
25. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2015;38(1):140-149.
26. Petznick A. Insulin management of type 2 diabetes mellitus. *Am Fam Physician*. 2011;84(2):183-190.
27. Red Book online. <http://truvenhealth.com/products/micromedex/product-suites/clinical-knowledge/red-book> [login required]. Accessed September 30, 2016.
28. Horvath K, Jeitler K, Berghold A, et al. Long-acting insulin analogues versus NPH insulin (human isophane insulin) for type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2007;(2):CD005613.
29. Siebenhofer A, Plank J, Berghold A, et al. Short acting insulin analogues versus regular human insulin in patients with diabetes mellitus. *Cochrane Database Syst Rev*. 2006;(2):CD003287.
30. Mooradian AD, Bernbaum M, Albert SG. Narrative review: a rational approach to starting insulin therapy. *Ann Intern Med*. 2006;145(2):125-134.
31. Rosenstock J, Davies M, Home PD, Larsen J, Koenen C, Scherthanner G. A randomised, 52-week, treat-to-target trial comparing insulin detemir with insulin glargine when administered as add-on to glucose-

## OUTPATIENT INSULIN MANAGEMENT

- lowering drugs in insulin-naïve people with type 2 diabetes. *Diabetologia*. 2008;51(3):408-416.
32. Elgart JF, González L, Prestes M, Rucci E, Gagliardino JJ. Frequency of self-monitoring blood glucose and attainment of HbA1c target values. *Acta Diabetol*. 2016;53(1):57-62.
  33. U.K. Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risks of complications in patients with type 2 diabetes (UKPDS 33) [published correction appears in *Lancet*. 1999; 354(9178):602]. *Lancet*. 1998;352(9131):837-853.
  34. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34) [published correction appears in *Lancet*. 1998;352(9139):1558]. *Lancet*. 1998;352(9131): 854-865.
  35. Patel A, MacMahon S, Chalmers J, et al.; ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2008;358(24):2560-2572.
  36. Duckworth W, Abraira C, Moritz T, et al.; VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes [published correction appears in *N Engl J Med*. 2009;361(10):1028]. *N Engl J Med*. 2009;360(2):129-139.
  37. Hemmingsen B, Lund SS, Gluud C, et al. Intensive glycaemic control for patients with type 2 diabetes: systematic review with meta-analysis and trial sequential analysis of randomised clinical trials. *BMJ*. 2011; 343:d6898.
  38. de la Peña A, Seger M, Soon D, et al. Bioequivalence and comparative pharmacodynamics of insulin lispro 200U/mL relative to insulin lispro (Humalog®) 100U/mL. *Clin Pharmacol Drug Dev*. 2016;5(1):69-75.
  39. Humalog U-200 website. <http://www.humalog.com/humalog-u200-kwikpen.aspx?WT.srch=1>. Accessed March 14, 2016.
  40. Afrezza website. <https://www.afrezza.com/>. Accessed March 14, 2016.
  41. Nuffer W, Trujillo JM, Ellis SL. Technosphere insulin (Afrezza): a new, inhaled prandial insulin. *Ann Pharmacother*. 2015;49(1):99-106.
  42. Humulin R U-500 website. <http://www.humulin.com>. Accessed April 10, 2016.
  43. Reutrakul S, Wroblewski K, Brown RL. Clinical use of U-500 regular insulin: review and meta-analysis. *J Diabetes Sci Technol*. 2012;6(2): 412-420.
  44. Toujeo website. <https://www.toujeo.com>. Accessed March 14, 2016.
  45. Ritzel R, Roussel R, Bolli GB, et al. Patient-level meta-analysis of the EDITION 1, 2 and 3 studies: glycaemic control and hypoglycaemia with new insulin glargine 300 U/ml versus glargine 100 U/ml in people with type 2 diabetes. *Diabetes Obes Metab*. 2015;17(9):859-867.
  46. Riddle MC, Yki-Järvinen H, Bolli GB, et al. One-year sustained glycaemic control and less hypoglycaemia with new insulin glargine 300 U/ml compared with 100 U/ml in people with type 2 diabetes using basal plus meal-time insulin: the EDITION 1 12-month randomized trial, including 6-month extension. *Diabetes Obes Metab*. 2015;17(9): 835-842.
