OPTUMRx

Therapeutic Class Overview
Cystic Fibrosis – Inhaled Antibiotics

INTRODUCTION

- Cystic fibrosis (CF) is the most common fatal genetic disease, affecting approximately 30,000 patients in the United States (U.S.) (*National Institutes of Health 2013*). It is caused by mutations in the CF transmembrane conductance regulator (*CFTR*) gene, which encodes for the CFTR protein. This protein acts as an ion channel regulating salt and fluid homeostasis, and defects are associated with thickened secretions, obstruction, and damage to several organs (*Ong et al 2016*). Respiratory manifestations are a significant feature of the disease, and respiratory failure is the most common cause of death in patients who do not receive a lung transplant (*Elborn 2016*).
  - CF is an autosomal recessive disorder; 2 copies of an abnormal gene must be present for the disease to develop (*Elborn 2016*). Patients may have 2 copies of the same mutation (homozygous) or 2 different mutations (heterozygous) (*Ong et al 2016*). Approximately 2000 mutations have been identified in the *CFTR* gene, of which more than 300 have been confirmed to cause CF (*CFTR2 2019*, *Quon and Rowe 2016*). In general, these mutations either reduce the amount of CFTR protein that reaches the cell membrane surface or reduce the function of CFTR as a chloride channel (*Egan 2016*).
  - There are 6 known classes of mutations that can cause CF. Classes I through III are associated with minimal CFTR function and most patients with these mutations have a severe CF phenotype (pancreatic insufficient and more severe lung disease). In contrast, class IV and V mutations are associated with some residual CFTR function and a milder phenotype (pancreatic sufficient and improved pulmonary outcomes and survival). Reports on the risk level for class VI mutations vary (*Egan 2016, Elborn 2016, Sosnay et al 2016*).
- Treatment of CF has traditionally been limited to addressing disease manifestations in specific organs (*Quon and Rowe 2016*).
  - Inhaled antibiotics have been commonly used to treat persistent airway infection with *Pseudomonas aeruginosa*, which contributes to lung damage in patients with CF; a reduction of bacterial load in the lungs decreases inflammation and the deterioration of lung function (*Smith et al 2018a*).
    - The 2013 CF Foundation (CFF) guidelines recommend chronic inhaled antibiotics, including tobramycin and aztreonam, for patients > 6 years of age with mild to severe disease with persistent colonization of *P. aeruginosa* to improve lung function, improve quality of life, and/or reduce exacerbations (*Mogayzel et al 2013*).
  - Inhaled dornase alfa, hypertonic saline, and mannitol have been used to enhance airway mucociliary clearance, while oral macrolide antibiotics and high-dose ibuprofen have been used to reduce inflammation (*Quon and Rowe 2016*).
  - More recently, CFTR modulators have been made available that act on the basic defect(s) in CFTR function; these include Kalydeco (ivacaftor), Orkambi (lumacaftor/ivacaftor), Symdeko (tezacaftor/ivacaftor), and Trikafta (elexacaftor/tezacaftor/ivacaftor) (*Drugs@FDA 2020, Elborn 2016*). Eligibility for CFTR modulator therapy depends on the patient's age and CF-causing mutation(s), and these products are used in conjunction with traditional therapies in patients who are eligible.
- This review includes the inhaled aminoglycoside antibiotic tobramycin and the inhaled monobactam antibiotic aztreonam.
  - Inhaled tobramycin is indicated for the management of CF patients with *P. aeruginosa*, is available in a variety of formulations, and may be administered via nebulization or dry powder inhalation.
  - Inhaled aztreonam is indicated to improve respiratory symptoms in CF patients with *P. aeruginosa* and may be administered via inhaled nebulization.
- Medispan classes: Anti-Infective Agents – Aminoglycosides (tobramycin); Anti-Infective Agents – Miscellaneous (aztreonam)

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Tobramycin inhaled agents	
Bethkis (tobramycin) 300 mg/4 mL inhalation solution	-
Kitabis Pak (tobramycin) 300 mg/5 mL inhalation solution co-packaged with a Pari LC Plus reusable nebulizer	-
Tobi (tobramycin) 300 mg/5 mL inhalation solution	✔
Tobi Podhaler (tobramycin) 28 mg inhalation capsule	-
Aztreonam inhaled agent	
Cayston (aztreonam) 75 mg inhalation solution	-

