HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use AFREZZA® safely and effectively. See full prescribing information for AFREZZA.

AFREZZA® (insulin human) inhalation powder, for oral inhalation use
Initial U.S. Approval: 2014

WARNING: RISK OF ACUTE BRONCHOSPASM IN PATIENTS WITH CHRONIC LUNG DISEASE
See full prescribing information for complete boxed warning.

- **Acute bronchospasm has been observed in AFREZZA-treated patients with asthma and Chronic Obstructive Pulmonary Disease (COPD). (*5.1*)**
- **AFREZZA is contraindicated in patients with chronic lung disease such as asthma or COPD. (*4*)**
- **Before initiating AFREZZA, perform a detailed medical history, physical examination, and spirometry (FEV_1) to identify potential lung disease in all patients. (*2.1*), (*5.1*)**

----------RECENT MAJOR CHANGES----------

Indications and Usage (*1*)	5/2026
Dosage and Administration:	
Important Administration Information (*2.2*)	5/2026
Recommended Starting Mealtime Dosage of AFREZZA (*2.3*)	1/2026

----------INDICATIONS AND USAGE----------
AFREZZA® is a rapid acting inhaled human insulin indicated to improve glycemic control in adult and pediatric patients 6 years of age and older with diabetes mellitus. (1)

Limitations of Use:
- Not recommended for the treatment of diabetic ketoacidosis (DKA) (1)
- Not recommended in patients who smoke or who have recently stopped smoking (1)

----------DOSAGE AND ADMINISTRATION----------
- Only administer via oral inhalation using the AFREZZA inhaler (2.2)
- Administer at the beginning of each meal (2.2)
- See full prescribing information for the recommended starting mealtime dosage in insulin-naïve patients and patients who are using subcutaneous mealtime insulin, or pre-mixed insulin (2.3)
- Modify the mealtime AFREZZA dosage based on the patient's metabolic needs, blood glucose monitoring results, and glycemic control goal (2.4)
- If blood glucose control is not achieved with increased AFREZZA dosages, consider discontinuing AFREZZA (2.4)

----------DOSAGE FORMS AND STRENGTHS----------
Inhalation powder in single-use cartridges of: 4 units, 8 units, or 12 units (3)

----------CONTRAINDICATIONS----------
- During episodes of hypoglycemia (4)
- Chronic lung disease, such as asthma, or COPD (4)
- Hypersensitivity to any regular human insulin product or any of the inactive ingredients in AFREZZA (4)

----------WARNINGS AND PRECAUTIONS----------
- *Hypoglycemia or Hyperglycemia with Changes in Insulin Regimen*: Make necessary changes to a patient's insulin regimen under close medical supervision with increased frequency of blood glucose monitoring. For patients with type 2 diabetes mellitus, oral antidiabetic treatment dosage modifications may be needed. (5.2)
- *Hypoglycemia* (may be life-threatening): Increase frequency of glucose monitoring in patients at higher risk for hypoglycemia and those who have reduced symptomatic awareness of hypoglycemia. (5.3)
- *Decline in Pulmonary Function*: Assess pulmonary function (e.g., spirometry (FEV_1)) at baseline, after 6 months of therapy, and annually, even in the absence of pulmonary symptoms. In patients who have a decline of ≥ 20% in FEV_1 from baseline, consider discontinuing AFREZZA. Consider more frequent monitoring of pulmonary function in patients with pulmonary symptoms (5.4)
- *Lung Cancer*: In patients with active lung cancer, a prior history of lung cancer, or in patients at risk for lung cancer, consider whether the benefits of AFREZZA use outweigh this potential risk. (5.5)
- *Diabetic Ketoacidosis*: In patients at risk for DKA, increase the frequency of glucose monitoring and consider changing to alternate route of insulin delivery. (5.6)
- *Hypersensitivity Reactions*: Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with AFREZZA. If hypersensitivity reactions occur, discontinue AFREZZA, treat per standard of care and monitor until symptoms and signs resolve. (5.7)
- *Hypokalemia* (may be life-threatening): Monitor potassium levels in patients at risk of hypokalemia. (5.8)
- *Fluid Retention and Heart Failure with Concomitant Use of PPAR-gamma Agonists:* Observe for signs and symptoms of heart failure; consider dosage reduction or discontinuation if heart failure occurs. (5.9)

----------ADVERSE REACTIONS----------
The most common adverse reactions associated with AFREZZA (2% or greater incidence) are hypoglycemia, cough, and throat pain or irritation (6)

To report SUSPECTED ADVERSE REACTIONS, contact MannKind at 1-877-323-8505 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- See full prescribing information for details regarding concomitant use of drugs that may (7):
  - Decrease blood glucose lowering effect of AFREZZA
  - Increase or decrease the blood glucose lowering effect of AFREZZA
  - Blunt signs and symptoms of hypoglycemia

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 05/2026

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

WARNING: RISK OF ACUTE BRONCHOSPASM IN PATIENTS WITH CHRONIC LUNG DISEASE

- **Acute bronchospasm has been observed in AFREZZA-treated patients with asthma and Chronic Obstructive Pulmonary Disease (COPD) *[see Warnings and Precautions (5.1)]*.**
- **AFREZZA is contraindicated in patients with chronic lung disease such as asthma or COPD *[see Contraindications (4)]*.**
- **Before initiating AFREZZA, perform a detailed medical history, physical examination, and spirometry (FEV_1) to identify potential lung disease in all patients *[see Dosage and Administration (2.1), Warnings and Precautions (5.1)]*.**

1 INDICATIONS AND USAGE

AFREZZA® is indicated to improve glycemic control in adult and pediatric patients 6 years of age and older with diabetes mellitus.

Limitations of Use:

- AFREZZA is not recommended for the treatment of diabetic ketoacidosis (DKA) *[see Warnings and Precautions (5.6)]*.
- The safety and effectiveness of AFREZZA in patients who smoke have not been established. The use of AFREZZA is not recommended in patients who smoke or who have recently stopped smoking *[see Warnings and Precautions (5.5)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Lung Function Assessment Prior to Administration

AFREZZA is contraindicated in patients with chronic lung disease because of the risk of acute bronchospasm in these patients. Before initiating AFREZZA, perform a medical history, physical examination and spirometry (FEV_1) in all patients to identify potential lung disease *[see Contraindications (4) and Warnings and Precautions (5.1)]*.

2.2 Important Administration Information

Prior to initiation, train patients and/or their caregiver(s) on proper administration of AFREZZA. After training, adult and pediatric patients aged 10 and older may self-administer AFREZZA if the healthcare provider determines that it is appropriate.

Refer patients to the Instructions for Use for detailed instructions and visuals on how to prepare, administer, and store AFREZZA; use the AFREZZA cartridges; and use the AFREZZA inhaler.

- Only administer AFREZZA via oral inhalation using the AFREZZA Inhaler.
- Administer AFREZZA at the beginning of each meal.
- Administer AFREZZA using a single inhalation per cartridge (if the dose is greater than the contents of a single cartridge, more than one cartridge is needed) *[see Dosage and Administration (2.3), Dosage Forms and Strengths (3)]*.
- To administer AFREZZA:
    - Keep the inhaler level with the white mouthpiece on top and purple base on the bottom after a cartridge has been inserted into the inhaler. Loss of drug effect can occur if the inhaler is turned upside down, held with the mouthpiece pointing down, shaken, or dropped after the cartridge has been inserted but before the dose has been administered. If any of the above occur, replace the cartridge before use.
    - Hold the inhaler away from the mouth and fully exhale.

- After the inhaler is placed in the mouth and the lips form a seal, tilt the inhaler down towards the chin while keeping the head level.
- With the mouth closed around the mouthpiece, inhale deeply through the inhaler.
- Hold the breath for as long as comfortable and at the same time remove the inhaler from the mouth.
- After holding the breath, exhale and continue to breathe normally.

