Drug Monograph

Drug/Drug Class:	**Afrezza™ (insulin human) inhalation/ Rapid Acting Insulin**
Prepared for:	MO HealthNet
Prepared by:	Xerox Heritage, LLC

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms & Manufacturer:	Afrezza™ is available as 4 unit and 8 unit single-use cartridges. It is available in a kit containing 90-4 unit cartridges and 2 inhalers, a kit containing 60-4 unit cartridges and 30-8 unit cartridges and 2 inhalers, and a kit containing 30-4 unit cartridges and 60-8 unit cartridges and 2 inhalers. Manufactured by: MannKind Corporation, Danbury, CT 06810 Distributed by: Sanofi-Aventis U.S. LLC., Bridgewater, NJ 08807
Summary of Findings:	The efficacy of Afrezza™ inhaled insulin was demonstrated in two randomized clinical trials in adults with diabetes mellitus. In patients with type 1 diabetes (n=344), the adjusted mean reduction in HbA1c from baseline with basal insulin plus Afrezza™ inhaled insulin (-0.21%) was noninferior to the reduction with basal insulin plus insulin aspart (-0.4%), but only 13.8% of those who received Afrezza™ inhaled insulin achieved an HbA1c of 7% or less compared with 27.1% who received insulin aspart. In patients with type 2 diabetes who were uncontrolled on metformin alone or a combination of at least 2 oral medications (n=479), the addition of Afrezza™ inhaled insulin significantly reduced the adjusted mean HbA1c from baseline compared with placebo (-0.82% vs -0.42%) at 24 weeks.
Status Recommendation:	☐ Prior Authorization (PA) Required ☐ Open Access ☐ Clinical Edit ☒ PDL
Type of PA Criteria:	☐ Increased Risk of ADE ☐ Preferred Agent ☐ Appropriate Indications ☒ Under Solicitation

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payors are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction[2]

Diabetes is a disease in which your blood glucose, or blood sugar, levels are too high. Glucose comes from the foods you eat. Insulin is a hormone that helps the glucose get into your cells to give them energy. With type 1 diabetes, your body does not make insulin. With type 2 diabetes, the more common type, your body does not make or use insulin well. Without enough insulin, the glucose stays in your blood. Over time, having too much glucose in your blood can cause serious problems. It can damage your eyes, kidneys, and nerves. Diabetes can also cause heart disease, stroke and even the need to remove a limb.

Dosage Form(s) [1]

Afrezza™ is available as 4 unit and 8 unit single-use cartridges. It is available in a kit containing 90-4 unit cartridges and 2 inhalers, a kit containing 60-4 unit cartridges and 30-8 unit cartridges and 2 inhalers, and a kit containing 30-4 unit cartridges and 60-8 unit cartridges and 2 inhalers.

Manufacturer [1]

Manufactured by: MannKind Corporation, Danbury, CT 06810
Distributed by: Sanofi-Aventis U.S. LLC., Bridgewater, NJ 08807

Indication(s) [1]

Afrezza™ is indicated to improve glycemic control in adults with diabetes mellitus.

Clinical Efficacy [1,2] (mechanism of action/pharmacology, comparative efficacy)

Insulin stimulates peripheral glucose uptake in skeletal muscle and fat and inhibits hepatic glucose production. Insulin also inhibits proteolysis, lipolysis in adipocytes, and enhances protein synthesis.

Pharmacokinetics

	Afrezza*
Half-life	28-39 minutes

*Inhaled human insulin has similar metabolism and elimination to regular human insulin.

Afrezza™ Inhaled insulin was noninferior to insulin aspart in reducing mean HbA1c, but was not as effective as insulin aspart in achieving an HbA1c of 7% or less in patients with type 1 diabetes mellitus.

STUDY DESIGN	Randomized, open-label, active-controlled, 24-week clinical trial (n=344).
INCLUSION CRITERIA	Patients with inadequately controlled type 1 diabetes.
EXCLUSION CRITERIA	Not specified.
TREATMENT REGIMEN	Patients underwent a 4-week optimization period with basal insulin and then were randomized to receive Afrezza™ inhaled insulin (n=174) or insulin aspart (n=170) at every meal, with doses titrated for 12 weeks followed by stable doses for another 12 weeks.
RESULTS	The adjusted mean reduction in HbA1c from baseline with basal insulin plus Afrezza™ inhaled insulin (-0.21%) was noninferior to the reduction with basal insulin plus insulin aspart (-0.4%) at 24 weeks. Significantly less (13.8%) patients who received Afrezza™ inhaled insulin achieved an HbA1c of 7% or less compared with insulin aspart (27.1%).
SAFETY	Not specified.

The addition of inhaled insulin to oral antidiabetic agents significantly reduced the adjusted mean HbA1c from baseline compared with placebo.

STUDY DESIGN	Randomized, double-blind, placebo-controlled, 24-week clinical trial (n=479).
INCLUSION CRITERIA	Patients with type 2 diabetes who were uncontrolled on metformin alone or a combination of two or more oral medications.
EXCLUSION CRITERIA	Not specified.
TREATMENT REGIMEN	Patients were randomized to receive Afrezza™ inhaled insulin (n=177) or placebo (n=176), with insulin doses titrated for 12 weeks followed by stable doses for another 12 weeks. Doses of oral antidiabetic agents were kept stable throughout the study.
RESULTS	The addition of Afrezza™ inhaled insulin significantly reduced the adjusted mean HbA1c from baseline compared with placebo (-0.82% vs -0.42%) at 24 weeks. Of patients who received Afrezza™ inhaled insulin,

	32.2% achieved an HbA1c of 7% or less compared with 15.3% of patients who received placebo.
SAFETY	Not specified.

