Therapeutic Class Overview
Insulins

INTRODUCTION

- Diabetes mellitus is defined as a group of metabolic disorders characterized by hyperglycemia that result from defects in the secretion and action of insulin (American Diabetes Association [ADA] Diabetes Basics, 2016).
- The classification of diabetes includes four clinical classes: 1) Type 1 diabetes which results from beta-cell (β-cell) destruction, usually leading to absolute insulin deficiency, 2) Type 2 diabetes which results from a progressive insulin secretory defect on the background of insulin resistance, 3) Other specific types of diabetes due to other causes, e.g., genetic defects in β-cell function, genetic defects in insulin action, diseases of the exocrine pancreas (such as cystic fibrosis), and drug- or chemical-induced (such as in the treatment of HIV/AIDS or after organ transplantation, and 4) Gestational diabetes mellitus (diabetes diagnosed during pregnancy that is not clearly overt diabetes) (ADA, 2016).
- In 2012, an estimated 29.1 million people, or 9.3% of the U.S. population, had diabetes, of which, 8.1 million were estimated to be undiagnosed (ADA Diabetes Basics, 2016; Centers for Disease Control [CDC], 2014).
- The insulin products are approved for use in the management of both types 1 and 2 diabetes. Other pharmacologic options for type 2 diabetes include sulfonylureas, biguanides, thiazolidinediones, meglitinides, alpha-glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) analogs, amylinomimetics, sodium-glucose cotransporter 2 (SGLT2) inhibitors, and combination products.
- Insulin is used as replacement therapy in patients with diabetes, replacing deficient endogenous insulin and temporarily restoring the ability of the body to properly utilize carbohydrates, fats, and proteins. Insulin is secreted by the β-cells in the pancreas and lowers blood glucose by facilitating peripheral glucose uptake into cells and by inhibiting gluconeogenesis in the liver. In addition to its glycemic effects, insulin has anabolic properties, enhancing protein synthesis, inhibiting lipolysis in adipocytes, and stimulating lipogenesis.
- The first insulin products were derived from animal sources, primarily pork and beef; however, they are no longer available in the United States (US). These older products have been replaced with human insulin and insulin analogs. Human insulin is biosynthesized utilizing recombinant deoxyribonucleic acid (DNA) with strains of *Escherichia coli* or *Saccharomyces cerevisiae* (baker's yeast) and is structurally identical to endogenous insulin. Insulin analogs are also derived from recombinant DNA technology. They are structurally different from human insulin but have comparable glucose-lowering effects. The insulin analogs differ in the addition, deletion, or substitution of amino acids on the B chain. Insulin analogs available today include insulin aspart, insulin degludec, insulin detemir, insulin glargine, insulin glulisine, and insulin lispro. The primary differences between commercially available insulin products revolve around pharmacodynamic and pharmacokinetic properties, particularly onset and duration of action. Individual insulin products are often classified into categories based on their onset and duration of action.
  - Bolus insulin products, also known as rapid- or short-acting insulin, include insulin aspart, insulin glulisine, insulin lispro, and certain human insulins. Unique formulations within this category include a rapid-acting, human insulin inhalation powder, and a higher strength of rapid-acting insulin lispro that provides 200 units per milliliter (U-200).
  - Basal insulin products, also known as intermediate- or long-acting insulin, include NPH, insulin degludec, insulin detemir, and insulin glargine. Unique products within this category include a long-acting formulation of insulin glargine that provides 300 units of insulin glargine per milliliter and enables patients to utilize a higher dose in one injection. Additionally, a new insulin glargine product, BASAGLAR® (LY insulin glargine) was approved under the abbreviated 505(b)(2) pathway based on safety and effectiveness data for LANTUS® (insulin glargine). BASAGLAR was not approved as a biosimilar product, but is considered a "follow-on biologic" to LANTUS (BASAGLAR Food and Drug Administration [FDA] press release, 2015; Drugs@FDA, 2016; BASAGLAR FDA approval letter, 2015). Under a settlement agreement with Sanofi, the US launch of BASAGLAR is scheduled for December 15, 2016 (Eli Lilly press release, 2015; BASAGLAR website, 2016).
- Insulin therapy is usually administered by subcutaneous injection, which allows for prolonged absorption and less pain compared to intramuscular injection. Currently there are no generic insulin products available. Of note, insulin products are available by prescription, as well as over-the-counter (short- and intermediate-acting products only).
- This review will focus on the insulin preparations outlined in Table 1 for their respective FDA-approved indications. FDA-approved products that do not have upcoming launch plans, such as RYZODEG® 70/30 (insulin degludec/insulin aspart), have been excluded from this review (RYZODEG 70/30 FDA press release, 2015).
- Medispan class: Antidiabetics, Insulin

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
Rapid-Acting Insulins			
AFREZZA® (insulin human) inhalation powder	MannKind	07/27/2014 (4 and 8 units/inhalation) 04/17/2015 (12 units/inhalation)	-
APIDRA® (insulin glulisine)	Sanofi	04/16/2004	-
APIDRA SoloStar® (insulin glulisine)	Sanofi	02/24/2009	-
HUMALOG® (insulin lispro)	Lilly	06/14/1996	-
HUMALOG Kwikpen® (insulin lispro)	Lilly	09/06/2007 (100 units/mL) 05/26/2015 (200 units/mL)	-
NOVOLOG®, NOVOLOG PenFill® (insulin aspart)	Novo Nordisk	06/07/2000	-
NOVOLOG FlexPen® (insulin aspart)	Novo Nordisk	01/19/2001	-
NOVOLOG FlexTouch® (insulin aspart)	Novo Nordisk	10/31/2013	-
Short-Acting Insulins			
HUMULIN R (insulin, regular, human recombinant)	Lilly	10/28/1982	-
HUMULIN® R U-500 (insulin, regular, human recombinant)	Lilly	03/31/1994	-
HUMULIN R U-500 Kwikpen (insulin, regular, human recombinant)	Lilly	12/29/2015	-
NOVOLIN® R (insulin, regular, human recombinant)	Novo Nordisk	06/25/1991	-
Intermediate-Acting Insulins			
HUMULIN N, HUMULIN N Kwikpen (insulin, NPH human recombinant isophane)	Lilly	10/28/1982	-
NOVOLIN N (insulin, NPH human recombinant isophane)	Novo Nordisk	07/01/1991	-
Long-Acting Insulins			
BASAGLAR (LY insulin glargine)	Lilly	12/16/2015	-
LANTUS (insulin glargine)	Sanofi	04/20/2000	-
LANTUS SoloStar (insulin glargine)	Sanofi	04/27/2007	-
LEVEMIR® (insulin detemir)	Novo Nordisk	06/16/2005	-
LEVEMIR FlexTouch (insulin detemir)	Novo Nordisk	10/31/2013	-
TOUJEO® (insulin glargine U-300)	Sanofi	02/25/2015	-
TRESIBA® (insulin degludec)	Novo Nordisk	09/25/2015	-