(*Drugs@FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Inhaled tobramycin agents*				Inhaled aztreonam agent*
	Bethkis (tobramycin)	Kitabis Pak (tobramycin)	Tobi (tobramycin)	Tobi Podhaler (tobramycin)	Cayston (aztreonam)
Management of CF patients with *P. aeruginosa* in patients ≥ 6 years of age†	✔	✔	✔	✔	
To improve respiratory symptoms in CF patients with *P. aeruginosa* in patients ≥ 7 years of age†					✔

Abbreviations: CF = cystic fibrosis, FEV_1 = forced expiratory volume in 1 second, $ppFEV_1$ = percent predicted FEV_1
* For Bethkis, safety and efficacy have not been demonstrated in patients with $ppFEV_1$ < 40% or > 80%; for Tobi Podhaler, safety and efficacy have not been demonstrated in patients with $ppFEV_1$ < 25% or > 80%; and for Cayston, Kitabis Pak, and Tobi, safety and efficacy have not been demonstrated in patients with $ppFEV_1$ < 25% or > 75%.
† Safety and efficacy have not been demonstrated in patients colonized with *Burkholderia cepacia*.

(*Prescribing information: Bethkis 2019, Cayston 2019, Kitabis Pak 2019, Tobi 2018, Tobi Podhaler 2015*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- A systematic review and meta-analysis of 18 trials (N = 3042), including 12 trials with tobramycin and 2 trials with aztreonam, evaluated the effects of long-term inhaled antibiotic therapy in patients with CF on clinical outcomes, quality of life, and adverse events (*Smith et al 2018a*).
  - There was no subgroup analysis of individual drugs or combinations due to the small number of trials, different duration of trials, different methods of expressing outcome results, and absence of variance in results.
  - Results showed that treatment with inhaled antibiotics improved lung function (4 trials; n = 814) and reduced the frequency of exacerbations (3 trials; n = 946) vs placebo. There were insufficient data to determine an effect on nutritional outcomes, survival, or quality of life.
    - Of the 8 trials that compared different inhaled antibiotics, 1 trial (N = 273; *Assael et al 2013*) demonstrated that aztreonam improved lung function significantly more than tobramycin inhalation solution, but the method of defining the outcome was different vs the remaining trials, and patients were exposed to tobramycin for a long period. No significant differences were found in the remaining trials with regard to lung function.
  - Important adverse events related to the treatment were uncommon, but were less common with tobramycin vs other antibiotics.

- Overall, the analysis determined that treatment with inhaled anti-pseudomonal antibiotics likely improved lung function and reduced exacerbation rates; however, the pooled estimates of the level of benefit were very limited. The best evidence was for inhaled tobramycin.

