Clinical Policy: Tobramycin (Bethkis, Kitabis Pak, TOBI, TOBI Podhaler)

Reference Number: ERX.SPA.26
Effective Date: 07.01.16
Last Review Date: 02.22
Line of Business: Commercial, Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description
Tobramycin (Bethkis®, Kitabis™ Pak, TOBI®, TOBI® Podhaler™) is an aminoglycoside antibacterial drug.

FDA Approved Indication(s)
Bethkis, Kitabis Pak, TOBI, and TOBI Podhaler are indicated for the management of cystic fibrosis (CF) in patients with *Pseudomonas aeruginosa*. Kitabis Pak and TOBI are specifically indicated for patients 6 years of age and older.

Limitation(s) of use: Safety and efficacy have not been demonstrated in patients under the age of 6 years, patients with forced expiratory volume in one second (FEV_1) < 25% or > 75% predicted (< 40% or > 80% predicted for Bethkis), or patients colonized with *Burkholderia cepacia*.

Policy/Criteria
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that Bethkis, Kitabis Pak, TOBI, and TOBI Podhaler are **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Cystic Fibrosis (must meet all)**:**

1. Diagnosis of CF;
2. Prescribed by or in consultation with a pulmonologist, an infectious disease specialist, or an expert in treatment of cystic fibrosis;
3. Age ≥ 6 years;
4. *Pseudomonas aeruginosa* is present in at least one airway culture;
5. If tobramycin is prescribed concurrently (or for alternating use) with Cayston®, documentation supports inadequate response to either agent alone (e.g., deteriorating pulmonary status, recurrent pulmonary exacerbations);
6. If request is for Bethkis, Kitabis Pak, or Tobi, member must use generic tobramycin nebulized solution, unless contraindicated or clinically significant adverse effects are experienced;
7. Dose does not exceed one of the following (a or b):
   a. Inhalation solution (Bethkis, Kitabis Pak, TOBI): 600 mg per day administered on a 28 days on/28 days off cycle;
   b. Inhalation powder (TOBI Podhaler): 224 mg per day administered on a 28 days on/28 days off cycle.

Approval duration: 6 months

B. Other diagnoses/indications

1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. Cystic Fibrosis (must meet all)**:**

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. Member is responding positively to therapy as evidenced by reduction in respiratory symptoms (e.g., cough, wheezing, sputum production, or pulmonary exacerbations due to Pseudomonas aeruginosa);
3. If request is for Bethkis, Kitabis Pak, or Tobi, member must use generic tobramycin nebulized solution, unless contraindicated or clinically significant adverse effects are experienced;
4. If tobramycin is prescribed concurrently (or for alternating use) with Cayston, documentation supports inadequate response to either agent alone (e.g., deteriorating pulmonary status, recurrent pulmonary exacerbations);
5. If request is for a dose increase, new dose does not exceed one of the following (a or b):
   a. Inhalation solution (Bethkis, Kitabis Pak, TOBI): 600 mg per day administered on a 28 days on/28 days off cycle;
   b. Inhalation powder (TOBI Podhaler): 224 mg per day administered on a 28 days on/28 days off cycle.

Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off-label use policy – ERX.PA.01 or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key
CF: cystic fibrosis
FDA: Food and Drug Administration
FEV_1: forced expiratory volume in one second

Appendix B: Therapeutic Alternatives
Not applicable

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s): known hypersensitivity to any aminoglycoside
- Boxed warning(s): none reported

Appendix D: General Information

- Tobramycin is recommended for chronic use in both mild and moderate-to-severe disease per the American Thoracic Society 2013 CF guidelines. Severity of lung disease is defined by FEV_1 predicted as follows: normal, > 90% predicted; mildly impaired, 70-89% predicted; moderately impaired, 40-69% predicted; and severely impaired, < 40% predicted.
- The use of continuous alternating therapy (i.e., alternating different inhaled antibiotics in order to provide continuous therapy) lacks sufficient evidence. The efficacy of this practice was evaluated in a randomized, double-blind, phase 3 trial. A total of 90 patients received 28-days inhaled tobramycin alternating with either 28-days inhaled aztreonam or placebo. Although the study found reduced exacerbation and respiratory hospitalization rates with the alternating

tobramycin/aztreonam regimen compared to tobramycin/placebo, it was underpowered, and these results were not statistically significant.

V. Dosage and Administration

Drug Name	Dosing regimen	Maximum Dose
Tobramycin inhalation solution (Bethkis, Kitabis Pak, TOBI)	300 mg inhaled BID for 28 days (followed by 28 days off tobramycin therapy)	600 mg/day
Tobramycin inhalation powder (TOBI Podhaler)	112 mg (4 capsules) inhaled BID for 28 days (followed by 28 days off tobramycin therapy)	224 mg/day

VI. Product Availability

Drug Name	Availability
Tobramycin inhalation solution (Bethkis)	4 mL single-dose ampule: 300 mg
Tobramycin inhalation solution (Kitabis Pak)	5 mL single-dose ampule: 300 mg Co-packaged with a PARI LC PLUS Reusable Nebulizer
Tobramycin inhalation solution (TOBI)	5 mL single-dose ampule: 300 mg
Tobramycin inhalation powder (TOBI Podhaler)	Capsule: 28 mg

VII. References

1. Bethkis Prescribing Information. Woodstock, IL: Catalent Pharm Solutions, LLC; December 2019. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/201820s005lbl.pdf. Accessed October 22, 2021.
2. Kitabis Pak Prescribing Information. Woodstock, IL: Catalent Pharm Solutions, LLC; December 2019. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/205433s005lbl.pdf. Accessed October 22, 2021.
3. TOBI Prescribing Information. East Hanover, NJ: Novartis Pharmaceuticals Corporation; October 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/050753s022lbl.pdf. Accessed October 22, 2021.
4. TOBI Podhaler Prescribing Information. East Hanover, NJ: Novartis Pharmaceuticals Corporation; July 2020. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/201688s010lbl.pdf. Accessed October 22, 2021.
5. 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.* April 1, 2013; 187 (7): 680-689.
6. Flume PA, Clancy JP, Retsch-Bogart GZ, et al. Continuous alternating inhaled antibiotics for chronic pseudomonal infection in cystic fibrosis. J Cyst Fibrosis. 2016; 15(6): 809-815.
7. Kapnadak SG, Dimango E, Hadjiliadis D, et al. Cystic Fibrosis Foundation consensus guidelines for the care of individuals with advanced cystic fibrosis lung disease. *J Cyst Fibros* 2020 May;19(3):344-354. doi: 10.1016/j.jcf.2020.02.015.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
1Q18 annual review: Added Bethkis. Added allowance for concurrent/alternating use with aztreonam pending supportive documentation of inadequate response to either agent alone. Added Appendix C: General Information.	10.26.17	02.18
1Q 2019 annual review: no significant changes; references reviewed and updated.	10.17.18	02.19
1Q 2020 annual review: no significant changes; references reviewed and updated.	10.28.19	02.20

Reviews, Revisions, and Approvals	Date	P&T Approval Date
1Q 2021 annual review: added prescriber restrictions of pulmonologist, infection disease specialist, or an expert in treatment of cystic fibrosis; added positive response to therapy examples: reduction in respiratory symptoms (e.g., cough, wheezing, sputum production, or pulmonary exacerbations due to Pseudomonas aeruginosa) in continuation criteria; updated Appendix D; references reviewed and updated.	01.07.21	02.21
1Q 2022 annual review: no significant changes; added redirection to generic nebulized solution for Bethkis, Kitabis, and Tobi requests; references reviewed and updated.	10.22.21	02.22

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.