Clinical Policy Title:	tobramycin
Policy Number:	RxA.193
Drug(s) Applied:	Bethkis®, Kitabis® Pak, TOBI®, TOBI® Podhaler®
Original Policy Date:	02/07/2020
Last Review Date:	06/10/2021
Line of Business Policy Applies to:	All lines of business

Background

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

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:

- TOBI®: 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 or patients colonized with *Burkholderia cepacia*.
- TOBI® Podhaler®: Safety and efficacy have not been demonstrated in patients under the age of 6 years, patients with forced expiratory volume in 1 second (FEV1) <25% or >80%, or patients colonized with *Burkholderia cepacia.*
- Bethkis®: Safety and efficacy have not been demonstrated in patients under the age of six years, patients with a forced expiratory volume in one second (FEV1) less than 40% or greater than 80% predicted, or patients colonized with *Burkholderia cepacia.*

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
tobramycin inhalation solution (Bethkis®, Kitabis® Pak, TOBI®)	Cystic fibrosis	300 mg inhaled twice daily for 28 days (followed by 28 days off tobramycin therapy)	600 mg/day
tobramycin inhalation powder (TOBI® Podhaler®)	Cystic fibrosis	112 mg (4 capsules) inhaled twice daily for 28 days (followed by 28 days off tobramycin therapy)	224 mg/day

Dosage Forms

- 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

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria. The provision of provider samples does not guarantee coverage under the terms of the pharmacy benefit administered by RxAdvance. All criteria for initial approval must be met in order to obtain coverage.

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
Commercial: 6 months
Medicaid: 6 months

II. Continued Therapy Approval

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

1. Member is currently receiving tobramycin that has been authorized by RxAdvance or the member has met initial approval criteria listed in this policy;
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
Commercial: 12 months

Medicaid: 12 months

III. Appendices

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

Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

Drug Name	Dosing Regimen	Maximum Dose
aztreonam (Cayston®)	Inhalation via nebulizer: 75 mg 3 times daily (at least 4 hours apart) for 28 days; administer in repeated cycles of 28 days on drug, followed by 28 days off drug	75 mg per dose 225 mg per day
azithromycin (Zithromax®)	(Off-label) Oral: 250 mg (< 40 kg) or 500 mg (≥ 40 kg) 3 times weekly **or** 250 mg once daily	See dosing regimen

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

APPENDIX C: Contraindications/Boxed Warnings

- Contraindication(s):
  - Known hypersensitivity to any aminoglycoside.

- Boxed Warning(s):
  - None.

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, 7089% 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.
- Due to risks as well as clinical efficacy, tobramycin is the preferred aminoglycoside for exacerbations in individuals with Pseudomonas.

References

1. Bethkis® Prescribing Information. Woodstock, IL: Catalent Pharm Solutions, LLC; December 2019. Available at http://www.bethkis.com. Accessed April 01, 2021.

2. Kitabis® Pak Prescribing Information. Woodstock, IL: Catalent Pharm Solutions, LLC; November 2019. Available at http://kitabis.com. Accessed April 01, 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 April 01, 2021.
4. TOBI® Podhaler® Prescribing Information. East Hanover, NJ: Novartis Pharmaceuticals Corporation; July 2020. Available at https://www.TOBI Podhaler.com. Accessed April 01, 2021.
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.
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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.
8. 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. Epub 2020 Feb 27. PMID: 32115388.

Review/Revision History	Review/Revised Date	P&T Approval Date
Policy established.	01/2020	02/07/2020
Policy was reviewed: 1. Policy description table was updated. 2. Limitation(s) of use was added for TOBI®, TOBI® Podhaler® & Bethkis® separately per latest package insert. 3. Continuation therapy criteria II.A.1. was rephrased to "Member is currently receiving medication that has been authorized by RxAdvance…". 4. Appendix B, therapeutic alternative was rephrased to "none". 5. Appendix C, boxed warning was rephrased to "none". 6. Initial therapy and continued therapy approval duration for "Commercial" was updated from length of benefit to 6 months and 12 months respectively; added approval duration for "HIM". 7. References were updated.	06/19/2020	09/14/2020

Policy was reviewed: 1. Dosing frequency abbreviations were expanded. 2. Clinical policy section standard verbiage was updated to include “The provision of provider samples…”. 3. Approval duration section was updated to remove HIM from initial and continued therapy approval. 4. Appendix B for therapeutic alternatives was updated to add information. 5. Appendix D for general information was updated to add “Due to risks as well as clinical efficacy…”. 6. References were updated.	04/01/2021	06/10/2021