

A second-generation inhaled insulin for diabetes mellitus

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The Food and Drug Administration (FDA) recently approved a new inhaled insulin product: Afrezza (insulin human) Inhalation Powder, also known as Technosphere Insulin. Afrezza (MannKind Corporation, Valencia, CA) is a novel ultrarapid-acting insulin formulation recommended for use before meals for the management of type 1 and type 2 diabetes mellitus.

Insulin is a 5700 molecular weight protein that has been a leading candidate for noninvasive delivery since its initial use by injection in 1921 for the management of diabetes.^{1,2} However, noninvasive delivery of insulin has a history of failure despite much research effort, particularly with oral and nasal approaches, because the nasal and gastrointestinal epithelia are functionally impermeable to insulin.^{3,4} The lungs, which are naturally permeable to some proteins, have become a target for insulin delivery. In the early 2000s, 10 pharmaceutical companies were developing, individually or collaboratively, seven different inhaled insulin products.⁵ Pfizer's Exubera was the first inhaled insulin product

Purpose. The pharmacologic properties of a recently approved inhaled insulin product, its unique delivery system, and the results of clinical safety and efficacy trials are reviewed.

Summary. Afrezza (also called Technosphere Insulin, MannKind Corporation, Valencia, CA) is a novel ultrarapid-acting insulin formulation indicated for use in improving glycemic control in selected patients with type 1 or type 2 diabetes mellitus. Afrezza is not intended as a substitute for traditional basal therapy with injectable long-acting insulin but may be used to provide prandial insulin coverage; it must be used in combination with long-acting insulin in patients with type 1 diabetes. Administered before meals using a dry-powder inhalation device, Afrezza is formulated with a novel excipient (fumaryl diketopiperazine) that dissolves instantly in lung fluid and

releases recombinant human insulin for absorption. In clinical trials, rates of hypoglycemia in Afrezza-treated patients were significantly lower than rates reported in comparator groups receiving injectable insulin products. The most commonly reported adverse effect of Afrezza is coughing, which tends to occur shortly after inhalation and is typically mild. Afrezza is not recommended for use in patients who smoke (or have recently stopped smoking) and those with a chronic lung disease such as asthma or chronic obstructive pulmonary disease. Afrezza is not recommended for the treatment of diabetic ketoacidosis.

Conclusion. Afrezza is a safe and effective treatment for selected adults with type 1 or type 2 diabetes, potentially providing an alternative to injectable insulin for prandial blood glucose control.

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to be marketed (FDA approved its labeling in January 2006).

First-generation inhaled insulin

Despite the long-term benefits for patients reluctant to take multiple insulin injections throughout the day for blood glucose control, Pfizer

announced the decision to withdraw Exubera from the market after only 13 months.⁶ From the product's initial market introduction, the health-care community and patients were not very supportive of the product because of its complicated large delivery device and high cost. These

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two factors resulted in very disappointing sales for Pfizer, especially since the initial sales prediction was \$2 billion per year. In April 2008, Pfizer released a warning disclosing an increased risk of lung cancer among patients who were treated with inhaled insulin.⁷ The warning was issued as a consequence of a clinical trial in which 6 out of 4740 patients treated with inhaled insulin developed lung cancer; only 1 of the 4292 patients not treated developed lung cancer.⁷ A closer look at the clinical trial study design revealed that the group treated with inhaled insulin included regular smokers, who were enrolled with the goal of studying the effect of smoking on the safety and efficacy of inhaled insulin. After the warning from Pfizer and its huge financial loss with Exubera, all other companies except MannKind Corporation discontinued further development of inhaled insulin products.

Comparison of Afrezza and Exubera

Although their excipients are different, Afrezza and Exubera have comparable particle sizes that are within the respirable range.⁸⁻¹⁰ One of the most notable differences between these two products is their respective delivery devices. MannKind developed a patient-friendly device called Dreamboat. The inhaler for Afrezza is easier and quicker to use (i.e., it does not require inhalation after “standing cloud formation,” as with Exubera), and its smaller size allows for more discreet usage.¹¹ Insulin doses contained in Afrezza cartridges are labeled in International Unit equivalents to doses of subcutaneously administered insulin to help ease the transition from the injectable to the inhaled product; Exubera dosages were labeled in milligrams, necessitating an extra dose-conversion step in order to determine the equivalent units of insulin.

