Afrezza (Insulin Human) Inhalation Powder

A New Inhaled Insulin for the Management Of Type-1 or Type-2 Diabetes Mellitus

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INTRODUCTION

According to the National Diabetes Statistics Report, 29.1 million people have diabetes mellitus (DM) in the U.S., or approximately 9.3% of the population.[1] DM imposes a financial burden on both patients and the health care economy, with direct and indirect costs totaling $245 billion in 2012.[1] All patients with type-1 DM (T1DM) require insulin therapy. Patients with type-2 DM (T2DM) may also become dependent on exogenous insulin as their disease progresses.[2] Approximately 6 million people in the U.S. require insulin therapy.[1] Insulin therapy allows for better glycemic control, but patients are often hesitant to make the transition to insulin because of its adverse-event profile (e.g., hypoglycemia, weight gain) and because of fear of injections.[3]

Since injectable insulin was introduced into clinical practice in 1922, other routes of administration have been explored.[4] Inhaled insulin, for example, offers the advantage of a larger area of absorption—approximately 70 to 140 square meters, or half of a tennis court.[4] In 1924, the first study of inhaled insulin was conducted in human subjects at doses 30 times higher than that of the subcutaneous (SC) route of administration.[4,5] In 2006, the Food and Drug Administration (FDA) approved the first inhaled insulin for patients with T1DM or T2DM. Exubera (Nektar Therapeutics/Pfizer) was derived from recombinant human insulin (rDNA origin), with

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a bioavailability of approximately 60%.[4,6] It was available as a spray-dried insulin powder packaged in blisters containing 1 mg or 3 mg of insulin.[6] Despite the promise of a new delivery system, Exubera did not find a profitable niche in the insulin market. Twenty-one months after its approval, the product was voluntarily withdrawn from the market because of low sales.[7] The failure of Exubera may have resulted from several factors, including the high cost of the inhaler; dosing in milligrams, which may have confused patients who had been receiving conventional insulin therapy that was measured in units; the large size of the device; and an FDA warning regarding the potential for primary lung cancer.[7,8]

Novel strategies for the administration of inhaled insulin continued to be investigated, and in July 2014 the FDA approved Afrezza (insulin human) inhalation powder (MannKind Corp./Sanofi-Aventis US) for patients with T1DM and T2DM.[9] Afrezza employs the new Gen2 inhaler (Figure 1), which is smaller and easier to use than the previously available Exubera device.[10–12]

This article reviews the pharmacol-ogy, pharmacokinetics, drug interactions, clinical efficacy, dosage and administration, safety profile, and place in therapy of Afrezza.
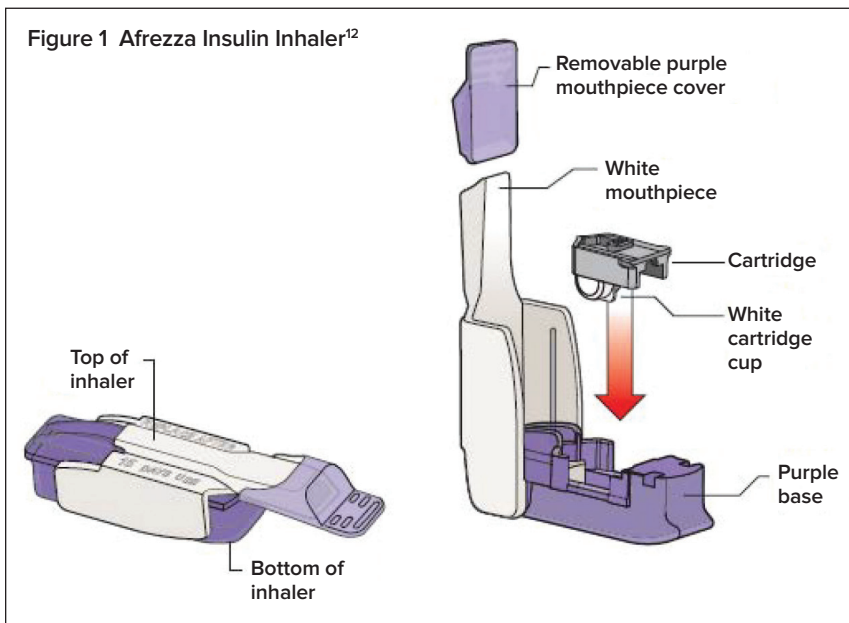
PHARMACOLOGY

