PRIOR AUTHORIZATION POLICY

POLICY: Antibiotics (Inhaled) – Arikayce Prior Authorization Policy
- Arikayce® (amikacin liposome inhalation suspension for oral inhalation – Insmed)

REVIEW DATE: 10/28/2020

OVERVIEW

Arikayce is indicated for the treatment of ***Mycobacterium avium* complex (MAC) lung disease**, in adults who have limited or no alternative treatment options, as part of a combination antibacterial regimen in patients who do not achieve negative sputum cultures after at least six consecutive months of a background multidrug regimen (MDR) therapy.[1] As only limited clinical safety and efficacy data is available, reserve Arikayce for adults with limited or no other treatment options.

This indication is approved under accelerated approval based on achieving sputum culture conversion (defined as three consecutive negative monthly sputum cultures) by Month 6.[1]

Limitation of Use: Arikayce has only been studied in patients with refractory MAC lung disease defined as not achieving culture negativity after at least 6 months of background MDR treatment.[1] Arikayce is not recommended in patients with non-refractory MAC lung disease.

Disease Overview

Nontuberculous mycobacteria (NTM) are ubiquitous environmental microorganisms that are routinely found in soil and water, including both natural and treated water.[2-4] In susceptible people, NTM can cause pulmonary and extra-pulmonary disease.[2] MAC is by far, the most common NTM causing pulmonary nontuberculosis mycobacterial disease (PNTM) with *M. kansassii* and *M. abscessus* the second and third most common causes of PNTM.[2] The prevalence is higher in women than men,[2,3,5] and in the Southeast and the West.[3] The prevalence of PNTM increases with increasing age,[3] is associated with chronic obstructive pulmonary disease (COPD),[4] and 90% of the cases of PNTM occur in Caucasians, followed by Asians/Pacific Islanders and Blacks in the US.[3] Studies from North America have found the annual rate of isolation of NTM to range from 6 to 22 per 100,000 persons and the annual rate of PNTM to range from 5 to 10 per 100,000 persons.[5]

Treatment recommendations for MAC lung disease are based on disease severity and previous therapies received and almost all are three drug regimens.[6] For those with nodular/bronchiectatic disease or with fibrocavitary disease who cannot tolerate daily treatment, a three times weekly (TIW), three-drug regimen is recommended. The TIW regimen consists of azithromycin 500 to 600 mg or clarithromycin 1,000 mg, ethambutol 25 mg/kg, and rifampin 600 mg. For select patients with nodular/bronchiectatic disease (mild disease, medication intolerance, or goal of therapy is disease suppression), a two drug regimen consisting of azithromycin or clarithromycin plus ethambutol daily is acceptable. For patients with fibrocavitary disease or severe nodular/bronchiectatic disease, daily administration of azithromycin 250 to 300 mg or clarithromycin 500 to 1,000 mg, ethambutol 15 mg/kg, and rifampin 600 mg is recommended. Treatment recommendations for patients with severe or previously treated disease include azithromycin 250 to 300 mg or clarithromycin 500 to 1,000 mg, ethambutol 15 mg/kg, and rifabutin 150 to 300 mg or rifampin 600 mg daily. Intermittent IV amikacin or streptomycin are recommended for the first 2 to 3 months in patients with cavitary disease, or previous treatment failure. Patients should be treated for 12 months beyond the time that the sputum cultures convert to negative. For most patients conversion occurs within 6 months of initiation of treatment.

Guidelines
The American Thoracic Society (ATS), the European Respiratory Society (ERS), the European Society of Clinical Microbiology and Infectious Disease (ESCMID), and the Infectious Disease Society of America (IDSA) developed clinical practice guidelines for the treatment of nontuberculous mycobacterial pulmonary disease (2020 version).[6] The guidelines recommend the addition of liposomal amikacin to guideline-based therapy, in patients with MAC pulmonary disease who have failed treatment after ≥ 6 months of treatment with guideline-based therapy. Liposomal amikacin is not recommended for the initial treatment of MAC pulmonary disease.

The US Cystic Fibrosis Foundation and the European Cystic Fibrosis Society (2016 version) developed consensus recommendations on the treatment of NTM lung disease in which nebulized amikacin is listed as a treatment option for MAC and *M. abscessus* lung disease in cystic fibrosis (CF) patients.[7] The guidelines recommend that inhaled amikacin be used in conjunction with other NTM antibiotics.