  47. U.S. Food and Drug Administration. FDA approves Basaglar, the first "follow-on" insulin glargine product to treat diabetes. <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm477734.htm>. Accessed March 14, 2016.
  48. Bode BW, Chaykin LB, Sussman AM, et al. Efficacy and safety of insulin degludec 200 U/ml and insulin degludec 100 U/ml in patients with type 2 diabetes (begin: compare). *Endocr Pract*. 2014;20(8):785-791.
  49. Korsatko S, Deller S, Koehler G, et al. A comparison of the steady-state pharmacokinetic and pharmacodynamic profiles of 100 and 200 U/mL formulations of ultra-long-acting insulin degludec. *Clin Drug Investig*. 2013;33(7):515-521.
  50. Meneghini L, Atkin SL, Gough SC, et al.; NN1250-3668 (BEGIN FLEX) Trial Investigators. The efficacy and safety of insulin degludec given in variable once-daily dosing intervals compared with insulin glargine and insulin degludec dosed at the same time daily: a 26-week, randomized, open-label, parallel-group, treat-to-target trial in individuals with type 2 diabetes. *Diabetes Care*. 2013;36(4):858-864.
  51. Garber AJ, King AB, Del Prato S, et al.; NN1250-3582 (BEGIN BB T2D) Trial Investigators. Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 2 diabetes (BEGIN Basal-Bolus Type 2): a phase 3, randomized, open-label, treat-to-target non-inferiority trial. *Lancet*. 2012; 379(9825):1498-1507.
  52. Zinman B, Philis-Tsimikas A, Cariou B, et al.; NN1250-3579 (BEGIN Once Long) Trial Investigators. Insulin degludec versus insulin glargine in insulin-naïve patients with type 2 diabetes: a 1-year, randomized, treat-to-target trial (BEGIN Once Long). *Diabetes Care*. 2012;35(12): 2464-2471.
  53. Gough SC, Bhargava A, Jain R, Mersebach H, Rasmussen S, Bergenstal RM. Low-volume insulin degludec 200 units/ml once daily improves glycemic control similarly to insulin glargine with a low risk of hypoglycemia in insulin-naïve patients with type 2 diabetes: a 26-week, randomized, controlled, multinational, treat-to-target trial: the BEGIN LOW VOLUME trial. *Diabetes Care*. 2013;36(9):2536-2542.
  54. Onishi Y, Iwamoto Y, Yoo SJ, Clauson P, Tamer SC, Park S. Insulin degludec compared with insulin glargine in insulin-naïve patients with type 2 diabetes: a 26-week, randomized, controlled, Pan-Asian, treat-to-target trial. *J Diabetes Investig*. 2013;4(6):605-612.
  55. Ratner RE, Gough SC, Mathieu C, et al. Hypoglycaemia risk with insulin degludec compared with insulin glargine in type 2 and type 1 diabetes: a pre-planned meta-analysis of phase 3 trials. *Diabetes Obes Metab*. 2013;15(2):175-184.
  56. Rodbard HW, Cariou B, Zinman B, et al.; BEGIN Once Long trial investigators. Comparison of insulin degludec with insulin glargine in insulin-naïve subjects with type 2 diabetes: a 2-year randomized, treat-to-target trial. *Diabet Med*. 2013;30(11):1298-1304.
  57. Tresiba website. <https://www.tresiba.com>. Accessed March 14, 2016.
  58. Christiansen JS, Niskanen L, Rasmussen S, Johansen T, Fulcher G. Lower rates of hypoglycemia during maintenance treatment with insulin degludec/insulin aspart versus biphasic insulin aspart 30: a combined analysis of two phase 3a studies in type 2 diabetes. *J Diabetes*. 2016;8(5):720-728.
  59. Ryzodeg 70/30 prescribing information. [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2015/203313lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/203313lbl.pdf). Accessed March 14, 2016.
  60. Mayfield JA, White RD. Insulin therapy for type 2 diabetes: rescue, augmentation, and replacement of beta-cell function [published correction appears in *Am Fam Physician*. 2004;70(11):2079-2080]. *Am Fam Physician*. 2004;70(3):489-500.

