Afrezza (regular human insulin, inhaled) Prior Authorization with Quantity Limit Program Summary

POLICY REVIEW CYCLE

Effective Date 04-01-2025 **Date of Origin**

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Afrezza® (regular human insulin, inhaled) Inhaled powder	To improve glycemic control in adult patients with diabetes mellitus. Limitations of use: • Not recommended for the treatment of diabetic ketoacidosis. • Not recommended in patients who smoke or who have recently stopped smoking.		1

See package insert for FDA prescribing information: https://dailymed.nlm.nih.gov/dailymed/index.cfm

CLINICAL RATIONALE

Diabetes	The American Diabetes Association (ADA) Standards of Medical Care in Diabetes recommends the following therapy for type 1 diabetes mellitus:(2) • Most individuals with type 1 diabetes should be treated with multiple daily injections of prandial and basal insulin, or continuous subcutaneous insulin infusion. • Most individuals with type 1 diabetes should use rapid-acting insulin analogs to reduce hyperglycemia risk. • Individuals with type 1 diabetes should receive education on how to match mealtime insulin doses to carbohydrate intake, fat and protein content, and anticipated physical activity. For type 2 diabetes mellitus (T2DM), the American Diabetes Association recommends the following:(2) • First-line therapy depends on comorbidities, patient-centered treatment factors, and management needs and generally includes metformin and comprehensive lifestyle modification. • The early introduction of insulin should be considered if there is evidence of ongoing catabolism (weight loss), if symptoms of hyperglycemia are present, or when A1C levels (greater than 10% [86 mmol/mol]) or blood glucose levels (greater than or equal to 300 mg/dL [16.7 mmol/L]) are very high. • Early combination therapy can be considered in some patients at treatment initiation to extend the time to treatment failure. • A patient-centered approach should guide the choice of pharmacologic agents. Consider the effects on cardiovascular and renal comorbidities,

	efficacy, hypoglycemia risk, impact on weight, cost and access, risk for side effects, and patient preferences. It has been shown that inhaled rapid-acting insulin used before meals in type 1 diabetes was shown to be noninferior for A1C lowering when compared with aspart insulin, with less hypoglycemia observed with inhaled insulin therapy. There was, however, a greater mean reduction in A1C with insulin aspart than with inhaled insulin (20.21% with inhaled vs. 20.40% with aspart, satisfying the noninferiority margin of 0.4%), and more patients in the insulin aspart group achieved A1C goals of less than or equal to 7.0% and less than or equal to 6.5%.(3) A pilot study found evidence that compared with injectable rapid-acting insulin, supplemental doses of inhaled insulin taken based on post-prandial glucose levels may improve blood glucose management without additional hypoglycemia or weight gain, although results from a larger study are needed for confirmation.(4) The American Association of Clinical Endocrinologists and American College of Endocrinology states that patients taking 2 oral antihyperglycemic agents who have an A1C greater than 8.0% and/or long standing T2DM are less likely to reach their target A1C with a third oral antihyperglycemic agent. Although adding a GLP1 receptor agonist as the third agent may successfully lower glycemia, eventually many patients will still require insulin. When insulin becomes necessary, a single daily dose of basal insulin should be added to the regimen. Patients whose glycemia remains uncontrolled while receiving basal insulin in combination with oral agents or GLP1 receptor agonists may require mealtime insulin to cover postprandial hyperglycemia. Rapid-acting injectable insulin analogs (lispro, glulisine, aspart, or fast-acting aspart) or inhaled insulin are preferred over regular human insulin because the former have a more rapid onset and offset of action and are associated with less hypoglycemia.(5) For the treatment of T1DM, regimens that provide both basal and prandial insulin should be used for most patients.(6)
Efficacy	Afrezza was studied in adults with type 1 diabetes in combination with basal insulin. The efficacy of Afrezza in type 1 diabetes patients 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. The efficacy of Afrezza in patients who smoke has not been established.(1)
Safety	Afrezza contains the following black box warning concerning patients with chronic lung disease:(1) • Acute bronchospasm has been observed in patients with asthma and COPD using Afrezza • Afrezza is contraindicated in patients with chronic lung disease such as asthma or COPD • Before initiating Afrezza, perform a detailed medical history, physical examination, and spirometry (FEV1) to identify potential lung disease in all patients. Acute bronchospasm has been observed following Afrezza dosing in patients with asthma and patients with COPD. In a study of patients with asthma, bronchoconstriction and wheezing following Afrezza dosing was reported in 29% (5 out of 17) and 0% (0 out of 13) of patients with and without a diagnosis of asthma, respectively. In this study, a mean decline in FEV1 of 400 mL was observed 15 minutes after a single dose in patients with asthma. In a study of patients with COPD (n=8), a mean decline in FEV1 of 200 mL was observed 18 minutes after a single dose of Afrezza. The long-term safety and efficacy of AFREZZA in patients with chronic lung disease has not been established.(1) Afrezza causes a decline in lung function over time as measured by FEV1. 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 FEV1 decline than comparator-treated patients. The FEV1 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 FEV1 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 FEV1 after discontinuation of Afrezza. The observed changes in FEV1 were similar in patients with type 1 and type 2 diabetes. 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 greater than or equal to 20% in FEV1 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.(1) Contraindications to Afrezza include:(1) • Use during episodes of hypoglycemia • Chronic lung disease, such as asthma, or chronic obstructive pulmonary disease • Hypersensitivity to regular insulin or any of the inhaled regular human insulin excipients