Formulation

Afrezza is a microparticle formulation. The proprietary name of the particle is Technosphere, and the proprietary name of the formulation is Technosphere Insulin. The main excipient in Afrezza is a novel non-toxic proprietary compound called fumaryl diketopiperazine (FDKP). FDKP is water soluble at neutral to basic pH, and FDKP molecules self-assemble under a controlled, mildly acidic pH environment into particles with a high internal porosity. The particles are often described as “microcrystalline plates” that associate to form the microparticles.¹² The final formulation is a crystalline dry powder of FDKP and 18% insulin (rDNA origin) with residual amounts of water and polysorbate 80. These 2- to 3- μm particles (average diameter, 2.5 μm) are ideally sized to reach all areas of the lung. In the final powder, at least 90% of the particles are within the respirable range for deep lung penetration (i.e., 1–5 μm). FDKP is a safe delivery vehicle, with more than 95% of intravenously administered FDKP excreted intact through the renal system (more than 90% within the first 8 hours). FDKP has no oral bioavailability.¹² When inhaled, the formulation rapidly dissolves at the physiological pH within the lungs, whereupon insulin is rapidly absorbed into the systemic circulation; the emitted dose is 65% of the initial powder within the cartridge. Of the emitted dose, 30% is deposited in the oropharynx, 11% is swallowed, and 59% is delivered to the lungs.¹³ Both insulin and FDKP are nearly completely cleared from the lungs within 12 hours of inhalation.¹⁴

Delivery device

Afrezza consists of Technosphere Insulin prefilled cartridges and the reusable breath-powered Dreamboat plastic inhaler (Figure 1). It is recommended that the Dreamboat device be discarded and replaced every 15 days. The small device does not re-

quire cleaning between uses. Over 5000 devices were dispensed during clinical trials, and 88% of patients responded favorably to the ease of use of the device.¹⁵ The prefilled cartridges are labeled as containing four units (blue) and eight units (green), have a shelf-life of 24 months when stored under refrigeration, and should not be stored for more than 10 days at room temperature.¹⁶

Clinical trials

The safety and efficacy of Afrezza have been studied in a total of approximately 6500 healthy adult volunteers and patients with type 1 and type 2 diabetes.¹⁵ These individuals were exposed to Afrezza for at least 2 weeks. Four Phase III clinical trials to evaluate Afrezza's efficacy included a total of 883 patients with type 1 diabetes who were on a basal-bolus insulin regimen and a total of 971 patients with type 2 diabetes who were either insulin naive, with inadequate glycemic control on oral antidiabetic drugs, or had received prior insulin therapy.¹⁵ All of these trials were randomized controlled multicenter trials involving 24 or 52 weeks of treatment. All four trials compared Afrezza with standard-of-care comparator agents or placebo use. All comparator trials had an open-label design, and the placebo-controlled trial had a double-blind design.

The pharmacokinetic properties of Afrezza were evaluated extensively in 31 trials involving healthy volunteers and patients with type 1 or type 2 diabetes.¹⁵ Selected pharmacokinetic and pharmacodynamic characteristics of Afrezza relative to those of rapid-acting insulin analogs and recombinant human insulin are summarized in Table 1. Plasma concentration–time profiles after Afrezza administration in doses ranging from 10 to 80 units were comparable to the observed profile after subcutaneous administration of 15 units of recombinant human insulin in a pharmacokinetic trial.¹⁵

In this trial, the time to maximum concentration ($t_{\max}$) after administration of inhaled insulin was 12–15 minutes, in contrast to a $t_{\max}$ of 120 minutes after subcutaneous injection of recombinant human insulin. Insulin concentrations returned to baseline within three hours of inhalation, compared with an interval of over six hours after subcutaneous delivery of recombinant human insulin. The observed $t_{\max}$ was consistent throughout the trial and independent of the given dose.