Drug	Manufacturer	FDA Approval Date	Generic Availability
Combination Insulins, Rapid-Acting and Intermediate-Acting			
HUMALOG Mix 50/50™ (50% insulin lispro protamine/ 50% insulin lispro)	Lilly	12/22/1999	-
HUMALOG Mix 50/50 Kwikpen (50% insulin lispro protamine/ 50% insulin lispro)	Lilly	09/06/2007	-
HUMALOG Mix 75/25™ (75% insulin lispro protamine/ 25% insulin lispro)	Lilly	12/22/1999	-
HUMALOG Mix 75/25 Kwikpen (75% insulin lispro protamine/ 25% insulin lispro)	Lilly	09/06/2007	-
NOVOLOG Mix 70/30 (70% insulin aspart protamine/ 30% insulin aspart)	Novo Nordisk	11/01/2001	-
NOVOLOG Mix 70/30 FlexPen (70% insulin aspart protamine/ 30% insulin aspart)	Novo Nordisk	05/03/2002	-
Combination Insulins, Short-Acting and Intermediate-Acting			
HUMULIN 70/30 (70% NPH, human insulin isophane/ 30% regular human insulin)	Lilly	04/25/1989	-
NOVOLIN 70/30 (70% NPH, human insulin isophane/ 30% regular human insulin)	Novo Nordisk	06/25/1991	-

(DRUGS@FDA, 2016)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Product	Adjunct to diet and exercise to improve glycemic control in adults and children with type 1 and type 2 diabetes mellitus	Control of hyperglycemia in patients with diabetes mellitus	Improve glycemic control in patients with diabetes mellitus	Improve glycemic control in adults and children with diabetes mellitus
Rapid-Acting Insulins				
AFREZZA			✔ £	
APIDRA				✔
HUMALOG				✔
NOVOLOG				✔
Short-Acting Insulins				
HUMULIN R	✔ *			
NOVOLIN R				✔
Intermediate-Acting Insulins				
HUMULIN N				✔
NOVOLIN N			✔	
Long-Acting Insulins**				
BASAGLAR				✔ ±
LANTUS				✔ ±
LEVEMIR				✔
TOUJEO			✔	
TRESIBA			✔	

Product	Adjunct to diet and exercise to improve glycemic control in adults and children with type 1 and type 2 diabetes mellitus	Control of hyperglycemia in patients with diabetes mellitus	Improve glycemic control in patients with diabetes mellitus	Improve glycemic control in adults and children with diabetes mellitus
Combination Insulins, Rapid-Acting and Intermediate-Acting				
HUMALOG Mix 50/50 HUMALOG Mix 75/25		✔		
NOVOLOG Mix 70/30			✔	
Combination Insulins, Short-Acting and Intermediate-Acting				
HUMULIN 70/30			✔	
NOVOLIN 70/30			✔	

*HUMULIN R U-500 is useful for the treatment of insulin-resistant patients with diabetes requiring daily doses of more than 200 units. HUMULIN R U-100 may also be administered intravenously under proper medical supervision in a clinical setting for glycemic control.
**Limitations of use: Not recommended for treating diabetic ketoacidosis. Use intravenous, rapid-acting or short-acting insulin instead.
± Not indicated for children with type 2 diabetes.
£ Limitations of use: Must use with a long-acting insulin in patients with type 1 diabetes. Not recommended for treating diabetic ketoacidosis. Not recommended in patients who smoke.

(Prescribing information: AFREZZA, 2016; APIDRA, 2015; BASAGLAR, 2016; HUMALOG, 2015; HUMALOG Mix 50/50, 2015; HUMALOG MIX 75/25, 2015; HUMULIN 70/30, 2015; HUMULIN N, 2015; HUMULIN R U-100, 2015; HUMULIN R U-500, 2016; LANTUS, 2015; LEVEMIR, 2015; NOVOLIN 70/30, 2016; NOVOLIN N, 2016; NOVOLIN R, 2016; NOVOLOG, 2015; NOVOLOG Mix 70/30, 2015; TOUJEO, 2015; TRESIBA, 2016)