Researchers have investigated insulin delivery through dermal, oral, and nasal routes, with pulmonary administration offering the greatest potential.[13] Circumventing physiological barriers, such as peptidases in the gastrointestinal tract and first-pass metabolism, the lungs offer the advantage of a vast alveolar medium for the absorption of insulin into the systemic circulation.[14,15] Technosphere technology has been used as a drug carrier for the pulmonary delivery of insulin.[14] This approach uses the excipient fumaryl diketopiperazine, which has a median diameter of approximately 2.0 mcm to 2.5 mcm, to adhere to and microencapsulate rapid-acting insulin.[12,16] The human insulin used in this technology is derived from nonpathogenic *Escherichia coli* and recombinant DNA technology,[17] and a powder suitable for inhalation is produced

Figure 1 Afrezza Insulin Inhaler[12]

Removable purple mouthpiece cover

White mouthpiece

Cartridge

White cartridge cup

Purple base

Top of inhaler

Bottom of inhaler

using a freeze-drying process.[12] When inhaled, Technosphere insulin (TI) particles dissolve in the neutral pH of the lung and enter the mucous layer of the alveoli, where they are rapidly absorbed into the circulation.[12,14] Both the inhaled TI powder and its delivery device are included under the trade name Afrezza.

PHARMACOKINETICS

An open-label, randomized, crossover study compared the pharmacokinetic profiles of three different single doses of inhaled TI (25, 50, or 100 units) with that of a single dose of SC regular human insulin (RHI; 10 international units [IUs]) in healthy, nonsmoking volunteers. Patients with T1DM or T2DM, human insulin antibodies, or tobacco or nicotine use in the past 12 months were excluded from the trial. Based on data from 11 subjects, the mean time to maximum or peak serum concentration (T_{max}) was achieved sooner in the inhaled TI groups (25 units = 12 ± 6 minutes, 50 units = 15 ± 5 minutes, and 100 units = 17 ± 5 minutes) than in the SC RHI group (134 ± 87 minutes). Moreover, higher mean maximum plasma concentrations (C_{max}) were achieved with inhaled TI (25 units = 54.6 ± 39 mcU/mL, 50 units = 105.0 ± 40 mcU/mL, and 100 units = 181.0 ± 98 mcU/mL) than with SC RHI (26.9 ± 10 mcU/mL). The relative difference in bioavailability among the different doses of inhaled TI averaged 23%. The area under the serum concentration–time curve (AUC) from 0 to 360 minutes increased linearly in the three TI dosing groups.[17]

An open-label, single-dose, parallel-controlled study evaluated the pharmacokinetic parameters of inhaled TI in nondiabetic patients with chronic obstructive pulmonary disorder (COPD). The study used a hyperinsulinemic–euglycemic clamp in 18 nondiabetic patients with mild-to-moderate COPD and in 20 nonsmoking, healthy patients without COPD. Two subjects withdrew from the trial because of severe hypoglycemia or the detection of low insulin concentrations. Thus, pharmacokinetic parameters were evaluated in a total of 36 patients (17 with COPD and 19 without COPD). Patients were excluded from the study if they were active smokers; had quit smoking within the previous six months; had been exposed to inhaled insulin within the past 30 days; or had clinically significant

pulmonary conditions. A single dose of 30 units of TI was used during the glucose clamp procedure. The mean C_{max} results were 34.7 mcU/mL and 39.5 mcU/mL in the COPD and non-COPD groups, respectively (P = 0.29). T_{max} was also similar in the two groups (15 minutes versus 12 minutes, respectively; P = 0.24). The AUC from 0 to 240 minutes was 2,037 mcU/mL/min in COPD patients and 2,279 mcU/mL/min in non-COPD patients (P = 0.47).[18]

The insulin contained in Afrezza is RHI.[12] Peak effects may be observed in approximately 53 minutes, with a duration of activity of approximately 160 to 180 minutes. The bioavailability of RHI in Afrezza is 21% to 30%. Its elimination half-life is 28 to 39 minutes, and the T_{max} is 12 to 15 minutes.[19] The fumaryl diketopiperazine excipient undergoes primarily renal elimination after systemic absorption.[19,20]