REFERENCES

Number	Reference
1	Afrezza prescribing information. Mannkind Corporation. February 2023.
2	ElSayed NA, Aleppo G, Bannuru RR, et al. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2024. Diabetes Care. 2023;47(Supplement_1):S158-S178. doi:10.2337/dc24-s009.
3	Bode BW, McGill JB, Lorber DL, et al. Inhaled Technosphere Insulin Compared With Injected Prandial Insulin in Type 1 Diabetes: A Randomized 24-Week Trial. *Diabetes Care* 2015;38:2266-2273. https://care.diabetesjournals.org/content/38/12/2266.full-text.pdf.
4	Akturk HK, Snell-Bergeon JK, Rewers A, et al. Improved Postprandial Glucose with Inhaled Technosphere Insulin Compared with Insulin Aspart in Patients with Type 1 Diabetes on Multiple Daily Injections: The STAT Study. Diabetes Technol Ther 2018 Oct;20(10):639-647. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6161328/
5	Garber AJ, Handelsman Y, Grunberger G, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Comprehensive Type 2 Diabetes Management Algorithm - 2020 Executive Summary. *Endocr Pract.* 2020 Jan;26(1):107-139. https://www.aace.com/pdfs/diabetes/algorithm-exec-summary.pdf.
6	American Association of Clinical Endocrinologists (AACE) Diabetes Resource Center. Treatment of Type 1 Diabetes. https://www.aace.com/disease-and-conditions/diabetes/type-1-diabetes.

POLICY AGENT SUMMARY PRIOR AUTHORIZATION

Target Brand Agent(s)	Target Generic Agent(s)	Strength	Targeted MSC	Available MSC	Final Age Limit	Preferred Status
Afrezza	insulin regular (human) inh powd ; insulin regular (human) inhal powd ; insulin regular (human) inhalation powder	12 UNIT ; 4 UNIT ; 60x4 &60x8 & 60x12 UNIT ; 8 UNIT ; 90 x 4 UNIT & 90x8 UNIT ; 90 x 8 UNIT & 90x12 UNIT	M ; N ; O ; Y	N		

POLICY AGENT SUMMARY QUANTITY LIMIT

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	QL Amount	Dose Form	Day Supply	Duration	Addtl QL Info	Allowed Exceptions	Targeted NDCs When Exclusions Exist
Afrezza	Insulin Regular (Human) Inh Powd 4 & 8 & 12 Unit/Cart (60)	60x4 &60x8 & 60x12 UNIT	1260	Cartridges	30	DAYS			
Afrezza	Insulin Regular (Human) Inh Powd 90 x 8 Unit & 90 x 12 Unit	90 x 8 UNIT & 90x12 UNIT	1080	Cartridges	30	DAYS			
Afrezza	Insulin Regular (Human) Inhal Powd 90 x 4 Unit & 90 x 8 Unit	90 x 4 UNIT & 90x8 UNIT	1800	Cartridges	30	DAYS			
Afrezza	Insulin Regular (Human) Inhalation Powder 12 Unit/Cartridge	12 UNIT	900	Cartridges	30	DAYS			
Afrezza	Insulin Regular (Human) Inhalation Powder 4 Unit/Cartridge	4 UNIT	2520	Cartridges	30	DAYS			
Afrezza	Insulin Regular (Human) Inhalation Powder 8 Unit/Cartridge	8 UNIT	1260	Cartridges	30	DAYS			

