Therapeutic Class Overview
Inhaled Aminoglycosides

INTRODUCTION

- Cystic fibrosis (CF) is the most common fatal genetic disease, affecting approximately 29,000 patients in the United States (U.S.) (*Hamed et al 2017, National Institutes of Health 2013*). It is caused by mutations in the *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, and more than 200 of these mutations have been confirmed to cause CF (*Quon et al 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 et al 2016*).
  - 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 et al 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 2018*).
  - 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), and Symdeko (tezacaftor/ivacaftor) (*Drugs@FDA 2018, Elborn 2016*). However, not all CF patients are eligible for treatment with CFTR modulators, and these products are used in conjunction with traditional therapies in patients who are eligible.
  - The 2013 CF Foundation (CFF) guidelines recommend the inhaled antibiotics for patients > 6 years of age with CF to improve lung function, improve quality of life, and/or reduce exacerbations, including chronic inhaled tobramycin for patients with mild, moderate, or severe disease with persistent colonization of *P. aeruginosa* (*Mogayzel et al 2013*).
- This review includes the inhaled aminoglycoside antibiotic, tobramycin, indicated for the treatment of CF patients with *P. aeruginosa*. Inhaled tobramycin is available in a variety of formulations and may be administered via nebulization or dry powder inhalation.
- Medispan classes: Anti-Infective Agents – Aminoglycosides (tobramycin)

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Bethkis (tobramycin)	-
Kitabis Pak (tobramycin)	-
Tobi (tobramycin)	✔
Tobi Podhaler (tobramycin)	-

(*Drugs@FDA 2018, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2018*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Drug*	Management of CF patients with *P. aeruginosa*†
Bethkis (tobramycin)	✔ (age ≥ 6 years)
Kitabis Pak (tobramycin)	✔ (age ≥ 6 years)
Tobi (tobramycin)	✔ (age ≥ 6 years)
Tobi Podhaler (tobramycin)	✔ (age ≥ 6 years)

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 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 2017, Kitabis Pak 2014, Tobi 2015, 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, 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 2018*).
  - 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, 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 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 (TIP), 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 (TIS) 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 TIS vs placebo, and ppFEV$_1$ was a significant predictor of HRQoL improvement (*Quitner and Buu 2002*).
  - A safety and efficacy trial determined that treatment with Bethkis nebulization solution 300 mg/4 mL demonstrated similar improvement in ppFEV$_1$ over 8 weeks of treatment compared with Tobi 300 mg/5 mL nebulization 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.
- TIP delivered via the Tobi Podhaler has been shown to have similar efficacy vs TIS; long-term safety and efficacy studies have shown that treatment with TIP 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 TIP 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 TIP vs TIS (*Konstan et al 2011b*).
- A systematic review of 6 trials (N = 208) evaluated the effectiveness of inhaled antibiotics for the treatment of pulmonary exacerbations in patients with CF (*Ryan et al 2012*). The effectiveness of these agents 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 no high level evidence to support the use of inhaled antibiotics for 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.

CLINICAL GUIDELINES

- **Cystic Fibrosis Foundation (CFF) – CF pulmonary guidelines: chronic medications for maintenance of lung health** (*Mogayzel et al 2013*)
  - The guideline provided several new recommendations when published in 2013, in addition to reaffirming several recommendations from a previous (2007) version of the guideline. Guideline recommendations specific to inhaled antibiotics and treatment of *P. aeruginosa* are included in Table 3.
  - For these guidelines, the severity of lung disease is defined by ppFEV$_1$ as follows: normal, > 90% ppFEV$_1$; mildly impaired, 70 to 89% ppFEV$_1$; moderately impaired, 40 to 69% ppFEV$_1$; and severely impaired, < 40% ppFEV$_1$.
  - Level of evidence and strength of recommendations is based on the U.S. Preventive Services Task Force system.

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 and older, 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 and older, 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 and older, 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 and older, 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, ceftazidime, colistin, gentamicin) to improve lung function and quality of life, or reduce exacerbations.	Low	--	I
Oral antipseudomonal antibiotics	For individuals with CF, 6 years of age and older, 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 and older, 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 and older, 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*.
  - Level of evidence and strength of recommendations is based on the U.S. Preventive Services Task Force system.

Table 4. Summary of recommendations from the CFF for medication use in preschoolers age 2 to 5 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.
  - Level of evidence and strength of recommendations is based on the U.S. Preventive Services Task Force system.

Table 5. Summary of recommendations from the CFF 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 *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

- 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.
- Fetal harm: can occur when aminoglycosides are 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.

DOSING AND ADMINISTRATION

Table 6. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments*
Bethkis	Inhalation nebulization 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 over an approximately 15-minute period, using the Pari LC Plus Reusable Nebulizer and DeVilbiss PulmoAide compressor.
Kitabis Pak	Inhalation nebulization 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 over an approximately 15-minute period, using the Pari LC Plus Reusable Nebulizer and DeVilbiss PulmoAide compressor. Kitabis Pak is a co-packaging of tobramycin inhalation solution with a Pari LC Plus Reusable Nebulizer.
Tobi	Inhalation nebulization 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 over an approximately 15-minute period, using the Pari LC Plus Reusable Nebulizer and DeVilbiss PulmoAide compressor.
Tobi Podhaler	Inhalation powder: 28 mg capsules	Oral inhalation	Four 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 capsule.

* Doses for all agents should be taken as close to 12 hours apart as possible; but not less than 6 hours apart; 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. 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 2004*).

- 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 have been 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 has supported the efficacy of the various inhaled tobramycin formulations for the management of CF patients with *P. aeruginosa*, and efficacy appears comparable among agents.
- Chronic use of inhaled tobramycin is recommended in patients with CF aged 6 years 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.
- 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.
- All inhaled tobramycin agents are administered twice daily. Bethkis, Kitabis Pak, and Tobi are administered via a 15-minute nebulization, and use of the nebulizer requires additional steps for cleaning and set-up. In contrast, Tobi Podhaler inhalation powder takes less time to administer, is given via a total of 8 breath-activated inhalations (2 inhalations of the contents of 4 dry powder capsules), and does not require disinfection.

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