Table 1 summarizes the key pharmacokinetic characteristics of Afrezza and other rapid-acting insulin analogs.[19]

CLINICAL TRIALS

Until 2010, clinical studies of TI used the MedTone inhalation device. MannKind Corp. subsequently developed a second-generation Gen2 inhaler (also known as the Dreamboat device). The FDA requested additional clinical data on the efficacy and safety of TI using this newer inhalation device. In response, MannKind conducted two phase 3 trials (Affinity 1 and Affinity 2). In reviewing the data from studies of both inhalers, the

FDA agreed to accept the Gen2 inhaler trials as the source of pivotal efficacy data for the approval of TI.[21] The present review therefore focuses on those studies (Table 2).[22–25]

Affinity 1

The Affinity 1 trial was a 24-week, open-label, noninferiority study that compared the efficacy of TI using the Gen2 inhaler with that of an SC rapid-acting insulin analog in T1DM patients with hemoglobin A_{1c} (HbA_{1c}) ranging from 7.5% to 10%. The patients included in the study were nonsmokers who had a body mass index (BMI) of 38 kg/m^2 or less; had been stable on an insulin regimen for up to three months; and had a fasting plasma glucose (FPG) level of less than 220 mg/dL. Most baseline characteristics were similar across treatment arms, but those who received SC aspart insulin weighed less and had a diagnosis of diabetes for a longer period (P values were not provided).[22]

The patients were randomly assigned to receive either TI Gen2 therapy (n = 174) or SC insulin therapy (n = 171). Both groups were treated with basal insulin at the doses used before enrollment. To evaluate the pulmonary safety of the TI Gen2 inhaler, the study enrolled 173 patients into a third treatment arm in which TI was administered using the MedTone inhaler (discussed in the Safety Profile section, below). The study protocol allowed doses of prandial insulin to be titrated during the first 12 weeks, but the

Table 1 Key Pharmacokinetic Characteristics of Rapid-Acting Insulin Analogs[19]				
	Afrezza[a] (Insulin Human)	**Novolog[b]** (Insulin Aspart)	**Humalog[c]** (Insulin Lispro)	**Apidra[d]** (Insulin Glulisine)
Route of administration	Inhaled	Subcutaneous		
Onset of action (hours)	~1	1 to 3	0.25 to 0.50	1.6 to 2.8
Duration of action (hours)	2.5 to 3.0	3 to 5	~5	3 to 4
Half-life (minutes)	28 to 39	81	~60	42
T_{max} (minutes)	12 to 15	40 to 50	30 to 90	36 to 120
[a] MannKind Corp./Sanofi-Aventis US [b] Novo Nordisk [c] Eli Lilly [d] Sanofi-Aventis US T_{max} = time to peak plasma concentration				

Table 2 Summary of Afrezza Pivotal Trials			
	Affinity 1[22,23]	**Affinity 2**[22,24]	**Rosenstock et al.**[25]
Methods			
Design	Open-label, noninferiority	Double-blind, superiority	Open-label, noninferiority
Duration of therapy	24 weeks	24 weeks	52 weeks
TI inhaler	Gen2 and MedTone	Gen2	MedTone
Treatment arms	TI vs. RAIA	TI vs. TP	TI vs. biaspart insulin 70/30
Adjunctive therapy	Basal insulin (varied among patients)	Oral antihyperglycemic drug	Insulin glargine
Inclusion criterion: HbA_{1c} (%)	≥ 7.5 and ≤ 10	≥ 7.5 and ≤ 10	> 7 and ≤ 11
Results			
Mean percentage-point change in HbA_{1c} from baseline	• TI: −0.21 • RAIA: −0.40 • P = n/a	• TI: −0.82 • TP: −0.42 • $P < 0.001$	• TI: −0.68 • Biaspart insulin: −0.76 • P = n/a
Mean change in fasting plasma glucose	• TI: −25.3 mg/dL • RAIA: −10.2 mg/dL • P = 0.0009	• TI: −11.2 mg/dL • TP: −3.8 mg/dL • P = 0.1698	• TI: −36 mg/dL • Biaspart insulin: −18 mg/dL • P = 0.0029
Percentage of patients achieving HbA_{1c} of less than 7%	• TI: 18.3% • RAIA: 30.7% • P = 0.0158	• TI: 32.2% • TP: 15.3% • P = 0.0002	• TI: 22% • Biaspart insulin: 27% • P = 0.2793

