



Effective Date 9/1/2023
Next Review Date... 9/1/2024
Coverage Policy Number IP0094

Tobramycin Inhalation Solution

Table of Contents

Overview 1
Medical Necessity Criteria 1
Reauthorization Criteria 2
Authorization Duration 2
Conditions Not Covered..... 3
Background..... 3
References 4

Related Coverage Resources

INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This policy supports medical necessity review for the following tobramycin inhalation solution products:

- Bethkis® (tobramycin 300mg/4ml inhalation solution)
Kitabis™ Pak (tobramycin 300mg/5ml inhalation solution pak)
TOBI® (tobramycin 300mg/5ml inhalation solution)
tobramycin 300mg/4ml inhalation solution (generic for Bethkis)
tobramycin 300mg/5ml inhalation solution (generic for TOBI)
tobramycin pak 300mg/5ml inhalation solution (generic for Kitabis Pak)

Receipt of sample product does not satisfy any criteria requirements for coverage.

Medical Necessity Criteria

Tobramycin inhalation solution products are considered medically necessary when ONE of the following is met (1, 2, or 3):

1. **Cystic Fibrosis.** Individual meets **ALL** of the following criteria (A, B, and C):
 - A. Documentation of *Pseudomonas aeruginosa* in airway cultures (for example, sputum culture, oropharyngeal culture, bronchoalveolar lavage culture)
 - B. The medication is prescribed by, or in consultation with, a pulmonologist or a physician who specializes in the treatment of cystic fibrosis.
 - C. Individual meets the preferred covered alternative(s) criteria as indicated in the table below

2. **Non-Cystic Fibrosis Bronchiectasis.** Individual meets **ALL** of the following criteria (A, B, C, and D):
 - A. Individual is 18 years of age or older
 - B. Documentation of *Pseudomonas aeruginosa* in airway cultures (for example, sputum culture, oropharyngeal culture, bronchoalveolar lavage culture)
 - C. The medication is prescribed by, or in consultation with, a pulmonologist
 - D. Individual meets the preferred covered alternative(s) criteria as indicated in the table below

3. **Continuation of Tobramycin Inhalation Solution Therapy.** Individual meets **ALL** of the following criteria (A, B and C):
 - A. Individual was started on tobramycin inhalation solution and is continuing the course of therapy
 - B. The medication is prescribed by, or in consultation with, a pulmonologist
 - C. Individual meets the preferred covered alternative(s) criteria as indicated in the table below

Coverage varies across plans and requires the use of preferred products. Refer to the customer's benefit plan document for coverage details.

Employer Group Non-Covered Products and the Preferred Covered Alternatives:

Non-Covered Product	Criteria
Bethkis (tobramycin 300mg/4ml inhalation solution)	There is documentation of the following: <ol style="list-style-type: none"> A. The individual has tried <u>tobramycin 300mg/4ml inhalation solution</u> (the bioequivalent generic product) AND cannot take due to a formulation difference in the inactive ingredient(s) which would result in a significant allergy or serious adverse reaction [may require prior authorization]
TOBI (tobramycin 300mg/5ml inhalation solution)	There is documentation of the following: <ol style="list-style-type: none"> A. The individual has tried <u>tobramycin 300mg/5ml inhalation solution</u> (the bioequivalent generic product) AND cannot take due to a formulation difference in the inactive ingredient(s) which would result in a significant allergy or serious adverse reaction [may require prior authorization]

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Reauthorization Criteria

Tobramycin inhalation solution products are considered medically necessary for continued use when initial criteria are met AND there is documentation of beneficial response.

Authorization Duration

Initial approval duration: up to 12 months
Reauthorization approval duration: up to 12 months

Conditions Not Covered

Any other use is considered experimental, investigational or unproven, including the following (this list may not be all inclusive):

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

Background

OVERVIEW

TOBI, Kitabis, and Bethkis, tobramycin inhalation solutions, are aminoglycoside antibiotics indicated for the management of **cystic fibrosis (CF)** in patients with *Pseudomonas aeruginosa*.¹⁻³ TOBI and Kitabis are indicated for the management of CF in patients ≥ 6 years of age.^{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 is indicated for the management of CF patients with *P. aeruginosa*.³ Safety and efficacy have not been demonstrated in patients < 6 years of age, patients with FEV₁ $< 40\%$ or $> 80\%$ predicted, or patients colonized with *B. cepacia*.

