This program applies to FlexRx Open, FlexRx Closed, GenRx Open and GenRx Closed formularies.

This is a FlexRx Standard and GenRx Standard program.

The BCBS MN Step Therapy Supplement also applies to this program for all Commercial/HIM lines of business.

Program specific denial language for prerequisite step therapy component does not apply. Instead, supplemental program denial language will apply.

**FDA LABELED INDICATIONS**

<table>
<thead>
<tr>
<th>Insulin Product</th>
<th>Indication</th>
<th>Dosage and Administration</th>
<th>Limitation of Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afrezza® (regular human insulin, inhaled)</td>
<td>Rapid acting insulin indicated to improve glycemic control in adult patients with diabetes mellitus.</td>
<td>Administer using a single inhalation per cartridge.</td>
<td>Patients with type 1 diabetes, must use with a long-acting insulin.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Administer at the beginning of a meal.</td>
<td>Not recommended for the treatment of diabetic ketoacidosis.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dosing must be individualized.</td>
<td>Not recommended in patients who smoke or who have recently stopped smoking.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>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.</td>
<td></td>
</tr>
</tbody>
</table>

**CLINICAL RATIONALE**

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

- 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 (≥300mg/dl) or A1C (≥10%)
- If noninsulin monotherapy at maximum tolerated dose does not achieve or maintain the A1C target over 3 months, then add a second agent, (sulfonylurea, thiazolidinedione, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 receptor agonist, or basal insulin), keeping patient factors in mind
• A patient-centered approach should be used to guide the choice of pharmacological agents. Considerations include efficacy, hypoglycemia risk, history of atherosclerotic cardiovascular disease, impact on weight, potential side effects, renal effects, delivery method (oral versus subcutaneous) cost, and patient preferences.
• For patients with type 2 diabetes who are not achieving glycemic goals, drug intensification, including consideration of 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 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 ≤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
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
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.

References:
Afrezza® Prior Authorization with Quantity Limit

OBJECTIVE
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)

PROGRAM PRIOR AUTHORIZATION AND QUANTITY LIMITS

<table>
<thead>
<tr>
<th>Brand (generic)</th>
<th>GPI</th>
<th>Multisource Code</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afrezza (human insulin, inhaled)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 units cartridge packs</td>
<td>27104010002940</td>
<td>M, N, O, Y</td>
<td>2,520 cartridges / 30 days</td>
</tr>
<tr>
<td>8 unit cartridge packs</td>
<td>27104010002950</td>
<td>M, N, O, Y</td>
<td>1,260 cartridges / 30 days</td>
</tr>
<tr>
<td>12 unit cartridge packs</td>
<td>27104010002955</td>
<td>M, N, O, Y</td>
<td>900 cartridges / 30 days</td>
</tr>
<tr>
<td>30 x 4 unit cartridge mix packs</td>
<td>27104010002970</td>
<td>M, N, O, Y</td>
<td>1,530 cartridges / 30 days</td>
</tr>
<tr>
<td>60 x 4 unit cartridge mix packs</td>
<td>27104010002975</td>
<td>M, N, O, Y</td>
<td>1,890 cartridges / 30 days</td>
</tr>
<tr>
<td>60 x 8 unit cartridge mix packs</td>
<td>27104010002986</td>
<td>M, N, O, Y</td>
<td>1,080 cartridges / 30 days</td>
</tr>
<tr>
<td>90 x 4 unit cartridge mix packs</td>
<td>27104010002978</td>
<td>M, N, O, Y</td>
<td>1,800 cartridges / 30 days</td>
</tr>
<tr>
<td>60 x 4 unit cartridge mix packs</td>
<td>27104010002990</td>
<td>M, N, O, Y</td>
<td>1,260 cartridges / 30 days</td>
</tr>
<tr>
<td>90 x 8 unit cartridge mix packs</td>
<td>27104010002988</td>
<td>M, N, O, Y</td>
<td>1,080 cartridges / 30 days</td>
</tr>
</tbody>
</table>

PRIOR AUTHORIZATION AND QUANTITY LIMIT CRITERIA FOR APPROVAL

Target Agent 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)

3. The patient has not smoked in the past 6 months

4. The patient does not have any FDA labeled contraindication(s) to Afrezza

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

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 which has been reviewed and approved by the Clinical Review pharmacist

**Length of Approval:** 12 months
Step Therapy Supplement

This program applies to FlexRx Closed, FlexRx Open, GenRx Closed, GenRx Open, Health Insurance Marketplace, FocusRx and KeyRx formularies.

Please note, this does not include or apply to quantity limit questions.

STEP THERAPY SUPPLEMENT

OBJECTIVE
The intent of the Step Therapy Supplement is to provide additional questions, to ensure compliance to MN Statute 62Q.184. These questions will apply if the step therapy component within a Prior Authorization or Step Therapy program is not able to be approved.

CONDITIONS FOR APPROVAL
The requested agent will be approved when ONE of the following are met:

1. The patient is currently being treated with the requested agent as indicated by ALL of the following:
   a. A statement by the prescriber that the patient is currently taking the requested agent
   AND
   b. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent
   AND
   c. The prescriber states that a change in therapy is expected to be ineffective or cause harm

   OR

2. The patient’s medication history include the required prerequisite/preferred agent(s) as indicated by:
   a. Evidence of a paid claim(s) within the past 999 days
   OR
   b. The prescriber has stated that the patient has tried the required prerequisite/preferred agent(s) in the past 999 days AND the required prerequisite/preferred agent(s) was discontinued due to lack of effectiveness or an adverse event

   OR

3. The prescriber has provided documentation that the required prerequisite/preferred agent(s) cannot be used due to a documented medical condition or comorbid condition that is likely to cause an adverse reaction, decrease ability of the patient to achieve or maintain reasonable functional ability in performing daily activities or cause physical or mental harm

Length of Approval: As per program specific criteria