BlueCross BlueShield of Alabama

Inhaled Antibiotics Duplicate Therapy Prior Authorization Program Summary

This prior authorization applies to Commercial, GenPlus, and Health Insurance Marketplace formularies.

OBJECTIVE
The intent of the Inhaled Antibiotics Duplicate Therapy program is to encourage use of inhaled antibiotic therapy for Cystic Fibrosis according to the Food and Drug Administration (FDA) approved labeling and/or clinical practice guidelines. The program will require the patient has a diagnosis of cystic fibrosis and is not using tobramycin inhalation and aztreonam inhalation concomitantly. The program will review the prescription claims history for members seeking use of either tobramycin inhalation or aztreonam inhalation with the other agent. If dual therapy is found, the claim will reject.

TARGET DRUGS
Bethkis® (tobramycin solution for inhalation)
Cayston® (aztreonam lysine inhalation solution)
Kitabis Pak (tobramycin inhalation solution with PARI LC PLUS Reusable Nebulizer)
[a]**TOBI®** (tobramycin solution for inhalation)
TOBI® Podhaler™ (tobramycin inhalation powder)
[a] – generic available

Brand (generic)	GPI	Multi source code
Bethkis (tobramycin)		
300 mg/4 mL nebulizer	07000070002530	M, N, O, or Y
Cayston (aztreonam)		
75 mg inhalation solution	16140010402120	M, N, O, or Y
Kitabis Pak (tobramycin inhalation solution)		
300 mg/5 mL nebulizer	07000070002520	M, N, O, or Y
TOBI (tobramycin solution for inhalation)		
300 mg/5 mL nebulizer	07000070002520	M, N,O, or Y
TOBI Podhaler (tobramycin inhalation powder)		
28 mg inhalation capsule	07000070000120	M, N, O, or Y

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL
Bethkis (tobramycin solution for inhalation), Cayston (aztreonam lysine inhalation solution), Kitabis Pak (tobramycin inhalation solution with PARI LC PLUS Reusable Nebulizer), TOBI (tobramycin solution for inhalation) or TOBI Podhaler (tobramycin inhalation powder) will be approved when BOTH of the following are met:

1. The patient has a diagnosis of cystic fibrosis
   AND
2. ONE of the following:
   a. The patient is not currently (within the previous 60 days) treated with another inhaled antibiotic for Cystic Fibrosis
      OR
   b. The patient is currently (within the previous 60 days) treated with another inhaled antibiotic for Cystic Fibrosis and the prescriber states that prior therapy

with the other agent will be discontinued and that therapy will be continued only with the requested agent

Length of Approval: 12 months

This pharmacy policy is not an authorization, certification, explanation of benefits or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All pharmacy policies are based on (i) information in FDA approved package inserts (and black box warning, alerts, or other information disseminated by the FDA as applicable); (ii) research of current medical and pharmacy literature; and/or (iii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

The purpose of Blue Cross and Blue Shield of Alabama's pharmacy policies are to provide a guide to coverage. Pharmacy policies are not intended to dictate to physicians how to practice medicine. Physicians should exercise their medical judgment in providing the care they feel is most appropriate for their patients.

Neither this policy, nor the successful adjudication of a pharmacy claim, is guarantee of payment.

FDA APPROVED INDICATION[1,2,13,14,15]

Drug	Management of cystic fibrosis patients with *Pseudomonas aeruginosa*	Administration and Dosing[f]
Bethkis [tobramycin solution for inhalation] 300 mg/4 mL	✓[a]	300 mg (one single-use ampule) twice daily for 28 days. Administered in repeated cycles of 28 days on/28 days off.[g]
Cayston [aztreonam lysine inhalation solution (AZLI)] 75 mg	✓[c]	75 mg (one single-use vial) three times daily for 28 days[d,e] Follow with 28 days off therapy
Kitabis Pak [co-packaging of tobramycin inhalation solution with PARI LC PLUS Reusable Nebulizer]	✓[a]	300 mg (one single-use ampule) twice daily in alternating periods of 28 days on drug, followed by 28 days off drug[b]
***TOBI** [tobramycin solution for inhalation (TSI)] 300 mg	✓[a]	300 mg (one single-use ampule) every 12 hours[b] for 28 days Follow with 28 days off therapy, and then resume for the next 28 day on/28 day off cycle
TOBI Podhaler [tobramycin inhalation powder]	✓[a]	Inhale 4 – 28 mg capsules twice daily for 28 days[h]. Follow with 28 days off therapy then resume next cycle