Information on indications, mechanism of action, pharmacokinetics, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Clinical trials conducted with the newer insulin analogs have shown that they are at least as effective as the older insulin formulations. A large meta-analysis revealed that both insulin aspart and insulin lispro produced comparable lowering of glycosylated hemoglobin (HbA1c) in patients with type 2 diabetes compared to regular insulin (Plank et al, 2005). In patients with type 1 diabetes, insulin lispro and insulin aspart produced small, but significant differences in lowering HbA1c compared to regular insulin. Clinical trials comparing insulin glulisine to regular insulin demonstrate similar results, with at least comparable decreases in HbA1c and a few trials reporting a significantly greater decrease in HbA1c when compared to regular insulin in patients with type 1 and 2 diabetes (Dailey et al, 2004; Garg et al, 2005; Rayman et al, 2007).
- The rapid-acting analogs have demonstrated a more favorable post-prandial glycemic profile compared to regular insulin in patients with type 1or 2 diabetes (Anderson et al, 1997a; Chen et al, 2006; Dailey et al, 2004; Raskin et al, 2000; Vignati et al, 1997). Most trials reported comparable rates of hypoglycemia between rapid-acting insulin analogs and regular insulin (Anderson et al, 1997b; Bretzel et al, 2004; Chen et al, 2006; Colquitt et al, 2003; Dailey et al, 2004; Fairchild et al, 2000; Garg et al, 2005; Home et al, 2006; McSorley et al, 2002; Mortensen et al, 2006; Plank et al, 2005; Raskin et al, 2000; Vignati et al, 1997). One large trial of patients with type 1 diabetes reported a 12% lower incidence of hypoglycemia with insulin lispro compared to regular insulin (P<0.001) (Anderson et al, 1997a). In another trial, significantly lower frequencies and monthly rates of severe symptomatic hypoglycemia and nocturnal hypoglycemia were reported in patients with type 2 diabetes patients with insulin glulisine compared to regular insulin (Rayman et al, 2007).
- Head-to-head trials of rapid-acting analogs suggest comparable effectiveness in terms of decreasing HbA1c, achieving similar self-monitored glucose profiles, rates of hypoglycemia, and achieving glycemic goals in patients with type 1 diabetes (Dreyer et al, 2005; Philotheou et al, 2011; Van Ban et al, 2011).
- In a 24-week, open-label, active-controlled, non-inferiority study, patients with type 1 diabetes on basal insulin were randomized to treatment with AFREZZA or insulin aspart administered at each meal of the day. At 24 weeks, treatment with mealtime AFREZZA provided a mean reduction in HbA1c that met the prespecified non-inferiority margin of 0.4%. However, reductions from baseline HbA1c were significantly less with AFREZZA compared to insulin aspart (-0.21% vs -0.4%, respectively; difference, 0.19%; 95% confidence interval [CI] 0.02 to 0.36). Fewer patients in the AFREZZA group achieved the HbA1c target of <7% compared to patients in the insulin aspart group (13.8% vs 27.1%, respectively; P-value not reported) (Bode et al, 2015).

- Patients with type 2 diabetes who were inadequately controlled on oral antidiabetic agents (OAD) were enrolled in a 24-week, double-blind, placebo-controlled study. Patients were randomized to receive treatment with AFREZZA or an inhaled placebo powder. At week 24, treatment with AFREZZA provided a mean reduction in HbA1c that was significantly greater compared to the reductions observed in the placebo group (-0.82 vs -0.42 respectively; difference, -0.4; 95% CI, -0.57 to -0.23; P<0.0001). A greater percentage of patients achieved the HbA1c target of ≤7% in the AFREZZA group compared to patients in the placebo group (38% vs 19%, respectively; P=0.0005) (Rosenstock et al, 2015[a]).
- While not consistently demonstrated, data suggest that long-acting insulin analogs are superior to isophane (NPH) insulin in decreasing HbA1c, as well as the incidence of hypoglycemia in patients with types 1 and 2 diabetes as demonstrated by the results of several active-comparator trials and meta-analyses (Bartley et al, 2008; Bozzano et al, 2008; Buse et al, 2009; Chase et al, 2008; De Leeuw et al, 2005; Dunbar et al, 2009; Eliaschewitz et al, 2006; Fritsche et al, 2003; Garber et al, 2007; Haak et al, 2005; Heller et al, 2009; Hermansen et al, 2004; Hermansen et al, 2006; Home et al, 2004; Horvath et al, 2007; Kølendorf et al, 2006; Lee et al, 2012; Montañana et al, 2008; Pan et al, 2007; Pieber et al, 2005; Philis-Tsimikas et al, 2006; Raslová et al, 2007; Ratner et al, 2000; Riddle et al, 2003; Robertson et al, 2007; Rosenstock et al, 2005; Russell-Jones et al, 2004; Siegmund et al, 2007; Standl et al, 2004; Tan et al, 2004; Tricco et al, 2014; Vague et al, 2003; Yenigun et al, 2009; Yki-Järvinen et al, 2000; Yki-Järvinen et al, 2006).
- The safety and efficacy of the long-acting analog insulin glargine U-300 (TOUJEO) have been compared to that of insulin glargine U100 (LANTUS) in open-label randomized, active-controlled, parallel studies of up to 26 weeks in patients with type 1 and type 2 diabetes mellitus. The reduction in HbA1c and fasting plasma glucose with insulin glargine U-300 was found to be similar to that of insulin glargine. As of yet, however, only the studies in patients with type 2 diabetes are published (Bolli et al, 2015; Riddle et al, 2014[b]; Yki-Järvinen et al, 2014).
- Insulin degludec (TRESIBA) was evaluated in more than 5,600 type 1 and type 2 diabetic patients throughout nine pivotal studies and five extension studies (BEGIN clinical program). In eight of the pivotal trials, insulin degludec was non-inferior to insulin glargine (LANTUS) or insulin detemir (LEVEMIR) in lowering HbA1c from baseline, with similar rates of hypoglycemia; in five trials, the rate of nocturnal hypoglycemia was significantly lower with insulin degludec compared to insulin glargine or insulin detemir. The mean difference in HbA1c at study end for insulin degludec versus insulin glargine or detemir ranged from -0.09 to 0.17% (Davies et al, 2014; Garber et al, 2012; Gough et al, 2013; Heller et al, 2012; Mathieu et al, 2013; Meneghini et al, 2013[a]; Onishi et al, 2013; Zinman et al, 2012). It is noteworthy that two of the eight insulin degludec trials resulted in a nominally lower reduction in HbA1c for insulin degludec compared to the active comparator basal insulin agents (Davies et al, 2014; Heller et al, 2012). The HbA1c and hypoglycemia trends were also observed in the published extension trials (Bode et al, 2013; Davies et al, 2016; Hollander et al, 2015; Mathieu et al, 2013; Rodbard et al, 2013). In the ninth pivotal trial, insulin degludec lowered HbA1c significantly more than oral sitagliptin 100 mg once daily in patients with type 2 diabetes who were receiving one or two concomitant background OAD agents (treatment difference, -0.43; 95% CI, -0.61 to -0.24; P<0.001), but there were significantly more episodes of overall confirmed hypoglycemia (P<0.0001) (Philis-Tsimikas et al, 2013).
- Across the BEGIN trials, a consistently increased risk of major adverse cardiovascular events (MACE) was observed with insulin degludec. At the request of an FDA Advisory Committee, Novo Nordisk conducted a pre-specified meta-analysis of MACE, which included 8,068 patients from 16 Phase 3 trials conducted for insulin degludec (TRESIBA) and insulin degludec/insulin aspart (RYZODEG).According to the 2012 analysis, there was a consistent trend towards harm in the pooled insulin degludec groups compared to active comparators (HR, 1.67; 95% CI, 1.01 to 2.75). Additional post-hoc analyses consistently trended towards harm regardless of endpoint, effect measure, analysis method, and subgroup analyses (FDA Briefing Document, 2012; Novo Nordisk Briefing Document, 2012). The DEVOTE trial was subsequently initiated to prospectively compare the cardiovascular (CV) safety of insulin degludec to insulin glargine in patients with type 2 diabetes at high risk of CV events. In 2015, insulin degludec was FDA-approved based on efficacy and safety data from the BEGIN clinical program and interim data from the DEVOTE trial; however, the DEVOTE data will not be shared publically until the trial publication in the second half of 2016 in order to maintain study integrity (Clinicaltrials.gov [NCT01959529], 2016; Novo Nordisk press release, 2015).
- The safety and efficacy of LY insulin glargine (BASAGLAR) compared to insulin glargine (LANTUS) were evaluated in 2 pivotal studies enrolling 534 and 744 patients with type 1 (ELEMENT 1 trial) and type 2 (ELEMENT 2 trial) diabetes mellitus, respectively. Both trials were multicenter, parallel group, randomized controlled trials; ELEMENT 1 was open-label and ELEMENT 2 was double-blinded. Both trials were conducted over 24 weeks; however, ELEMENT 1 also included a 28-week comparative safety extension period. Mealtime insulin lispro was administered 3 times daily in both groups within the ELEMENT 1 trial. Oral antidiabetic medication was permitted in conjunction with insulin treatment within the ELEMENT 2 trial. The primary efficacy endpoint tested the non-inferiority of agents by the

