



Insulin Human (Afrezza®) New Drug Update

Drug Name:	Insulin human
Trade Name (Manufacturer):	Afrezza (Sanofi-Aventis)
Form:	Inhalation powder
Strength:	4 unit (blue) and 8 unit (green) single-use cartridges
FDA Approval:	June 12, 2014
Market Availability:	Anticipated 1 st quarter 2015
FDA Approval Classification:	Standard Review
Classification:	Specific Therapeutic Class (HIC3): Hypoglycemics, Insulin and Related Agents (C4G)

INDICATION^{1,2,3}

Insulin inhalation powder (Afrezza) is a rapid-acting, orally inhaled insulin indicated to improve glycemic control in adults with Type 1 or Type 2 diabetes mellitus (T1DM, T2DM).

Insulin inhalation powder must be used with a long-acting insulin in patients with T1DM. It is not recommended for the treatment of diabetic ketoacidosis (DKA). Insulin inhalation powder should not be used in patients who smoke or who have recently stopped smoking, as safety and efficacy has not been established in this population.

PHARMACOKINETICS

Afrezza consists of Technosphere® insulin inhalation powder and the breath-powered Gen 2 inhaler. The Technosphere particles contain an inert excipient, fumaryl diketopiperazine (FDKP), which carries the insulin to the lungs. The insulin is rapidly absorbed across the alveolar wall and has a similar pharmacokinetic profile as endogenous insulin. The bioavailability of insulin inhalation powder is approximately 20-30 percent of subcutaneously administered insulin. Insulin inhalation powder has a more rapid absorption and onset of action and a shorter duration of action compared to subcutaneous (SC) regular human insulin (RHI) and rapid-acting analogues (RAA). The time to maximum plasma concentration (Tmax) is 12-15 minutes. The mean peak metabolic effect is 53 minutes for insulin inhalation powder versus three to four hours for RHI and 108 minutes for insulin lispro, respectively. The duration of action of insulin inhalation powder is 2.5-3 hours. Insulin inhalation powder is nearly completely cleared from the lungs within 12 hours.

CONTRAINDICATIONS/WARNINGS

A boxed warning instructs that insulin inhalation powder is contraindicated in patients with chronic lung disease, such as asthma or chronic obstructive pulmonary disease (COPD), since acute bronchospasm has been experienced in these patients. Prior to initiating therapy, all patients should be evaluated for potential lung disease, including detailed medical history, physical examination, and spirometry. The Food and Drug Administration requires a Risk Evaluation and Mitigation Strategy (REMS) program regarding use in patients with chronic lung disease and the need for evaluation of pulmonary function prior to start of therapy.⁴

Insulin inhalation powder is also contraindicated during episodes of hypoglycemia and in patients with a hypersensitivity to regular human insulin.

In long-term (up to two years) clinical studies, patients without chronic lung disease experienced a small decline (40 mL) in lung function as measured by forced expiratory volume in one second (FEV₁). This decline was observed within the first three months of therapy and persisted throughout the studies. Impact of treatment longer than two years and reversal of impairment after discontinuation has not been assessed. Pulmonary function should be monitored at baseline, after six months of therapy, and annually in all patients; or more frequently in those with symptoms such as wheezing, bronchospasm, cough, or difficulty breathing. Alternative therapy should be considered in patients who experience a decline of at least 20 percent in FEV₁ from baseline.

In clinical trials, the incidence of lung cancer reported in patients treated with Technosphere insulin inhalation powder (0.8 cases per 1,000 patient-years) did not exceed the rate that is expected in individuals with diabetes (one to two cases per 1,000 patient-years). Caution should be used in patients with current or previous lung cancer or who are at increased risk for lung cancer.

In clinical trials with T1DM patients, more patients using insulin inhalation powder experienced DKA than those receiving comparators (0.43 versus 0.14 percent, respectively). In patients at risk for DKA, such as those with an acute illness or infection, carefully monitor blood glucose and switch to an alternate route of administration if necessary.

As in all patients on antidiabetic therapy, glucose monitoring should be performed particularly when changes in insulin strengths, manufacturer, type, or method of administration are made.

