Inhaled Antibiotics Duplicate Therapy Quantity Limit Program Summary

This program applies to Medicaid

POLICY REVIEW CYCLE

Effective Date	Date of Origin
04-01-2024	04-01-2024

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Bethkis® (tobramycin inhalation solution)* Oral inhalation	Management of cystic fibrosis patients with *Pseudomonas aeruginosa.* Safety and efficacy have not been demonstrated in patients under the age of six years, patients with a forced expiratory volume in one second (FEV1) less than 40% or greater than 80% predicted, or patients colonized with *Burkholderia cepacia.*	*generic available	1
Cayston® (aztreonam inhalation solution) Oral inhalation	To improve respiratory symptoms in cystic fibrosis (CF) patients with *Pseudomonas aeruginosa.* Safety and effectiveness have not been established in pediatric patients below the age of 7 years, patients with FEV1 less than 25% or greater than 75% predicted, or patients colonized with *Burkholderia cepacia.*		5
Kitabis® Pak, Tobramycin Inhalation Solution Pak Oral inhalation	Management of cystic fibrosis in adults and pediatric patients 6 years of age and older with *Pseudomonas aeruginosa*. Safety and efficacy and have been demonstrated in patients under the age of 6 years, patients with FEV1 less than 25% or greater than 75% predicted, or patients colonized with *Burkholderia cepacia.*		3
TOBI® Podhaler® (tobramycin inhalation powder) Oral inhalation	Management of cystic fibrosis patients with *Pseudomonas aeruginosa.* Safety and efficacy have not been demonstrated in patients under the age of 6 years, patients with FEV1 less than 25% or greater than 80%, or patients colonized with *Burkholderia cepacia.*		2
TOBI® (tobramycin inhalation solution)* Oral inhalation	Management of cystic fibrosis in adults and pediatric patients 6 years of age and older with *Pseudomonas aeruginosa*. Safety and efficacy have not been demonstrated in patients under the age of 6 years, patients with forced expiratory volume in 1 second (FEV1) less than 25% or greater than 75% predicted, or patients colonized with *Burkholderia cepacia.*	*generic available	4

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

CLINICAL RATIONALE

Cystic Fibrosis	Cystic fibrosis (CF) is a multi-system disorder caused by mutations in the gene for the CF transmembrane conductance regulator (CFTR), which encodes an ion channel protein in epithelial cells on the airway surface.(6) Defects in the ion channel protein cause abnormal ion transport which alters antimicrobial airway defenses. This impaired host defense results in chronic lower airway bacterial infections, the most common of which are *Pseudomonas aeruginosa* and *Staphylococcus aureus*. *P. aeruginosa*, in particular, is linked to greater airway inflammation and overall decline in health.(9,10) Pulmonary disease remains the leading cause of morbidity and mortality in patients with CF.(6,9) The approach to treating infection in CF lung disease is multifaceted, involving antibiotics, chest physiotherapy, inhaled medications to promote secretion clearance, and anti-inflammatory agents.(6) It is hypothesized that *P. aeruginosa* infections initially occur transiently before progressing to chronic infection. Over time, *P. aeruginosa* adapts to the airway by developing a "mucoid" phenotype that exists within a biofilm, which contributes to the development of chronic, difficult-to-eradicate infection. However, there is evidence that early antibiotic therapy has the potential to clear or "eradicate" initial *P. aeruginosa* infection and to postpone chronic infection with this organism.(10) Specifically, both inhaled tobramycin and aztreonam are highly effective at eradicating first or very early infection with *P. aeruginosa*. Success rates are greater than 75%, and this is seen as important progress in treating CF.(6,9,10) The prevalence of chronic *P. aeruginosa* infection in the United States CF population has steadily decreased over the last several years, with the greatest reductions observed in younger populations where successful eradication strategies may have played a pivotal role.(9) Undoubtedly, improved use of antibiotics is responsible for a substantial portion of the increased survival that has occurred in patients with CF.(6,9) Prophylactic use of antibiotics to prevent *P. aeruginosa* acquisition is not recommended, as clinical trials of this approach did not show benefit.(6,7,10) Once *P. aeruginosa* becomes established in the CF airway, the organisms are difficult to eliminate. Chronic infection is associated with poor growth, more rapid decline in lung function, increased need for antibiotic treatment and hospitalization, and earlier death.(6,10) Eradication remains an important goal, but patients unable to clear *P. aeruginosa* infection can often be adequately treated for many years with cycled or continuous alternating use of existing antibiotic options.(6,8,9) Chronic treatment with inhaled antibiotics helps to reduce the *Pseudomonas* bacterial burden and thus lessen its impact. Because most classes of antibiotics that show in vitro activity against *P. aeruginosa* are ineffective when administered orally, delivery by inhalation presents an attractive alternative since relatively high drug concentrations can be delivered to the site of lung infection with minimal systemic absorption.(6,8) Guidelines for treatment of CF *P. aeruginosa* infection recommend the use of inhaled tobramycin and inhaled aztreonam.(6,7,9) Tobramycin is recommended as first-line because of the extensive information supporting its safety and efficacy.(6,7,9,10) Trials have demonstrated that chronic treatment with inhaled tobramycin improves lung function, reduces acute pulmonary exacerbations, and improves quality-of-life outcomes.(1-4,6,9,10) Treatment is routinely administered for 28 days on therapy alternating with 28 days off. Inhaled aztreonam can be used as an alternative to inhaled tobramycin in select patients.(6,7,9,10) Trials have demonstrated that chronic treatment with inhaled aztreonam improves lung function, reduces pulmonary exacerbations, and improves quality-of-life outcomes.(5,6,7,10) Candidates for aztreonam include patients who cannot tolerate tobramycin, patients whose pulmonary status is deteriorating despite tobramycin use, patients who are or are planning to become pregnant, or patients who prefer the use of aztreonam to tobramycin.(6) Treatment is routinely administered for 28 days on therapy alternating with 28 days off.(6) For patients with deteriorating pulmonary status and/or recurrent pulmonary exacerbations despite cycling between 28 days on and 28 days off of a single inhaled antibiotic, it has become common practice for clinicians to prescribe continuous