*-generic available
a – Patients 6 years of age and older. Safety and efficacy not demonstrated in patients with FEV_1 < 40% or >80% (for Bethkis), <25% or >75% (for TOBI), and <25% or >80% (for TOBI Podhaler) predicted or patients colonized with *Burkholderia cepacia.*
b – Administer over 15 minutes. Take doses as close to 12 hours apart as possible and at least 6 hours apart. Use only with a PARI LC PLUS™ Reusable Nebulizer and a DeVilbiss® Pulmo-Aide® air compressor.
c – Patients 7 years of age and older. Safety and efficacy not demonstrated in patients with FEV_1 <25% or >75% predicted or patients colonized with *Burkholderia cepacia.*
d – Administer over 2-3 minutes. Take at least 4 hours apart. Reconstitute with 1 mL of sterile diluent (0.17% sodium chloride) and use immediately. Use only with an Altera Nebulizer System.
e – Use bronchodilator before administration of Cayston. Short-acting bronchodilators can be taken between 15 minutes and 4 hours prior to each dose of Cayston. Alternatively, long-acting bronchodilators can be taken between 30 minutes and 12 hours prior to administration of Cayston.
f – Dosage is not based on weight or adjusted for age.
g - must be administered with a PARI LC Plus reusable nebulizer with a PARI Vios Air compressor. Administered over a 15 minute period. The doses should be taken as close to 12 hours apart as possible and not less than 6 hours apart.
h-use with Podhaler device; each dose of 4 capsules should be taken as close to 12 hours apart as possible and should not be taken less than 6 hours apart.

CLINICAL RATIONALE

Cystic fibrosis (CF) is an autosomal recessive disease characterized by pancreatic insufficiency and thick persistent pulmonary secretions, which often lead to airway infection.[3] The most common airway pathogen in patients with CF is *Pseudomonas aeruginosa*.[4,6] *P. aeruginosa* is found in about 80% of patients with CF by 18 years of age; overall around 50% of the patients are infected.[6] Chronic infection is associated with poor growth, more rapid

decline in lung function, increased need for antibiotic treatment and hospitalization, and earlier death.[7,8] Pulmonary Clinical Practice Guidelines for Cystic Fibrosis recommend the chronic use of inhaled tobramycin, inhaled aztreonam, dornase alfa, and ivacaftor in patients 6 years of age and older. The CF Foundation has recommended the following order of inhaled medications: bronchodilator; hypertonic saline; dornase alfa; airway clearance; and aerosolized antibiotic.[4]

Tobramycin
Guidelines developed by the Pulmonary Therapies Committee of the Cystic Fibrosis Foundation made the following recommendations for tobramycin solution for inhalation (TSI) (written prior to the approval of aztreonam lysine inhalation solution (AZLI)):[4]

- Moderate to severe lung disease (≥6 years of age): For patients colonized with *P. aeruginosa*, the chronic use of TSI is strongly recommended to improve lung function and reduce exacerbations (grade A recommendation).
- Mild lung disease or asymptomatic (≥6 years of age): For patients colonized with *P. aeruginosa*, the chronic use of TSI is recommended to reduce exacerbations (grade B recommendation).

Cystic Fibrosis Foundation Evidence-based guidelines for the management of infants with CF recommend that for infants under 2 years of age who remained colonized with *pseudomonas aeruginosa* be treated chronically with alternate month TSI.[12]

In the pivotal trial that evaluated the intermittent use of TSI in cystic fibrosis patients, TSI treatment produced significant improvements in pulmonary function test results, reduced sputum levels of *P. aeruginosa*, and resulted in a 26% reduction in the probability of hospitalization.[9] Safety and efficacy have not been demonstrated in patients less 6 years of age.

