



## Drug Coverage Policy

Effective Date .....06/15/2025

Coverage Policy Number.....IP0094

Policy Title.....Tobramycin Inhalation Solution

# Antibiotics (Inhaled) – Tobramycin Inhalation Solution

- Bethkis® (tobramycin inhalation solution – Chiesi, generic)
- Kitabis® (tobramycin inhalation solution – Pari, authorized generic)
- TOBI® (tobramycin inhalation solution – Mylan, generic)

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### 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. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment where appropriate and have discretion in making individual coverage determinations. Where coverage for care or services does not depend on specific circumstances, reimbursement will only be provided if a requested service(s) is submitted in accordance with the relevant criteria outlined in the applicable Coverage Policy, including covered diagnosis and/or procedure code(s). Reimbursement is not allowed for services when billed for conditions or diagnoses that are not covered under this Coverage Policy (see "Coding Information" below). When billing, providers must use the most appropriate codes as of the effective date of the submission. Claims submitted for services that are not accompanied by covered code(s) under the applicable Coverage Policy will be denied as not covered. 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.*

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### OVERVIEW

The tobramycin inhalation solutions are aminoglycoside antibiotics indicated for the management of **cystic fibrosis (CF)** in patients with *Pseudomonas aeruginosa*.<sup>1-3</sup> TOBI (generic) and Kitabis (authorized generic) are indicated for the management of CF in patients  $\geq 6$  years of age.<sup>1,2</sup> Safety and efficacy have not been demonstrated in patients  $< 6$  years of age, patients with forced expiratory volume in 1 second (FEV<sub>1</sub>)  $< 25\%$  or  $> 75\%$  predicted, or patients colonized with *Burkholderia cepacia*. Bethkis (generic) is indicated for the management of CF patients with *P. aeruginosa*.<sup>3</sup> Safety and efficacy have not been demonstrated in patients  $< 6$  years of age, patients with FEV<sub>1</sub>  $< 40\%$  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).<sup>4</sup> In patients  $\geq 6$  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 and quality of life, and reduce exacerbations. For mild disease, the Committee recommends chronic use of inhaled tobramycin for patients  $\geq 6$  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).<sup>5</sup> 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.<sup>12</sup>

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.<sup>6</sup> At Week 4, the TIS group had a mean 4.54 log<sub>10</sub> 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.<sup>7</sup> 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.<sup>8</sup> 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.<sup>9</sup> 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.<sup>13</sup> 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.<sup>10</sup> 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 recommends patients with a new isolate of *P. aeruginosa* be offered eradication antibiotic treatment which includes nebulized antibiotics (e.g., colistin, gentamicin, tobramycin).<sup>11</sup> 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.

## Coverage Policy

### POLICY STATEMENT

Prior Authorization is required 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.

**Tobramycin inhalation solution (Bethkis, Kitabis, TOBI, generics) is considered medically necessary when ONE of the following is met (1, 2, or 3)**

### FDA-Approved Indication

**1. Cystic Fibrosis.** Approve for 1 year if the patient meets BOTH of the following (A, B, and C):

- 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)** The medication is prescribed by or in consultation with a pulmonologist or a physician who specializes in the treatment of cystic fibrosis.
- C)** Preferred product criteria is met for the product(s) as listed in the below table(s) for **Cystic Fibrosis.**

#### Other Uses with Supportive Evidence

- 2. Bronchiectasis, Non-Cystic Fibrosis.** Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
  - A)** Patient is  $\geq 18$  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)** The medication is prescribed by or in consultation with a pulmonologist.
  - D)** Preferred product criteria is met for the product(s) as listed in the below table(s) for **Bronchiectasis, Non-Cystic Fibrosis.**
- 3. Continuation of Tobramycin Inhalation Solution Therapy (for conditions other than Cystic Fibrosis or Bronchiectasis, Non-Cystic Fibrosis).** Approve for 1 month if the patient meets BOTH of the following (A and B):
  - A)** Patient was started on tobramycin inhalation solution and is continuing a course of therapy; AND
  - B)** Preferred product criteria is met for the product(s) as listed in the below table(s) for **Continuation of Therapy.**