HbA_{1c} = hemoglobin A_{1c}; n/a = not available; RAIA = rapid-acting insulin analog (subcutaneous aspart); TI = Technosphere insulin; TP = Technosphere placebo

doses were kept stable for the remaining 12 weeks.[23]

The study's primary efficacy endpoint was the percentage change in HbA_{1c} between the TI Gen2 and SC insulin aspart groups at 24 weeks. At the end of the study, the mean decrease in HbA_{1c} was greater in the insulin aspart group (–0.40%) than in the TI Gen2 group (–0.21%), with a treatment difference of 0.19 percentage points (95% confidence interval, 0.02 to 0.36). While the percent reduction in HbA_{1c} with TI was significantly less than that in the aspart arm, it met the study's criteria for noninferiority. The doses of basal insulin used were higher in the TI groups than in the aspart group. At week 24, the median daily basal insulin dose for the TI Gen2 group was 32 units (increased by 4 units from baseline), and the median daily basal insulin dose for the SC insulin aspart group was 26 units (increased by 1 unit from baseline). The percentage of patients who achieved an HbA_{1c} level of 7.0% or less at week 24 was significantly greater in the SC insulin aspart group compared with the

TI group (30.7% versus 18.3%, respectively; P = 0.0158). The proportion of subjects achieving an HbA_{1c} level of 6.5% or less at week 24 was not significantly different between the two treatment groups (12.7% versus 7.6%, respectively, P = 0.2144).[22,23]

Affinity 2

The Affinity 2 trial was a 24-week, randomized, double-blind, placebo-controlled study involving insulin-naïve T2DM patients whose disease was uncontrolled with metformin alone or with at least two oral antidiabetic agents (50% of the maximum approved dose of sulfonylurea; the maximum approved dose of dipeptidyl peptidase-4 [DPP-4] inhibitors; or the maximum tolerated dose of meglitinides or alpha-glucosidase inhibitors).[24] The patients were nonsmokers who had HbA_{1c} levels of 7.5% to 10% and a BMI of 45 kg/m^{2} or less; who had been receiving stable doses of oral antidiabetic agents for three months; who had an FPG of 270 mg/dL or less; and who did not have a history of chronic insulin use. The study

included a six-week run-in period, during which the patients remained on their prior treatment regimens, were advised to perform more frequent self-monitoring of blood glucose, and received nutritional and physical-activity counseling. Patients who were able to achieve an HbA_{1c} of less than 7.5% during the run-in period were excluded from the study.[22,24]

After the six-week run-in period, eligible patients were randomly assigned to receive either TI (n = 164) or Technosphere placebo (TP; n = 164). Both groups used the Gen2 inhaler device. The patients participated in a 12-week prandial-insulin titration phase, which was followed by a 12-week period of stable dosing. Throughout the trial, patients with persistent hyperglycemia received open-label rescue therapy in addition to their study treatment. The patients who entered the study while receiving metformin were given glimepiride as a rescue medication, and those who entered the trial while receiving two or more oral agents were given SC insulin glargine as needed.[22]

The TI arm demonstrated a significantly greater reduction in HbA_{1c} at week 24 compared with the TP arm, with a difference of –0.40 percentage points ($P < 0.001$). A larger percentage of patients in the TI group achieved the desired HbA_{1c} goal of less than 7% compared with the TP group (37.7% versus 19.0%, respectively; P = 0.0005). The mean change in FPG levels was not significantly different between the two groups.[24] During the 24-week study period, the patients receiving TI experienced a mean 0.49-kg weight gain, whereas those in the placebo group lost an average of 1.13 kg; the between-group treatment difference was 1.62 kg ($P < 0.0001$).[22]

Rosenstock et al.