## OUTPATIENT INSULIN MANAGEMENT

**eTABLE A**

### Pharmacokinetic Profiles of Insulin Products

Insulin	Onset	Peak	Duration
<b>Rapid acting</b>			
Aspart (Novolog)	10 to 20 minutes	40 to 50 minutes	3 to 5 hours
Glulisine (Apidra)	25 minutes	45 to 48 minutes	4 to 5 hours
Lispro (Humalog)	15 to 30 minutes	0.5 to 2.5 hours	3 to 6.5 hours
Human (Afrezza)	15 to 30 minutes	53 minutes	2.6 hours
<b>Short acting</b>			
Regular (Humulin R) U-100	30 to 60 minutes	2 to 4 hours	5 to 8 hours
<b>Intermediate acting</b>			
Isoophane (NPH; Humulin N)	1 to 3 hours	8 hours	12 to 16 hours
<b>Long acting</b>			
Detemir (Levemir)	3 to 4 hours	3 to 9 hours	6 to 23 hours
Glargine (Lantus, Basaglar)	3 to 4 hours	None	11 to > 24 hours
Glargine (Toujeo Solostar)	6 hours	None	> 24 hours
<b>Ultra-long acting</b>			
Regular U-500	30 minutes	8 hours	24 hours
Degludec (Tresiba FlexTouch)	0.5 to 1.5 hours	9 hours	42 hours
<b>Premixed</b>			
70% isophane/30% regular (Humulin 70/30)	30 to 60 minutes	Varies	10 to 16 hours
70% isophane/30% regular (Novolin 70/30)	30 to 60 minutes	Varies	10 to 16 hours
70% aspart protamine/30% aspart (Novolog Mix 70/30)	5 to 15 minutes	Varies	10 to 16 hours
50% lispro protamine/50% lispro (Humalog Mix 50/50)	10 to 15 minutes	Varies	10 to 16 hours
75% lispro protamine/25% lispro (Humalog Mix 75/25)	10 to 15 minutes	Varies	10 to 16 hours
70% degludec/30% aspart (Ryzodeg)	See individual components		

## OUTPATIENT INSULIN MANAGEMENT

**eTABLE B**

### Shelf Life After Insulin Product Reaches Room Temperature

Insulin	Shelf life	
	Vials	Pens
<b>Rapid acting</b>		
Aspart (Novolog)	28 days	28 days
Glulisine (Apidra)	28 days	28 days
Lispro (Humalog)	28 days	28 days
<b>Short acting</b>		
Regular (Humulin R) U-100	31 to 42 days, depending on the brand	—
<b>Intermediate acting</b>		
Isoophane (NPH; Humulin N)	31 to 42 days, depending on the brand	14 days
<b>Long acting</b>		
Detemir (Levemir)	6 weeks	6 weeks
Glargine (Lantus, Basaglar)	4 weeks	4 weeks
Glargine (Toujeo Solostar)	—	6 weeks
<b>Ultra-long acting</b>		
Regular U-500	40 days	4 weeks
Degludec (Tresiba FlexTouch)	—	8 weeks
<b>Premixed</b>		
70% isophane/30% regular (Humulin 70/30)	31 days	10 days
70% isophane/30% regular (Novolin 70/30)	42 days	—
70% aspart protamine/30% aspart (Novolog Mix 70/30)	28 days	14 days
50% lispro protamine/50% lispro (Humalog Mix 50/50)	28 days	10 days
75% lispro protamine/25% lispro (Humalog Mix 75/25)	28 days	10 days
70% degludec/30% aspart (Ryzodeg)	—	28 days

**eTABLE C**

### Dosing Conversion from Rapid- Acting U-100 Injectable Insulin to Inhaled Insulin (Afrezza)

Rapid-acting U-100 injectable insulin dose (units)	Afrezza dose (units)
Up to 4	4
5 to 8	8
9 to 12	12
13 to 16	16
17 to 20	20
21 to 24	24

*Information from Afrezza prescribing information. <https://www.afrezza.com/hcp/>. Accessed March 14, 2016.*