#### Employer Plans:

Product	Criteria
<b>Bethkis</b> (tobramycin 300mg/4ml inhalation solution)	<b>1. <u>Cystic Fibrosis.</u></b> <b>A)</b> Patient meets BOTH of the following (i <u>and</u> ii): <ul style="list-style-type: none"> <li><b>i.</b> Patient meets the above medical necessity criteria; AND</li> <li><b>ii.</b> Patient has tried tobramycin inhalation solution (generics for Bethkis, Kitabis Pak, or TOBI solution) or TOBI Podhaler.</li> </ul> <b>2. <u>Bronchiectasis, Non-Cystic Fibrosis.</u></b> <b>A)</b> Patient meets BOTH of the following (i <u>and</u> ii): <ul style="list-style-type: none"> <li><b>i.</b> Patient meets the above medical necessity criteria; AND</li> <li><b>ii.</b> Patient has tried tobramycin inhalation solution (generics for Bethkis, Kitabis Pak, or TOBI solution).</li> </ul> <b>3. <u>Continuation of Therapy (for conditions other than Cystic Fibrosis or Bronchiectasis, Non-Cystic Fibrosis).</u></b> <b>A)</b> Patient is continuing a course of therapy and meets BOTH of the following (i <u>and</u> ii):

Product	Criteria
	<ul style="list-style-type: none"> <li>i. Patient meets the above medical necessity criteria; AND</li> <li>ii. Patient has tried tobramycin inhalation solution (generics for Bethkis, Kitabis Pak, or TOBI solution).</li> </ul>
<b>TOBI</b> (tobramycin 300mg/5ml inhalation solution)	<p><b>1. <u>Cystic Fibrosis.</u></b></p> <p><b>A)</b> Patient meets BOTH of the following (i <u>and</u> ii):</p> <ul style="list-style-type: none"> <li>i. Patient meets the above medical necessity criteria; AND</li> <li>ii. Patient has tried tobramycin inhalation solution (generics for Bethkis, Kitabis Pak, or TOBI solution) or TOBI Podhaler.</li> </ul> <p><b>2. <u>Bronchiectasis, Non-Cystic Fibrosis.</u></b></p> <p><b>A)</b> Patient meets BOTH of the following (i <u>and</u> ii):</p> <ul style="list-style-type: none"> <li>i. Patient meets the above medical necessity criteria; AND</li> <li>ii. Patient has tried tobramycin inhalation solution (generics for Bethkis, Kitabis Pak, or TOBI solution).</li> </ul> <p><b>3. <u>Continuation of Therapy (for conditions other than Cystic Fibrosis or Bronchiectasis, Non-Cystic Fibrosis).</u></b></p> <p><b>A)</b> Patient is continuing a course of therapy and meets BOTH of the following (i <u>and</u> ii):</p> <ul style="list-style-type: none"> <li>i. Patient meets the above medical necessity criteria; AND</li> <li>ii. Patient has tried tobramycin inhalation solution (generics for Bethkis, Kitabis Pak, or TOBI solution).</li> </ul>

#### Individual and Family Plans:

Product	Criteria
<b>Bethkis</b> (tobramycin 300mg/4ml inhalation solution)	<p><b>1. <u>Cystic Fibrosis.</u></b></p> <p><b>A)</b> Patient meets BOTH of the following (i <u>and</u> ii):</p> <ul style="list-style-type: none"> <li>i. Patient meets the above medical necessity criteria; AND</li> <li>ii. Patient has tried tobramycin inhalation solution 300mg/5ml (generics for Kitabis Pak or TOBI solution)</li> </ul> <p><b>2. <u>Bronchiectasis, Non-Cystic Fibrosis.</u></b></p> <p><b>A)</b> Patient meets BOTH of the following (i <u>and</u> ii):</p> <ul style="list-style-type: none"> <li>i. Patient meets the above medical necessity criteria; AND</li> <li>ii. Patient has tried tobramycin inhalation solution 300mg/5ml (generics for Kitabis Pak or TOBI solution).</li> </ul> <p><b>3. <u>Continuation of Therapy (for conditions other than Cystic Fibrosis or Bronchiectasis, Non-Cystic Fibrosis).</u></b></p> <p><b>A)</b> Patient is continuing a course of therapy and meets BOTH of the following (i <u>and</u> ii):</p> <ul style="list-style-type: none"> <li>i. Patient meets the above medical necessity criteria; AND</li> <li>ii. Patient has tried tobramycin inhalation solution 300mg/5ml (generics for Kitabis Pak or TOBI solution).</li> </ul>
<b>Kitabis Pak</b> (tobramycin 300mg/5ml)	<p><b>1. <u>Cystic Fibrosis.</u></b></p> <p><b>A)</b> Patient meets BOTH of the following (i <u>and</u> ii):</p> <ul style="list-style-type: none"> <li>i. Patient meets the above medical necessity criteria; AND</li> </ul>