reduction in HbA1c from baseline to 24 weeks. A non-inferiority margin for the 95% CI upper limit was pre-specified at 0.4%. If this was met, a non-inferiority margin of 0.3% was also tested. Key secondary endpoints included hypoglycemia rates and mean weight change. In both ELEMENT 1 and ELEMENT 2, LY insulin glargine and insulin glargine had similar and significant (P<0.001) within-group decreases in HbA1c values from baseline. LY insulin glargine met non-inferiority criteria compared to insulin glargine for change in HbA1c from baseline to 24 weeks in both trials (ELEMENT 1: -0.35% vs. -0.46%, respectively; least squares mean difference, 0.108%; 95% CI, -0.002 to 0.219; P>0.05; ELEMENT 2: -1.29% vs. -1.34%, respectively; least squares mean difference, 0.052%; 95% CI, -0.07 to 0.175; P>0.05). There were no statistically significant differences between treatment groups for the rate of each category of hypoglycemia (total, nocturnal, severe), adjusted for 1 year, at 24 or 52 weeks in ELEMENT 1 and at 24 weeks in ELEMENT 2 (P>0.05 for all treatment comparisons). No significant differences between treatment groups were seen for change from baseline in body weight (ELEMENT 1, week 24 and 52: both P>0.05; ELEMENT 2, week 24: P>0.05) (Blevins et al, 2015; Rosenstock et al, 2015[b]).

- At this time, there is a lack of substantial head-to-head data demonstrating the superiority of one long-acting insulin analog over another. When comparing the long-acting analogs head-to-head, several trials have demonstrated non-inferiority between the products in the same outcomes when used in the management of type 1 diabetes and as add-on therapy in patients with type 2 diabetes (Heller et al, 2009; Hollander et al, 2008; Pieber et al, 2007; Raskin et al, 2009; Rosenstock et al, 2008; Swinnen et al, 2010). In one head-to-head trial of insulin glargine and metformin versus insulin detemir and metformin, insulin glargine lowered HbA1c more than insulin detemir (Meneghini et al, 2013[b]). In clinical trials and using indirect comparisons, long-acting insulin agents appear to be similarly effective in achieving and maintaining glycemic control:
- A 2011 Cochrane review (included 4 trials; n = 2250 patients) found that LANTUS and LEVEMIR are equally effective in achieving and maintaining glycemic control (HbA1c). The review also found no differences in overall, nocturnal, and severe hypoglycemic events (Swinnen et al, 2011).
- To further inform the differences between basal insulin agents, a network meta-analysis (included 41 trials, of which 25 trials included patients on basal-oral therapy; n = 15,746) evaluated the safety and efficacy of insulin glargine U-300 (TOUJEO) vs. other basal insulin therapies in the treatment of T2DM. The authors found that the change in HbA1c was comparable between TOUJEO and LEVEMIR (difference, -0.08; 95% credible interval [CrI], -0.4 to 0.24) and TRESIBA (difference, -0.12; CrI, -0.42 to 0.2). Additionally, there were no differences in nocturnal or documented symptomatic hypoglycemic events (Freemantle et al, 2016).
- A direct comparative trial evaluating two types of premixed biphasic insulin demonstrated similar results in terms of reducing HbA1c (Domeki et al, 2014). Another trial comparing biphasic insulin to basal plus prandial insulin in type 2 diabetes mellitus demonstrated that basal plus prandial insulin therapy is slightly more effective than premixed insulin with less hypoglycemia (Riddle et al, 2014[a]).
- Insulin therapies have been compared to GLP-1 agonists. The study results are mixed. A study comparing glycemic control with insulin glargine versus exenatide demonstrated that better glycemic control was sustained with exenatide (Diamant et al, 2012). Other studies have demonstrated that GLP-1 agonists are statistically noninferior to insulin glargine for the change in HbA1c (Inagaki et al, 2012, Weissman et al, 2014). Also, a study comparing the addition of albiglutide to insulin glargine was found to be noninferior to the addition of insulin lispro to insulin glargine (Rosenstock et al, 2014).
- In terms of clinical outcomes, the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) have demonstrated that intensive glycemic control with insulin significantly reduces the rate of onset and progression of diabetic complications when compared to standard therapy (DCCT, 1993; UKPDS, 1998). Neither trial indicated the specific insulin formulations utilized; however, in the UKPDS, the risk reduction in microvascular complications was related more toward tight glycemic control rather than to one specific therapy (UKPDS, 1998).
- Refer to the Conclusions section for treatment guideline recommendations.