- A systematic review of 4 randomized controlled trials (N = 167) was conducted to determine if treatment of pulmonary exacerbations with inhaled antibiotics in patients with CF improved quality of life, reduced time off school or work and improved long-term survival (*Smith et al 2018b*). Data on the effectiveness of inhaled antibiotics for long-term suppression of respiratory infection has suggested there may also be benefit for treatment of exacerbations, with the strongest evidence supporting inhaled tobramycin. However, the review found little useful high-level evidence to support the use of inhaled antibiotics for the treatment of pulmonary exacerbations, as the included trials were inadequate for a valid analysis.
  - An inhaled aminoglycoside may be useful when an intravenous aminoglycoside is contraindicated due to renal impairment or risk of drug-induced hearing loss.
- A systematic review of 7 trials (N = 744) evaluated whether antibiotic treatment of early *P. aeruginosa* infection in patients with CF resulted in clinical improvements, and whether treatment with any particular antibiotic strategy (ie, combinations of inhaled, oral or intravenous antibiotics) was superior compared to other strategies or placebo (*Langton Hewer et al 2017*).
  - Most trials included inhaled tobramycin as a comparator.
  - The analysis determined that nebulized antibiotics, alone or in combination with oral antibiotics, were better vs no treatment for early infection with *P. aeruginosa*, and eradication may be sustained for up to 2 years.
  - There was insufficient evidence to determine whether antibiotic treatment for the eradication of early *P. aeruginosa* decreased mortality or morbidity, improved quality of life, or was associated with adverse events vs placebo or standard treatment.
  - Overall, there was insufficient evidence to state which antibiotic strategy should be used for the eradication of early *P. aeruginosa* infection in patients with CF.
- A network meta-analysis of 11 randomized controlled trials evaluated the effectiveness of inhaled antibiotics, including Bethkis, Tobi, tobramycin inhalation powder, and aztreonam, for the treatment of chronic *P. aeruginosa* lung infection in patients with CF (*Littlewood et al 2012*).
  - The analysis concluded that the studied antibiotics had comparable efficacies for the treatment of chronic *P. aeruginosa* lung infection in CF, as measured by improvements in change from baseline in percent predicted forced expiratory volume in 1 second ($ppFEV_1$), *P. aeruginosa* sputum density, and acute exacerbations.
  - The analyses suggested that all treatments improved clinical outcomes vs placebo. Treatment with the inhaled tobramycin formulations provided potentially clinically meaningful improvement in lung function over inhaled aztreonam, but differences were not statistically significant.
  - Prior exposure to an active drug was identified as a key factor affecting outcomes, yet this was not typically reported in trials as a predictive factor. Most trials involved the first use of the active drug, and therefore had a population who was naïve to the active drug.
- Multiple clinical trials have shown that the efficacy of tobramycin inhalation solution was significantly better vs placebo, as demonstrated by improved FEV_1, reduced sputum *P. aeruginosa* density, decreased relative risk of hospitalization for respiratory and other reasons, and decreased use of other antibiotics (*Chuchalin et al 2007, Lenoir et al 2007, Máiz et al 2013, Mazurek et al 2011, Murphy et al 2004, Ramsey et al 1999, Quittner and Buu 2002*).
  - Reported improvements in health-related quality of life (HRQoL) were significantly more likely in patients treated with tobramycin inhalation solution vs placebo, and $ppFEV_1$ was a significant predictor of HRQoL improvement (*Quittner and Buu 2002*).
  - A safety and efficacy trial determined that treatment with Bethkis inhalation solution 300 mg/4 mL demonstrated similar improvement in $ppFEV_1$ over 8 weeks of treatment compared with Tobi 300 mg/5 mL inhalation solution (*Mazurek et al 2014*). Lung function improvement with Bethkis continued throughout a 48-week extension phase, and was also associated with a favorable tolerability profile.
- Tobramycin inhalation powder delivered via the Tobi Podhaler has been shown to have similar efficacy vs the tobramycin inhalation solution; long-term safety and efficacy studies have shown that treatment with tobramycin inhalation powder was well tolerated with no unexpected adverse events and had sustained efficacy in patients with CF (*Hamed et al 2017, Máiz et al 2013, Sommerwerck et al 2016*).
  - The Phase 3 EVOLVE and EDIT clinical trials demonstrated that treatment with Tobi Podhaler significantly improved $ppFEV_1$ vs placebo at 28 days, and also reduced sputum *P. aeruginosa* density, respiratory-related hospitalizations,

and antipseudomonal antibiotic use (*Galeva et al 2013, Konstan et al 2011a*). Improvements in lung function and a decrease in sputum *P. aeruginosa* density from baseline were sustained in patients treated with up to 7 cycles of tobramycin inhalation powder over a period of at least 1 year (*Hamed et al 2017, Konstan et al 2016*).
  - The Phase 3 open-label EAGER trial demonstrated similar increases in $ppFEV_1$ and mean reduction in sputum *P. aeruginosa* density over 24 weeks (3 cycles) of treatment with tobramycin inhalation powder vs tobramycin inhalation solution (*Konstan et al 2011b*).
- Multiple clinical trials, including 3 pre-approval studies and 7 post-approval trials, have demonstrated that inhaled aztreonam is a safe and effective antimicrobial treatment for the eradication of newly acquired *P. aeruginosa* and long-term suppressive therapy of chronic endobronchial infection among patients with CF (*Elson et al 2019*).
  - Two Phase 3, double-blind, placebo-controlled, randomized-controlled trials (AIR-CF1, N = 164; AIR-CF2, N = 211) demonstrated improvements in lung function, decreased pulmonary exacerbations, reduced sputum *P. aeruginosa* density, and improvement in respiratory symptoms compared with placebo when aztreonam was administered in 28-day cycles as suppressive therapy (*McCoy et al 2008, Retsch-Bogart et al 2009*).
  - A long-term, 18-month, open-label study (AIR-CF3, N = 274) in patients who completed these 2 trials demonstrated that aztreonam use was also associated with consistent, sustained weight gain among CF patients (*Oermann et al 2010*).

CLINICAL GUIDELINES

- **Cystic Fibrosis Foundation (CFF) – CF pulmonary guidelines: chronic medications for maintenance of lung health** (*Mogayzel et al 2013*)
  - This guideline provided several new recommendations when published in 2013, in addition to reaffirming several recommendations from a previous (2007) version of the guideline.
  - For these guidelines, the severity of lung disease is defined by $ppFEV_1$ as follows: normal, > 90% predicted; mildly impaired, 70 to 89% predicted; moderately impaired, 40 to 69% predicted; and severely impaired, < 40% predicted.
  - The level of evidence and strength of recommendations are based on the U.S. Preventive Services Task Force system.
  - Recommendations specific to inhaled antibiotics and treatment of *P. aeruginosa* are included in Table 3.