Product	Criteria
	<p>ii. Patient has tried tobramycin inhalation solution 300mg/5ml (generics for Kitabis Pak or TOBI solution).</p> <p><b>2. <u>Bronchiectasis, Non-Cystic Fibrosis.</u></b>  <b>A)</b> Patient meets BOTH of the following (i <u>and</u> ii):  i. Patient meets the above medical necessity criteria; AND  ii. Patient has tried tobramycin inhalation solution 300mg/5ml (generics for Kitabis Pak or TOBI solution).</p> <p><b>3. <u>Continuation of Therapy (for conditions other than Cystic Fibrosis or Bronchiectasis, Non-Cystic Fibrosis).</u></b>  <b>A)</b> Patient is continuing a course of therapy and meets BOTH of the following (i <u>and</u> ii):  i. Patient meets the above medical necessity criteria; AND  ii. Patient has tried tobramycin inhalation solution 300mg/5ml (generics for Kitabis Pak or TOBI solution).</p>
<b>TOBI</b> (tobramycin 300mg/5ml inhalation solution)	<p><b>1. <u>Cystic Fibrosis.</u></b>  <b>A)</b> Patient meets BOTH of the following (i <u>and</u> ii):  i. Patient meets the above medical necessity criteria; AND  ii. Patient has tried tobramycin inhalation solution 300mg/5ml (generics for Kitabis Pak or TOBI solution).</p> <p><b>2. <u>Bronchiectasis, Non-Cystic Fibrosis.</u></b>  <b>A)</b> Patient meets BOTH of the following (i <u>and</u> ii):  i. Patient meets the above medical necessity criteria; AND  ii. Patient has tried tobramycin inhalation solution 300mg/5ml (generics for Kitabis Pak or TOBI solution).</p> <p><b>3. <u>Continuation of Therapy (for conditions other than Cystic Fibrosis or Bronchiectasis, Non-Cystic Fibrosis).</u></b>  <b>A)</b> Patient is continuing a course of therapy and meets BOTH of the following (i <u>and</u> ii):  i. Patient meets the above medical necessity criteria; AND  ii. Patient has tried tobramycin inhalation solution 300mg/5ml (generics for Kitabis Pak or TOBI solution).</p>
<b>tobramycin 300mg/4ml</b>	<p><b>1. <u>Cystic Fibrosis.</u></b>  <b>A)</b> Patient meets BOTH of the following (i <u>and</u> ii):  i. Patient meets the above medical necessity criteria; AND  ii. Patient has tried tobramycin inhalation solution 300mg/5ml (generics for Kitabis Pak or TOBI solution)</p> <p><b>2. <u>Bronchiectasis, Non-Cystic Fibrosis.</u></b>  <b>A)</b> Patient meets BOTH of the following (i <u>and</u> ii):  i. Patient meets the above medical necessity criteria; AND  ii. Patient has tried tobramycin inhalation solution 300mg/5ml (generics for Kitabis Pak or TOBI solution).</p> <p><b>3. <u>Continuation of Therapy (for conditions other than Cystic Fibrosis or Bronchiectasis, Non-Cystic Fibrosis).</u></b></p>

Product	Criteria
	<p><b>A)</b> Patient is continuing a course of therapy and meets BOTH of the following (i <u>and</u> ii):</p> <ul style="list-style-type: none"> <li><b>i.</b> Patient meets the above medical necessity criteria; AND</li> <li><b>ii.</b> Patient has tried tobramycin inhalation solution 300mg/5ml (generics for Kitabis Pak or TOBI solution).</li> </ul>

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.

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

**Tobramycin inhalation solution (Bethkis, Kitabis, TOBI, generics) for any other use is considered not medically necessary, including the following (this list may not be all inclusive; criteria will be updated as new published data are available):**

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

## References

1. TOBI® inhalation solution [prescribing information]. Morgantown, WV: Mylan; February 2023.
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3. Bethkis® inhalation solution [prescribing information]. Woodstock, IL: Chiesi; February 2023.
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11. Polverino E, Goeminne PC, McDonnell, et al. European Respiratory Society guidelines for the management of adult bronchiectasis. *Eur Respir J*. 2017;50:1700629.

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## Revision Details

Type of Revision	Summary of Changes	Date
Annual Revision	<p><b>For all indications:</b> Added medical necessity criteria, including preferred products, for Individual and Family Plans to the policy.</p> <p><b>Cystic Fibrosis:</b> Added TOBI Podhaler as another preferred alternative option for Employer Plans.</p> <p><b>Continuation of Tobramycin Inhalation Solution Therapy (for conditions other than Cystic Fibrosis or Bronchiectasis, Non-Cystic Fibrosis) :</b> Updated authorization duration to 1 month, was previously 12 months.</p>	7/1/2024
Annual Revision	No criteria changes	6/15/2025

The policy effective date is in force until updated or retired.

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