Medical Policy

BlueCross BlueShield of Kansas
An independent licensee of the Blue Cross Blue Shield Association

Title: Afrezza (human insulin)

- **Prime Therapeutics will review Prior Authorization requests**

Prior Authorization Form:
http://www.bcbsks.com/CustomerService/Forms/pdf/PriorAuth-6146KS-AFRE.pdf

Link to Drug List (Formulary):
https://www.bcbsks.com/drugs/

Professional
Original Effective Date: January 23, 2015
Revision Date(s): June 1, 2015; October 1, 2015; April 15, 2016; April 29, 2016; September 1, 2016; February 1, 2017; April 1, 2017; July 15, 2017; April 1, 2018
Current Effective Date: April 1, 2018

Institutional
Original Effective Date: January 23, 2015
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Current Effective Date: April 1, 2018

State and Federal mandates and health plan member contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. To verify a member's benefits, contact Blue Cross and Blue Shield of Kansas Customer Service.

The BCBSKS Medical Policies contained herein are for informational purposes and apply only to members who have health insurance through BCBSKS or who are covered by a self-insured group plan administered by BCBSKS. Medical Policy for FEP members is subject to FEP medical policy which may differ from BCBSKS Medical Policy.

The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents of Blue Cross and Blue Shield of Kansas and are solely responsible for diagnosis, treatment and medical advice.

If your patient is covered under a different Blue Cross and Blue Shield plan, please refer to the Medical Policies of that plan.

DESCRIPTION

The intent of the Afrezza prior authorization with quantity limit is to encourage appropriate use and the use of cost-effective preferred rapid acting insulin product(s). The program defines appropriate use of Afrezza as requiring patients to have a diagnosis of diabetes mellitus type 1 who are on concomitant long acting insulin therapy or diagnosis of diabetes mellitus type 2; who has received a detailed medical history, physical examination, and spirometry with Forced Expiratory Volume in 1 second (FEV1) to identify potential lung disease; who have not smoked in the past 6 months; and who do not have contraindications to Afrezza. The program also requires the patient to have a documented intolerance, FDA labeled contraindication, or hypersensitivity to the preferred rapid acting insulin product(s) that is not expected to occur with the requested product(s). The program will also accommodate for those with a documented needle phobia and for those with a physical or mental disability that will prevent the patient from using the preferred rapid acting insulin product(s). The program will also support a quantity limit of 10,080 units of insulin every 30 days. Requests for Afrezza will be reviewed when patient-specific documentation is provided.

Target Agents

- **Afrezza**® (regular human insulin inhaled)

FDA Labeled Indications[1]

Insulin Product	Indication	Dosage and Administration	Limitation of Use
Afrezza® (regular human insulin, inhaled)	Rapid acting insulin indicated to improve glycemic control in adult patients with diabetes mellitus.	Administer using a single inhalation per cartridge. Administer at the beginning of a meal. Dosing must be individualized. Before initiating, perform a detailed medical history, physical examination, and spirometry with Forced Expiratory Volume in 1 second (FEV1) in all patients to identify potential lung disease.	Patients with type 1 diabetes, must use with a long-acting insulin. Not recommended for the treatment of diabetic ketoacidosis. Not recommended in patients who smoke or who have recently stopped smoking.

POLICY

Prior Authorization and Quantity Limit Criteria for Approval

Afrezza will be approved when ALL of the following are met:

1. The patient has ONE of the following diagnoses:
   a. The patient has a diagnosis of diabetes mellitus type 1 AND the patient is on concurrent long acting insulin therapy in the past 90 days
      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. The patient does not have any FDA labeled contraindication(s) to Afrezza
   AND
5. ONE of the following:
   a. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to the preferred rapid acting insulin product(s) that is not expected to occur with the requested product
      OR
   b. The prescriber has documented that the patient has a physical or a mental disability that would prevent him/her from using a preferred rapid acting insulin product(s)
      OR
   c. The patient has a documented needle phobia
   AND
6. ONE of the following:
   a. The quantity requested is less than or equal to the program quantity limit
      OR
   b. The quantity (dose) requested is greater than the program quantity limit and the prescriber has submitted documentation in support of therapy with a higher dose/ quantity for the intended diagnosis

Length of Approval: 12 months

FDA Labeled Contraindications	
Agent	**Contraindications**
Afrezza	▪ During episodes of hypoglycemia ▪ Chronic lung disease, such as asthma, or chronic obstructive pulmonary disease ▪ Hypersensitivity to regular human insulin or any of the Afrezza excipients