Rosenstock and colleagues compared TI with premixed insulin in a 52-week open-label trial involving 677 adults with T2DM. All of the subjects were poorly controlled on insulin therapy (HbA_{1c} = 7% to 11%) with or without oral antidiabetic agents. They were randomly assigned to receive TI plus SC insulin glargine (n = 334) or SC premixed biaspart insulin (70% insulin aspart protamine suspension and 30% insulin aspart; n = 343). Those in the TI-plus-glargine arm received half of their daily insulin dose as glargine and the other half as TI; TI was admin-

istered 90 seconds before each meal. Patients in the biaspart group injected insulin 15 minutes before breakfast and dinner. Both treatment groups were allowed to continue taking metformin and thiazolidinediones.[25]

The study's primary efficacy endpoint was the change in HbA_{1c} at 52 weeks. Secondary endpoints at 52 weeks included the change from baseline in the plasma glucose concentration after a standardized liquid meal; the proportion of patients achieving an HbA_{1c} level of 7.0% or less; the change in FPG; the one-hour and two-hour postprandial glucose levels; and the change in weight. The mean changes in HbA_{1c} were similar between the two treatment groups and met the study's criteria for noninferiority. The mean change from baseline in FPG levels at week 52 was significantly higher in the TI group compared with the insulin biaspart group (2.0 mmol/L [36 mg/dL] versus 1.0 mmol/L [18 mg/dL]; $P = 0.0029$). Patients in the TI group had significantly lower one-hour postprandial glucose levels compared with those in the biaspart group (9.5 mmol/L [171.2 mg/dL] versus 11.6 mmol/L [209.0 mg/dL]; $P = 0.0001$). The proportion of patients achieving HbA_{1c} of 7% or less and the two-hour postprandial glucose levels were similar between the two treatment groups. Weight gain was significantly lower in the TI group compared with the biaspart group (0.9 kg versus 2.5 mg, respectively; $P = 0.0002$).[25]

SAFETY PROFILE
Hypoglycemia

As with other insulin products, the most common adverse event associated with Afrezza is hypoglycemia.[12] A 12-week, double-blind, placebo-controlled, randomized, parallel-group study compared the efficacy, safety, and tolerability of TI with that of TP in insulin-naïve patients with T2DM whose disease was suboptimally controlled with oral antidiabetic agents. There was no significant difference in the rates of hypoglycemic events between the TI (n = 26) and TP (n = 22) groups at the end of the study (43% versus 36%, respectively; $P = 0.321$).[26] In the 52-week trial by Rosenstock and colleagues, the rate of mild-to-moderate hypoglycemia was lower in patients treated with TI plus SC glargine (n = 155) compared with those receiving SC premixed insulin ana-

log (n = 228) (48% versus 69%, respectively). The rate of severe hypoglycemia was also lower with TI plus SC glargine (n = 14) than with SC premixed insulin analog (n = 33) (4% versus 10%, respectively).[25] In the Affinity 2 trial, however, the rate of hypoglycemia (of any severity) was significantly higher in the TI group than in the TP group (68% versus 31%, respectively; $P < 0.0001$).[22,24]

Pulmonary Function

Raskin and colleagues conducted a prospective, open-label study to evaluate pulmonary function during two years of treatment with Afrezza in patients with T1DM or T2DM. Nondiabetic patients were also included in the study (about 10% of the total cohort). Patients were excluded if they had significant pulmonary, cardiac, hepatic, or renal disease; significant chest radiograph abnormalities; a history of malignancy within the last five years; severe complications of uncontrolled diabetes; or current illicit drug or alcohol use. In the intent-to-treat population (n = 1,699), 730 diabetes patients received TI; 824 diabetes patients received usual diabetes care; and 145 patients did not have diabetes. During the two-year study, all of the patient cohorts experienced a decline in pulmonary function from baseline. TI was noninferior to usual care for the mean change in the forced expiratory volume in one second (FEV_1) from baseline to month 24 (0.037 L). The percentages of patients with a decrease of 15% or more in FEV_1 were 5.6% (42 of 730) and 3.3% (27 of 824) in the TI and usual-care groups, respectively.[27]

In another study, 12 weeks of treatment with TI or TP resulted in mean changes from baseline in FEV_1 of –0.04 L ($P = 0.143$) and –0.01 L ($P = 0.74$), respectively.[26] FEV_1 changes were also reported in a head-to-head comparison of TI administered with the Gen2 inhaler and TI administered with the MedTone inhaler. The authors reported no statistically significant difference between the two treatment groups in terms of the mean change from baseline in FEV_1 (–0.07 for Gen2 and –0.08 for MedTone; $P = 0.5364$).[12,23]

Cough

Cough is commonly associated with the use of Afrezza. In the prospective, open-label study by Raskin et al., 28%

