PRIOR AUTHORIZATION POLICY

POLICY: Antibiotics (Inhaled) – Tobramycin Inhalation Solution Prior Authorization Policy
- Bethkis® (tobramycin inhalation solution – Chiesi/Catalent)
- Kitabis™ (tobramycin inhalation solution – Catalent, authorized generic)
- TOBI® (tobramycin inhalation solution – Novartis, generic)

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OVERVIEW

TOBI and Kitabis, aminoglycoside antibiotics, are indicated for the management of **cystic fibrosis** (CF) in adults and pediatric patients ≥ 6 years of age with *Pseudomonas aeruginosa*.[1,2] Safety and efficacy have not been demonstrated in patients < 6 years of age, patients with forced expiratory volume in 1 second (FEV1) < 25% or > 75% predicted, or patients colonized with *Burkholderia cepacia.*

Bethkis, an aminoglycoside antibiotic, is indicated for the management of **CF** patients with *P. aeruginosa*.[3] Safety and efficacy have not been demonstrated in patients < six years of age, patients with FEV1 < 40% or > 80% predicted, or patients colonized with *B. cepacia*.

Disease Overview

CF is a complex, chronic, multi-organ, inherited disorder.[4] Lung disease accounts for nearly 85% of mortality in patients with CF. Lung destruction in CF is caused by obstruction of the airways due to dehydrated and thickened secretions, resultant endobronchial infection, and an exaggerated inflammatory response leading to development of bronchiectasis and progressive obstructive airway diseases. In patients with CF, there are a number of maintenance treatments that may be prescribed, including inhaled antibiotics.

Aerosolized delivery of antimicrobial agents for pulmonary infections provides an ideal method for achieving high local drug concentration in the lungs while minimizing systemic exposure.[5] It has been estimated that by 18 years of age, 80% of patients with CF have *P. aeruginosa* infection. Once *P. aeruginosa* is established in the respiratory tract of a patient with CF, the clinical course of the disease can worsen. Although many organisms can be found in the lower respiratory tract of patients who have CF, infection with mucoid *P. aeruginosa* is common and is associated with poorer outcomes.[6] Infection with chronic mucoid *P. aeruginosa* is associated with poor growth, more rapid decline in lung function, increased need for antibiotic treatment and hospitalization, and earlier death. In addition, mucoid *P. aeruginosa* (characterized by its biofilm) is more resistant to antibiotics than non-mucoid *P. aeruginosa*. Therefore, effective antimicrobial therapies targeting *P. aeruginosa* are central to the management of CF.

Guidelines

The Cystic Fibrosis Foundation (CFF) established a Pulmonary Therapeutics Committee which provided recommendations, based on available evidence (2007) for the use of medications intended to maintain lung health.[4] In 2013 the Committee published updated recommendations for the use of chronic medications in the management of CF lung disease.[7] In patients ≥ 6 years of age with CF and moderate-to-severe lung disease with *P. aeruginosa* persistently present in cultures of the airways, the chronic use of inhaled tobramycin is strongly recommended to improve lung function, quality of life and reduce exacerbations. For mild disease, the Committee recommends chronic use of inhaled tobramycin for patients with CF ≥ 6 years of age with *P. aeruginosa* persistently present in cultures of the airways, to reduce exacerbations.

The CFF published a systematic review of the literature regarding eradication of initial *P. aeruginosa* infections to develop guidelines for effective prevention (2014).[8] The recommendations pertaining to inhaled antibiotics are as follows: 1) Inhaled antibiotic therapy is recommended for the treatment of initial or new growth of *P. aeruginosa* (the favored antibiotic regimen is tobramycin [300 mg BID] for 28 days); and 2) Prophylactic antipseudomonal antibiotics to prevent the acquisition of *P. aeruginosa* are not recommended.

Other Uses With Supportive Evidence

A few trials support the efficacy of tobramycin inhalation solution (TIS) for the treatment of bronchiectasis with *P. aeruginosa* infection. In a randomized, double-blind, placebo-controlled study, patients received either TIS 300 mg (n = 37) or placebo (n = 37) twice daily (BID) for 4 weeks and were followed for an additional 2 weeks off treatment.[9] At Week 4, the TIS group had a mean 4.54 $\log_{10}$ decrease in *P. aeruginosa* colony-forming units (CFU)/g of sputum compared with no change in the placebo group ($P < 0.01$). At Week 6, complete eradication of *P. aeruginosa* occurred in 35% of the patients in the TIS group compared with none in the placebo group, and 62% of patient in the TIS group vs. 38% of the placebo group had improvements in their general health (odds ratio 2.7; 95% confidence interval: 1.1, 6.9).