- The AFREZZA Inhaler can be used for up to 15 days from the date of first use. After 15 days of use, discard the inhaler and replace it with a new inhaler.

2.3 Recommended Starting Mealtime Dosage of AFREZZA

Insulin naïve patients

The initial dosage of AFREZZA is 4 units inhaled at the beginning of each meal.

Switching from Other Mealtime (prandial) Insulin Regimens to AFREZZA

When switching from another insulin to AFREZZA, a different insulin dosage may be needed and increased frequency of blood glucose monitoring and monitoring for signs and symptoms of hypoglycemia may be needed *[see Warnings and Precautions (5.2, 5.3), Clinical Pharmacology (12.2, 12.3)].*

Subcutaneous, Mealtime (prandial) Insulin:

Follow the recommendations in Table 1 to convert each injected mealtime insulin dosage (or bolus dosage for patients using insulin pumps) to the recommended mealtime dosage of AFREZZA.

Subcutaneous, Pre-Mixed Insulin:

- Refer to the prescribing information for the pre-mixed insulin to estimate the mealtime subcutaneous insulin dosage based on the product's pharmacokinetic and pharmacodynamic properties.
- Follow the recommendations in Table 1 to convert each estimated injected mealtime dosage to an AFREZZA mealtime dose.
- If basal insulin is clinically indicated, refer to the prescribing information for the chosen basal insulin for dosage recommendations.

Table 1. Recommended Starting Mealtime Dosage of AFREZZA when Switching from Other Mealtime Insulin Regimens

Current Subcutaneous Mealtime Insulin Dosage	Starting Dosage of AFREZZA
Up to 3 units	4 units
4 to 5 units	8 units
6 to 7 units	12 units
8 or more units	16 units

* For AFREZZA doses exceeding the contents of a single cartridge at mealtime, use more than one cartridge. To achieve the required total mealtime dosage, use a combination of 4 unit, 8 unit, and 12 unit cartridges. When titrating dosages above 16 units after the initial conversion dosage, use combinations of different cartridges *[see Dosage and Administration (2.4), Dosage Forms and Strengths (3), How Supplied/Storage and Handling (16)]*.

2.4 Mealtime AFREZZA Dosage Modification

- Modify the mealtime AFREZZA dosage based on the patient's metabolic needs, blood glucose monitoring results, and glycemic control goal.
- Dosage modifications may be needed with changes in physical activity, changes in meal patterns (i.e., macronutrient content or timing of food intake), changes in renal or hepatic function or during acute illness *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.6, 8.7)].*
- Increase the frequency of blood glucose monitoring during titration of AFREZZA. If blood glucose control is not achieved with increased AFREZZA dosages, consider discontinuing AFREZZA.

2.5 Dosage Modifications for Drug Interactions
Dosage modification may be needed when:

- AFREZZA is used concomitantly with certain drugs that increase and/or decrease the glucose lowering effect *[see Drug Interactions (7)]*.
- Switching from another insulin to AFREZZA *[see Dosage and Administration (2.3) and Warnings and Precautions (5.2)]*

3 DOSAGE FORMS AND STRENGTHS

Inhalation Powder: 3 single-use cartridges of insulin human as white powder labeled “afrezza”. Each AFREZZA inhalation cartridge delivers:

- 4 units (blue cartridge)
- 8 units (green cartridge)
- 12 units (yellow cartridge)

4 CONTRAINDICATIONS

AFREZZA is contraindicated:

- During episodes of hypoglycemia *[see Warnings and Precautions (5.3)]*.
- In patients with chronic lung disease, such as asthma or COPD, because of the risk of acute bronchospasm *[see Warnings and Precautions (5.1)]*.
- In patients with a previous severe hypersensitivity reaction to any regular human insulin product or any of the inactive ingredients in AFREZZA. Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with AFREZZA *[see Warnings and Precautions (5.7)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Acute Bronchospasm in Patients with Chronic Lung Disease
Because of the risk of acute bronchospasm, AFREZZA is contraindicated in patients with chronic lung disease such as asthma or COPD *[see Contraindications (4)]*. Before initiating therapy with AFREZZA, evaluate patients with a medical history, physical examination, and spirometry (FEV_1) to identify potential underlying lung disease.

Acute bronchospasm has been observed in AFREZZA-treated patients with asthma and COPD. In a study of patients with asthma whose bronchodilators were temporarily withheld for assessment, bronchoconstriction and wheezing following AFREZZA dosing was reported in 29% (5/17) and 0% (0/13) of patients with and without a diagnosis of asthma, respectively. In this study, a mean decline in FEV_1 of 400 mL was observed 15 minutes after a single AFREZZA dose in patients with asthma. In a subset study of 8 patients with COPD, a mean decline in FEV_1 of 200 mL was observed 18 minutes after a single AFREZZA dose.

5.2 Hypoglycemia or Hyperglycemia with Changes in Insulin Regimen
Changes in an insulin regimen (e.g., insulin strength, manufacturer, injection site or type, or method of administration) may affect glycemic control and predispose to hypoglycemia *[see Warnings and Precautions (5.3)]* or hyperglycemia. If clinically indicated, make any necessary changes to a patient’s insulin regimen under close medical supervision with increased frequency of blood glucose monitoring. For patients with type 2 diabetes mellitus, dosage modifications of concomitant oral antidiabetic treatment may be needed *[see Drug Interactions (7)]*.

5.3 Hypoglycemia
Hypoglycemia is the most common adverse reaction associated with insulins, including AFREZZA. Severe hypoglycemia can cause seizures, may be life-threatening, or cause death. Hypoglycemia can impair concentration ability and reaction time; this may place an individual and others at risk in situations where these abilities are important (e.g., driving or operating other machinery).

AFREZZA's time action profile impacts the timing of hypoglycemia following inhalation of the drug product *[see Clinical Pharmacology (12.3)]*. Hypoglycemia can occur suddenly, and symptoms may differ across patients and change over time in the same patient. Symptomatic awareness of hypoglycemia may be less pronounced in patients with longstanding diabetes mellitus, in patients with diabetic nerve disease, in patients using medications that block the sympathetic nervous system (e.g., beta-blockers) *[see Drug Interactions (7)],* or in patients who experience recurrent hypoglycemia.

Risk Factors and Mitigation Strategies for Hypoglycemia

The risk of hypoglycemia after use of AFREZZA is related to the duration of action of the insulin and, in general, is highest when the glucose lowering effect of the insulin is maximal *[See Clinical Pharmacology (12.3)]*. The glucose lowering effect time course of AFREZZA may vary in different individuals or at different times in the same individual and depends on many conditions *[see Clinical Pharmacology (12.2)]*. Other factors which may increase the risk of hypoglycemia include changes in meal pattern (e.g., macronutrient content or timing of meals), changes in level of physical activity, or changes to concomitantly administered medication *[see Drug Interactions (7)].* Patients with renal or hepatic impairment may be at higher risk of hypoglycemia *[see Use in Specific Populations (8.6, 8.7)].* Advise patients to recognize and manage hypoglycemia and self-monitor glucose. In patients at higher risk for hypoglycemia and patients who have reduced symptomatic awareness of hypoglycemia, increased frequency of glucose monitoring is recommended.

5.4 Decline in Pulmonary Function

AFREZZA causes a decline in pulmonary function over time as measured by FEV_1. In clinical trials excluding patients with chronic lung disease and lasting up to 2 years, AFREZZA-treated patients experienced a small [40 mL (95% CI: -80, -1)] but greater FEV_1 decline than comparator-treated patients. The FEV_1 decline was noted within the first 3 months, and persisted for the entire duration of therapy (up to 2 years of observation). In this population, the annual rate of FEV_1 decline did not appear to worsen with increased duration of use. The effects of AFREZZA on pulmonary function for treatment duration longer than 2 years has not been established. There are insufficient data in long term studies to draw conclusions regarding reversal of the effect on FEV_1 after discontinuation of AFREZZA. The observed changes in FEV_1 were similar in patients with type 1 and type 2 diabetes mellitus.

