Drug Monograph

Drug/Drug Class:	**Arikayce® (amikacin) liposome suspension for inhalation / Inhaled Antibiotics**
Prepared for:	MO HealthNet
Prepared by:	Conduent

☒ **New Criteria** ☐ **of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms & Manufacturer:	Arikayce® is available as a sterile, aqueous, liposome suspension for oral inhalation in a unit-dose glass vial containing amikacin 590 mg/8.4 mL Manufactured by: Insmed Incorporated, Bridgewater, NJ 08807-3365
Summary of Findings:	The efficacy of Arikayce® was assessed in an open-label, randomized, multi-center trial in adult patients with refractory *Mycobacterium avium* complex (MAC) lung disease. The proportion of patient achieving culture conversion by Month 6 was significantly ($p<0.0001$) greater for Arikayce® plus background regimen (65/224, 29%) compared to background regimen alone (10/112, 8.9%).
Status Recommendation:	☐ Prior Authorization (PA) Required ☐ Open Access ☐ Clinical Edit ☒ PDL
Type of PA Criteria:	☐ Increased Risk of ADE ☒ Under Solicitation ☐ Appropriate Indications ☐ No PA Required

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [2,3]

Mycobacterium avium complex (MAC) are the most common pulmonary nontuberculous mycobacterial (NTM) pathogens in almost all regions of the world. Primarily, there are three species that cause disease in humans within this complex; *M. avium, M. intracellulare, and M. chimaera.* These pathogens are commonly found in water and soil. Symptoms of MAC infection includes persistent cough, fatigue, weight loss, night sweats, and possible shortness of breath and coughing up of blood. With antimycobacterial treatment being prolonged, potentially difficult to tolerate, and modest long-term response rates, not all patients at time of diagnosis warrant treatment. Incidence of MAC is 1 case per 100,000 persons per year.

Dosage Form [1]

Arikayce® is available as a sterile, aqueous, liposome suspension for oral inhalation in a unit-dose glass vial containing amikacin 590 mg/8.4 ml (equivalent to amikacin sulfate 623 mg/8.4 mL).

Manufacturer [1]

Manufactured by: Insmed Incorporated, Bridgewater, NJ 08807-3365

Indication(s) [1]

LIMITED POPULATION: Arikayce® is an aminoglycoside antibacterial indicated in adults who have limited or no alternative treatment options, for the treatment of *Mycobacterium avium* complex (MAC) lung disease as part of a combination antibacterial drug regimen in patients who do not achieve negative sputum cultures after a minimum of 6 consecutive months of a multidrug background regimen therapy.

As only limited clinical safety and effectiveness data for Arikayce® are currently available, reserve Arikayce® for use in adults who have limited or no alternative treatment options. This drug is indicated for use in a limited and specific population of patients. This indication is approved under accelerated approval based on achieving sputum culture conversion (defined as 3 consecutive negative monthly sputum cultures) by month 6. Clinical benefit has not yet been established.

Limitation of Use: Arikayce® has only been studied in patients with refractory MAC lung disease defined as patients who did not achieve negative sputum cultures after a minimum of 6 consecutive months of a multidrug background regimen therapy. The use of Arikayce® is not recommended for patients with non-refractory MAC lung disease

Clinical Efficacy [1,2] (mechanism of action/pharmacology, comparative efficacy)

Amikacin is a polycationic, semisynthetic, bactericidal aminoglycoside. Amikacin enters the bacterial cell by binding to negatively charged components of the bacterial cell wall disrupting the overall architecture of the cell wall. The primary mechanism of action is the disruption and inhibition of protein synthesis in the target bacteria by binding to the 30S ribosomal subunit.

Pharmacokinetics:

	Arikayce®
Protein Binding	≤ 10%
Bioavailability	Vary primarily from individual differences in nebulizer efficiency and airway pathology
Metabolism	does not undergo appreciable metabolism
Excretion (Renal)	Urine, average, 7.42% (ranging from 0.72 to 22.60%; n=14) unchanged drug
Half-life	5.9 to 19.5 hours

Efficacy of Arikayce®

STUDY DESIGN	Open-label, randomized (2:1), multi-center trial (n=336)
INCLUSION CRITERIA	Refractory *Mycobacterium avium* complex (MAC) lung disease confirmed by at least 2 sputum culture results, refractory disease was defined as not achieving negative sputum cultures after a minimum duration of 6 consecutive months of background regimen therapy that was either ongoing or stopped no more than 12 months before the patient's screening visit
EXCLUSION CRITERIA	Patients not meeting the inclusion criteria.
TREATMENT REGIMEN	Patients were randomized to Arikayce® plus background regimen (n=224) or background regimen alone (n=112). At baseline, background regimens included macrolide (91.9%), a rifamycin (85.7%), or ethambutol (80.3%). 54.9% of patients were receiving triple regiment therapy of a macrolide, a rifamycin, and ethambutol. The surrogate endpoint for assessing efficacy was based on achieving culture conversion (3 consecutive monthly negative sputum cultures) by month 6.
RESULTS	The proportion of patient achieving culture conversion by month 6 was significantly ($p<0.0001$) greater for Arikayce® plus background regimen (65/224, 29%) compared to background regimen alone (10/112, 8.9%). Clinical benefit was not demonstrated in additional endpoints by month 6 of change from baseline in six-minute walk test distance and the Saint George's Respiratory Questionnaire.

SAFETY	Not specified.