The relative bioavailability of inhaled versus subcutaneously administered insulin was also evaluated in this pharmacokinetic trial.¹⁵ The median relative bioavailability of inhaled insulin was 24%, with a range of 20–27%. Relative to subcutaneous insulin delivery, use of inhaled insulin resulted in a more rapid increase in serum insulin concentrations (within 15 minutes of delivery) and a more rapid onset of action (within approximately 25–30 minutes), which better mimic the normal physiological response to glucose absorption after meals.^{15,17} In fact, the rapid onset of action of inhaled insulin is comparable to that of intravenously administered insulin, making it the first formulation whose effects mimic physiological early insulin release.¹⁸ The relative bioavailability

of Afrezza was further evaluated in a second trial¹⁵; after the administration of 20 units of inhaled Afrezza, the observed bioavailability relative to that of 8 units of a subcutaneously delivered rapid-acting insulin analog was 33%. Overall, the results of pharmacokinetic studies showed a bioavailability of about 30% for Afrezza in comparison with subcutaneously administered regular human insulin (recombinant human insulin) and rapid-acting insulin analogs.

Type 1 diabetes

Two Phase III clinical trials (24 and 52 weeks) were conducted to study the safety and efficacy of Afrezza in the treatment of type 1 diabetes.¹⁵ In both trials, the median age of participants was 36 years (range, 18–76 years), and the median body mass index (BMI) was 25 kg/m²; diabetes duration ranged from 1 to 64 years. The study participants had pretreatment glycosylated hemoglobin (HbA_{1c}) values of 7.5–10.0% (in the

Figure 1. Dreamboat reusable inhaler device (left) and Afrezza cartridges containing four units (blue) and eight units (green) of Technosphere Insulin. Photo courtesy of MannKind Corporation, Valencia, CA.



Table 1.

Comparison of Inhaled Insulin, Subcutaneous Rapid-Acting Insulin Analogs, and Subcutaneous Regular Human Insulin

Product	Time to Onset of Effect (min)	Time to Peak Plasma Concentration (min)	Time to Maximum Effect (hr)	Duration of Action (hr)	Recommended Time of Administration
Inhaled insulin (Afrezza) ¹⁵	15–30	12–15	~0.9	3	At the beginning of a meal
Insulin aspart (NovoLog) ^{17,18}	12–18	40–50	1–3	3–5	Immediately (5–10 min) before a meal
Insulin lispro (Humalog) ^{18,19}	15–30	30–90	0.5–2.5	2–4	15 min before or immediately after a meal
Insulin glulisine (Apidra) ^{18,20}	12–30	40–120	1.6–2.8	3–4	Within 15 min before or within 20 min after starting a meal
Regular insulin (Humulin, Novolin) ^{18,21,22}	~30	60–239	2.5–5.0	3–14	Approximately 30 min before a meal

24-week trial) and 7–11% (in the 52-week trial) and baseline fasting plasma glucose (FPG) concentrations of ≤ 180 mg/dL. Both of these trials were active-control trials conducted with the goal of demonstrating the non-inferiority of Afrezza to comparator insulin therapies. A standard basal insulin regimen (isophane insulin human, insulin glargine, or insulin detemir) was used in the 24-week trial, and insulin glargine was used in the 52-week trial. In the 24-week trial, patients in each treatment group received basal insulin and were randomly assigned to receive either prandial Afrezza therapy or prandial subcutaneous injections of the rapid-acting analog insulin aspart; in the 52-week trial, patients in each treatment group received insulin glargine and were randomly assigned to receive either prandial Afrezza or prandial insulin aspart. The primary efficacy endpoint in both trials was the mean change from baseline in HbA_{1c} concentration, and the secondary efficacy endpoint was the mean change in FPG concentration from baseline to the end of the trial period. Statistical analysis of the efficacy data was performed using mixed-model repeated measures in the 24-week trial, and analysis of covariance (ANCOVA) was used in the 52-week trial. In both trials, the prespecified noninferiority margin was 0.4%; thus, for demonstration of noninferiority, the upper limit of the 95% confidence interval (CI) for the between-group difference had to be below that threshold value. In the 24-week trial, HbA_{1c} reductions from the mean baseline value of 7.9% were, on average, comparable between the Afrezza group and the comparator group, with a mean change of -0.21% (i.e., -0.21 percentage point) (95% CI, -0.33% to -0.09%) versus a mean change of -0.40% (95% CI, -0.52% to -0.28%). In the 52-week trial, average HbA_{1c} reductions from the mean baseline of 8.4% were also comparable in the Afrezza and