Table 3. Summary of recommendations from the CFF for chronic medications in CF treatment

Treatment	Recommendation	Certainty of net benefit	Estimate of net benefit	Strength of Recommendation*
2007 recommendations, reaffirmed in 2013 without changes				
Inhaled tobramycin – moderate-to-severe disease	For individuals with CF, ≥ 6 years of age, with moderate-to-severe lung disease and *P. aeruginosa* persistently present in cultures of the airways, the CFF strongly recommends the chronic use of inhaled tobramycin to improve lung function and quality of life, and reduce exacerbations.	High	Substantial	A
Inhaled tobramycin – mild disease	For individuals with CF, ≥ 6 years of age, with mild lung disease and *P. aeruginosa* persistently present in cultures of the airways, the CFF recommends the chronic use of inhaled tobramycin to reduce exacerbations.	Moderate	Moderate	B
Azithromycin with *P. aeruginosa*	For individuals with CF, ≥ 6 years of age, with *P. aeruginosa* persistently present in cultures of the airways, the CFF recommends the chronic use of azithromycin to improve lung function and reduce exacerbations.	High	Moderate	B
Other inhaled antibiotics	For individuals with CF, ≥ 6 years of age, with *P. aeruginosa* persistently present in cultures of the airways, the CFF concludes that the evidence is insufficient to recommend for or against the chronic use of other inhaled antibiotics (ie, carbenicillin,	Low	--	I

	ceftazidime, colistin, gentamicin) to improve lung function and quality of life, or reduce exacerbations.			
Oral antipseudomonal antibiotics	For individuals with CF, ≥ 6 years of age, with *P. aeruginosa* persistently present in cultures of the airways, the CFF concludes that the evidence is insufficient to recommend for or against the routine use of chronic oral antipseudomonal antibiotics to improve lung function and quality of life, or reduce exacerbations.	Low	--	I
2013 new or modified recommendations				
Inhaled aztreonam – moderate-to-severe disease	For individuals with CF, ≥ 6 years of age, with moderate-to-severe lung disease and *P. aeruginosa* persistently present in cultures of the airways, the CFF strongly recommends the chronic use of inhaled aztreonam to improve lung function and quality of life.	High	Substantial	A
Inhaled aztreonam – mild disease	For individuals with CF, ≥ 6 years of age, with mild lung disease and *P. aeruginosa* persistently present in cultures of the airways, the CFF recommends the chronic use of inhaled aztreonam to improve lung function and quality of life.	Moderate	Moderate	B

* **A**: The committee strongly recommends that clinicians routinely provide this therapy. There is high certainty that the net benefit is substantial. **B**: The committee recommends that clinicians routinely provide this therapy. There is high certainty that the net benefit is moderate, or there is moderate certainty that the net benefit is moderate to substantial. **I**: The committee concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.

- **CFF - Clinical practice guidelines from the CFF for preschoolers with CF** (*Lahiri et al 2016*)
  - This guideline focuses on the care of preschool children 2 to 5 years of age with CF. It includes recommendations in the areas of routine surveillance for pulmonary disease, therapeutics, and nutritional and gastrointestinal care. Table 4 highlights recommendations relevant to inhaled antibiotics and treatment of *P. aeruginosa*.
  - The level of evidence and strength of recommendations are based on the U.S. Preventive Services Task Force system.

Table 4. CFF recommendations for inhaled antibiotics in preschoolers 2 to 5 years of age with CF

Topic	Recommendation	Grade or consensus		
		Certainty of net benefit	Estimate of net benefit	Strength of Recommendation*
Exacerbations	The CFF recommends the use of oral, inhaled, and/or intravenous antibiotics to treat pulmonary exacerbations.	Consensus Recommendation		
Chronic *Pseudomonas* infection	The CFF recommends that children who remain persistently infected with *P. aeruginosa* be treated chronically with alternate-month inhaled antipseudomonal antibiotics.	Moderate	Moderate	B

* **B**: The committee recommends that clinicians routinely provide this therapy. There is high certainty that the net benefit is moderate, or there is moderate certainty that the net benefit is moderate to substantial.