Contraindications [(1)]

- Chronic lung disease (eg, asthma or COPD); risk of acute bronchospasm
- During episodes of hypoglycemia
- Hypersensitivity to regular human insulin or other components of the product

Warnings and Precautions [(1)]

- Acute bronchospasm has been reported in patients with asthma and COPD; use contraindicated in this population; screening required in all patients.
- Fluid retention and heart failure may occur when used in combination with thiazolidinediones; monitoring required.
- Hypoglycemia, including severe cases, may occur, especially in patients with longstanding diabetes, diabetic nerve disease, hepatic or renal impairment, or changes in meal patterns, physical activity, or concomitant medication; monitoring required.
- Hyperglycemia may occur; monitoring required.
- Diabetic ketoacidosis has been reported, increased risk in patients with acute illness or infection; monitoring recommended.
- Hypokalemia may occur, especially in patients receiving potassium-lowering medication, medications sensitive to serum potassium concentrations, and IV insulin; monitoring recommended.
- Use caution in patients with hepatic impairment; monitoring recommended and dosage adjustment may be necessary.
- Hypersensitivity reactions, sometimes severe or life-threatening (eg, anaphylaxis), may occur.
- Use caution in patients with renal impairment; monitoring recommended and dosage adjustment may be necessary.
- Decline in pulmonary function has been reported; monitoring recommended.
- Consider risk vs benefits of treatment in patients with active lung cancer, a previous history of lung cancer, or who are at risk for lung cancer.

Adverse Effects [1]

Most common, ≥ 2%	Afrezza™ (n=1991)	Placebo (n=290)
Cough	25.6%	19.7%
Throat pain/irritation	4.4%	3.8%
Headache	3.1%	2.8%
Diarrhea	2.7%	1.4%
Productive cough	2.2%	1%
Fatigue	2%	0.7%
Nausea	2%	0.3%

Hypoglycemia	Afrezza™ (n=177)	Placebo (n=176)
Non-severe hypoglycemia	67%	30%
Severe hypoglycemia	5.1%	1.7%

Drug Interactions [1]

- Albuterol
- Antidiabetic agents
- Antihypertensive agents
- Disopyramide
- Fibrates
- Fluoxetine
- Lithium
- Monoamine oxidase inhibitors
- Pentamidine
- Pentoxifylline
- Pramlintide
- Propoxyphene
- Salicylates
- Somatostatin analogues: octreotide
- Sulfonamide antibiotics

Dosage and Administration [1]

The recommended starting dose is 4 units via oral inhalation at the beginning of each meal; adjust as clinically indicated.

Cost

GENERIC NAME	BRAND NAME	MANUFACTURER	STRENGTH	COST/ PACKAGE	COST*/ UNIT
Insulin human inhaled	Afrezza	MannKind	90-4 unit cartridges	$225.90	$0.63
			60-4 unit cartridges 30-8 unit cartridges	$252	$0.53
			30-4 unit cartridges 60-8 unit cartridges	$278.10	$0.46
Insulin aspart	Novolog	Novo Nordisk	100 units/mL, 10 mL vial	$203.20	$0.20
			100 units/mL, 3 mL pen cartridge, 5 pens	$392.55	$0.26

*WholesaleAcquisitionCost

Conclusion

Afrezza™ is a rapid-acting inhaled insulin indicated to improve glycemic control in adults with diabetes mellitus. It is administered in an inhaler that is breath-activated by a patient and used at the start of meals. The efficacy of Afrezza™ inhaled insulin was demonstrated in two randomized clinical trials. In patients with type 1 diabetes (n=344), the adjusted mean reduction in HbA1c from baseline with basal insulin plus Afrezza™ inhaled insulin (-0.21%) was noninferior to the reduction with basal insulin plus insulin aspart (-0.4%) at 24 weeks, but only 13.8% of those who received Afrezza™ inhaled insulin achieved an HbA1c of 7% or less compared with 27.1% who received insulin aspart. In patients with type 2 diabetes who were uncontrolled on metformin alone or a combination of at least two oral medications (n=479), the addition of Afrezza™ inhaled insulin significantly reduced the adjusted mean HbA1c from baseline compared with placebo (-0.82% vs -0.42%) at 24 weeks. Of patients who received Afrezza™ inhaled insulin, 32.2% achieved an HbA1c of 7% or less compared with 15.3% of patients who received placebo. Afrezza™ inhaled insulin is not a substitute for long-acting insulin and in patients with type 1 diabetes, it must be used with long-acting insulin. Afrezza™ Inhaled insulin should not be used to treat diabetic ketoacidosis and its use is not recommended in smokers or those who recently stopped smoking. Spirometry must be performed in all patients prior to initiating treatment as Afrezza™ inhaled insulin is contraindicated in patients with chronic lung disease due to the risk of acute bronchospasm.

Recommendation

This drug is being considered for inclusion in the state specific Preferred Drug List

References

1. Product Information: Afrezza™, insulin human inhalation powder. MannKind Corporation, Danbury, CT, 06/2014
2. Diabetes. Retrieved March 12, 2015 from http://www.nlm.nih.gov

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