All insulin products, including inhaled insulin, can lead to a hypokalemia. Serum potassium levels should be monitored in all patients at risk for hypokalemia, such as those using potassium-lowering medications, since.

Thiazolidinediones (TZDs) can cause dose-related fluid retention, particularly when used in combination with insulin, including insulin inhalation powder. Consider stopping TZD therapy if heart failure occurs.

DRUG INTERACTIONS

Many drugs can affect glucose metabolism and concurrent use with insulin products may require insulin dose adjustment.

Concomitant use of insulin inhalation powder with other antidiabetic agents, angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blocking (ARB) agents, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors (MAOIs), pentoxifylline, pramlintide, propoxyphene,

salicylates, octreotide, and sulfonamide antibiotics may increase the risk of hypoglycemia. Dose adjustments and increased frequency of glucose monitoring may be needed.

The glucose lowering effect of insulin inhalation powder may be decreased with concurrent use of atypical antipsychotics, corticosteroids, danazol, diuretics, estrogens, isoniazid, niacin, oral contraceptives, phenothiazines, protease inhibitors, somatropin, sympathomimetic agents and thyroid hormones. Dose adjustment and increased frequency of glucose monitoring may be needed.

Alcohol, beta-blockers, clonidine, and lithium salts may increase or decrease the efficacy of insulin inhalation powder. In addition, beta-blockers, clonidine, guanethidine, and reserpine may blunt the signs and symptoms of hypoglycemia when co-administered with insulin inhalation powder.

COMMON ADVERSE EFFECTS

The most common adverse events reported in clinical trials is hypoglycemia (mild-moderate in 95.4 percent of T1DM patients; severe in 18.4 percent of T1DM patients; non-severe in 67 percent of patients with T2DM; severe 5.1 percent of patients with T2DM), cough (26.9 percent) and throat pain or irritation (4.8 percent). Cough usually occurred within 10 minutes, was generally mild, dry, intermittent, and tended to decrease over time.

Clinical trials in subjects with T1DM, noted modest weight loss with insulin inhalation powder in contrast to weight gain with comparator insulin. In insulin-using T2DM subjects, insulin inhalation powder was associated with a more modest weight gain than comparator over the 52-week trial duration.

Increases in anti-insulin antibodies have been reported more frequently with insulin inhalation powder use as compared to SC administered mealtime insulins; however this was not associated with reduced efficacy.

SPECIAL POPULATIONS

Pregnancy

Pregnancy Category C.

Pediatrics

Safety and efficacy of insulin inhalation powder have not been established in pediatric patients.

Geriatrics

No overall differences in safety and efficacy have been observed between elderly and younger patients.

Hepatic Impairment

The effect of hepatic impairment on insulin inhalation powder therapy has not been studied. Dose adjustments and frequent blood glucose monitoring may be necessary.

Renal Impairment

The effect of renal impairment on insulin inhalation powder therapy has not been studied. Dose adjustments and frequent blood glucose monitoring may be necessary.

DOSAGES

Insulin inhalation powder (Afrezza) should only be administered via oral inhalation using the breath-powered inhaler provided. Insulin inhalation powder is administered at the beginning of the meal. The recommended initial mealtime dose is as listed:

- Insulin-naïve Individuals: 4 U at each meal.
- Individuals using SC mealtime insulin: Determine the insulin inhalation powder dose for each meal by using the dose conversion table provided in the package insert.
 - ❑ 4 U injected mealtime insulin dose = 4 U inhaled mealtime insulin dose
 - ❑ Round up to the nearest 4 U of insulin inhalation powder
- Individuals using SC pre-mixed insulin:
 - ❑ Estimate the mealtime injected dose by dividing half of the total daily injected pre-mixed insulin dose equally among the three meals of the day.
 - ❑ Convert each estimated injected mealtime dose to an appropriate insulin inhalation powder dose as outlined in the package insert dose conversion table.
 - ❑ Administer half of the total daily injected pre-mixed dose as an injected basal insulin dose.

Adjust dosage based on the patient's glycemic goal, blood glucose monitoring, and metabolic needs.