SAFETY SUMMARY

- Contraindications:
  - Insulins are contraindicated during episodes of hypoglycemia and with hypersensitivity to any ingredient of the product.
  - In addition, AFREZZA is also contraindicated in patients with chronic lung disease, such as asthma or chronic obstructive pulmonary disease (COPD), because of the risk of acute bronchospasm.
- Boxed Warnings
  - AFREZZA has a Boxed Warning for the risk of acute bronchospasm in patients with chronic lung disease.

- Warnings/Precautions:
    - Insulin pens must never be shared between patients, even if the needle is changed. Patients using insulin vials must never reuse or share needles or syringes with another person. Sharing poses a risk for transmission of blood-borne pathogens.
    - Frequent glucose monitoring and insulin dose reduction may be required in patients with renal or hepatic impairment.
    - All insulins can cause hypokalemia, which if untreated, may result in respiratory paralysis, ventricular arrhythmia, and death.
    - Long-term use of insulin can cause lipodystrophy at the site of repeated insulin injections.
    - Accidental mix-ups between basal insulin products and other insulins, particularly rapid-acting insulins, have been reported. To avoid medication errors, patients should be instructed to always check the insulin label before each injection.
    - AFREZZA has additional respiratory-related warnings and precautions associated with its use including acute bronchospasm in patients with chronic lung disease, decline in pulmonary function, and lung cancer.
- Adverse Events:
    - Hypoglycemia is the most commonly observed adverse reaction. Hypoglycemia can impair concentration ability and reaction time which may place an individual and others at risk in situations where these abilities are important. Severe hypoglycemia can cause seizures, may be life-threatening, or cause death. Self-monitoring of blood glucose plays an essential role in the prevention and management of hypoglycemia.
    - Weight gain, sodium retention and edema, and injection site reactions can occur.
    - Additional adverse events observed with the inhaled insulin, AFREZZA, include cough, throat pain or irritation, headache, diarrhea, productive cough, fatigue, nausea, decreased pulmonary function test, bronchitis, and urinary tract infection.
- Drug Interactions:
    - β-blockers, clonidine, guanethidine, and reserpine may all mask hypoglycemic reactions.
    - Thiazolidinediones can cause dose-related fluid retention, particularly when used in combination with insulin.
    - Refer to prescribing information for all drugs that can increase or reduce the glucose-lowering ability of insulin.
- Risk Evaluation and Mitigation Strategy (REMS)
    - The FDA requires a communication plan to inform health care professionals about the serious risk of acute bronchospasm associated with AFREZZA.
    - The FDA includes risk mitigation strategies for hypoglycemia in the prescribing information for the insulin glargine formulations (LANTUS, LANTUS SoloStar, and TOUJEO). Patients and caregivers must be educated to recognize and manage hypoglycemia. Self-monitoring of blood glucose plays an essential role in the prevention and management of hypoglycemia. In patients at higher risk for hypoglycemia and patients who have reduced symptomatic awareness of hypoglycemia, increased frequency of blood glucose monitoring is recommended. The long-acting effect of insulin glargine may delay recovery from hypoglycemia. Also, to minimize the risk of hypoglycemia with these products, do not administer them intravenously, intramuscularly, or in an insulin pump or dilute or mix them with other insulin products or solutions.