- **CFF - CF pulmonary guideline: pharmacologic approaches to prevention and eradication of initial *P. aeruginosa* infection** (*Mogayzel et al 2014*)
  - This guideline focuses on the prevention of *P. aeruginosa* infection, the treatment of initial *P. aeruginosa* infection, and the use of bronchoscopy to obtain routine airway cultures in individuals with CF. Guideline recommendations specific to inhaled antibiotics and prevention of *P. aeruginosa* are included in Table 5.
  - The level of evidence and strength of recommendations are based on the U.S. Preventive Services Task Force system.

Table 5. CFF recommendations for pharmacologic approaches to eradication and prevention of initial *P. aeruginosa* infection

Treatment	Recommendation	Certainty of net benefit	Estimate of net benefit	Strength of Recommendation*
Inhaled antibiotics	The CFF strongly recommends inhaled antibiotic therapy for the treatment of initial or new growth of *P. aeruginosa* from an airway culture. The favored antibiotic regimen is inhaled tobramycin (300 mg twice daily) for 28 days.	High	Substantial	A
Prophylactic antipseudomonal antibiotics	The CFF recommends against the use of prophylactic antipseudomonal antibiotics to prevent the acquisition of *P. aeruginosa*.	Moderate	Zero	D

* **A**: The committee strongly recommends that clinicians routinely provide this therapy. There is high certainty that the net benefit is substantia. **D**: The committee recommends against the therapy. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits. Clinicians should discourage the use of this therapy.

SAFETY SUMMARY

Tobramycin inhaled agents

- The inhaled tobramycin agents are contraindicated in patients with hypersensitivity or allergy to components of the product(s).
- Key warnings and precautions are similar among the inhaled tobramycin products, and generally include:
  - Bronchospasm: Can occur with inhalation of tobramycin.
  - Ototoxicity: Tinnitus and hearing loss have been reported in patients receiving tobramycin inhalation.
  - Nephrotoxicity: Has been associated with aminoglycosides as a class.
  - Neuromuscular disorders: Aminoglycosides may aggravate muscle weakness because of a potential curare-like effect on neuromuscular function.
  - Embryo-fetal toxicity: Aminoglycosides can cause fetal harm when administered to a pregnant woman.
- Adverse events associated with the inhaled tobramycin agents include:
  - Common adverse events (> 5%) occurring more frequently in Bethkis-treated patients: decreased FEV, rales, increased red blood cell sedimentation rate, and dysphonia.
  - Common adverse events (> 5%) in patients treated with Kitabis Pak and Tobi inhalation solution: cough, pharyngitis, and increased sputum.
  - Common adverse events (≥ 10%) in patients treated with Tobi Podhaler: cough, lung disorder, productive cough, dyspnea, pyrexia, oropharyngeal pain, dysphonia, hemoptysis, and headache.
    - Cough was the most common adverse event and was reported more frequently with Tobi Podhaler vs nebulized tobramycin (48% vs 31%, respectively) in clinical trials.

Aztreonam inhaled agent

- Inhaled aztreonam is contraindicated in patients with a known allergy to aztreonam.
- Key warnings and precautions for aztreonam include risk of allergic reactions, bronchospasm, decreases in FEV_1 after a 28-day treatment cycle, and development of drug-resistant bacteria.
- Common adverse events (> 5%) with aztreonam include cough, nasal congestion, wheezing, pharyngolaryngeal pain, pyrexia, chest discomfort, abdominal pain and vomiting.

DOSING AND ADMINISTRATION

Table 6. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments*
Bethkis (tobramycin)	Inhalation solution: 300 mg/4 mL ampules	Oral inhalation	Twice daily in repeated cycles of 28 days on drug, followed by 28 days off	• Dose should be administered using the hand-held Pari LC Plus Reusable Nebulizer with a Pari Vios air compressor.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments*
Kitabis Pak (tobramycin)	Inhalation solution: 300 mg/5 mL ampules	Oral inhalation	Twice daily in repeated cycles of 28 days on drug, followed by 28 days off	• Dose should be administered using the hand-held Pari LC Plus Reusable Nebulizer. • Kitabis Pak is a co-packaging of tobramycin inhalation solution with a Pari LC Plus Reusable Nebulizer.
Cayston (aztreonam)	Inhalation solution: 75 mg single-use vials of lyophilized powder packaged with sterile saline diluent	Oral Inhalation	Three times daily in repeated cycles of 28 days on drug, followed by 28 days off	• Dose should be reconstituted with 1 mL of sterile diluent. • Dose should be administered over an approximate 2 to 3 minute period using the Altera Nebulizer System. • Patients should use a bronchodilator before administration.
Tobi (tobramycin)	Inhalation solution: 300 mg/5 mL ampules	Oral inhalation	Twice daily in repeated cycles of 28 days on drug, followed by 28 days off	• Dose should be administered using the hand-held Pari LC Plus Reusable Nebulizer and DeVilbiss PulmoAide compressor.
Tobi Podhaler (tobramycin)	Inhalation powder: 28 mg capsules	Oral inhalation	4 capsules twice daily in repeated cycles of 28 days on drug, followed by 28 days off	• Capsules are for use with the Podhaler device only. • The contents of each capsule are administered through a deep inhalation with a single breath; the patient must inhale 2 times from each of the 4 capsules (ie, a total of 8 breath-activated inhalations)