comparator groups (mean change, -0.13% [95% CI, -0.24% to -0.01%] versus -0.37% [95% CI, -0.49% to -0.25%]). In the 24-week trial, the mean changes from baseline in FPG levels were -25.27 mg/dL in the Afrezza group and -10.15 mg/mL in the comparator group. In the 52-week trial, the mean FPG changes from baseline in the Afrezza and comparator groups were -35.5 and -20.6 mg/mL, respectively.

Type 2 diabetes

The safety and efficacy of Afrezza in the treatment of type 2 diabetes were studied in two Phase III clinical trials lasting 24 and 52 weeks.¹⁵ The 24-week study was a placebo-controlled superiority trial, while the longer study was a comparator trial. The participants in the 24-week trial were 26–75 years of age, with diabetes durations ranging from 2 to 12 years.²⁵ A total of 328 participants were enrolled in this trial; all were insulin naive, had been previously treated with either metformin monotherapy or a combination of two or more oral antidiabetic drugs, and were on a stable regimen for at least three months before enrollment. All participants had a BMI of <45 kg/m² and an HbA_{1c} value of 7.5–10.0%. The patients were randomly assigned to receive cartridges containing either 10 units of inhaled insulin (assumed bioavailability, 26%) or non-insulin-containing Technosphere powder (as a placebo) for mealtime administration. The primary efficacy endpoint was the change in HbA_{1c} from baseline to study end (24 weeks). The secondary efficacy endpoints were HbA_{1c} goal attainment and changes from baseline in FPG and weight. Statistical analyses of primary and secondary efficacy endpoints were performed using a one-sided, one-sample *t* test for within-group variations and a one-sided, two-sample *t* test for between-group variations. At randomization, the adjusted mean baseline HbA_{1c} levels were compa-

rable in the two groups (8.25% in the Afrezza group and 8.27% in the placebo group). The primary efficacy comparison showed that Afrezza was superior to the placebo in lowering the mean HbA_{1c} concentration, with a between-group difference of -0.40% (95% CI, -0.57% to -0.23% ; $p < 0.001$). Comparative data on the secondary efficacy endpoints showed that Afrezza-treated patients were more likely than placebo recipients to reach one or both of the prespecified HbA_{1c} goals. Almost 38% of patients in the Afrezza group achieved an HbA_{1c} of $\leq 7\%$, and four times as many Afrezza-treated patients as placebo users had an HbA_{1c} value below 6.5% by the end of the 24-week trial.¹⁵ A modest weight gain (0.49 kg) was reported in the Afrezza group over the 24-week study duration, whereas the mean weight change in the placebo group was -1.13 kg (95% CI, -2.34 to -0.90 kg). A greater mean FPG reduction was reported in the Afrezza group (-11.20 mg/dL) compared with the placebo group (-3.78 mg/dL) at the end of the trial.

The second Phase III trial of Afrezza in patients with type 2 diabetes was a 52-week comparator trial involving participants previously treated with insulin.¹⁵ This trial compared the effects of Afrezza plus subcutaneous basal insulin with those of subcutaneous injections of a premixed biphasic rapid-acting (BPR) insulin analog composed of 70% insulin aspart protamine suspension and 30% insulin aspart (“BPR 70/30”) given twice daily. The ages of the participants were between 19 and 79 years; the duration of diabetes ranged from 1 to 52 years. A total of 618 participants were enrolled in this trial. Similar to the 24-week trial, participants were included if they had a BMI greater than 45 kg/m² and an HbA_{1c} of 7.0–11.0%. The treatment group participants were randomly assigned to receive either prandial Afrezza plus subcutaneous basal insulin (insulin glargine) or