Multiple cartridges are necessary for insulin inhalation powder dosages above 8 U. Administer a single inhalation per cartridge. Only one inhaler should be used at a time. Replace the inhaler every 15 days.

Cartridges should be kept refrigerated and must be used within ten days at room temperature and three days if foil package is opened.

To administer, fully exhale, close lips around the mouthpiece, tilt the inhaler downward while keeping the head level, inhale deeply and hold breath as long as comfortable.

To avoid loss of drug powder once the drug cartridge has been inserted into the inhaler, the inhaler must be kept level and white mouthpiece on top and purple base on the bottom, the inhaler must not be shaken or dropped. If any of the above occurs, the cartridge should be replaced before use.

CLINICAL TRIALS

A literature search was performed using “insulin inhalation powder” and “technosphere”. Placebo-controlled trials were included in the absence of comparative trials.

It is important to note that in clinical studies 10 U and 20 U cartridges were used which is equivalent to approximately 4 IU and 8 IU subcutaneous insulin, respectively. To minimize confusion, the FDA agreed that the Afrezza cartridges would be labeled as 4 U and 8U, respectively.

Type 1 Diabetes

A 24-week open-label, active-controlled study enrolled patients with inadequately controlled T1DM to evaluate the glucose lowering effect of mealtime insulin inhalation powder used in combination with a basal insulin. During a four-week run-in period subjects were converted to mealtime insulin aspart using a one-to-one unit conversion and titrated their basal insulin dosage to achieve a fasting plasma glucose (FPG) < 120 mg/dL and ≥ 100 mg/dL (and not to exceed 180 mg/dL for eligibility). All subjects remained on their prior basal insulin (NPH, glargine, or detemir) throughout the study. After the run-in

period, 344 patients were randomized 1:1 to insulin inhalation powder or insulin aspart administered at each meal of the day. During the first 12 weeks mealtime and basal insulin doses were titrated to pre-specified glycemic goals, after which doses remained relatively unchanged and adjusted only for safety or change in patients' clinical status such as infection. Supplemental insulin doses were allowed in the inhaled insulin group. At week 24, the mean daily doses for inhaled insulin increased by 30.7 U (equivalent to approximately 7.7 U SC insulin) and for insulin aspart by 1.6 U. The mean daily basal insulin dose was also higher in the inhaled insulin group than the insulin aspart group, 37.1 U versus 31.6 U, respectively. At Week 24, treatment with basal insulin plus mealtime inhaled insulin provided less HbA1c reduction than insulin aspart (-0.21% versus -0.4%, respectively), and the difference (-0.19%) was statistically significant (95% CI 0.02 to 0.36). The mean reduction provided by basal insulin plus inhaled insulin narrowly met the pre-specified non-inferiority margin of 0.4%. A greater proportion of patient in the insulin aspart group achieved the HbA1c target of $\leq 7\%$ (30.7 versus 18.3 percent; $p=0.0158$). Patients treated with insulin inhalation powder experienced a mean decrease in weight of 0.39 kg, while those treated with insulin aspart showed a mean increase of 0.93 kg. Severe hypoglycemia was experienced in 18.4 percent of subjects on inhaled insulin and 29.2 percent of those on insulin aspart; the incidence of mild to moderate hypoglycemia was similar between the groups (96 and 99.6 percent, respectively). The most common respiratory adverse reaction was cough, which was reported in 31.6 percent of subjects in the inhaled insulin group and 2.3 percent for the insulin aspart group. Cough was generally mild and intermittent, but led to study discontinuation in 5.7 percent of subjects that received inhaled insulin and zero subjects on insulin aspart.

In a 52-week, open-label trial 539 patients with T1DM were randomized to insulin glargine (basal) plus either insulin inhalation powder or insulin aspart. Dose titration was permitted during the entire trial based on pre-meal and postprandial blood glucose levels. This trial did not meet its primary efficacy endpoint of noninferiority margin of 0.4% for insulin inhalation powder compared with insulin aspart. At Week 52 mean change in HbA1c was -0.13% and -0.37% for insulin inhalation powder and insulin aspart, respectively (difference 0.24; 95% CI 0.08, 0.404). A similar proportion of patients achieved HbA1c $\leq 7\%$ in both groups (16.3 versus 16 percent, respectively). Patients treated with insulin inhalation powder reported a mean decrease in weight of 0.5 kg, while those treated with insulin aspart showed a mean increase of 1.4 kg. Incidence of hypoglycemia was reported in 0.08 events/subject-month for the inhaled insulin group and 0.1 events/subject-month for the insulin aspart group.

