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

Reference Number: PA.CP.PHAR.211
Effective Date: 01/18
Last Review Date: 01/19

Coding Implications
Revision Log

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 is 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
It is the policy of Pennsylvania Health and Wellness that tobramycin inhalation solution 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. Age ≥ 6 years;
3. Pseudomonas aeruginosa is present in at least one airway culture;
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. 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: Refer to PA.CP.PMN.53

II. Continued Approval

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

1. Currently receiving medication via Pennsylvania Health and Wellness benefit or member has previously met all initial approval criteria or the Continuity of Care Policy (PA.LTSS.PHAR.01) applies;

2. Member is responding positively to therapy;
3. 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);
4. 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 (1 or 2)**:**

1. Currently, receiving medication via Pennsylvania Health and Wellness benefit and documentation supports positive response to therapy or the Continuity of Care Policy (PA.LTSS.PHAR.01) applies.

Approval duration: Duration of request or 6 months (whichever is less); or

2. Refer to PA.CP.PMN.53

Background

Description/Mechanism of Action:

Tobramycin is an aminoglycoside antimicrobial produced by Streptomyces tenebrarius. It acts primarily by disrupting protein synthesis leading to altered cell membrane permeability, progressive disruption of the cell envelope, and eventual cell death. When inhaled, tobramycin is concentrated in the airways.

III. 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. 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.

IV. 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

V. 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

Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J7682	Tobramycin, inhalation solution, FDA-approved final product, noncompounded, unit dose form, administered through DME, per 300 mg
J7685	Tobramycin, inhalation solution, compounded product, administered through DME, unit dose form, per 300 mg

Reviews, Revisions, and Approvals	Date	Approval Date
Removed baseline FEV requirement. Added allowance for concurrent/alternating use with aztreonam pending supportive documentation of inadequate response to either agent alone. References reviewed and updated		

Reviews, Revisions, and Approvals	Date	Approval Date
1Q 2019 annual review: references reviewed and updated.	01/19	

References

1. Bethkis Prescribing Information. Woodstock, IL: Catalent Pharm Solutions, LLC; July 2017. Available at http://www.bethkis.com. Distribution network available at https://bethkis.com/wp-content/uploads/2015/10/BETHKIS-SpecialtyPharmacyInsert_R1-PRB.pdf. Accessed November 9, 2018.
2. Kitabis Pak Prescribing Information. Woodstock, IL: Catalent Pharm Solutions, LLC; November 2014. Available at http://kitabis.com. Accessed November 9, 2018.
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 November 9, 2018.
4. TOBI Podhaler Prescribing Information. East Hanover, NJ: Novartis Pharmaceuticals Corporation; October 2015. Available at https://www.tobipodhaler.com. Accessed November 9, 2018.
5. Flume PA, Mogayzel PJ, Robinson KA, et al. Cystic fibrosis pulmonary guidelines. Treatment of pulmonary exacerbations. Am J Respir Crit Care Med. 2009; 180: 802-808.
6. 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.
7. 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.