DOSING AND ADMINISTRATION

Table 3a. Dosing and Administration

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
Rapid-Acting Insulins				
AFREZZA (insulin human)	Single-use cartridges: 4 units (0.35 mg insulin), 8 units (0.7 mg insulin), 12 units (1 mg insulin)	Starting mealtime dose: Insulin naïve individuals: 4 units of AFREZZA at each meal. Individuals using subcutaneous prandial insulin: determine the appropriate AFREZZA dose for each meal by converting from the injected dose using the dose conversion table (see Table 3b). Individuals using subcutaneous pre-mixed insulin: estimate the mealtime injected dose by dividing half of the total daily injected pre-mixed insulin dose equally among the three meals of the day. Convert each estimated mealtime dose to an appropriate AFREZZA dose using the dose conversion table (see Table 3b). Administer half of the total daily injected pre-mixed dose as an injected basal insulin dose.	Dosage adjustment may be needed when switching from another insulin to AFREZZA or due to drug interactions. AFREZZA should only be administered via oral inhalation using the AFREZZA Inhaler. See prescribing information for further dosing information in other situations.	Administer at the beginning of a meal. AFREZZA is administered using a single inhalation per cartridge. For doses exceeding 12 units, inhalations from multiple cartridges are required. Keep the inhaler level with the white mouthpiece on top and purple base on bottom after a cartridge have been inserted into the inhaler to prevent loss of drug effect.
APIDRA (insulin glulisine)	100 units/mL: Cartridge (OptiClik® delivery device): 3 mL Pen (SoloStar® prefilled): 3 mL Vial: 10 mL	Dose and frequency are individualized per patient needs. Use in a regimen with intermediate- or long-acting insulin.	Administer within 15 minutes before a meal or within 20 minutes after starting a meal. Must not be mixed or diluted when used in an external insulin infusion pump.	Injection sites should be rotated within the same region (abdomen, thigh or upper arm) from one injection to the next to reduce the risk of lipodystrophy. APIDRA-specific information should be followed for in-use time, frequency of changing infusion sets, or other details specific to APIDRA usage.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
HUMALOG (insulin lispro)	100 units/mL: Cartridge: 3 mL KwikPen (prefilled): 3 mL Vial: 3 mL, 10 mL 200 units/mL: KwikPen (prefilled): 3 mL	Dose and frequency are individualized per patient needs. Use in a regimen with intermediate- or long-acting insulin.	Administer within 15 minutes before a meal or immediately after a meal. HUMALOG U-100 by subcutaneous injection may be mixed with NPH only. Must not be mixed or diluted when used in an external insulin infusion pump. Do not mix HUMALOG U-200 with any other insulin. Do not perform dose conversion when using either strength of the KwikPen.	Injection sites should be rotated within the same region (abdomen, thigh, buttocks or upper arm) from one injection to the next to reduce the risk of lipodystrophy. Do not administer HUMALOG U-200 by continuous subcutaneous or intravenous infusion.
NOVOLOG (insulin aspart)	100 units/mL: Cartridge (PenFill): 3 mL FlexPen: 3 mL FlexTouch: 3 mL Vial: 10 mL	Dose and frequency are individualized per patient needs. Use in a regimen with intermediate- or long-acting insulin.	Should be injected immediately (within 5-10 minutes) before a meal. Must not be mixed or diluted when used in an external insulin infusion pump.	Injection sites should be rotated within the same region (abdomen, thigh, buttocks, or upper arm) from one injection to the next to reduce the risk of lipodystrophy.
Short-Acting Insulins				
HUMULIN R (insulin, regular, human recombinant)	100 units/mL: Vial: 3 mL, 10 mL 500 units/mL: Vial: 20 mL	When given SQ, generally given three or more times daily before meals. U-500: Generally given two to three times daily before meals. Dose and frequency are individualized per patient needs. Often used concomitantly with intermediate- or long-acting insulin.	Injection should be followed by a meal within approximately 30 minutes of administration. U-500 should only be given SQ and should not be mixed with other insulins.	Injection sites should be rotated within the same region (abdomen, thigh, gluteal region or upper arm) from one injection to the next to reduce the risk of lipodystrophy.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
NOVOLIN R (insulin, regular, human recombinant)	100 units/mL: Vial: 10 mL	Dose and frequency are individualized per patient needs. Often used in combination with intermediate- or long-acting insulin.	Injection should be followed by a meal within approximately 30 minutes of administration.	Injection sites should be rotated within the same region (abdomen, thigh, buttocks, or upper arm) from one injection to the next to reduce the risk of lipodystrophy.
Intermediate-Acting Insulins				
HUMULIN N, (insulin, NPH, human recombinant isophane)	100 units/mL: KwikPen (prefilled): 3 mL Vial: 3 mL, 10 mL	Generally given in one to two injections per day. Dose and frequency are individualized per patient needs.	Administer 30 to 60 minutes before a meal or bedtime.	Injection sites should be rotated within the same region (abdomen, thigh, buttocks, or upper arm) from one injection to the next to reduce the risk of lipodystrophy.
NOVOLIN N (insulin, NPH, human recombinant isophane)	100 units/mL: Vial: 3 mL, 10 mL	Generally given in one to two injections per day. Dose and frequency are individualized per patient needs.	Administer 30 to 60 minutes before a meal or bedtime.	Injection sites should be rotated within the same region (abdomen, thigh, buttocks, or upper arm) from one injection to the next to reduce the risk of lipodystrophy.
Long-Acting Insulins				
BASAGLAR (LY insulin glargine)	100 units/mL: KwikPen (prefilled): 3 mL	Administer between 1 and 80 units per injection SQ once daily into the thigh, upper arm, or abdomen. Dose is individualized based on patient needs. Type 1 diabetes: Starting dose in insulin-naïve patients is approximately one-third of the total daily insulin dose. Short- or rapid-acting, pre-meal insulin should be used to satisfy the remainder of the daily insulin requirements. Type 2 diabetes: Starting dose in insulin-naïve patients is 0.2 units/kg or up to 10 units once daily.	May be administered at any time of day, but at same time every day. Do not administer intravenously or use in insulin pumps.	Injection sites should be rotated within the same region (abdomen, thigh or upper arm) from one injection to the next to reduce the risk of lipodystrophy.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
LANTUS (insulin glargine)	100 units/mL: Cartridge (for use with OptiClik): 3 mL SoloStar (disposable device): 3 mL Vial: 10 mL	Recommended starting dose in insulin-naïve type 2 diabetes patients: 0.2 units/kg or up to 10 units SQ once daily. Dose is individualized based on patient needs.	May be administered at any time of day, but at same time every day. Do not administer intravenously or use in insulin pumps. See full prescribing information when converting to once daily LANTUS from other insulin therapies.	Injection sites should be rotated within the same region (abdomen, thigh or upper arm) from one injection to the next to reduce the risk of lipodystrophy.
LEVEMIR (insulin detemir)	100 units/mL: FlexPen: 3 mL FlexTouch: 3 mL Vial: 10 mL	Administer SQ once or twice daily. Dose is individualized based on patient needs.	Once daily administration should be given with evening meal or at bedtime. Twice daily administration should be given in the morning and then 12 hours later with evening meal or at bedtime. Do not use in insulin pumps.	Injection sites should be rotated within the same region (abdomen, thigh or upper arm) from one injection to the next to reduce the risk of lipodystrophy.
TOUJEO (insulin glargine U-300)	300 units/mL: Pen (SoloStar prefilled): 1.5 mL	Administer SQ once daily. Dose is individualized based on patient needs. The dose of TOUJEO ranges from 1 to 80 units per one injection. Type 1 diabetes: Starting dose in insulin-naive patients is approximately one-third to one-half the total daily insulin dose. The remainder of the total daily insulin dose should be given as a short-acting insulin and divided between each daily meal. Type 2 diabetes: Starting dose in insulin-naïve	Administer at the same time each day. When changing patients to TOUJEO, monitor glucose frequently in the first weeks of therapy. To minimize the risk of hypoglycemia, titrate the dose of TOUJEO no more frequently than every 3 to 4 days. Do not administer TOUJEO intravenously, intramuscularly, or in an insulin pump.	Injection sites should be rotated within the same region (abdomen, thigh, or upper arm) from one injection to the next to reduce the risk of lipodystrophy. Do not mix with any other insulin products or solutions.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		patients is 0.2 units per kilogram of body weight once daily.		
TRESIBA (insulin degludec)	100 units/mL: FlexTouch: 3 mL 200 units/mL: FlexTouch: 3 mL	Administer SQ once daily. Dose is individualized based on patient needs. Type 1 diabetes: Starting dose in insulin-naïve patients is approximately one-third to one-half of the total daily insulin dose. The remainder of the total daily insulin dose should be given as a short-acting insulin and divided between each daily meal. Type 2 diabetes: Starting dose in insulin-naïve patients is 10 units once daily. Patients already on insulin therapy: Start at the same unit dose as the total daily long- or intermediate-acting insulin unit dose.	May be administered at any time of day. The recommended number of days between dose increases is 3 to 4 days. Do not administer intravenously, intramuscularly, or in an insulin infusion pump.	Injection sites should be rotated within the same region (abdomen, thigh, or upper arm) from one injection to the next to reduce the risk of lipodystrophy. Do not dilute or mix with any other insulin products or solutions.
Combination Insulins, Rapid-Acting and Intermediate-Acting				
HUMALOG Mix 50/50, HUMALOG Mix 75/25 (insulin lispro protamine/ insulin lispro)	100 units/mL: Vial: 10 mL KwikPen (prefilled): 3 mL	Dose and frequency are individualized per patient needs.	Administer within 15 minutes before meals. Do not use in insulin pumps.	Injection sites should be rotated within the same region (abdomen, thigh or upper arm) from one injection to the next to reduce the risk of lipodystrophy.
NOVOLOG Mix 70/30 (insulin aspart protamine/ insulin aspart)	100 units/mL: FlexPen: 3 mL Vial: 10 mL	Typically dosed on a twice daily basis. Dose and frequency are individualized per patient needs.	Administer within 15 minutes before meals for type 1 diabetes. Administer within 15 minutes before or after meals for type 2 diabetes. Do not use in insulin pumps.	Injection sites should be rotated within the same region (abdomen, thigh, buttocks or upper arm) from one injection to the next to reduce the risk of lipodystrophy.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
Combination Insulins, Short-Acting and Intermediate-Acting				
HUMULIN 70/30 (NPH, human insulin isophane/ regular human insulin)	100 units/mL: KwikPen (prefilled): 3 mL Vial: 3 mL, 10 mL	Generally given in two injections per day. Dose and frequency are individualized per patient needs.	Administer 30 to 60 minutes before a meal.	Injection sites should be rotated within the same region (abdomen, thigh, buttocks, or upper arm) from one injection to the next to reduce the risk of lipodystrophy.
NOVOLIN 70/30 (NPH, human insulin isophane/ regular human insulin)	100 units/mL: Vial: 10 mL	Generally given in two injections per day. Dose and frequency are individualized per patient needs.	Administer 30 to 60 minutes before a meal.	Injection sites should be rotated within the same region (abdomen, thigh, buttocks, or upper arm) from one injection to the next to reduce the risk of lipodystrophy.

