PRIOR AUTHORIZATION POLICY

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

REVIEW DATE: 10/23/2024

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 6 consecutive months of a background multidrug regimen (MDR) therapy.[1] As only limited clinical safety and efficacy data are available, reserve Arikayce for adults with limited or no other treatment options.

This indication was 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.

Efficacy

The efficacy of Arikayce was established in one open-label, randomized (2:1), multi-center trial in patients with refractory MAC lung disease as confirmed by at least 2 sputum culture results (n = 336).[7] Patients were considered to have refractory MAC lung disease if they did not achieve negative sputum cultures after a minimum duration of 6 consecutive months of background regimen therapy that was either ongoing or stopped ≤ 12 months before the screening visit. The surrogate efficacy endpoint was based on achieving culture conversion (3 consecutive monthly negative sputum cultures) by Month 6. Patients who achieved culture conversion by Month 6 were continued on Arikayce plus background multidrug regimen or background multidrug regimen alone based on their randomization for a total of 12 months after the first negative sputum culture. At baseline, 329 patients were on a multidrug background regimen that included a macrolide (93.3%), a rifamycin (86.3%), or ethambutol (81.4%). The proportion of patients achieving culture conversion by Month 6 was significantly greater with Arikayce plus background multidrug regimen vs. background multidrug regimen alone (29% vs. 8.9%, respectively; $P < 0.0001$). Among patients who achieved culture conversion by Month 6, 55.4% of patients in the Arikayce group vs. no patients in the background multidrug regimen only group had sustained and durable conversion ($P = 0.0017$).[8] Relapse rates through 3 months after treatment were 9.2% in the Arikayce group vs. 30.0% in the background therapy only group.

Guidelines

The American Thoracic Society, the European Respiratory Society, the European Society of Clinical Microbiology and Infectious Disease, and the Infectious Disease Society of America developed clinical practice guidelines for the treatment of nontuberculous mycobacterial (NTM) pulmonary disease (2020).[2] Treatment recommendations for MAC lung disease are based on disease severity and previous therapies received and almost all are three drug regimens. Typical regimens involve azithromycin or clarithromycin; ethambutol; and rifampin. For select patients, a two-drug regimen consisting of azithromycin or clarithromycin plus ethambutol daily is acceptable. Liposomal amikacin is not recommended for the initial treatment of MAC pulmonary disease. The guidelines recommend the addition of liposomal amikacin to guideline-based therapy in patients with MAC pulmonary disease who have failed treatment (failure to

convert sputum culture) after ≥ 6 months of treatment with guideline-based therapy. Patients should be treated for ≥12 months after culture conversion. The breakpoint for resistance to amikacin is ≥ 64 mcg/mL for parenteral amikacin and ≥ 128 mcg/mL for amikacin liposome inhalation suspension, and finding these MICs would lead to cessation of therapy. In patients with MAC pulmonary disease, guidelines suggest susceptibility-based treatment for macrolides and amikacin over empiric therapy (conditional recommendation, very low certainty in estimates of effect).

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.[3] 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 patients with CF has been assessed in three studies.[4] In a Phase III, randomized, open-label, non-inferiority study, patients with CF were randomized to Arikayce 590 mg once daily (QD) or tobramycin inhalation solution (TIS) 300 mg twice daily (n = 302). 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). FEV_1 improvement at Day 168 with Arikayce was non-inferior to TIS (mean difference -1.31%). More patients receiving Arikayce experienced pulmonary exacerbations compared with TIS; however, fewer patients required all-cause hospitalization. Change in CF Questionnaire Revised 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 with CF and chronic *P. aeruginosa* infection from two Phase Ib/IIa pharmacokinetic/pharmacodynamic studies.[5] 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*.[6] Patients received 70-, 140-, 280- or 560-mg of liposomal amikacin or placebo QD for 28 days and were 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. In cases where the approval duration is authorized in months, 1 month is equal to 30 days. 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, initial 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 one of the following criteria:

FDA-Approved Indication

1. ***Mycobacterium avium* Complex Lung Disease.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 1 year of the patient meets ALL of the following (i, ii, iii, iv, v, and vi):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Patient has completed ≥ 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).
     - **iii.** Patient has a positive sputum culture for *Mycobacterium avium* complex; AND
       Note: Any positive sputum culture taken after the patient has completed ≥ 6 consecutive months of a background multidrug regimen fulfills this criterion.
     - **iv.** The *Mycobacterium avium* complex isolate is susceptible to amikacin, according to the laboratory report; AND
     - **v.** The medication will be used in conjunction with a background multidrug regimen; AND
       Note: A multidrug regimen typically includes a macrolide (azithromycin or clarithromycin), ethambutol, and a rifamycin (rifampin or rifabutin).
     - **vi.** The medication is prescribed by a pulmonologist, infectious diseases physician, or a physician who specializes in the treatment of *Mycobacterium avium* complex lung infections.
   - **B)** Patient is Currently Receiving Arikayce. Approve for the duration noted below if the patient meets BOTH of the following (i and ii):
     - **i.** The medication will be used in conjunction with a background multidrug regimen; AND
       Note: A multidrug regimen typically includes a macrolide (azithromycin or clarithromycin), ethambutol, and a rifamycin (rifampin or rifabutin).
     - **ii.** Patient meets ONE of the following (a or b):
       - **a)** Approve for 1 year if patient has not achieved negative sputum cultures for *Mycobacterium avium* complex; OR
       - **b)** Approve for 1 year (total) if patient has achieved negative sputum cultures for *Mycobacterium avium* complex for less than 12 months.
         Note: Approve enough Arikayce to complete 12 months of therapy following a negative sputum culture for *Mycobacterium avium* complex.

Other Uses with Supportive Evidence

2. **Cystic Fibrosis**. Approve for 1 year if the patient meets the following (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

1. Arikayce® suspension for oral inhalation [prescribing information]. Bridgewater, NJ: Insmed; February 2023.
2. Daley CL, Iaccarino JM, Lange C, et al. Treatment of nontuberculous mycobacterial pulmonary disease: An official ATS/ERS/ESCMID/IDSA clinical practice guideline. *Eur Respir J*. 2020;56:2000535.
3. 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.
4. Bilton D, Pressler T, Fajac I, et al. Amikacin liposome inhalation suspension for chronic *Pseudomonas aeruginosa* infection in cystic fibrosis. *J Cyst Fibros*. 2020;19:284-291.
5. Okusanya OO, Bhavnani SM, Hammel J, et al. Pharmacokinetic and pharmacodynamic evaluation of liposomal amikacin for inhalation in cystic fibrosis patients with chronic Pseudomonal infection. *Antimicrob Agents Chemother*. 2009;53:3847-3854.
6. 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.
7. Griffith DE, Eagle G, Thomson R et al; for the CONVERT Study Group. Amikacin liposome inhalation suspension for treatment-refractory lung disease caused by *Mycobacterium avium* complex (CONVERT) a prospective, open-label, randomized study. *Am J Respir Crit Care Med.* 2018;198(12):1559-1569.
8. Griffith DE, Thomson R, Flume P et al; for the CONVERT Study Group. Amikacin liposome inhalation suspension for refractory *Mycobacterium avium* complex lung disease. *Chest*. 2021;160(3):831-842.