Assess pulmonary function (e.g., spirometry) at baseline, after the first 6 months of therapy, and annually thereafter, even in the absence of pulmonary symptoms. In patients who have a decline of ≥ 20% in FEV_1 from baseline, consider discontinuing AFREZZA. Consider more frequent monitoring of pulmonary function in patients with pulmonary symptoms such as wheezing, bronchospasm, breathing difficulties, or persistent or recurring cough. If symptoms persist, discontinue AFREZZA *[see Adverse Reactions (6.1)]*.

5.5 Lung Cancer

In clinical trials, two cases of lung cancer, one in controlled trials and one in uncontrolled trials (2 cases in 2,750 patient-years of exposure), were observed in patients exposed to AFREZZA while no cases of lung cancer were observed in patients exposed to comparators (0 cases in 2,169 patient-years of exposure). In both cases, a prior history of heavy tobacco use was identified as a risk factor for lung cancer. Two additional cases of lung cancer (squamous cell and lung blastoma) occurred in non-smokers exposed to AFREZZA and were reported by investigators after clinical trial completion. These data are insufficient to determine whether AFREZZA has an effect on lung or respiratory tract tumors.

In patients with active lung cancer, a prior history of lung cancer, or in patients at risk for lung cancer, consider whether the benefits of AFREZZA use outweigh this potential risk.

5.6 Diabetic Ketoacidosis

In clinical trials enrolling patients with type 1 diabetes mellitus, DKA was more common in AFREZZA-treated patients (0.43%; n=13) than in comparator-treated patients (0.14%; n=3). Patients with type 1 diabetes mellitus should always use AFREZZA concomitantly with basal insulin. In patients at risk for DKA, such as those with an acute illness or infection, increase the frequency of glucose monitoring and consider discontinuing AFREZZA and giving insulin using an alternate route of administration.

5.7 Hypersensitivity Reactions
Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with AFREZZA.

If hypersensitivity reactions occur, discontinue AFREZZA, treat per standard of care and monitor until symptoms and signs resolve *[see Adverse Reactions (6.1)]*. AFREZZA is contraindicated in patients with a previous severe hypersensitivity reaction to any regular human insulin product or any of the inactive ingredients in AFREZZA *[see Contraindications (4)]*.

5.8 Hypokalemia
All insulin products, including AFREZZA, cause a shift in potassium from the extracellular to intracellular space, possibly leading to hypokalemia. Untreated hypokalemia may cause respiratory paralysis, ventricular arrhythmia, and death.

Monitor potassium levels in AFREZZA-treated patients at risk for hypokalemia (e.g., patients using potassium-lowering medications, patients taking medications sensitive to serum potassium concentrations and patients receiving intravenously administered insulin).

5.9 Fluid Retention and Heart Failure with Concomitant Use of PPAR-gamma Agonists
Thiazolidinediones (TZDs), which are peroxisome proliferator-activated receptor (PPAR)-gamma agonists, can cause dose-related fluid retention, particularly when used in combination with insulin. Fluid retention may lead to or exacerbate heart failure.

Patients treated with insulin, including AFREZZA, and a PPAR-gamma agonist should be observed for signs and symptoms of heart failure. If heart failure develops, manage according to current standards of care, and consider discontinuing or reducing the dosage of the PPAR-gamma agonist.

6 ADVERSE REACTIONS
The following serious adverse reactions are described below and elsewhere in the labeling:

- Acute bronchospasm in patients with chronic lung disease *[see Warnings and Precautions (5.1)]*
- Hypoglycemia *[see Warnings and Precautions (5.3)]*
- Decline in pulmonary function *[see Warnings and Precautions (5.4)]*
- Lung cancer *[see Warnings and Precautions (5.5)]*
- Diabetic ketoacidosis *[see Warnings and Precautions (5.6)]*
- Hypersensitivity reactions *[see Warnings and Precautions (5.7)]*

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse Reactions in Clinical Trials in Adults with Type 1 or Type 2 Diabetes Mellitus

The data described below reflect exposure of 3,017 adult patients to AFREZZA and include 1,026 patients with type 1 diabetes mellitus and 1,991 patients with type 2 diabetes mellitus. The mean exposure duration was 8.2 months for patients with type 1 diabetes mellitus and those with type 2 diabetes mellitus *[see Clinical Studies (14.2, 14.3)]*. In the overall population:

- 1,874 patients with type 1 or type 2 diabetes mellitus were exposed to AFREZZA for 6 months and 724 patients for greater than one year.
- 620 and 1,254 patients with type 1 or type 2 diabetes mellitus, respectively, were exposed to AFREZZA for up to 6 months.
- 238 and 486 patients with type 1 or type 2 diabetes mellitus, respectively, were exposed to AFREZZA for greater than one year (median exposure was 1.8 years).

AFREZZA was studied in placebo and active-controlled adult trials (n = 3 and n = 10, respectively).

The mean age of the adult population was 50 years and 20 patients were older than 75 years of age; 51% of the population were males; 83% were White, 5% were Black or African American, and 2% were Asian; 10% were Hispanic or Latino ethnicity. At baseline, the type 1 diabetes mellitus population had diabetes mellitus for an average of 17 years and had a mean HbA1c of 8.3%, and the type 2 diabetes mellitus population had diabetes mellitus for an average of 11 years and had a mean HbA1c of 8.8%. At baseline, 33% of the population reported peripheral neuropathy, 32% reported retinopathy and 20% had a history of cardiovascular disease.

Table 2 shows the frequency of common adverse reactions, excluding hypoglycemia, associated with the use of AFREZZA in the pool of controlled trials in adults with type 2 diabetes mellitus patients that occurred more commonly on AFREZZA than on placebo and/or comparator and occurred in at least 2% of patients treated with AFREZZA.

Table 2. Common Adverse Reactions That Occurred in ≥ 2% in Adult Patients with Type 2 Diabetes Mellitus (excluding Hypoglycemia) Treated with AFREZZA

Adverse Reaction	AFREZZA (n = 1,991) %	Placebo[a] (n = 290) %	Non-placebo comparators (n=1,363) %
Cough	26	20	5
Throat pain or irritation	4	4	1
Headache	3	3	2
Diarrhea	3	1	2
Productive cough	2	1	1
Fatigue	2	1	1
Nausea	2	0.3	1

[a] Carrier particle without insulin was used as placebo *[see Description (11.1)]*.

Table 3 shows the frequency of common adverse reactions, excluding hypoglycemia, associated with the use of AFREZZA in the pool of active-controlled trials in adults with type 1 diabetes mellitus. These adverse reactions occurred more commonly on AFREZZA than on comparator and occurred in at least 2% of patients treated with AFREZZA.

Table 3. Common Adverse Reactions That Occurred in ≥ 2% in Adult Patients with Type 1 Diabetes Mellitus (excluding Hypoglycemia) Treated with AFREZZA

Adverse Reaction	AFREZZA (n=1,026) %	Subcutaneous Insulin (n = 835) %
Cough	29	5
Throat pain or irritation	6	2
Headache	5	3
Pulmonary function test decreased	3	1
Bronchitis	3	2
Urinary tract infection	2	2

Hypoglycemia

Hypoglycemia is the most commonly observed adverse reaction in patients treated with AFREZZA *[see Warnings and Precautions (5.3)].* The rates of reported hypoglycemia depend on the definition of hypoglycemia used, diabetes type, insulin dose, intensity of glucose control, background therapies, and other intrinsic and extrinsic patient factors. For these reasons, comparing rates of hypoglycemia across clinical trials of AFREZZA or with the incidence of hypoglycemia for other insulin products may be misleading and also, may not be representative of hypoglycemia rates that will occur in clinical practice.