In a randomized, single-blind study, patients received TIS 300 mg (n = 16) or placebo (n = 19) BID for 3 months following a 14-day course of intravenous ceftazidime and tobramycin and were followed for an additional 12 months.[10] At the end of the study, 54.5% of the TIS group (n = 6/11) and 29.4% of the placebo group (n = 5/17) were free of *P. aeruginosa* ($P = 0.048$). In addition, patients in the TIS group had significantly fewer exacerbations (1.27 vs. 2.5; $P = 0.044$), hospital admissions (0.06 vs. 0.47; $P = 0.037$), and hospital days (0.9 vs. 13.56; $P = 0.034$) than the placebo group, respectively. No significant difference was found in pulmonary function tests.

A double-blind, placebo-controlled, crossover study randomized 30 patient to initial TIS 300 mg or placebo BID for 6 months, followed by a 1 month washout period and 6 months of therapy with the other treatment.[11] During the first treatment period, TIS treatment resulted in a significant reduction in *P. aeruginosa* density compared with placebo ($P = 0.038$). During both treatment periods, patients treated with TIS had fewer admissions (0.15 vs. 0.75; $P = 0.038$) and hospital days (2.05 vs. 12.65; $P = 0.047$) than patients treated with placebo, respectively. No significant changes occurred with number of exacerbations and pulmonary function tests.

In an open-label trial, 41 patients received three cycles of TIS 300 mg BID for 14 days followed by 14 days off therapy.[12] Patients were followed for an additional 40 weeks after the three cycles of treatment with TIS. At Week 10, there was a significant improvement from baseline (mean change 1.5 points; $P = 0.006$) in the composite pulmonary symptom score which included cough, shortness of breath, sputum production, fatigue, and wheezing. Quality of life, assessed using the St. George's Respiratory Questionnaire, was significantly improved at Week 10 (mean change 9.8; $P < 0.001$) compared with baseline. At Week 12, 22.2% of patients (n = 6/27) were considered to have *P. aeruginosa* eradicated from sputum cultures.

The American Thoracic Society (ATS) published a clinical review (2013) of non-cystic fibrosis bronchiectasis on their webpage.[13] The review lists nebulized antibiotics (e.g., colistin, gentamicin, tobramycin) as treatment options for the eradication or suppression of *P. aeruginosa*. The European Respiratory Society (ERS) have published guidelines (2017) for the management of adult bronchiectasis and recommend patients with a new isolate of *P. aeruginosa* be offered eradication antibiotic treatment which includes nebulized antibiotics (e.g., colistin, gentamicin, tobramycin).[14] While both the ATS and ERS list nebulized colistin and gentamicin as treatment options for non-cystic fibrosis bronchiectasis, neither drug has a commercially available formulation for nebulization.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of tobramycin inhalation solution. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with tobramycin inhalation solution as well as the monitoring required for adverse events and long-term efficacy, approval requires tobramycin inhalation solution to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of tobramycin inhalation solution is recommended in those who meet one of the following criteria:

FDA-Approved Indication

1. **Cystic Fibrosis.** Approve for 1 year if the patient meets the following criteria (A and B):
   - **A)** Patient has *Pseudomonas aeruginosa* in culture of the airway; AND
     Note: Examples of culture of the airway include sputum culture, oropharyngeal culture, bronchoalveolar lavage culture.
   - **B)** Tobramycin inhalation solution is prescribed by or in consultation with a pulmonologist or a physician who specializes in the treatment of cystic fibrosis.

Other Uses with Supportive Evidence

2. **Bronchiectasis, Non-Cystic Fibrosis**. Approve for 1 year if the patient meets the following criteria (A, B, and C):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has *Pseudomonas aeruginosa* in culture of the airway; AND
     Note: Examples of culture of the airway include sputum culture, oropharyngeal culture, bronchoalveolar lavage culture.
   - **C)** Tobramycin inhalation solution is prescribed by or in consultation with a pulmonologist.

3. **Continuation of Tobramycin Inhalation Solution Therapy**. Approve for 1 month if the patient was started on tobramycin inhalation solution and is continuing course of therapy.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of tobramycin inhalation solution is not recommended in the following situations:

1. **Nasal Rinse**. Tobramycin inhalation solution is not approvable for compounding of tobramycin nasal rinse.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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2. Kitabis™ inhalation solution [prescribing information]. Woodstock, IL: Catalent; December 2019.

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