(257 of 923) of the patients treated with TI experienced cough compared with 4% (42 of 949) of those who received usual diabetes care and 3% of those who did not have diabetes.[27] Similarly, in the 52-week study by Rosenstock and colleagues, 33% (106 of 323) of patients who received TI in addition to SC glargine insulin experienced cough compared with 6% (20 of 331) of those treated with SC premixed insulin analog. Cough often resulted in the discontinuation of therapy.[25]

Other Adverse Events

Other adverse outcomes reported during treatment with Afrezza include diabetic ketoacidosis (DKA), lung cancer, hypokalemia, fluid retention, and heart failure when combined with thiazolidinediones.[12] The most common Afrezza-related adverse events are listed in Table 3.[12,19]

WARNINGS AND PRECAUTIONS

Afrezza is contraindicated in patients with chronic lung disease because of the potential for acute bronchospasm. Patients should be evaluated for underlying lung disease, such as asthma or COPD, before treatment is initiated. In addition, pulmonary function should be assessed at baseline, after the first six months, and annually thereafter.[12]

Consideration should be given to discontinuing therapy in patients with a decline of 20% or more from baseline in

Table 3 Most-Common Adverse Events Associated With Afrezza in Clinical Trials[12,19]

Adverse Event	Rate
Hypoglycemia	67%
Acute bronchospasm in asthmatics	29%
Cough	26% to 29%
Productive cough	2%
Throat pain or irritation	6%
15% or more decrease in FEV_1	6%
Headache	5%
Reduced lung function	3%
Bronchitis	3%
Fatigue	2%
Urinary-tract infection	2%
FEV_1 = forced expiratory volume in one second	

FEV_1. Frequent monitoring is indicated in diabetes patients with pulmonary symptoms, such as wheezing, cough, or bronchospasm.[12]

Afrezza therapy is contraindicated in patients with a history of hypersensitivity to RHI or to excipients of Afrezza. The product should not be used during episodes of hypoglycemia, and it is not recommended for patients who smoke or for the management of DKA.[12]

DOSAGE AND ADMINISTRATION

Before patients begin treatment with Afrezza, clinicians must perform a thorough medical history, physical examination, and spirometry testing (FEV_1) to rule out the presence of chronic lung diseases, such as asthma or COPD. Afrezza is administered to adults (18 years of age or older) at the beginning of a meal using a single inhalation per cartridge. Initial dosing recommendations are as follows:[12]

- In insulin-naïve patients, initiate 4 units of TI at each meal.
- In patients receiving SC prandial insulin, use the dose-conversion table (Table 4) to determine the appropriate TI dose at each meal.
- In patients receiving SC premixed insulin, determine the total daily dose of premixed insulin and divide half of this dose equally into three meals a day. The estimated SC meal-time dose should then be converted to an appropriate TI dose using Table 4. The remaining half of the total daily insulin dose should be given as a basal insulin dose.

Subsequent TI doses are adjusted according to the patient's overall glycemic control, metabolic requirements, and blood-glucose monitoring results. Glycemic control should be monitored closely in patients requiring high doses of Afrezza. SC prandial insulin should be considered in patients who require high doses of TI and are not achieving adequate glycemic control.[12]

Patients receiving Afrezza therapy must be instructed on how to properly use the product (e.g., select the appropriate cartridge, remove the cartridge, load the cartridge into the inhaler, inhale the product, and store the product).[12]

USE IN SPECIAL POPULATIONS

Afrezza is a Pregnancy Category C drug. It should not be used in pregnant women unless the potential benefits of treatment clearly outweigh the risks. Afrezza has not been studied in lactating mothers. In view of the high likelihood that insulin and carrier molecules may be excreted into human milk, clinicians must decide whether Afrezza or nursing should be suspended.[12]

No differences in the safety and efficacy of Afrezza have been observed between patients older than 65 years of age and younger patients. The use of Afrezza is limited to adults because it has not been studied in patients younger than 18 years of age. The effects of renal or hepatic impairment on the pharmacokinetics of Afrezza have not been studied.[12]

DRUG–DRUG INTERACTIONS

Certain drugs may increase the risk of hypoglycemia associated with Afrezza; may increase or decrease the blood-glucose-lowering affect of Afrezza; or may affect the signs and symptoms of hypoglycemia (Table 5). Dosing adjustments and increased glucose monitoring may be warranted when Afrezza is coadministered with these agents.[12]