The incidence of severe and non-severe hypoglycemia in AFREZZA-treated patients versus placebo-treated patients with type 2 diabetes mellitus is shown in Table 4. A hypoglycemic episode was recorded if a patient reported symptoms of hypoglycemia with or without a blood glucose value consistent with hypoglycemia. Severe hypoglycemia was defined as an event with symptoms consistent with hypoglycemia requiring the assistance of another person and associated with either a blood glucose value consistent with hypoglycemia or prompt recovery after treatment for hypoglycemia.

Table 4. Incidence of Severe and Non-Severe Hypoglycemia in a Placebo-Controlled Study of Adult Patients with Type 2 Diabetes Mellitus

Hypoglycemia Severity	AFREZZA (N=177)	Placebo (N=176)
Severe Hypoglycemia	5%	2%
Non-Severe Hypoglycemia	67%	30%

Other Adverse Reactions in Adults with Type 1 or Type 2 Diabetes Mellitus

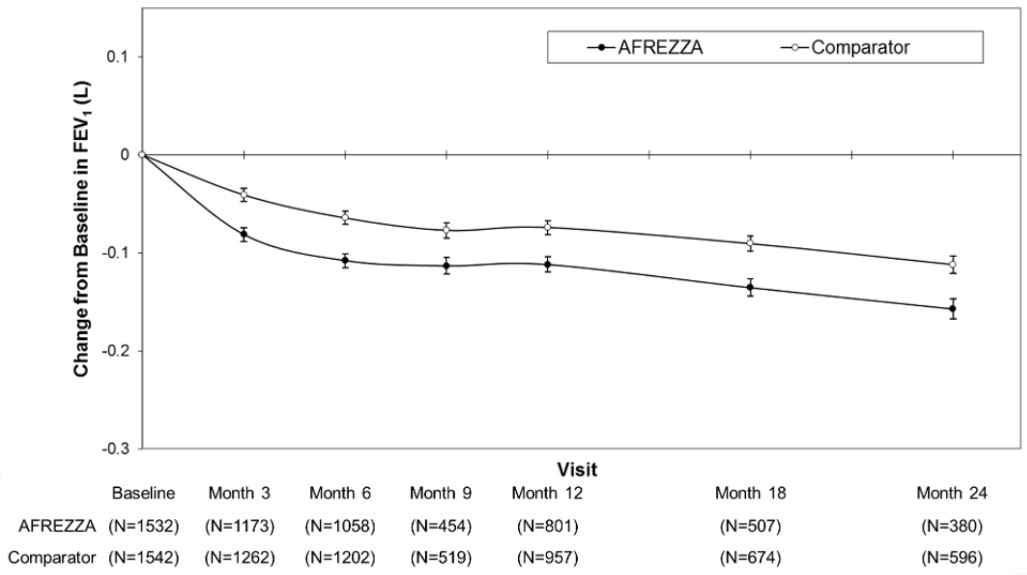
Cough

Approximately 27% of adults treated with AFREZZA reported cough, compared to approximately 5% of patients treated with comparator. In clinical trials, cough was the most common reason for discontinuation of AFREZZA therapy (3% of adult AFREZZA-treated patients).

Pulmonary Function Decline

In clinical trials lasting up to 2 years, excluding patients with chronic lung disease, adults treated with AFREZZA had a 40 mL (95% CI: -80, -1) greater decline from baseline in forced expiratory volume in one second (FEV_1) compared to patients treated with comparator anti-diabetes treatments. The decline occurred during the first 3 months of therapy and persisted over 2 years (Figure 1). A decline in FEV_1 of ≥ 15% occurred in 6% of AFREZZA-treated patients compared to 3% of comparator-treated patients *[see Warnings and Precautions (5.4)]*.

Figure 1. Mean (+/-SE) Change in FEV_1 (Liters) from Baseline for Adult Patients with Type 1 and Type 2 Diabetes Mellitus



Weight Gain

Weight gain has occurred with some insulin therapies, including AFREZZA. Weight gain has been attributed to the anabolic effects of insulin and the decrease in glycosuria. In a clinical trial of adult patients with type 2

diabetes mellitus *[see Clinical Studies (14.3)]*, there was a mean 0.49 kg weight gain among AFREZZA-treated patients compared with a mean 1.13 kg weight loss among placebo-treated patients.

Adverse Reactions in the Clinical Trial in Pediatric Patients Aged 6 Years and Older with Type 1 or 2 Diabetes Mellitus

A 26-week open-label, randomized clinical trial evaluated the safety of AFREZZA versus rapid-acting insulin analog (RAA), both in combination with basal insulin, in 230 pediatric patients with type 1 or type 2 diabetes mellitus *[see Clinical Studies (14.4)]*. The trial was followed by a 26-week safety extension. The mean age of patients was 12.6 years (range: 4 to 17 in the RAA arm, 6 to 17 in the AFREZZA arm). The majority (97.8%) had type 1 diabetes mellitus; a small subset (2.2%) had type 2 diabetes mellitus *[see Clinical Studies (14.4)]*. The trial population had the following characteristics: 38% were female, 77% were White, 10% were Black or African American, 3% were Asian, 6% multiracial, and 20% were Hispanic or Latino ethnicity.

Table 5 shows the frequency of common adverse reactions, excluding hypoglycemia, associated with the use of AFREZZA during the pediatric clinical trial. Data observed for 52 weeks was consistent with the 26-week safety profile. These adverse reactions occurred more commonly on AFREZZA than the comparator and occurred in at least 5% of patients treated with AFREZZA. The overall safety profile was similar to that of adults. In this trial, the change in percent predicted FEV_1 from baseline to Week 26 was similar in both groups.

Table 5. Common Adverse Reactions That Occurred in ≥ 5% of Pediatric Patients Aged 6 Years and Older With Type 1 and Type 2 Diabetes Mellitus (excluding Hypoglycemia) Treated with AFREZZA and More Commonly on AFREZZA Than on RAA

Adverse Reaction[a]	**AFREZZA (n=117) %**	**RAA (n=113) %**
Cough	21	3
Upper respiratory tract infection	18	14
Oropharyngeal pain	11	4
Headache	8	5
Vomiting	5	3

[a] This study was not designed to evaluate meaningful comparisons of adverse reaction incidence between AFREZZA and RAA.

Hypoglycemia
In the pediatric clinical trial *[see Clinical Studies (14.4)],* events of severe hypoglycemia (level 3) were defined as an episode associated with severe cognitive impairment requiring external assistance for recovery. Level 3 hypoglycemia was reported in 2 (1.7%) AFREZZA-treated pediatric patients versus 1 (0.9%) RAA-treated patient during the randomized treatment period.

6.2 Postmarketing Experience

The following adverse reaction has been identified during post approval use of AFREZZA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure:
Respiratory: bronchospasm.

7 DRUG INTERACTIONS

Table 6 presents clinically significant drug interactions with AFREZZA.