NPH=neutral protamine Hagedorn, SQ=subcutaneous

Table 3b. Mealtime AFREZZA Dose Conversion Table

Injected Mealtime Insulin Dose	AFREZZA Dose	# of 4-unit cartridges needed	# of 8 unit cartridges needed	# of 12 unit cartridges needed
Up to 4 units	4 units	1		
5 to 8 units	8 units		1	
9 to 12 units	12 units	1*	1*	1
13 to 16 units	16 units		2	
17 to 20 units	20 units		1	1
21 to 24 units	24 units			2

*A 4-unit and 8-unit may be combined; alternatively, a single 12-unit may be used.

SPECIAL POPULATIONS

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
Rapid-Acting Insulins					
AFREZZA (insulin human)	No overall differences in safety or effectiveness were observed between patients over 65 and younger patients.	Safety and efficacy have not been established.	Safety and efficacy have not been established.	Safety and efficacy have not been established.	Pregnancy Category C* It is highly likely that the insulin and carrier in AFREZZA is excreted in human milk. A decision should be made whether to discontinue nursing or discontinue use of the drug.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
APIDRA (insulin glulisine)	Use caution with initial dosing and changes in dosing to avoid hypoglycemic reactions.	Safety and efficacy in children < 4 years with type 1 diabetes have not been established. Safety and efficacy in children with type 2 diabetes have not been established.	Renal dosage adjustment may be required.	Hepatic dosage adjustment may be required.	Pregnancy category C* Unknown; use with caution. Adjustment of insulin dose may be needed while breastfeeding.
HUMALOG (insulin lispro)	Use caution with initial dosing and changes in dosing to avoid hypoglycemic reactions.	Safety and efficacy in children < 3 years with type 1 diabetes have not been established. Safety and efficacy in children with type 2 diabetes have not been established.	Renal dosage adjustment may be required.	Hepatic dosage adjustment may be required.	Pregnancy category B* Unknown; use with caution. Adjustment of insulin dose may be needed while breastfeeding.
NOVOLOG (insulin aspart)	Use caution with initial dosing and changes in dosing to avoid hypoglycemic reactions.	Safety and efficacy in children < 2 years with type 1 diabetes have not been established. Safety and efficacy in children with type 2 diabetes have not been established.	Renal dosage adjustment may be required.	Hepatic dosage adjustment may be required.	Pregnancy category B* Unknown; use with caution. Adjustment of insulin dose may be needed while breastfeeding.
Short-Acting Insulins					
HUMULIN R (insulin, regular, human recombinant)	Use caution with initial dosing and changes in dosing to avoid hypoglycemic reactions.	Approved for use in children. U-500: Safety and efficacy in children have not been established.	Renal dosage adjustment may be required.	Hepatic dosage adjustment may be required.	Pregnancy category B* Unknown; use with caution. Adjustment of insulin dose may be needed while breastfeeding.
NOVOLIN R (insulin, regular, human recombinant)	Use caution with initial dosing and changes in dosing to avoid hypoglycemic reactions.	Safety and efficacy in children < 2 years with type 1 diabetes have not been established. Safety and efficacy in children with type 2 diabetes have not been established.	Renal dosage adjustment may be required.	Hepatic dosage adjustment may be required.	Pregnancy category B* Unknown; use with caution. Adjustment of insulin dose may be needed while breastfeeding.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
Intermediate-Acting Insulins					
HUMULIN N, NOVOLIN N (insulin, NPH, human recombinant isophane)	Use caution with initial dosing and changes in dosing to avoid hypoglycemic reactions.	Safety and efficacy in children have not been established.	Renal dosage adjustment may be required.	Hepatic dosage adjustment may be required.	Pregnancy category B* Unknown; use with caution. Adjustment of insulin dose may be needed while breastfeeding.
Long-Acting Insulins					
BASAGLAR (LY insulin glargine)	Use caution with initial dosing and changes in dosing to avoid hypoglycemic reactions.	Safety and efficacy in children < 6 years with type 1 diabetes have not been established. Safety and efficacy in children with type 2 diabetes has not been established.	Renal dosage adjustment may be required.	Hepatic dosage adjustment may be required.	Pregnancy category C* Unknown; use with caution. Adjustment of insulin dose may be needed while breastfeeding.
LANTUS (insulin glargine)	Use caution with initial dosing and changes in dosing to avoid hypoglycemic reactions.	Safety and efficacy in children < 6 years with type 1 diabetes have not been established. Safety and efficacy in children with type 2 diabetes have not been established.	Renal dosage adjustment may be required.	Hepatic dosage adjustment may be required.	Pregnancy category C* Unknown; use with caution. Adjustment of insulin dose may be needed while breastfeeding.
LEVEMIR (insulin detemir)	Use caution with initial dosing and changes in dosing to avoid hypoglycemic reactions.	Safety and efficacy in children < 2 years with type 1 diabetes have not been established. Safety and efficacy in children with type 2 diabetes have not been established.	Renal dosage adjustment may be required.	Hepatic dosage adjustment may be required.	Pregnancy category B* Unknown; use with caution. Adjustment of insulin dose may be needed while breastfeeding.
TOUJEO (insulin glargine U-300)	Use caution with initial dosing and changes in dosing to avoid hypoglycemic reactions.	Safety and efficacy have not been established.	Renal dosage adjustment may be required.	Hepatic dosage adjustment may be required.	There are no clinical studies of the use of TOUJEO in pregnant women. Female patients should be advised to tell their physicians if they intend to become, or if they become pregnant while taking TOUJEO.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
					Unknown; use with caution. Adjustment of insulin dose may be needed while breastfeeding.
TRESIBA (insulin degludec)	Use caution with initial dosing and changes in dosing to avoid hypoglycemic reactions.	Safety and efficacy have not been established.	Renal dosage adjustment may be required.	Hepatic dosage adjustment may be required.	Pregnancy category C* Unknown; use with caution. Adjustment of insulin dose may be needed while breastfeeding.
Combination Insulins, Rapid-Acting and Intermediate-Acting					
HUMALOG Mix 50/50, HUMALOG Mix 75/25 (insulin lispro protamine/ insulin lispro)	Use caution with initial dosing and changes in dosing to avoid hypoglycemic reactions.	Safety and efficacy in children have not been established.	Renal dosage adjustment may be required.	Hepatic dosage adjustment may be required.	Pregnancy category B* Unknown; use with caution. Adjustment of insulin dose may be needed while breastfeeding.
NOVOLOG Mix 70/30 (insulin aspart protamine/ insulin aspart)					
Combination Insulins, Short-Acting and Intermediate-Acting					
HUMULIN 70/30, NOVOLIN 70/30 (NPH, human insulin isophane/ regular human insulin)	Use caution with initial dosing and changes in dosing to avoid hypoglycemic reactions.	No information available.	Renal dosage adjustment may be required.	Hepatic dosage adjustment may be required.	Pregnancy category B* Unknown; use with caution. Adjustment of insulin dose may be needed while breastfeeding.