Program Quantity Limits	
Brand (generic)	**Quantity Limit**
Afrezza (human insulin, inhaled)	
4 units cartridge packs	2,520 cartridges / 30 days
8 unit cartridge packs	1,260 cartridges / 30 days
12 unit cartridge packs	900 cartridges / 30 days
30 x 4 unit cartridge + 60 x 8 unit cartridge mix packs	1,530 cartridges / 30 days
60 x 4 unit cartridge + 30 x 8 unit cartridge mix packs	1,890 cartridges / 30 days
60 X 8 unit cartridge + 30 x 12 unit cartridge mix packs	1,080 cartridges / 30 days
90 x 4 unit cartridge + 90 x 8 unit cartridge mix packs	1,800 cartridges / 30 days
60 x 4 unit cartridge + 60 x 8 unit cartridge + 60 x 12 unit cartridge mix packs	1,260 cartridges / 30 days

RATIONALE

The American Diabetes Association (ADA) Standards in diabetes mellitus recommend the following therapy for type 1 diabetes mellitus:[3]

- Use of multiple-dose insulin injections (3-4 injections per day of basal and prandial insulin) or continuous subcutaneous insulin infusion (CSII) therapy
- Matching prandial insulin to carbohydrate intake, pre-meal blood glucose, and anticipated activity
- Most patients should use insulin analogs to reduce hypoglycemic risk

For type 2 diabetes mellitus (T2DM), the American Diabetes Association recommends the following:

- Metformin, if not contraindicated and if tolerated, is the preferred initial pharmacological agent for type 2 diabetes
- Consider initiating insulin therapy (with or without additional agents) in patients with newly diagnosed type 2 diabetes and markedly symptomatic and/or elevated blood glucose levels or A1C
- If noninsulin monotherapy at maximum tolerated dose does not achieve or maintain the A1C target over 3 months, then add a second oral agent, a glucagon-like peptide 1 receptor agonist, or basal insulin
- A patient-centered approach should be used to guide the choice of pharmacological agents. Considerations include efficacy, cost, potential side effects, weight, comorbidities, hypoglycemia risk, and patient preferences.
- For patients with type 2 diabetes who are not achieving glycemic goals, insulin therapy should not be delayed

The ADA states that inhaled rapid-acting insulin used before meals in type 1 diabetes was shown to be non-inferior for A1C lowering when compared with aspart insulin, with less hypoglycemia. observed with inhaled insulin therapy. There was, however, a greater mean reduction 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 ≤7.0% and ≤6.5%. [3]

The AACE/ACE algorithm recommends insulin for T2DM when noninsulin antihyperglycemic therapy fails to achieve target glycemic control or when a patient has symptomatic hyperglycemia. Therapy with long-acting basal insulin is preferred. If glycemic control is not achieved with basal insulin, prandial insulin can be added. Preference should be given to rapid-acting insulins (the analogs lispro, aspart, and glulisine or inhaled insulin) over regular human insulin because the former have a more rapid onset and offset of acting and are associated with less hypoglycemia. For the treatment of T1DM, regimens that provide both basal and prandial insulin should be used.[2]

Efficacy[1]
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.

Safety[1]
Contraindications to Afrezza include:

- 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.

Afrezza contains the following black box warnings:

- 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.

The most common adverse reactions associated with Afrezza (2% or greater incidence) are hypoglycemia, cough, and throat pain or irritation.

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.

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 ≥ 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.

REVISIONS

01-23-2015	Afrezza added to New to Market Drug medical policy (effective 01-23-2015).
06-01-2015	Stand-alone policy published 04-21-2015.
10-01-2015	Published 11-10-2015. Administrative Update retro-effective to 10-01-2015.
	In Policy section: ▪ Updated Quantity Limit chart.
04-15-2016	Policy language reviewed with no changes
	Rationale section updated
	References updated
04-29-2016	Corrected Current Effective Date from 04-15-2016 to 10-01-2015 since no policy language changes were made.
09-01-2016	Published 10-12-2016. Retro-effective to 09-01-2016
	In Policy section: ▪ Updated Quantity Limit chart by adding a new product, 90x4 unit + 90x8 unit cartridge mix pack as a target
02-01-2017	Policy published 04-01-2017. Policy retro-effective to 02-01-2017.
	In Policy section: ▪ Quantity Limits chart updated with new package size of Afrezza.
04-01-2017	Description section updated
	Rationale section updated
	References updated
07-15-2017	Policy published 08-01-2017. Policy retro-effective to 07-15-2017.
	In Policy section: ▪ Added availability of 8u and 12u packs with specified quantity limits
04-01-2018	Description section updated.
	In Policy section: ▪ In Item 5 c removed "diagnosis" to read "The patient has a documented needle phobia"
	Rationale section updated
	References updated

REFERENCES

1. Afrezza prescribing information. Mannkind Corporation. September 2017.
2. Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm. 2017 Executive Summary. *Endocr Pract.* 2017 Feb;23(2):207-238.
3. American Diabetes Association. Standards of Medical Care in Diabetes-2017. *Diabetes Care* 2017;40 (Supp 1): S1-S135.