Type 2 Diabetes

A 24-week double-blind, placebo-controlled trial, enrolled adults with T2DM inadequately controlled on optimal or maximally tolerated doses of metformin monotherapy, or at least two oral antidiabetic agents. Following a six-week run-in period, 353 patients were randomized (1:1) to add-on therapy with insulin inhalation powder or an inhaled placebo powder. Insulin doses were titrated for the first 12 weeks and remained stable thereafter. Oral antidiabetic doses remained unchanged. Open-label rescue therapy (insulin glargine or glimepiride) in addition to the study treatment was allowed in patients who experienced persistent or worsening hyperglycemia greater than pre-specified thresholds. At Week 24, the insulin group reported statistically significantly greater mean reduction in HbA1c compared to the placebo group (0.82 versus 0.42 percent; $p<0.0001$). A greater proportion of patients in the insulin group achieved the HbA1c target of $\leq 7\%$ (32.2 versus 15.3 percent, respectively; $p=0.0005$). Patients in the insulin group experienced a mean increase in weight of 0.5 kg, while those in the placebo group reported a mean decrease of 1.1 kg. Severe hypoglycemia was reported in 5.7

percent of patients on inhaled insulin and 1.7 percent of those who received placebo. Cough was reported in 24 percent of the active treatment group and 20 percent of the placebo group.

A 52-week, open-label trial randomized 618 patients with T2DM who had been receiving SC insulin therapy to a basal/bolus regimen with insulin glargine plus insulin inhalation powder or to a twice daily regimen with 70/30 biphasic insulin. For patients assigned to insulin glargine plus inhaled insulin, half of the total daily pre-randomization insulin dose was replaced with mealtime inhaled insulin and the remaining was replaced by basal insulin glargine. Dose titration was permitted throughout the study. At Week 52, mean change in HbA1c were -0.59% and -0.71% for insulin glargine/inhaled insulin and biphasic insulin, respectively. Non-inferiority (margin 0.4%) of inhaled insulin plus basal insulin was demonstrated compared to biphasic insulin (difference 0.12%; 95% CI -0.05%-0.29%). A greater proportion of patients in the biphasic insulin group achieved the HbA1c target of $\leq 7\%$ (26.8 versus 22.1 percent, respectively; $p=0.28$). A lower incidence of severe hypoglycemia, defined as blood glucose < 37 mg/dL, was reported with inhaled insulin/insulin glargine than biphasic insulin (4.3 versus 10 percent, respectively; $p<0.01$). Patients in the inhaled insulin/insulin glargine group experienced a mean increase in weight of 0.9 kg and those in the biphasic insulin group reported a mean increase of 2.5 kg.

OTHER DRUGS USED FOR CONDITION

Insulin and amylin agonists [e.g., pramlintide (Symlin®)] are FDA approved for the treatment of patients with T1DM.

Various injectable and oral agents are approved for the management of T2DM. Oral agents include metformin, sulfonylureas, alpha-glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, meglitinides, sodium-glucose cotransporter (SGLT2) inhibitors, and TZDs. Injectable products include insulin analogs, glucagon-like peptide-1 (GLP-1) receptor agonists, and pramlintide.

Insulin analogs include rapid-acting insulin analogs (insulin aspart [Novolog®], insulin glulisine [Apidra®] and insulin lispro [Humalog®]), with onsets of action within 15 minutes and durations of action of three to five hours. Short-acting regular insulins (Humulin® R, Novolin® R) have an onsets of action between 30 and 60 minutes. Intermediate-acting NPH insulins (Humulin® N, Novolin® N) demonstrate onsets of action between two and four hours. Long-acting insulins, with onsets of action ranging between two and six hours include insulin detemir (Levemir®) and insulin glargine (Lantus®). Finally, biphasic insulins, such as Humulin 70/30 and Novolin 70/30 have onsets between 30 and 60 minutes, and Humalog and Novolog have onsets less than 15 minutes.