CLIENT SUMMARY – PRIOR AUTHORIZATION

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Afrezza	insulin regular (human) inh powd ; insulin regular (human) inhal powd ; insulin regular (human) inhalation powder	12 UNIT ; 4 UNIT ; 60x4 &60x8 & 60x12 UNIT ; 8 UNIT ; 90 x 4 UNIT & 90x8 UNIT ; 90 x 8 UNIT & 90x12 UNIT	Commercial ; HIM ; ResultsRx

CLIENT SUMMARY – QUANTITY LIMITS

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Afrezza	Insulin Regular (Human) Inh Powd 4 & 8 & 12 Unit/Cart (60)	60x4 &60x8 & 60x12 UNIT	Commercial ; HIM ; ResultsRx
Afrezza	Insulin Regular (Human) Inh Powd 90 x 8 Unit & 90 x 12 Unit	90 x 8 UNIT & 90x12 UNIT	Commercial ; HIM ; ResultsRx
Afrezza	Insulin Regular (Human) Inhal Powd 90 x 4 Unit & 90 x 8 Unit	90 x 4 UNIT & 90x8 UNIT	Commercial ; HIM ; ResultsRx
Afrezza	Insulin Regular (Human) Inhalation Powder 12 Unit/Cartridge	12 UNIT	Commercial ; HIM ; ResultsRx
Afrezza	Insulin Regular (Human) Inhalation Powder 4 Unit/Cartridge	4 UNIT	Commercial ; HIM ; ResultsRx
Afrezza	Insulin Regular (Human) Inhalation Powder 8 Unit/Cartridge	8 UNIT	Commercial ; HIM ; ResultsRx

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval

Preferred Agent(s)	Non-Preferred Agent(s)
Fiasp (insulin aspart) **Humalog** (insulin lispro) **Humalog U200** (insulin lispro) **Lyumjev** (insulin lispro-aabc) **NovoLog** (insulin aspart)	**Admelog** (insulin lispro) **Apidra** (insulin glulisine) **Insulin aspart** **Insulin lispro**

Initial Evaluation

Target Agent(s) will be approved when ALL of the following are met:

1. ONE of the following:
   A. The patient has a diagnosis of diabetes mellitus type 1 AND the patient is currently on long acting insulin therapy **OR**
   B. The patient has a diagnosis of diabetes mellitus type 2 **AND**
2. The patient has received ALL of the following to identify any potential lung disease:
   A. Detailed medical history review **AND**
   B. Physical examination **AND**
   C. Spirometry with Forced Expiratory Volume in 1 second (FEV1) **AND**
3. The patient has not smoked in the past 6 months **AND**
4. If the patient has an FDA labeled indication, then ONE of the following:
   A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR**
   B. There is support for using the requested agent for the patient's age for the requested indication **AND**
5. ONE of the following:
   A. The patient has an intolerance or hypersensitivity to a preferred rapid acting insulin agent that is not expected to occur with the requested agent **OR**
   B. The patient has an FDA labeled contraindication to a preferred rapid acting insulin agent **OR**
   C. There is support that the patient has a physical or a mental disability that would prevent them from using a preferred rapid acting insulin agent(s) **OR**
   D. The patient has a documented needle phobia **AND**
6. The patient does NOT have any FDA labeled contraindications to the requested agent

Length of Approval: 12 months

NOTE: Quantity Limit applies, please refer to Quantity Limit Criteria.

Renewal Evaluation

Target Agent(s) will be approved when ALL of the following are met:

1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND**
2. The patient has had clinical benefit with the requested agent **AND**
3. The patient has received ALL of the following to identify any potential lung disease:
   A. Detailed medical history review **AND**
   B. Physical examination **AND**
   C. Spirometry with Forced Expiratory Volume in 1 second (FEV1) **AND**
4. The patient has not smoked in the past 6 months **AND**
5. The patient does NOT have any FDA labeled contraindications to the requested agent

Module	Clinical Criteria for Approval
	Length of Approval: 12 months NOTE: Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
QL with PA	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose **AND** C. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **Length of Approval:** up to 12 months