Ototoxicity did not occur with TSI therapy during clinical studies. In post-marketing experience, some patients receiving TSI and extensive previous or concomitant parenteral aminoglycosides have reported hearing loss. Bronchospasm may occur with inhalation of TSI. The most common adverse reactions are dysphonia (13%) and tinnitus (3%). Emergence of tobramycin-resistant *P. aeruginosa* and increased isolation rate of *C. albicans* and *Aspergillus* spp. have been found in TSI treated patients.[10]

Aztreonam
The safety and efficacy of AZLI was evaluated over a period of 28 days of treatment in one pivotal, published, randomized, double-blind, placebo-controlled, multicenter trial that enrolled patients with CF and *P. aeruginosa* (n=164).[11] Patients 7 years of age and older and with FEV_1 of 25% to 75% predicted were enrolled. These patients were randomized in a 1:1 ratio to receive either AZLI (75 mg) or placebo administered by inhalation 3 times a day for 28 days. The primary efficacy endpoint was change in symptoms, assessed with CFQ-R-Respiratory scores (the questionnaire asks patient to report on symptoms like cough, wheezing, and sputum production; range, 0-100 points and increasing scores indicated improvement). Five-point changes in scores reflected improved or worsened respiratory symptoms detected by patients.

The adjusted mean CFQ-R-Respiratory scores increased for AZLI-treated patients and decreased for placebo-treated patients (day 28 treatment difference, 9.7 points; 95% confidence interval [CI], 4.3 to 15.1; $p < 0.001$). The adjusted mean FEV_1 increased for AZLI-treated patients and decreased for placebo-treated patients (day 28 treatment difference, 10.3%; 95% CI, 6.3 to 14.3; $p < 0.001$). The number of hospitalized patients did not differ significantly between the 2 groups.

The safety was evaluated in 344 patients from two placebo-controlled trials and one open-label follow-on trial.[2] In controlled trials, 146 patients with CF received 75 mg AZLI 3 times a day for 28 days. Most common adverse events were: cough (54%), nasal congestion (16%), wheezing (16%), pharyngolaryngeal pain (12%), and pyrexia (13%). Caution is advised when administering to patients if they have a history of beta-lactam allergy, although patients with a known beta-lactam allergy have received AZLI in clinical trials and no severe allergic reactions were reported. Prescribing AZLI in the absence of known *Pseudomonas aeruginosa* infection in patients with CF is unlikely to provide benefit and increases the risk of development of drug-resistant bacteria.

Inhaled azetreonam and tobramycin are currently FDA approved for use intermittently in the treatment of chronic pseudomonal infections in cystic fibrosis. However, use of continuous inhaled antibiotic regimens of differing combinations is growing in clinical practice. In an effort to evaluate the safety and efficacy of continuous use of inhaled antibiotics, a phase III trial with continuous use of inhaled tobromycin and aztreonam was conducted.[16.] This double-blind trial compared continuous alternating therapy (CAT) to an intermittent treatment regimen. Subjects were treated with 3 cycles of 28-days inhaled aztreonam (AZLI) or placebo 3-times daily alternating with 28-days open-label tobramycin inhalation solution (TIS). 90 subjects were randomized over 18 months. Study enrollment was limited, in part because of evolving practices by clinicians of adopting a CAT regimen in clinical practice; consequently the study was underpowered. AZLI/TIS treatment reduced exacerbation rates by 25.7% ($p = 0.25$; primary endpoint) and rates of respiratory hospitalizations by 35.8% compared with placebo/TIS ($p = 0.14$). AZLI/TIS CAT therapy was well tolerated.[16] With the trial failing to show statistical significance of CAT over intermittent therapy, more clinical trial are needed to establish safety and efficacy of CAT.

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