Contraindications [1]

- Known hypersensitivity to any aminoglycoside

Warnings and Precautions [1]

- Hypersensitivity Pneumonitis: Reported with Arikayce® treatment; if hypersensitivity pneumonitis occurs, discontinue Arikayce® and manage patients as medically appropriate.
- Hemoptysis: Higher frequency of hemoptysis has been reported with Arikayce® treatment. If hemoptysis occurs, manage the patients as medically appropriate.
- Bronchospasm: Higher frequency of bronchospasm has been reported with Arikayce® treatment. Treat patients as medically appropriate if this occurs during treatment with Arikayce®.
- Exacerbations of Underlying Pulmonary Disease: Higher frequency of exacerbations of underlying pulmonary disease has been reported with Arikayce® treatment. Treat patients as medically appropriate if this occurs during treatment with Arikayce®.
- Ototoxicity: Higher frequency of ototoxicity has been reported with Arikayce® treatment. Closely monitor patients with known or suspected auditory or vestibular dysfunction. If patients develop tinnitus this may be an early symptom of ototoxicity.
- Nephrotoxicity: Aminoglycosides can cause nephrotoxicity. Close monitoring of patients with known or suspected renal dysfunction may be needed when prescribing Arikayce®.
- Neuromuscular Blockade: Aminoglycosides may aggravate muscle weakness because of a potential curare-like effect on neuromuscular function. If neuromuscular blockade occurs, it may be reversed by the administration of calcium salts but mechanical assistance may be necessary.
- Embryo-Fetal Toxicity: Aminoglycosides can cause total, irreversible, bilateral congenital deafness in pediatric patients exposed in utero.

Adverse Effects [1]

Most common, ≥ 5%	**Arikayce® plus Background Regimen (n=223) %**	**Background Regimen Alone (n=112) %**
Dysphonia[a]	105(47)	1(1)
Cough[b]	87(39)	19(17)
Bronchospasm[c]	64(29)	12(11)
Hemoptysis	40(18)	14(13)
Ototoxicity[d]	38(17)	11(10)
Upper airway irritation[e]	37(17)	2(2)
Musculoskeletal pain[f]	37(17)	9(8)

Fatigue and asthenia	36(16)	11(10)
Exacerbation of underlying pulmonary disease[g]	33(15)	11(10)
Diarrhea	28(13)	5(5)
Nausea	26(12)	4(4)
Pneumonia[h]	22(10)	9(8)
Headache	22(10)	5(5)
Pyrexia	16(7)	5(5)
Vomiting[i]	15(7)	4(4)
Rash[j]	14(6)	2(2)
Weight decreased	14(6)	1(1)
Change in sputum[k]	12(5)	1(1)
Chest discomfort	12(5)	3(3)

Drug Interactions (1)

- Drugs with Neurotoxic, Nephrotoxic, or Ototoxic Potential: Avoid concomitant use of Arikayce® with medications associated with neurotoxicity, nephrotoxicity, and ototoxicity.
- Ethacrynic Acid, Furosemide, Urea, or Mannitol: Some diuretics can enhance aminoglycoside toxicity by altering aminoglycoside concentrations in serum and tissue. Avoid concomitant use of Arikayce® with ethacrynic acid, furosemide, urea, or intravenous mannitol.

Dosage and Administration (1)

The recommended dosage of Arikayce® in adults is once daily inhalation of the contents of one 590 mg/8.4 mL Arikayce® vial (590 mg of amikacin) using the Lamira Nebulizer System. Administer Arikayce® with the Lamira Nebulizer System only. Arikayce® should be at room temperature before use. Prior to opening, shake the Arikayce® vial well for at least 10 to 15 seconds until the contents appear uniform and well mixed. The Arikayce® vial is opened by flipping up the plastic top of the vial then pulling downward to loosen the metal ring. The metal ring and the rubber stopper should be removed carefully. The contents of the Arikayce® vial can then be poured into the medication reservoir of the nebulizer handset. If a daily dose of Arikayce® is missed, administer the next dose the next day. Do not double the dose to make up for the missed dose.

Cost

Generic Name	Brand Name	Manufacturer	Dose	Cost/Month**
Amikacin liposome inhalation suspension	Arikayce®	Insmed Inc.	590mg/8.4ml vial once daily	$10,162.88

** Maximum Allowable Cost

Lamira Nebulizer System sold separately

Conclusion [1,3]

Arikayce® has been approved for the treatment of lung disease caused by MAC in patients who do not respond to conventional therapy. This is the first medication to be approved under the Limited Population Pathway for Antibacterial and Antifungal Drugs (LAPD Pathway) established by Congress under the 21st Century Cures Act. This program involves smaller, shorter, or fewer clinical trials to streamline the development and approval process for antibacterial and antifungal medications to treat life-threatening infections in a limited population of patients with unmet need. Arikayce® labeling includes a black box warning for risk of increased respiratory adverse reactions. In the Arikayce® clinical trial, the proportion of patients achieving culture conversion by month 6 was significantly ($p<0.0001$) greater for Arikayce® plus background regimen (65/224, 29%) compared to background regimen alone (10/112, 8.9%).

Recommendation

This drug is being considered for inclusion in the state specific Preferred Drug List.

References

1) Product Information: Arikayce® (amikacin liposome inhalation suspension) Insmed Incorporated, 10 Finderne Ave, Bldg. 10, Bridgewater, NJ 08807-3365 9/2018.
2) Kasperbauer, S, Daley, C. Treatment of Mycobacterium avium complex lung infections in adults. Post TW, ed. UpToDate. Waltham, MA: UpToDate Inc. http://www.uptodate.com (Accessed on February 11, 2019.)
3) FDA News Release, 2018, September 28. *FDA approves a new antibacterial drug to treat a serious lung disease using a novel pathway to spur innovation.* Retrieved from www.fda.gov/News/Events/Newsroom/PressAnouncements/ucm622048.htm

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