Other Uses with Supportive Evidence
The efficacy of Arikayce in the treatment of *Pseudomonas aeruginosa* infection in CF patients has been assessed in three studies.[8] In a Phase III, randomized, open-label, non-inferiority study, 302 patients with CF were randomized to Arikayce 590 mg once daily (QD) or tobramycin inhalation solution (TIS) 300 mg twice daily. Patients received three cycles of treatment which consisted of 28 days on treatment followed by 28 days off treatment. The primary endpoint of the study was the relative change from baseline to the end of the 24-week study in forced expiratory volume in 1 second (FEV_1). Secondary endpoints included change in FEV_1 and forced expiratory volume % (FEV_1 %) predicted at various time points, change in CF Questionnaire-Revised (CFQ-R), time to first exacerbation, change in $\log_{10}$ colony-forming units (CFU), and all-cause hospitalization. The improvement in least squares mean FEV_1 at Day 168 was similar between Arikayce and TIS. The mean difference was -1.31% meeting the prespecified criteria for non-inferiority (lower bound of the 95% CI ≥ -5.0%). Change in FEV_1 at the end of each treatment course (Day 28, 84, and 140) and change in FEV_1 % predicted at the midpoint of cycle 1 (Day 14) and at the end of each treatment course were similar between treatment groups. More patients receiving Arikayce experienced pulmonary exacerbations compared with TIS; however, fewer patients required all-cause hospitalization. Change in CFQ-R was similar between groups at the end of each treatment course. Mean reductions in *P. aeruginosa* $\log_{10}$ CFU was similar for Arikayce and TIS at Day 28 and at Day 140.

A pooled report included 24 patients from two Phase Ib/IIa pharmacokinetic/pharmacodynamic studies with chronic *P. aeruginosa* infection.[9] Patients received liposomal amikacin 500 mg QD by inhalation for 14 days. Statistically significant changes from baseline to Days 7 and 14 were seen in FEV_1, FEV_1 % predicted, and forced expiratory flow between 25% and 75% of forced vital capacity. Another report included pooled data from two dose-ranging studies (one Phase Ib/IIa and one Phase IIa) in patients with CF (n = 105) chronically infected with *P. aeruginosa*.[9] Patients received 70, 140, 280 or 560 of liposomal amikacin or placebo QD for 28 days and followed for an additional 28 days. In repeated-measures mixed-effect models, the 560 mg dose was associated with statistically significant improvements in FEV_1, and FEV_1 % predicted and a reduction in $\log_{10}$ CFUs.

POLICY STATEMENT
Prior authorization is recommended for prescription benefit coverage of Arikayce. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Arikayce as well as the monitoring required for adverse events and long-term efficacy, approval requires Arikayce to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Arikayce is recommended in those who meet the following criteria:

FDA-Approved Indications

1. ***Mycobacterium avium* Complex (MAC) Lung Disease.** Approve for 1 year if the patient meets the following criteria (A, B, C, and D):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has NOT achieved negative sputum cultures for *Mycobacterium avium* complex within the past 3 months after completion of ≥ 6 consecutive months of a background multidrug regimen; AND
     Note: A multidrug regimen typically includes a macrolide (azithromycin or clarithromycin), ethambutol, and a rifamycin (rifampin or rifabutin).
   - **C)** Arikayce will be used in conjunction to a background multidrug regimen; AND
     Note: A multidrug regimen typically includes a macrolide (azithromycin or clarithromycin), ethambutol, and a rifamycin (rifampin or rifabutin).
   - **D)** The medication is prescribed by a pulmonologist, infectious diseases physician or a physician who specializes in the treatment of *Mycobacterium avium* complex lung infections.

Other Uses with Supportive Evidence

2. **Cystic Fibrosis**. Approve for 1 year if the patient meets the following criteria (A and B):
   - **A)** Patient has *Pseudomonas aeruginosa* in culture of the airway (e.g., sputum culture, oropharyngeal culture, bronchoalveolar lavage culture); AND
   - **B)** The medication is prescribed by or in consultation with a pulmonologist or a physician who specializes in the treatment of cystic fibrosis.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Arikayce is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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7. Floto RA, Olivier KN, Saiman L, et al. US Cystic Fibrosis Foundation and European Cystic Fibrosis Society consensus recommendations for the management of non-tuberculous mycobacteria in individuals with cystic fibrosis. *Thorax*. 2016;7:i1-i22.
8. Bilton D, Pressler T, Fajac I, et al. Amikacin liposome inhalation suspension for chronic *Pseudomonas aeruginosa* infection in cystic fibrosis. *J Cyst Fibros*. 2019; doi: 10.1016/j.jcf.2019.08.001. [Epub ahead of print].

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10. Okusanya OO, Bhavnani SM, Hammel JP, et al. Evaluation of the Pharmacokinetics and Pharmacodynamics of Liposomal Amikacin for Inhalation in Cystic Fibrosis Patients with Chronic Pseudomonal Infections Using Data from Two Phase 2 Clinical Studies. *Antimicrob Agents Chemother*. 2014;58:5005-5015.