AVAILABILITY AND COST

Afrezza powder for inhalation is available as single-use 4-unit, 8-unit, and 12-unit cartridges. Each blister strip contains three cartridges, and each card contains five blister strips. Each strip is perforated, allowing patients to remove a single strip of three cartridges at a time. There are 30 cartridges per foil package. Patients requiring more than 12 units of

Table 4 Afrezza Mealtime-Dose Conversion Table[12]

Injected Insulin Dose	Inhaled Afrezza Dose
Up to 4 units	4 units
5 to 8 units	8 units
9 to 12 units	12 units
13 to 16 units	16 units
17 to 20 units	20 units
21 to 24 units	24 units

Table 5 Potential Drug–Drug Interactions With Afrezza[12]

Outcomes	Examples
Drugs that may increase risk of hypoglycemia	• Antidiabetic drugs • Angiotensin-converting enzyme inhibitors • Angiotensin II receptor blockers • Fibrates • Fluoxetine • Monoamine oxidase inhibitors • Pentoxifylline • Salicylates • Sulfonamide antibiotics
Drugs that may decrease blood-glucose-lowering effect of Afrezza	• Atypical antipsychotics • Corticosteroids • Diuretics • Glucagon • Isoniazid • Niacin • Oral contraceptives • Protease inhibitors • Sympathomimetic agents (e.g., albuterol)
Drugs that may increase or decrease blood-glucose-lowering effect of Afrezza	• Alcohol • Beta blockers • Clonidine • Lithium salts • Pentamidine
Drugs that may affect signs and symptoms of hypoglycemia	• Beta blockers • Clonidine • Guanethidine • Reserpine

Table 6 Afrezza Configurations and Costs[12,28]			
National Drug Code	**Number of Cartridges**	**Product Configuration**	**Average Wholesale Price***
0024-5874-90	90	90 4-unit cartridges and two inhalers	$271
0024-5884-63	90	60 4-unit cartridges; 30 8-unit cartridges; and two inhalers	$303
0024-5882-36	90	30 4-unit cartridges; 60 8-unit cartridges; and two inhalers	$334
0024-5894-63	90	60 8-unit cartridges; 30 12-unit cartridges; and two inhalers	$380
* As of October 15, 2015 (rounded to the nearest dollar).			

Afrezza must use a combination of cartridges to achieve the target dose. Several configurations of Afrezza are available at average wholesale prices ranging from approximately $271 for 90 4-unit cartridges plus two inhalers to approximately $380 for 60 8-unit cartridges, 30 12-unit cartridges, and two inhalers (Table 6).[12]

STORAGE AND PRODUCT STABILITY
Insulin Cartridges
Sealed or unopened foil packages of Afrezza may be stored in a refrigerator at 36° F to 46° F (2° C to 8° C) until the expiration date. If a sealed foil package is not refrigerated, it must be used within 10 days. Once a foil package has been opened at room temperature, sealed blister cards and strips must be used within 10 days, and opened strips must be used within three days. Before use, the cartridges should be at room temperature for 10 minutes.[12]

Inhaler Device
The Afrezza inhaler should be stored at 36° F to 77° F (2° C to 25° C). Excursions are permitted. The inhaler should be at room temperature for 10 minutes before use. The same inhaler should be used to take the different cartridge strengths. The inhaler should be replaced every 15 days to maintain drug delivery.[12]

P&T COMMITTEE CONSIDERATIONS
Advantages
Afrezza inhalation powder is in the same therapeutic category as SC rapid-acting insulin analogs, such as Novolog (insulin aspart, Novo Nordisk), Humalog (insulin lispro, Eli Lilly), and Apidra (insulin glulisine, Sanofi-Aventis US). Certain differences in its pharmacokinetic profile, however, may be advantageous (see Table 1). For example, Afrezza has a reduced duration of action of two to three hours (compared with up to five hours with the rapid-acting insulin analogs) and a shorter half-life of 28 to 39 minutes (compared with up to 1.35 hours with the other products); this may lessen the potential for hypoglycemic events. Afrezza also offers a faster T_{max} of 12 to 15 minutes (compared with 30 minutes to two hours with the rapid-acting analogs).[12,19]