* Pregnancy Category B = No evidence of risk in humans, but there remains a remote possibility. Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women.
Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

(Clinical Pharmacology, 2016)

CONCLUSION

- The insulin products are approved for use in the management of both type 1 and 2 diabetes. The primary differences between commercially available insulin products revolve around pharmacodynamic and pharmacokinetic properties, particularly onset and duration of action.
- Individual insulin products are classified by their onset and duration of actions and may fall into one of four categories: rapid-, short-, intermediate-, or long-acting insulins. Insulin therapy is usually administered by subcutaneous injection, which allows for prolonged absorption and less pain compared to intramuscular injection. No generic insulin products are currently available.
- AFREZZA is a rapid-acting inhaled insulin. The inhalation route offers a less invasive alternative route of administration and improved convenience of administration compared with injectable rapid-acting insulins. Due to this

different route of administration, the most common adverse reactions associated with AFREZZA in clinical trials were hypoglycemia, cough, and throat pain or irritation.

- The safety and efficacy of insulin therapy in the management of diabetes are well established. Clinical trials have demonstrated that the newer rapid- and long-acting insulin analogs are as effective as regular and isophane (NPH) insulin in terms of glucose management. The data also suggests that long-acting insulin analogs are superior to NPH in decreasing HbA1c and are associated with a lower incidence of hypoglycemic events. Furthermore, head-to-head data does not consistently demonstrate the superiority of one rapid- or long-acting insulin analog over another.
- In terms of clinical outcomes, intensive glycemic control with insulin has been shown to significantly reduce the rate of onset and progression of diabetic complications when compared to standard therapy.
- Insulin is the mainstay of therapy for patients with type 1 diabetes. Current guidelines recommend that most people with type 1 diabetes be treated with multiple daily injections (three to four injections per day of basal and prandial insulin) or continuous subcutaneous insulin infusion. In addition, the guidelines suggest that most people with type 1 diabetes should use insulin analogs to reduce hypoglycemia risk. Rapid-acting inhaled insulin used before meals in type 1 diabetes patients leads to inferior HbA1c lowering when compared with insulin aspart, but with less hypoglycemia across all HbA1c target categories (ADA, 2016; Handelsman et al, 2015).
- According to current clinical guidelines regarding the management of type 2 diabetes, consideration should be given to initiating insulin therapy (with or without other agents) at the outset of treatment in newly diagnosed patients with markedly symptomatic and/or elevated blood glucose levels or HbA1c. Furthermore, due to the progressive nature of type 2 diabetes, insulin therapy is eventually indicated for many patients and should not be delayed in those who are not achieving glycemic goals with noninsulin therapies (ADA, 2016; Garber et al, 2016; Handelsman et al, 2015; Inzucchi et al, 2015).
- Guidelines suggests that an insulin treatment program be designed specifically for an individual patient, to match the supply of insulin to his or her dietary/exercise habits and prevailing glucose trends, as revealed through self-monitoring. Anticipated glucose-lowering effects should be balanced with the convenience of the regimen, in the context of an individual's specific therapy goals (ADA, 2016; Garber et al, 2016; Handelsman et al, 2015; Inzucchi et al, 2015).
- In general, no one specific insulin product among the various classifications is recommended or preferred over another. Insulin therapy must be individualized as the products within the different classifications play specific roles in achieving adequate glycemic control.

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