	treatment by alternating between two different antibiotics (e.g., tobramycin and aztreonam), each for a 28-day period. This approach was evaluated in a randomized clinical trial in patients with a wide range of pulmonary function (FEV1 25 to 75 percent predicted), in which 28 days of inhaled aztreonam or placebo alternated with 28-day cycles of inhaled tobramycin. The study was terminated early because of inability to meet recruitment targets, in part because many clinicians and patients had already adopted continuously alternating therapy into their treatment regimen. Due to early termination of the study, statistical significance was not reached; however, the study showed 25% reduction in pulmonary exacerbation, 36% reduction in hospitalization for a respiratory event, and median time to first exacerbation was increased. Nonetheless, due to the early termination of the study and lack of statistical significance, there is insufficient evidence for guidelines to support the practice of alternating inhaled antibiotics for all patients with chronic *P. aeruginosa* infection. Despite this, many experts feel that it is reasonable practice for patients with advanced lung disease or those with frequent pulmonary exacerbations or accelerated decline in pulmonary status.(6,8,9) For individuals with advanced cystic fibrosis lung disease, the Cystic Fibrosis Foundation Consensus Guidelines for the Care of Individuals with Advanced Cystic Fibrosis Lung Disease (2020), recommends a trial of continuous alternating inhaled antibiotics as dictated by bacterial pathogens identified in respiratory cultures.(11)

REFERENCES

Number	Reference
1	Bethkis prescribing information. Chiesi USA, Inc. February 2023.
2	TOBI Podhaler prescribing information. Mylan Pharmaceuticals Inc. February 2023.
3	Kitabis Pak prescribing information. Pari Respiratory Equipment, Inc. August 2023.
4	TOBI prescribing information. Mylan Specialty LP. February 2023.
5	Cayston prescribing information. Gilead Sciences, Inc. November 2019.
6	Simon RH, et al. Cystic Fibrosis: Antibiotic Therapy for Chronic Pulmonary Infection. UpToDate. Last updated August September 2023. Literature review current through September 2023.
7	Mogayzel PJ, Naureckas ET, Robinson KA, et al. Cystic Fibrosis Pulmonary Guidelines. Chronic Medications for Maintenance of Lung Health. Am J Respir Crit Care Med. 2013;187(7):680-689.
8	Flume PA, Clancy JP, Retsch-Bogart GZ, et al. Continuous Alternating Inhaled Antibiotics for Chronic Pseudomonal Infection in Cystic Fibrosis. J Cyst Fibros. 2016;15(6):809-815.
9	Nichols DP, Durmowicz AG, Field A, et al. Developing Inhaled Antibiotics in Cystic Fibrosis: Current Challenges and Opportunities. Ann Am Thorac Soc. 2019;16(5):534-539.
10	Mogayzel PJ, Naureckas ET, Robinson KA, et al. Cystic Fibrosis Foundation Pulmonary Guideline: Pharmacologic Approaches to Prevention and Eradication of Initial *Pseudomonas aeruginosa* Infection. Ann Am Thorac Soc. 2014;11(10):1640-1650.
11	Cystic Fibrosis Foundation Consensus Guidelines for the Care of Individuals with Advanced Cystic Fibrosis Lung Disease. J Cystic Fibrosis. 2020;19(3):344-354.

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
Bethkis	Tobramycin Nebu Soln 300 MG/4ML	300 MG/4ML	56	Ampules	56	DAYS			
Cayston	aztreonam lysine for inhal soln	75 MG	84	Vials	56	DAYS			

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
Kitabis pak ; Tobi	Tobramycin Nebu Soln 300 MG/5ML	300 MG/5ML	56	Ampules	56	DAYS			
Tobi podhaler	tobramycin inhal cap	28 MG	28	Blisters	56	DAYS			

CLIENT SUMMARY – QUANTITY LIMITS

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Bethkis	Tobramycin Nebu Soln 300 MG/4ML	300 MG/4ML	Medicaid
Cayston	aztreonam lysine for inhal soln	75 MG	Medicaid
Kitabis pak ; Tobi	Tobramycin Nebu Soln 300 MG/5ML	300 MG/5ML	Medicaid
Tobi podhaler	tobramycin inhal cap	28 MG	Medicaid

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	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 for the requested indication **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 **OR** 3. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** C. The prescriber has provided information in support of therapy with a higher dose for the requested indication **Length of Approval:** 12 months