Table 6. Clinically Significant Drug Interactions with AFREZZA

Antidiabetic agents, Angiotensin-Converting Enzyme Inhibitors, Angiotensin II Receptor Blocking Agents, Disopyramide, Fibrates, Fluoxetine, Monoamine Oxidase Inhibitors, Pentoxifylline, Pramlintide, Salicylates, Somatostatin Analogs (e.g., octreotide), and Sulfonamide Antibiotics	
Prevention or Management	Monitor blood glucose more frequently and modify AFREZZA dosage, as clinically indicated, when used concomitantly with these drugs.
Mechanism and Clinical Effect(s)	Concomitant use of these drugs with AFREZZA may increase the risk of hypoglycemia.
Atypical Antipsychotics (e.g., olanzapine and clozapine), Corticosteroids, Danazol, Diuretics, Estrogens, Glucagon, Isoniazid, Niacin, Oral Contraceptives, Phenothiazines, Progestogens (e.g., in oral contraceptives), Protease inhibitors, Somatropin, Sympathomimetic Agents (e.g., albuterol, epinephrine, terbutaline) and Thyroid Hormones.	
Prevention or Management	Monitor blood glucose more frequently and modify AFREZZA dosage, as clinically indicated, when used concomitantly with these drugs.
Mechanism and Clinical Effect(s)	Concomitant use of these drugs with AFREZZA may reduce the blood glucose lowering effect of AFREZZA.
Alcohol, Beta-blockers, Clonidine, and Lithium Salts	
Prevention or Management	Monitor blood glucose more frequently and modify AFREZZA dosage, as clinically indicated, when used concomitantly with these drugs.
Mechanism and Clinical Effect(s)	Concomitant use with AFREZZA may either increase or decrease the blood glucose lowering effect of AFREZZA.
Pentamidine	
Prevention or Management	Monitor blood glucose more frequently and modify AFREZZA dosage, as clinically indicated, when used concomitantly with these drugs.
Mechanism and Clinical Effect(s)	Concomitant use of pentamidine with AFREZZA may cause hypoglycemia, which may sometimes be followed by hyperglycemia
Beta-blockers, Clonidine, Guanethidine, and Reserpine	
Prevention or Management	Monitor blood glucose more frequently and modify AFREZZA dosage, as clinically indicated, when used concomitantly with these drugs.
Mechanism and Clinical Effect(s)	Concomitant use of these drugs with AFREZZA may blunt the signs and symptoms of hypoglycemia, making it more difficult to recognize

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited available data with AFREZZA use in pregnant women are insufficient to determine drug-associated risks for adverse developmental outcomes. Available information from published studies with human insulin use during pregnancy has not reported a clear association with human insulin and adverse developmental outcomes (*see Data*). There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy (*see Clinical Considerations*). In animal reproduction studies, there were no adverse developmental outcomes with subcutaneous administration of carrier particles (vehicle without insulin) to pregnant rats during organogenesis at doses 21 times the human daily dose of 99 mg AFREZZA, based on AUC *(see Data)*.

The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with HbA1c >7 and has been reported to be as high as 20-25% in women with HbA1c >10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Poorly controlled diabetes in pregnancy increases the maternal risk for DKA, pre-eclampsia, spontaneous abortions, preterm delivery, stillbirth, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia- related morbidity.

Data

Human Data

There are limited data with AFREZZA use in pregnant women. Published data do not report a clear association with human insulin and major birth defects, miscarriage, or adverse maternal or fetal outcomes when human insulin is used during pregnancy. However, these studies cannot definitely establish the absence of any risk because of methodological limitations including small sample size and lack of blinding.

Animal Data

In pregnant rats given subcutaneous doses of 10, 30, and 100 mg/kg/day of carrier particles (vehicle without insulin) from gestation day 6 through 17 (organogenesis), no major malformations were observed at doses up to 100 mg/kg/day (21 times the human systemic exposure at a daily dose of 99 mg AFREZZA, based on AUC).

In pregnant rabbits given subcutaneous doses of 2, 10, and 100 mg/kg/day of carrier particles (vehicle without insulin) from gestation day 7 through 19 (organogenesis), adverse maternal effects were observed in all dose groups (at human systemic exposure following a daily dose of 99 mg AFREZZA, based on AUC).
In pregnant rats given subcutaneous doses of 10, 30, and 100 mg/kg/day of carrier particles (vehicle without insulin) from gestation day 7 through lactation day 20 (weaning), decreased epididymis and testes weights were observed in F1 male offspring, however, no decrease in fertility was noted, and impaired learning were observed in F1 pups at $\geq$ 30 mg/kg/day (6 times the human systemic exposure at a daily dose of 99 mg AFREZZA, based on AUC).

8.2 Lactation

Risk Summary

There are no data on the presence of AFREZZA in human milk, the effects on the breastfed infant, or the effects on milk production. One small published study reported that exogenous subcutaneous insulin was present in human milk. No adverse effects in infants were noted. The carrier particles are present in rat milk (*see Data*). Potential adverse reactions that are related to inhalational administration of AFREZZA are unlikely to be associated with potential exposure of AFREZZA through breast milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for AFREZZA and any potential adverse effects on the breastfed infant from AFREZZA or from the underlying maternal condition.

Data

Subcutaneous administration of the carrier particle in lactating rats resulted in excretion of the carrier particle in rat milk at levels that were approximately 10% of the maternal exposure. Given the results of the rat study, it is highly likely that the insulin and carrier in AFREZZA are excreted in human milk.

8.4 Pediatric Use

The safety and effectiveness of AFREZZA to improve glycemic control have been established in pediatric patients 6 years of age and older with diabetes mellitus. Use of AFREZZA for this indication is supported by evidence from an adequate and well controlled trial in pediatric patients aged 6 years and older with type 1 or type 2 diabetes mellitus and from trials in adults with type 1 or type 2 diabetes mellitus *[see Adverse Reactions (6.1), Clinical Studies (14.2, 14.3, 14.4)]*.

The overall safety profile in pediatric patients was similar to adults *[see Adverse Reactions (6.1)]*.

The safety and effectiveness of AFREZZA have not been established in pediatric patients less than 6 years of age.

8.5 Geriatric Use
In the AFREZZA clinical studies, 671 (12%) patients were 65 years of age or older, of which 42 (0.8%) were 75 years of age or older. In these studies, 381 (13%) of AFREZZA-treated patients were 65 years of age or older, of which 20 (0.7%) were 75 years of age or older. No overall differences in effectiveness of AFREZZA have been observed between patients 65 years of age and older and younger adult patients *[see Clinical Studies (14)]*. Clinical studies of AFREZZA did not include sufficient numbers of patients 65 years of age and older to determine whether there were differences in safety between these patients and younger adult patients.

Pharmacokinetic and pharmacodynamic studies to assess the effect of age on pharmacokinetics or pharmacodynamics on insulin human, respectively, have not been conducted.

8.6 Hepatic Impairment
The effect of hepatic impairment on the pharmacokinetics of AFREZZA has not been studied. Frequent glucose monitoring and a lower dosage may be necessary in AFREZZA-treated patients with hepatic impairment *[see Dosage and Administration (2.2, 2.3) and Warnings and Precautions (5.3)]*.

8.7 Renal Impairment
The effect of renal impairment on the pharmacokinetics of AFREZZA has not been studied. Some studies with human insulin have shown increased circulating levels of insulin in patients with renal failure. Frequent glucose monitoring and a lower dosage may be necessary in AFREZZA-treated patients with renal impairment *[see Dosage and Administration (2.2, 2.3) and Warnings and Precautions (5.3)]*.

10 OVERDOSAGE

Excess insulin administration may cause hypoglycemia and hypokalemia *[see Warnings and Precautions (5.3, 5.8)]*.

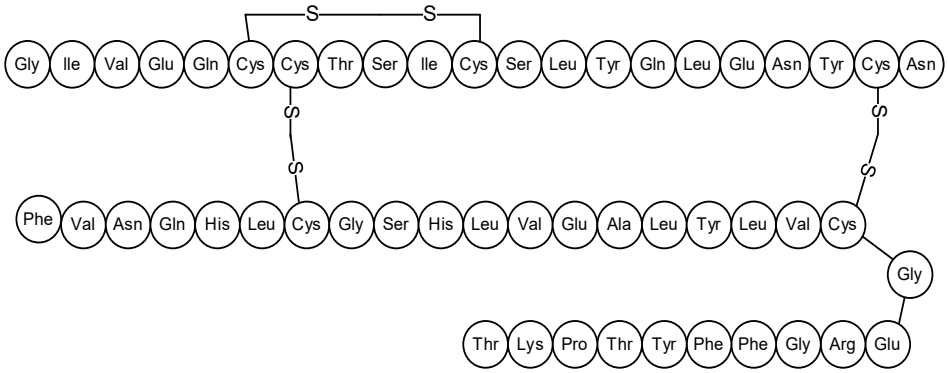
Mild episodes of hypoglycemia due to insulin overdose can usually be treated with oral glucose. Adjustments in drug dosage, meal patterns, or exercise, may be needed.