prandial BPR 70/30. The primary efficacy endpoint was the change in HbA_{1c} from baseline to study end (52 weeks). The secondary efficacy endpoints were HbA_{1c} goal attainment, FPG change, and weight change. Statistical analyses of primary and secondary efficacy endpoints were performed using ANCOVA. At randomization, the adjusted mean HbA_{1c} levels were comparable in the two groups. Analysis of data on the primary efficacy endpoints at 52 weeks showed that Afrezza was noninferior to BPR 70/30 with regard to the mean HbA_{1c} change from baseline, with a between-group difference of 0.12% (95% CI, -0.05% to 0.29%). In the Afrezza group, the baseline HbA_{1c} value was 8.69%, and the mean change was -0.59%; in the BPR 70/30 group, the baseline HbA_{1c} was 8.68%, and the mean change was -0.71%. Comparative data on the secondary efficacy endpoints showed that approximately the same percentages of patients in both groups reached the HbA_{1c} goal of ≤7% (22.1% in the Afrezza group and 26.8% in the BPR 70/30 group). At the end of the 52-week trial, a greater mean FPG change was observed in the Afrezza group (-26.7 mg/dL versus -12.9 mg/dL in the BPR 70/30 group). Significantly less weight gain was reported in the Afrezza group (0.9 kg; 95% CI, 0.3–1.5 kg) compared with the BPR 70/30 group (2.5 kg; 95% CI, 1.9–3.0 kg).

Adverse effects

Cough. In a 52-week trial of Afrezza involving patients with type 2 diabetes, the most common treatment-emergent adverse effect was cough.⁹ Approximately 32% of patients administered Afrezza experienced cough, which was generally mild and dry, and the number of events declined over time. The events of cough rarely led to trial discontinuation. Cough is an anticipated adverse effect of any inhaled dry-powder formulation.^{26,27}

Hypoglycemia. Managing hypoglycemia is always a challenge when managing antidiabetic medication therapy that includes insulin.²⁸ The rate of hypoglycemia in patients with type 2 diabetes treated with Afrezza was significantly lower than in those on an insulin comparator. The results of Phase III trials clearly showed a reduction of severe hypoglycemia after Afrezza administration compared with insulin aspart treatment (31% versus 49%).⁹ A similar observation was also reported in patients with type 1 diabetes treated with Afrezza compared with lispro insulin. Afrezza significantly reduced rates of mild-to-moderate hypoglycemia events (5.97 events per patient-month for the Afrezza group versus 8.01 events per patient-month for the comparator group).²⁹

Diabetic ketoacidosis. Diabetic ketoacidosis (DKA) is a potentially life-threatening complication resulting from a shortage of insulin in patients with diabetes. During the 52-week type 1 diabetes trial, a slightly higher rate of DKA events was reported in patients with type 1 diabetes who were treated with Afrezza, as compared with the comparator group.¹⁵ However, most DKA events were related to concurrent infection, treatment interruption, or reduced dosing; these events were later deemed to be manageable through investigative-site educational initiatives. The overall rates of DKA were 0.46% in the Afrezza group and 0.23% in the comparator group.¹⁵

Safety

Antiinsulin antibody development. Development of antiinsulin antibodies is a concern during insulin therapy, and it occurs to a greater extent during inhaled versus subcutaneous insulin therapy.³⁰ In a 24-week study of patients with type 1 diabetes, levels of antiinsulin antibodies increased threefold to fivefold in the Afrezza-treated group (from a median of 9.30 Kronus units/mL at

baseline to a median of 30.85 Kronus units/mL at week 24); antibody levels remained practically unchanged in the group treated with subcutaneous insulin.¹⁵ However, higher antibody levels were not correlated with any adverse effects. After discontinuation of treatment, antibody levels returned to normal. In a placebo-controlled 24-week study of patients with type 2 diabetes, the median antiinsulin antibody level did not change in the placebo group but was slightly increased in the Afrezza group (from 5.80 Kronus units/mL at baseline to 7.40 Kronus units/mL at week 24).¹⁵