PLACE IN THERAPY

According to the American Diabetes Association (ADA), most patients with T1DM should be treated with a multiple-dose insulin regimen or continuous subcutaneous insulin therapy.⁵ For patients with T2DM, insulin is recommended as add-on to an oral antidiabetic agent when an oral agent alone does not provide adequate glycemic control. Insulin therapy may be considered from the onset with or without other agents, in newly diagnosed T2DM patients with markedly symptomatic and/or elevated blood glucose level or HbA1c. In addition, many patients with T2DM may ultimately require insulin therapy. Insulin inhalation powder was not specifically discussed in this guidance.

In 2006 the FDA approved the first inhaled insulin product, Exubera® by Pfizer, for the management of T1DM and T2DM. However, due to lower than expected utilization, it was withdrawn from the market in 2007.

Differences between Afrezza and Exubera include pharmacokinetic profiles and delivery devices. Afrezza's pharmacokinetic profile mimics first phase insulin spike. Peak serum concentrations are 12-15 minutes for Afrezza and 30-90 minutes for Exubera. Peak metabolic effect is seen in less than one hour for Afrezza versus two hours for Exubera and subcutaneous regular human insulin. In addition, Afrezza's delivery device is more compact and easier to use than Exubera's inhaler. Exubera dosage was measured in milligrams rather than units. Both products required multiple cartridges or blisters to complete a dose.

Insulin inhalation powder (Afrezza) provides an alternative option for prandial (mealtime) insulin and should be prescribed with injectable basal insulin for T1DM and injectable basal insulin or oral antidiabetic agents for patients with T2DM. Inhaled insulin is associated with improved hypoglycemia profile and less weight gain/loss than comparators. The inhaled dosage form may be beneficial for adults with diabetes in whom the injectable administration is a barrier to insulin therapy, such as patients with visual impairment or neuropathy.

Afrezza is not a replacement for long- or intermediate-acting insulin therapy.

The FDA is requiring postmarketing studies including evaluating cardiovascular and long-term effects on pulmonary function, risk of pulmonary malignancy, as well as safety and efficacy in pediatrics.

SUGGESTED UTILIZATION MANAGEMENT

Anticipated Therapeutic Class Review (TCR) Placement	Hypoglycemics, Insulins
Clinical Edit	No history of smoking in the previous six months No history of chronic lung disease, such as asthma or COPD For patients with T1DM, verify concurrent use of a long-acting insulin
Quantity Limit	3 x 4 unit cartridges per day; 90 cartridges per 30 days 9 x 8 unit cartridges per day; 270 cartridges per 30 days
Duration of Approval	One year
Drug to Disease Hard Edit	Diabetes Mellitus (Types 1 and 2)

REFERENCES

1 Afrezza [package insert]. Danbury, CT; Mankind Corporation; June 2014.

2 Mankind Corp. Afrezza Briefing Document for Endocrine and Metabolic Drug Advisory Committee. April, 2014. Available at: <http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/endocrinologicandmetabolicdrugsadvisorycommittee/ucm390865.pdf>. Accessed January 5, 2015.

3 FDA Briefing Document – Endocrinology and Metabolic Drugs Advisory Committee Meeting. Afrezza. April 1, 2014. Available at: <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM390864.pdf>. Accessed January 19, 2015.

4 Federal Drug Administration. NDA 022472 Afrezza® (insulin human) Inhalation Powder Risk Evaluation and Mitigation Strategy. June, 2014. Available at: <http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM403785.pdf>. Accessed January 5, 2015.

5 American Diabetes Association Standards of Medical Care in Diabetes–2015, Approaches to Glycemic Treatment. Diabetes Care 2015 38:S5-S7; doi:10.2337/dc15-S004. Available at: http://care.diabetesjournals.org/content/38/Supplement_1. Accessed January 28, 2015.