Severe episodes of hypoglycemia (due to insulin overdose) with coma, seizure, or neurologic impairment may be treated with intramuscular or subcutaneous glucagon or concentrated intravenous glucose. After apparent clinical recovery from hypoglycemia, continued observation and additional carbohydrate intake may be necessary to avoid recurrence of hypoglycemia. Hypokalemia should be corrected appropriately.

In the event of an overdose of AFREZZA, consider contacting the Poison Help line (1-800-222-1222) or a medical toxicologist for additional overdosage management recommendations.

11 DESCRIPTION

11.1 AFREZZA Cartridges
Human insulin is a rapid acting human insulin produced by recombinant DNA technology utilizing a non-pathogenic laboratory strain of *Escherichia coli* (K12). Chemically, human insulin has the empirical formula $C_{257}H_{383}N_{65}O_{77}S_6$ and a molecular weight of 5808. Human insulin has the following primary amino acid sequence:



AFREZZA (human insulin) inhalation powder is available in single-use plastic cartridges filled with a white powder containing insulin (human), which is administered via oral inhalation using the AFREZZA Inhaler only.

Insulin is adsorbed onto carrier particles consisting of fumaryl diketopiperazine (FDKP) and polysorbate 80.

AFREZZA Inhalation Powder is a dry powder supplied as 4 unit, 8 unit or 12 unit cartridges.

11.2 AFREZZA Inhaler

The AFREZZA Inhaler is breath-powered by the patient. When the patient inhales through the device, the powder is aerosolized and delivered to the lung. The amount of AFREZZA delivered to the lung will depend on individual patient factors.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Insulin lowers blood glucose levels in adult patients with diabetes mellitus by stimulating peripheral glucose uptake by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin inhibits lipolysis in adipocytes, inhibits proteolysis, and enhances protein synthesis.

12.2 Pharmacodynamics

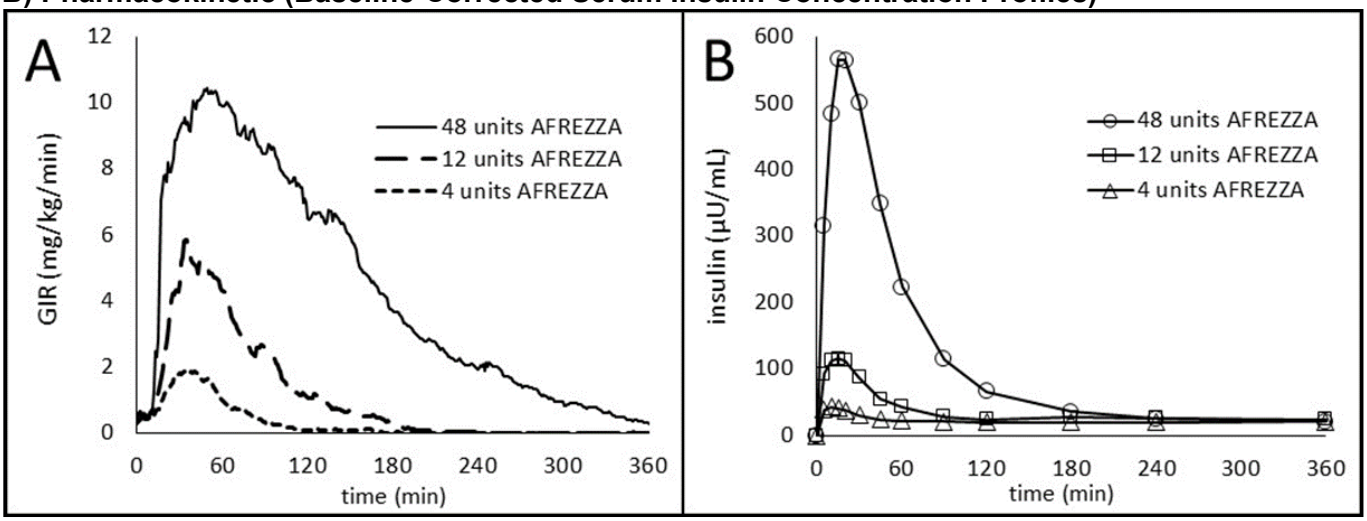
The time course of insulin action (i.e., glucose lowering) may vary considerably in different patients or within the same patient, or when switching from subcutaneous mealtime insulin to AFREZZA. The average pharmacodynamic profile [i.e., glucose lowering effect measured by glucose infusion rate (GIR) over time in a euglycemic clamp study] after administration of a single AFREZZA dose of 4, 12, and 48 units in 30 patients with type 1 diabetes mellitus is shown in Figure 2(A), and key characteristics regarding the timing of the effects are described in Table 7:

Table 7. Timing of Insulin Effect (i.e., mean pharmacodynamics effect) After Administration of a Single AFREZZA Dose in Patients (N=30) with Type 1 Diabetes Mellitus

Parameter for Insulin Effect	AFREZZA 4 units	AFREZZA 12 units	AFREZZA 48 units
Time to first measurable effect	~12 minutes	~12 minutes	~12 minutes
Time to peak effect	~35 minutes	~45 minutes	~55 minutes
Time for effect to return to baseline	~90 minutes	~180 minutes	~270 minutes

Figure 2. Results After Administration of AFREZZA 4, 12, and 48 Units in Patients with Type 1 Diabetes Mellitus (N=30)

A) Mean Insulin Effect (Baseline-Corrected Glucose Infusion Rate); and
B) Pharmacokinetic (Baseline-Corrected Serum Insulin Concentration Profiles)



On average, the pharmacodynamics effect of AFREZZA, measured as area under the glucose infusion rate – time curve (AUC GIR) increased linearly with doses up to 48 units (106, 387, and 1581 mg/kg for 4, 12, and 48 units doses, respectively).

Intrapatient variability in AUC GIR and GIR_{max} was approximately 28% (95% CI 21-42%) and 27% (95% CI 20-40%), respectively.

12.3 Pharmacokinetics

The area under the plasma concentration versus time curve (AUC) of insulin increased dose proportionally up to 48 units. Intrapatient variability of AUC and peak concentration (C_{max}) of insulin was approximately 16% (95% CI 12-23%) and 21% (95% CI 16-30%), respectively.

Absorption

The pharmacokinetic profiles for orally inhaled AFREZZA 4, 12, and 48 units from a study in 30 patients with type 1 diabetes mellitus are shown in Figure 2(B). A higher maximum plasma insulin concentration was achieved at an earlier timepoint in this study when patients were switched from subcutaneous mealtime insulin to AFREZZA *[see Dosage and Administration (2.3)].* The time to maximum serum insulin concentration (t_{max}) ranged from 10-20 minutes after oral inhalation of 4 to 48 units of AFREZZA.

Elimination

The apparent terminal half-life ranged from 120 to 206 minutes. Serum insulin concentrations declined to baseline by approximately 60 to 240 minutes.

Metabolism and Excretion

The metabolism and excretion of AFREZZA are comparable to regular human insulin.

Carrier Particles

Clinical pharmacology studies showed that carrier particles *[see Description (11.1)]* are not metabolized and are eliminated unchanged in the urine following the lung absorption. Following oral inhalation of AFREZZA, a mean of 39% of the inhaled dose of carrier particles was distributed to the lungs and a mean of 7% of the dose was swallowed. The swallowed fraction was not absorbed from the GI tract and was eliminated unchanged in the feces.

Specific Populations

Pediatric Patients

In pediatric patients aged 8 years and older, insulin serum concentration profiles (t_{max} and time decline to baseline) showed a similar time course between adult and pediatric patients following administration of AFREZZA. Insulin C_{max} and AUC increased in a dose-dependent manner following a single dose of 4 units to 12 units.