Pulmonary safety. Lung function. Lung function was evaluated in a 24-month prospective study in patients with type 1 or type 2 diabetes receiving Afrezza ($n = 730$) or usual diabetes care ($n = 824$) and a cohort without diabetes who did not receive any specific treatment ($n = 145$).³¹ The evaluation was performed by measuring forced expiratory volume in one second (FEV₁), which is the volume of air that can forcibly be blown out in one second after full inspiration. A slight change in FEV₁ values was observed with Afrezza use at the beginning of the study (mean decline, 0.037 L; 95% CI, 0.014–0.060 L), but FEV₁ values subsequently stabilized for the rest of the trial period. The difference in the mean FEV₁ values in the Afrezza and comparator groups disappeared within 1 month of Afrezza discontinuation. Similar observations were reported in trials involving smokers.¹⁵

Cancer. Two cases of lung cancer have been reported in trials of Afrezza, but both participants were ex-smokers. Overall, rates of lung cancers (and other cancers) reported among Afrezza-treated patients in clinical trials have been consistent with rates observed in the general U.S. population.³² A postmarketing observational cohort trial is planned to further evaluate the long-term risk of lung cancer with Afrezza use.

Safety in patients with lung disease. The safety of Afrezza in diabetic patients with lung diseases has not been studied. However, based on the observation of adverse events in small clinical pharmacology studies in nondiabetic patients with asthma and chronic obstructive pulmonary disease, Afrezza is not recommended for patients with lung diseases.¹⁵

Administration and dosage

Afrezza is administered via oral inhalation at the beginning of a meal to control postprandial glucose levels in type 1 and type 2 diabetes.¹⁹ The patient is still required to use a long-acting insulin product to maintain his or her glucose level throughout the day. Afrezza is available in four- and eight-unit cartridges. The cartridges are labeled with the equivalent subcutaneous dose to help patients and prescribers compare the Afrezza dose with the traditional subcutaneous insulin dose. A four-unit cartridge delivers the equivalent of four units of subcutaneously delivered insulin, and an eight-unit cartridge delivers the equivalent of eight units of subcutaneous insulin. Thus, in the prescribing information, the conversion factor for converting the smallest possible dose of Afrezza to a dose of subcutaneous insulin is 4; this value is based on the medication's documented 25–30% bioavailability relative to subcutaneous formulations of recombinant human insulin and rapid-acting insulin analogs.¹⁹

Recommended dose conversion guidelines

Patients using insulin for the first time for blood glucose control should start with 4 units of Afrezza at each meal.³³ For patients already using mealtime subcutaneous insulin, dose conversion should be performed as follows: up to 4 units of subcutaneous insulin $\approx$ 4 units of Afrezza, 5–8 units of subcutaneous insulin $\approx$ 8 units of Afrezza,

9–12 units of subcutaneous insulin $\approx$ 12 units of Afrezza, 13–16 units of subcutaneous insulin $\approx$ 16 units of Afrezza, 17–20 units of subcutaneous insulin $\approx$ 20 units of Afrezza, and 21–24 units of subcutaneous insulin $\approx$ 24 units of Afrezza.

Patients already using subcutaneous premixed insulin should administer half of their total daily subcutaneous dose as premixed basal insulin, divide the remainder of the total daily subcutaneous dose by three, and convert each of the three calculated doses to Afrezza doses as shown above.

Future perspective

The results of multiple international clinical trials established the safety and efficacy of Afrezza, leading to its approval by FDA. However, the product is approved only for adults; further studies are needed to establish its safety and efficacy in children. Despite the availability of numerous needle-free injector pens, many patients may benefit from the inhaled insulin product. Afrezza's dry-powder inhaler and ultrarapid release profile support the prediction that Afrezza will fare much better than Exubera, especially in those patients who are reluctant to take multiple daily insulin injections.

Conclusion

Afrezza is a safe and effective treatment for selected adults with type 1 or type 2 diabetes, potentially providing an alternative to insulin injections for prandial blood glucose control.

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