* Doses for all agents should be administered as close to 12 hours apart as possible; but not less than 6 hours apart for tobramycin agents and not < 4 hours apart for aztreonam; dose is not adjusted for age or weight.

See the current prescribing information for full details

- In general, aerosolized antibiotics require a compressor and nebulizer, and approximately 15 minutes per dose for administration of tobramycin and 2 to 3 minutes for aztreonam. Nebulizers require regular cleaning after each use to prevent device contamination; lack of regular cleaning may potentially lead to transport of pathogens to the lower airways (*Blau et al 2007, Lester et al 2012*).
- Phase 1 and Phase 3 studies of treatment with tobramycin administered via the Tobi Podhaler reported an administration time of 4 to 6 minutes in patients with CF (*Geller et al 2007, Konstan et al 2011a*). The Tobi Podhaler device does not require disinfection (*Hamed et al 2017, Vazquez-Espinosa et al 2016*).

CONCLUSION

- Inhaled antibiotics are commonly used to treat persistent airway infection with *P. aeruginosa*, which contributes to lung damage in patients with CF. Treatment with inhaled antibiotics reduces bacterial load in the lungs, and decreases inflammation and the deterioration of lung function.
- Current clinical evidence supports the efficacy of the various inhaled tobramycin formulations and inhaled aztreonam for the management of CF patients with *P. aeruginosa*. Efficacy appears comparable among agents, and data are limited regarding which antibiotic strategy may be more effective in improvement in lung function, reduction of exacerbation rates, and eradication of *P. aeruginosa* infection.

- Guidelines recommend chronic use of inhaled tobramycin or aztreonam in patients with CF 6 years of age and older, with mild or moderate-to-severe lung disease and *P. aeruginosa*, to improve lung function and quality of life, and reduce exacerbations.
  - Inhaled antibiotic therapy is strongly recommended for initial or new growth of *P. aeruginosa*, with inhaled tobramycin as the favored regimen.
  - Inhaled tobramycin agents are indicated in patients ≥ 6 years of age, while inhaled aztreonam is indicated in patients ≥ 7 years of age.
- Safety concerns with inhaled tobramycin agents include bronchospasm, ototoxicity, nephrotoxicity, and neuromuscular disorders.
  - In clinical trials, cough was reported more frequently with the Tobi Podhaler inhalation powder vs nebulized tobramycin or placebo.
- Safety concerns with inhaled aztreonam include bronchospasm, decreases in FEV_1, and development of drug-resistant bacteria.
- All inhaled tobramycin agents are administered twice daily. Bethkis, Kitabis Pak, and Tobi inhalation solution are administered via a 15-minute nebulization. In contrast, tobramycin inhalation powder administered via the Tobi Podhaler takes approximately 4 to 6 minutes to administer via a total of 8 breath-activated inhalations (2 inhalations of the contents of 4 dry powder capsules).
- Inhaled aztreonam is administered 3 times daily via a 2 to 3 minute nebulization; patients should use a bronchodilator before administration.
- Use of a nebulizer requires additional steps for set-up and regular cleaning after each use to prevent device contamination, while the Tobi Podhaler device does not require disinfection.