With respect to efficacy, pivotal clinical trials have established the ability of inhaled TI to improve glycemic variables, such as HbA$_{1c}$ and FPG, in patients with T1DM or T2DM (see Table 2).[22–25] For patients who are reluctant to use SC insulin products because of a fear of injections, Afrezza offers a noninvasive alternative. Moreover, the compact, hand-held Afrezza inhaler is relatively easy to use.[12]

Limitations
Considering the safety data for Afrezza presented previously, there are concerns of reduced pulmonary function and FEV$_1$, warranting patients to be pre-screened with a medical history, physical examination, and spirometry prior to initiation of therapy. Whether or not a patient develops pulmonary symptoms, spirometry testing needs to be performed periodically. Further studies are needed to evaluate the impact of Afrezza on pulmonary function beyond two years and the reversibility of FEV$_1$ changes upon discontinuation. Afrezza is, therefore, contraindicated in patients with chronic lung diseases such as asthma and COPD.[12]

Afrezza has not been studied in pediatric patients with diabetes mellitus and is approved for use in adults only. This product is not a substitute for long-acting insulin and must be used in combination with a long-acting insulin when managing patients with T1DM. Afrezza is also not recommended for the treatment of diabetic ketoacidosis, nor is it recommended for patients who smoke or recently stopped smoking.[12]

Treatment with Afrezza may carry a risk of lung cancer, although the data are limited. Two cases of lung cancer (in 2,750 patient-years of exposure) were observed in clinical trials of Afrezza, whereas no cases were observed with comparators (in 2,169 patient-years of exposure). In both cases, the subjects had a history of heavy tobacco use. Two additional cases of squamous-cell lung cancer were reported in nonsmokers exposed to Afrezza.[12]

Unlike SC rapid-acting insulin vials or pens, which may have in-use expiration periods of up to one month, Afrezza insulin cartridges must be used within 10 days after they have been removed from refrigeration (or within three days if the blister packaging has been opened).[12] This is an important counseling point for patients who are accustomed to SC insulin products.

To achieve Afrezza dosing targets, combinations of the different cartridge configurations (4 units, 8 units, and 12 units) are required for doses beyond 12 units (see Tables 4 and 6). Patients who require higher doses and are not achieving the desired glycemic effects will need to be evaluated for injectable insulin therapy as an alternative.[12,19]

It is difficult to compare the cost-effectiveness of Afrezza with that of current SC insulin products (multidose pens or vials) because of the variety of doses required by diabetes patients and the respective day's supply per product. See Table 6 for a list of the product configurations and average wholesale prices for Afrezza.

CONCLUSION
Afrezza is a new dry powder/inhaler system for the delivery of Technosphere insulin to patients with T1DM or T2DM. It provides a promising, noninvasive alternative to SC insulin analogs in this population (Table 7).

Table 7 Key Points Regarding Afrezza Inhalation Powder[12]

- Afrezza is an inhaled rapid-acting insulin.
- Perform thorough medical history, physical examination, and spirometry testing to rule out potential chronic lung diseases before initiating therapy.
- Assess pulmonary function (e.g., forced expiratory volume in one second) after six months of therapy and annually thereafter.
- May be used in adult patients with type-1 or type-2 diabetes mellitus.
- Must be used in combination with a long-acting insulin in type-1 diabetes mellitus patients.
- Not recommended for patients who smoke or for management of diabetic ketoacidosis.
- Contraindicated in patients with chronic lung diseases (e.g., asthma, chronic obstructive pulmonary disease).
- Most common adverse events include hypoglycemia and cough.
- A dose-conversion table is available for patients transitioning from subcutaneous prandial or premixed insulin (see Table 4).
- Screen patients for potential drug–drug interactions (see Table 5).
- Insulin cartridges are available in three strengths: 4 units, 8 units, and 12 units.
- Consider the patient's required mealtime dose when selecting the product configuration (see Table 6).
- Each cartridge is for single use only.
- Storage and product-expiration recommendations depend on whether the product is not in use versus in use; refrigerated versus room temperature; sealed versus opened (see "Storage and Product Stability" section).
- Cartridges and inhaler must be at room temperature for 10 minutes before use.
- After the cartridge has been inserted, the inhaler should be kept with the mouthpiece pointing upwards. Loss of the drug powder can occur if the inhaler is turned upside down, is held with the mouthpiece pointing down, or is shaken or dropped.

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