Guidelines

The Cystic Fibrosis Foundation (CFF) Pulmonary Therapeutics Committee published recommendations for the use of chronic medications in the management of CF lung disease (2013).⁴ In patients ≥ 6 years of age with CF and moderate-to-severe lung disease with *P. aeruginosa* persistently present in cultures of the airways, 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 ≥ 6 years of age with CF and *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).⁵ 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 twice daily {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. A literature review concluded that in patients with non-CF bronchiectasis and chronic *P. aeruginosa* infection, TIS is effective in reducing the density of bacteria in sputum, which may be associated with additional clinical benefit.¹²

In a randomized, double-blind, placebo-controlled study, patients received either TIS 300 mg (n = 37) or placebo (n = 37) (BID for 4 weeks and were followed for an additional 2 weeks off treatment).⁶ At Week 4, the TIS group had a mean 4.54 log₁₀ 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 patients in the TIS group vs. 38% of patients in 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.⁷ At the end of the study, 54.5% of patients in the TIS group (n = 6/11) and 29.4% of patients in 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 patients in the placebo group, respectively. No significant differences were found in pulmonary function tests.

A double-blind, placebo-controlled, crossover study randomized 30 patients 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.⁸ 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 hospital 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 in the number of exacerbations and/or pulmonary function tests were observed.

In an open-label trial, 41 patients received three cycles of TIS 300 mg BID for 14 days followed by 14 days off therapy.⁹ 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.

A Phase III, multicenter, double-blind, placebo-controlled trial randomized adults with symptomatic bronchiectasis with positive *P. aeruginosa* sputum culture to TIS 300 mg ($n = 167$) or placebo ($n = 172$) in addition to standard of care.¹³ Treatment was provided for two cycles, each consisting of 28 days on therapy and 28 days off therapy. At Week 16, there was a significant reduction in *P. aeruginosa* density with TIS vs. placebo (adjusted difference 1.74 \log_{10} CFU/g; $P < 0.001$) and a greater improvement in the quality of life bronchiectasis respiratory symptom score on Day 29 (adjusted mean difference 7.91; $P < 0.001$). Significantly more patients were culture negative for *P. aeruginosa* in the TIS group vs. placebo on Day 29 (29.3% vs. 10.6%, respectively).

The American Thoracic Society (ATS) published a clinical review (2013) of non-cystic fibrosis bronchiectasis.¹⁰ 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).¹¹ 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.

References

1. TOBI® inhalation solution [prescribing information]. Morgantown, WV: Mylan; February 2023.
2. Kitabis® inhalation solution [prescribing information]. Midlothian, VA: Pari; February 2023.
3. Bethkis® inhalation solution [prescribing information]. Woodstock, IL: Chiesi; February 2023.
4. 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;187:680-689.
5. Mogayzel PJ, Naureckas ET, Robinson KA, et al; and the Cystic Fibrosis Foundation Pulmonary Clinical Practice Guidelines Committee. Pharmacologic approaches to prevention and eradication of initial *Pseudomonas aeruginosa* infection. *Ann Am Thorac Soc*. 2014;11(10):1640-1650.
6. Barker AF, Couch L, Fiel SB, et al. Tobramycin solution for inhalation reduces sputum *Pseudomonas aeruginosa* density in bronchiectasis. *Am J Respir Crit Care Med*. 2000;162:481-485.
7. Orriols R, Hernando R, Ferrer A, et al. Eradication therapy against *Pseudomonas aeruginosa* in non-cystic fibrosis bronchiectasis. *Respiration*. 2015;90:299-305.
8. Drobic ME, Sune P, Montoro JB, et al. Inhaled tobramycin in non-cystic fibrosis patients with bronchiectasis and chronic bronchial infection with *Pseudomonas aeruginosa*. *Ann Pharmacother*. 2005;39:39-44.
9. Scheinberg P, Shore E. A pilot study of the safety and efficacy of tobramycin solution for inhalation in patients with severe bronchiectasis. *Chest*. 2005;127:1420-1426.
10. McShane PJ, Naureckas ET, Tino G, Strek ME. Non-cystic fibrosis bronchiectasis. *Am J Respir Crit Care Med*. 2013;188:647-656.
11. Polverino E, Goeminne PC, McDonnell, et al. European Respiratory Society guidelines for the management of adult bronchiectasis. *Eur Respir J*. 2017;50:1700629.

12. Elborn JS, Blasi F, Haworth CS, et al. Bronchiectasis and inhaled tobramycin: A literature review. *Respir Med.* [Epub ahead of print 2022 Jan 1].
13. Guan WJ, Xu JF, Luo H, et al. A double-blind randomized placebo-controlled Phase III trial of tobramycin inhalation solution in adults with bronchiectasis with *Pseudomonas aeruginosa* infection. *Chest.* 2023;163(1):64-76.

"Cigna Companies" refers to operating subsidiaries of Cigna Corporation. All products and services are provided exclusively by or through such operating subsidiaries, including Cigna Health and Life Insurance Company, Connecticut General Life Insurance Company, Evernorth Behavioral Health, Inc., Cigna Health Management, Inc., and HMO or service company subsidiaries of Cigna Health Corporation. © 2023 Cigna.