REFERENCES

- Assael BM, Pressler T, Bilton D, et al. Inhaled aztreonam lysine vs inhaled tobramycin in cystic fibrosis: a comparative efficacy trial. *J Cyst Fibros*. 2013;12:130-140.
- Bethkis [package insert], Woodstock, IL: Chiesi USA, Inc.; December 2019.
- Blau H, Mussaffi H, Mei Zahav M, et al. Microbial contamination of nebulizers in the home treatment of cystic fibrosis. *Child Care Health Dev*. 2007; 33: 491-495.
- Cayston [package insert], Foster City, CA: Gilead Sciences, Inc.; November 2019.
- CFTR2: Clinical and functional translation of CFTR; in collaboration with the Cystic Fibrosis Foundation and Johns Hopkins University. https://www.cftr2.org/mutations_history. March 2019. Accessed January 14, 2020.
- Chuchalin A, Csiszer E, Gyurkovics K, et al. A formulation of aerosolized tobramycin (Bramitob) in the treatment of patients with cystic fibrosis and Pseudomonas aeruginosa infection: a double-blind, placebo-controlled, multicenter study. *Paediatr Drugs*. 2007;9(Suppl 1):21-31.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed January 10, 2020.
- Egan ME. Genetics of cystic fibrosis: clinical implications. *Clin Chest Med*. 2016;37:9-16.
- Elborn JS. Cystic fibrosis. *Lancet*. 2016;388:2519-2531.
- Elson EC, Mermis J, Polineni D, Oermann CM. Aztreonam lysine inhalation solution in cystic fibrosis. *Clin Med Insights Circ Respir Pulm Med*. 2019;13:1179548419842822. doi: 10.1177/1179548419842822.
- Galeva I, Konstan MW, Higgins M, et al. Tobramycin inhalation powder manufactured by improved process in cystic fibrosis: the randomized EDIT trial. *Curr Med Res Opin*. 2013;29:947-956.
- Geller DE, Konstan MW, Smith J, et al. Novel tobramycin inhalation powder in cystic fibrosis subjects: pharmacokinetics and safety. *Pediatr Pulmonol*. 2007;42:307-313.
- Hamed K, Debonnett L. Tobramycin inhalation powder for the treatment of pulmonary Pseudomonas aeruginosa infection in patients with cystic fibrosis: a review based on clinical evidence. *Ther Adv Respir Dis*. 2017;11(5):193-209. doi: 10.1177/1753465817691239.
- Kitabis Pak [package insert], Midlothian, VA: Pari Respiratory Equipment; September 2019.
- Konstan MW, Flume PA, Galeva I, et al. One-year safety and efficacy of tobramycin powder for inhalation in patients with cystic fibrosis. *Pediatr Pulmonol*. 2016;51(4):372-378. doi: 10.1002/ppul.23358.
- Konstan MW, Flume PA, Kappler M, et al. Safety, efficacy and convenience of tobramycin inhalation powder in cystic fibrosis patients: The EAGER trial. *J Cyst Fibros*. 2011b;10(1):54-61. doi: 10.1016/j.jcf.2010.10.003.
- Konstan MW, Geller DE, Minic P, et al. Tobramycin inhalation powder for P. aeruginosa infection in cystic fibrosis: the EVOLVE trial. *Pediatr Pulmonol*. 2011a; 46:230–238.
- Lahiri T, Hempstead SE, Brady C, et al. Clinical practice guidelines from the Cystic Fibrosis Foundation for preschoolers with cystic fibrosis. *Pediatrics*. 2016;137(4):e20151784. doi: 10.1542/peds.2015-1784.
- Langton Hewer SC, Smyth AR. Antibiotic strategies for eradicating Pseudomonas aeruginosa in people with cystic fibrosis. *Cochrane Database Syst Rev*. 2017;4:CD004197. doi: 10.1002/14651858.CD004197.pub5.
- Lenoir G, Antypkin YG, Miano A, et al. Efficacy, safety, and local pharmacokinetics of highly concentrated nebulized tobramycin in patients with cystic fibrosis colonized with Pseudomonas aeruginosa. *Paediatr Drugs*. 2007;9(Suppl 1):11-20.
- Lester MK, Flume PA, Gray SL, et al. Nebulizer use and maintenance by cystic fibrosis patients: a survey study. *Respir Care*. 2004;49:1504–1508.
- Littlewood KJ, Higashi K, Jansen JP, et al. A network meta-analysis of the efficacy of inhaled antibiotics for chronic Pseudomonas infections in cystic fibrosis. *J Cyst Fibros*. 2012;11(5):419-426. doi: 10.1016/j.jcf.2012.03.010.