Drug Interaction Studies

Bronchodilators and Inhaled Steroids

Albuterol increased the AUC insulin after AFREZZA administration by 25% in patients with asthma *[see Drug Interactions (7)].* AFREZZA is contraindicated in patients with asthma.

In a study in healthy volunteers no significant change in insulin exposure was observed when fluticasone was administered following AFREZZA administration.

12.6 Immunogenicity

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, including those of insulin human or of other insulin human products.

Increases in anti-insulin antibody concentrations were observed in patients treated with AFREZZA. Increases in anti-insulin antibodies were observed more frequently in patients treated with AFREZZA than in patients treated with subcutaneously injected mealtime insulin. There was no clinically significant effect of anti-drug antibodies on safety or effectiveness (as measured by HbA1c and fasting plasma glucose) of AFREZZA over the treatment duration of the studies which spanned 3 to 24 months.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis

In a 104 week carcinogenicity study, rats were given doses up to 46 mg/kg/day of the carrier and up to 1.23 mg/kg/day of insulin, by nose-only inhalation. No increased incidence of tumors was observed at systemic exposures equivalent to the insulin at a daily AFREZZA dose of 99 mg, based on a comparison of relative body surface areas across species.

13.2 Mutagenesis

No increased incidence of tumors was observed in a 26 week carcinogenicity study in transgenic mice (Tg-ras-H2) given doses up to 75 mg/kg/day of carrier and up to 5 mg/kg/day of AFREZZA.

AFREZZA was not genotoxic in Ames bacterial mutagenicity assay and in the chromosome aberration assay, using human peripheral lymphocytes with or without metabolic activation. The carrier alone was not genotoxic in the in vivo mouse micronucleus assay.

13.3 Impairment of Fertility

In fertility study in male and female rats at subcutaneous doses of 10, 30, and 100 mg/kg/day of carrier (vehicle without insulin), there were no adverse effects on male fertility at doses up to 100 mg/kg/day. In female rats dosed 2 weeks prior to mating until gestation day 7, there was increased pre- and post-implantation loss at 100 mg/kg/day but not at 30 mg/kg/day (21 times and 6 times, respectively the human systemic exposure at a daily dose of 99 mg AFREZZA, based on AUC).

14 CLINICAL STUDIES

14.1 Overview of Clinical Studies of AFREZZA Adult and Pediatric Patients 6 Years of Age and Older with Diabetes Mellitus

AFREZZA has been studied in adults with type 1 diabetes mellitus in combination with basal insulin. The efficacy of AFREZZA, in combination with basal insulin, in adult patients with type 1 diabetes mellitus was compared to insulin aspart in combination with basal insulin.

AFREZZA has been studied in adults with type 2 diabetes in combination with oral antidiabetic drugs. The efficacy of AFREZZA in type 2 diabetes patients was compared to placebo inhalation.

AFREZZA has been studied in pediatric patients aged 6 to 17 years with type 1 and type 2 diabetes mellitus in combination with basal insulin. The efficacy of AFREZZA, in combination with basal insulin was compared to rapid-acting insulin analogs (RAA) in combination with basal insulin.

14.2 Adults with Type 1 Diabetes Mellitus

Patients with inadequately controlled type 1 diabetes mellitus participated in a 24-week, open-label, active-controlled study (NCT01445951) to evaluate the glucose lowering effect of mealtime AFREZZA used in combination with a basal insulin. Following a 4-week basal insulin optimization period, 344 patients were randomized to AFREZZA by oral inhalation (n=174) or insulin aspart given subcutaneously (n=170) at each meal of the day. All patients received basal insulin. Mealtime insulin doses were titrated to glycemic goals for the first 12 weeks and kept stable for the last 12 weeks of the study. The trial population had the following characteristics: mean age was 38, 56% were female, 96% were White, 3% were Black or African American, less than 1% were Asian, less than 1% were Native Hawaiian or Pacific Islander, less than 1% were other races, and 10% were Hispanic or Latino ethnicity.

Results

At Week 24, treatment with mealtime AFREZZA and basal insulin provided a mean reduction in HbA1c that met the pre-specified non-inferiority margin of 0.4%. AFREZZA and basal insulin provided less HbA1c reduction than insulin aspart and basal insulin, and the difference was statistically significant. More patients in the insulin aspart and basal insulin group achieved the HbA1c target of ≤7% (Table 8).

Table 8. Results at Week 24 in an Active-Controlled Study of Mealtime AFREZZA plus Basal Insulin in Adults with Type 1 Diabetes Mellitus

Efficacy Parameter	AFREZZA + Basal Insulin (N=174)	Insulin Aspart + Basal Insulin (N=170)
HbA1c (%)		
Baseline (adjusted mean[a])	7.94	7.92
Change from baseline (adjusted mean[a,b])	-0.21	-0.40
Difference from insulin aspart (adjusted mean[a,b]) (95% CI)	0.19 (0.02, 0.36)	
Percentage of patients achieving HbA1c ≤ 7%[c]	14%	27%
Fasting Plasma Glucose (mg/dL)		
Baseline (adjusted mean[a])	153.9	151.6
Change from baseline (adjusted mean[a, b])	-25.3	10.2
Difference from insulin aspart (adjusted mean[a, b]) (95% CI)	-35.4 (-56.3, -14.6)	

[a] Adjusted mean was obtained using a Mixed Model Repeated Measures (MMRM) approach with HbA1c or FPG as the dependent variable and treatment, visit, region, basal insulin stratum, and treatment by visit interaction as fixed factors, and corresponding baseline as a covariate. An autoregression (1) [AR(1)] covariance structure was used.
[b] Data at 24 weeks were available from 131 (75%) and 150 (88%) patients randomized to the AFREZZA and insulin aspart groups, respectively.
[c] The percentage was calculated based on the number of patients randomized to the trial.

14.3 Adults with Type 2 Diabetes Mellitus

A total of 479 adult patients with type 2 diabetes mellitus inadequately controlled on optimal/maximally tolerated doses of metformin only, or 2 or more oral antidiabetic (OAD) agents participated in a 24-week, double-blind, placebo-controlled study (NCT01451398). Following a 6-week run-in period, 353 patients were randomized to AFREZZA by oral inhalation (n=177) or an inhaled placebo powder without insulin (n=176). Insulin doses were titrated for the first 12 weeks and kept stable for the last 12 weeks of the study. OADs doses were kept stable in the study. The trial population had the following characteristics: mean age was 57, 56% were female, 87% were White, 11% were Black or African American, less than 1% were Asian, less than 1% were American Indian or Alaska Native, 1% were other races, and 24% were Hispanic or Latino ethnicity.

Results

At Week 24, treatment with AFREZZA plus OADs provided a mean reduction in HbA1c that was statistically significantly greater compared to the HbA1c reduction observed in the placebo plus OADs group (Table 9).

Table 9. Results at Week 24 in a Placebo-Controlled Study of AFREZZA in Adults with Type 2 Diabetes Mellitus Inadequately Controlled on Oral Antidiabetic Agents

Efficacy Parameter	AFREZZA + Oral Anti-Diabetic Agents (N=177)	Placebo + Oral Anti-Diabetic Agents (N=176)
HbA1c (%)		
Baseline (adjusted mean[a])	8.25	8.27
Change from baseline (adjusted mean[a,b])	-0.82	-0.42
Difference from placebo (adjusted mean[a,b]) (95% CI)	-0.40 (-0.57, -0.23)	
Percentage (%) of patients achieving HbA1C ≤7%[c]	32%	15%
Fasting Plasma Glucose (mg/dL)		
Baseline (adjusted mean[a])	175.9	175.2
Change from baseline (adjusted mean[a,b])	-11.2	-3.8
Difference from placebo (adjusted mean[a,b]) (95% CI)	-7.4 (-18.0, 3.2)	

[a] Adjusted mean was obtained using a Mixed Model Repeated Measures (MMRM) approach with HbA1c or FPG as the dependent variable and treatment, visit, region, and treatment by visit interaction as fixed factors, and corresponding baseline as a covariate. An autoregression (1) [AR(1)] covariance structure was used.
[b] Data at 24 weeks without rescue therapy were available from 139 (79%) and 129 (73%) patients randomized to the AFREZZA and placebo groups, respectively.
[c] The percentage was calculated based on the number of patients randomized to the trial.