- Máiz L, Girón RM, Olveira C, et al. Inhaled antibiotics for the treatment of chronic bronchopulmonary Pseudomonas aeruginosa infection in cystic fibrosis: systematic review of randomized controlled trials. *Expert Opin Pharmacother*. 2013;14(9):1135-1149. doi:10.1517/14656566.2013.790366.
- Mazurek H, Chiron R, Kucerova T, et al. Long-term efficacy and safety of aerosolized tobramycin 300 mg/4 ml in cystic fibrosis. *Pediatr Pulmonol*. 2014;49(11):1076-1089. doi: 10.1002/ppul.22989.
- Mazurek H, Lenoir G, Pelikan L, et al. Head-to-head comparison of two inhaled tobramycin solutions in cystic fibrosis (CF) patients with chronic Pseudomonas aeruginosa (Pa) infection. *J Cyst Fibros*. 2011;10(Suppl 1):S28.
- McCoy KS, Quittner AL, Oermann CM, et al. Inhaled aztreonam lysine for chronic airway *Pseudomonas aeruginosa* in cystic fibrosis. *Am J Respir Crit Care Med*. 2008;178(9):921-928. doi:10.1164/rccm.200712-1804OC.
- Mogayzel PJ Jr, Naureckas ET, Robinson KA, et al; Cystic Fibrosis Foundation Pulmonary Clinical Practice Guidelines Committee. Cystic Fibrosis Foundation pulmonary guideline: pharmacologic approaches to prevention and eradication of initial Pseudomonas aeruginosa infection. *Ann Am Thorac Soc*. 2014 Dec;11(10):1640-1650. doi: 10.1513/AnnalsATS.201404-166OC.
- Mogayzel PJ, Naureckas ET, Robinson KA, et al; Pulmonary Clinical Practice Guidelines Committee. Cystic fibrosis pulmonary guidelines: chronic medications for maintenance of lung health. *Am J Respir Crit Care Med*. 2013;187(7):680-689.
- Murphy TD, Anbar RD, Lester LA, et al. Treatment with tobramycin solution for inhalation reduces hospitalizations in young CF subjects with mild lung disease. *Pediatr Pulmonol*. 2004;38(4):314-320.
- National Institutes of Health; National Human Genome Research Institute. Learning about cystic fibrosis. https://www.genome.gov/10001213/. Updated December 27, 2013. Accessed January 14, 2020.
- Oermann CM, Retsch-Bogart GZ, Quittner AL, et al. An 18-month study of the safety and efficacy of repeated courses of inhaled aztreonam lysine in cystic fibrosis. *Pediatr Pulmonol*. 2010;45:1121-1134.
- Ong T, Ramsey BW. New therapeutic approaches to modulate and correct cystic fibrosis transmembrane conductance regulator. *Pediatr Clin N Am*. 2016;63:751-764.
- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed January 10, 2020.
- Quittner AL, Buu A. Effects of tobramycin solution for inhalation on global ratings of quality of life in patients with cystic fibrosis and Pseudomonas aeruginosa infection. *Pediatr Pulmonol*. 2002;33(4):269-276.
- Quon BS, Rowe SM. New and emerging targeted therapies for cystic fibrosis. *BMJ*. 2016;352:i859. doi: 10.1136/bmj.i859.
- Ramsey BW, Pepe MS, Quan JM, et al. Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. Cystic Fibrosis Inhaled Tobramycin Study Group. *N Engl J Med*. 1999;340(1):23-30.
- Retsch-Bogart GZ, Quittner AL, Gibson RL, et al. Efficacy and safety of inhaled aztreonam lysine for airway pseudomonas in cystic fibrosis. *Chest*. 2009;135(5):1223-1232. doi: 10.1378/chest.08-1421.
- Sosnay PR, Raraigh KS, Gibson RL. Molecular genetics of cystic fibrosis transmembrane conductance regulator: genotype and phenotype. *Pediatr Clin N Am*. 2016;63:585-598.
- Smith S, Rowbotham NJ, Regan KH. Inhaled anti-pseudomonal antibiotics for long-term therapy in cystic fibrosis. *Cochrane Database Syst Rev*. 2018a;3:CD001021. doi: 10.1002/14651858.CD001021.pub3.
- Smith S, Rowbotham NJ, Charbek E. Inhaled antibiotics for pulmonary exacerbations in cystic fibrosis. *Cochrane Database Syst Rev*. 2018b;10:CD008319. doi: 10.1002/14651858.CD008319.pub3.
- Sommerwerck U, Virella-Lowell I, Angyalosi G, et al. Long-term safety of tobramycin inhalation powder in patients with cystic fibrosis: phase IV (ETOILES) study. *Curr Med Res Opin*. 2016;32(11):1789-1795.
- Tobi [package insert], East Hanover, NJ: Novartis Pharmaceuticals Corporation; October 2018.
- Tobi Podhaler [package insert], East Hanover, NJ: Novartis Pharmaceuticals Corporation; October 2015.
- Vazquez-Espinosa E, Marcos C, Alonso T, et al. Tobramycin inhalation powder (TOBI Podhaler) for the treatment of lung infection in patients with cystic fibrosis. *Expert Rev Anti Infect Ther*. 2016;14(1):9-17. doi: 10.1586/14787210.2016.1118344.

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