14.4 Pediatric Patients 6 Years of Age and Older with Type 1 and Type 2 Diabetes Mellitus

The efficacy of AFREZZA was assessed in an open-label 26-week, randomized active-controlled trial in 230 pediatric patients with type 1 or type 2 diabetes mellitus (NCT04974528). All patients were required to take basal insulin during the study. Patients were randomized (1:1) to receive either mealtime AFREZZA or RAA (insulin aspart, lispro, or glulisine; per investigator's choice) for 26 weeks. The primary efficacy endpoint was change in HbA1c from baseline to Week 26, with a pre-specified non-inferiority margin of 0.4% for the between-group difference in HbA1c. The mean age of patients was 12.6 years (range: 4 to 17 years in the RAA arm; 6 to 17 years in the AFREZZA arm). The majority (97.8%) had type 1 diabetes mellitus; a small subset (2.2%) had type 2 diabetes mellitus. The trial population had the following characteristics: 38% were female, 77% were White, 10% were Black or African American, 3% were Asian, 6% were multiracial, and 20% were Hispanic or Latino ethnicity.

Results

At Week 26, treatment with mealtime AFREZZA and basal insulin did not meet the primary endpoint of noninferiority, based on a noninferiority margin of 0.4% (See Table 10). Treatment with mealtime AFREZZA resulted in nominally inferior mean levels of HbA1c compared to treatment with mealtime RAA (Week 26 HbA1c 8.41% in the AFREZZA group; 8.22% in the RAA group). The confidence interval of the between-group difference in mean HbA1c reduction exceeded the pre-specified non-inferiority margin.

Table 10. Results at Week 26 in an Active-Controlled Study of AFREZZA plus Basal Insulin in Pediatric Patients Aged 6 Years and Older with Type 1 or Type 2 Diabetes Mellitus

Efficacy Parameter **Intention-to-treat population** [a]	**AFREZZA** **(N=117)**	**RAA** **(N=113)**
HbA1c (%)		
Baseline (adjusted mean[b])	8.22 (0.87)	8.21 (0.96)
Change from baseline mean[b]	0.19 (0.09)	0.01 (0.09)
Difference from RAA [b,c] (95% CI)	0.18 (-0.07, 0.44)	
Patients (%) achieving HbA1c ≤ 7%[d]	12 (10.3)	12 (10.6)

[a] The intent-to-treat population consists of all randomly assigned participants. At Week 26, the HbA1c endpoint was missing for 10% and 7% of patients randomized to Afrezza and RAA, respectively. Missing Week 26 data were imputed using return-to-baseline multiple imputation.

[b] Least-squares mean from ANCOVA adjusted for baseline value and other stratification factors.

[c] One-sided adjusted p-value = 0.058 > 0.025 for non-inferiority versus RAA. Statistical significance of non-inferiority of Afrezza was not demonstrated.

[d] The number is calculated based on observed HbA1c values at Week 26. Missing Week 26 data were treated as non-responder.

16 HOW SUPPLIED/STORAGE AND HANDLING

AFREZZA (insulin human) Inhalation Powder is available as 4 unit, 8 unit and 12 unit single-use cartridges. Three cartridges are contained in a single cavity of a blister strip. Each card contains 5 blister strips (each containing three cartridges) separated by perforations for a total of 15 cartridges. Two cards of the same cartridge strength are packaged in a foil laminate overwrap (30 cartridges per foil package).

The cartridges are color-coded, blue for 4 units, green for 8 units and yellow for 12 units. Each cartridge is marked with “afrezza” and “4 units”, “8 units” or “12 units”.

The AFREZZA Inhaler is individually packaged in a clear overwrap. The inhaler is fully assembled with a removable mouthpiece cover. The AFREZZA Inhaler can be used for up to 15 days from the date of first use. After 15 days of use, the inhaler must be discarded and replaced with a new inhaler.

AFREZZA (insulin human) Inhalation Powder is available in the following configurations:

NDC	**Cartridge Strength**	**Quantity of Cartridges per Strength**	**Total Quantity of Cartridges per Kit**	**Total Units in Kit**	**Number of Inhalers**
47918-874-90	4 units	90	90	360 Units	2
47918-878-90	8 units	90	90	720 Units	2
47918-891-90	12 units	90	90	1,080 Units	2
47918-898-18	8 units, 12 units	90	180	1,800 Units	2
47918-880-18 (Titration Pack)	4 units, 8 units	90	180	1,080 Units	2
47918-902-18 (Titration Pack)	4 units, 8 units, 12 units	60	180	1,440 Units	2

Storage:

Not in Use: Refrigerated Storage 2ºC to 8ºC (36ºF to 46ºF)

Sealed (Unopened) Foil Package	May be stored until the Expiration Date*
Sealed (Unopened) Blister Cards and Strips	Must be used within 1 month*

* If a foil package, blister card or strip is not refrigerated, the contents must be used within 10 days.

In Use: Room Temperature Storage 25ºC (77ºF), excursions permitted 15ºC to 30ºC (59ºF to 86ºF)

Sealed (Unopened) Blister Cards and Strips	Must be used within 10 days
Opened Strips	Must be used within 3 days

Do not put a blister card or strip back into the refrigerator after being stored at room temperature.

Inhaler Storage:
Store refrigerated or at room temperature 2ºC to 25ºC (36ºF to 77ºF); excursions permitted. Inhaler may be stored refrigerated, but should be at room temperature before use.

Handling:
Before use, cartridges should be at room temperature for 10 minutes.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Instruct patients to use AFREZZA only with the AFREZZA inhaler.

Acute Bronchospasm in Patients with Chronic Lung Disease
Advise patients that if they experience any respiratory difficulty after inhalation of AFREZZA, they should report it to their healthcare provider immediately for assessment *[see Warnings and Precautions (5.1)]*.

Hypoglycemia
Instruct patients on self-management procedures including glucose monitoring, proper inhalation technique, and management of hypoglycemia and hyperglycemia, especially at initiation of AFREZZA therapy. Instruct patients on handling of special situations such as intercurrent conditions (illness, stress, or emotional disturbances), an inadequate or skipped insulin dose, inadvertent administration of an increased insulin dose, inadequate food intake, or skipped meals *[see Warnings and Precautions (5.3)]*.

Inform patients that their ability to concentrate and react may be impaired as a result of hypoglycemia. Advise patients who have frequent hypoglycemia or reduced or absent warning signs of hypoglycemia to use caution when driving or operating machinery.

Advise patients that changes in insulin regimen can predispose to hyperglycemia or hypoglycemia and that changes in insulin regimen should be made under close medical supervision *[see Warnings and Precautions (5.2)]*.

Decline in Pulmonary Function
Inform patients that AFREZZA can cause a decline in lung function *[see Warnings and Precautions (5.4)]*.

Lung Cancer
Inform patients to promptly report any signs or symptoms potentially related to lung cancer *[see Warnings and Precautions (5.5)]*.

Diabetic Ketoacidosis
Instruct patients to carefully monitor their blood glucose during illness, infection, and other risk situations for DKA and to contact their healthcare provider if their blood glucose control worsens *[see Warnings and Precautions (5.6)]*.

Hypersensitivity Reactions
Advise patients that hypersensitivity reactions can occur with insulin therapy including AFREZZA. Inform patients on the symptoms of hypersensitivity reactions *[see Warnings and Precautions (5.7)]*.

Manufactured by: MannKind Corporation, Danbury, CT 06810
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Patent: www.mannkindcorp.com/patent-notices