See 12- and 15-month conversion data on page 6

ARIKAYCE®
(amikacin liposome inhalation suspension)
590 mg/8.4 mL

Limited Population

Every villain has its weakness. And now refractory MAC lung disease has ARIKAYCE[1]

When MAC lung disease patients fail to respond after 6 months of standard therapy, it's time to add 2020 NTM Guideline-recommended ARIKAYCE[2]

In a Phase 3 trial, ARIKAYCE + standard therapy achieved **over a 3-fold increase** in the percentage of adult patients who experienced culture conversion by Month 6 vs those who received the standard therapy alone **(29.0% [65/224] vs 8.9% [10/112])** (*P*<0.0001).[1,3]

MAC=*Mycobacterium avium* complex; NTM=nontuberculous mycobacteria.

INDICATION

LIMITED POPULATION: ARIKAYCE® is 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. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

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.

IMPORTANT SAFETY INFORMATION

WARNING: RISK OF INCREASED RESPIRATORY ADVERSE REACTIONS

ARIKAYCE has been associated with an increased risk of respiratory adverse reactions, including hypersensitivity pneumonitis, hemoptysis, bronchospasm, and exacerbation of underlying pulmonary disease that have led to hospitalizations in some cases.

Please see full Important Safety Information on pages 21-22 and enclosed full Prescribing Information.

The 2020 NTM Treatment Guidelines recommend the following approach to treating MAC† lung disease

2020 GUIDELINES STRONGLY RECOMMEND ADDING ARIKAYCE AT 6 MONTHS WHEN PATIENTS REMAIN CULTURE POSITIVE[2]

- The 2020 Guidelines **strongly recommend** adding ARIKAYCE to treatment for patients with MAC lung disease who remain culture positive after 6 months of treatment[2]
- ARIKAYCE is the first and only therapy studied in and FDA-approved for patients who fail to achieve culture conversion after 6 months of initial standard therapy[1]

MAC lung disease diagnosed

Initiate multidrug regimen[2]

1→5 months after treatment initiation

Monitor response—obtain sputum cultures every 1 to 2 months[2]

6 months after treatment initiation

Is your patient responding to treatment?

~**30%** of MAC patients fail initial treatment and do not achieve conversion within 6 months[4]

NO → **Add ARIKAYCE at 6 months[2]**

ARIKAYCE® (amikacin liposome inhalation suspension) 590 mg/8.4 mL | Limited Population*

YES → **Continue multidrug regimen[2]**

The 2020 Guidelines recommend **treatment initiation rather than "watchful waiting" for certain diagnosed patients,** especially in those with positive AFB sputum smears and/or cavitary disease.[2]

The 2020 Guidelines recommend that MAC‡ lung disease should be treated with a multidrug regimen that includes at least a macrolide and ethambutol.[2]

- Guidelines recommend a 3-drug regimen of azithromycin, ethambutol, and rifampicin to treat MAC lung disease

The 2020 Guidelines recommend that sputum cultures be obtained every 1 to 2 months during the treatment of MAC lung disease to assess response and determine duration of therapy and whether the regimen needs to be adjusted.[2]

†*Mycobacterium avium* complex: Common MAC species include: *Mycobacterium avium*, *Mycobacterium intracellulare*, and *Mycobacterium chimaera*.[2]

‡In patients with macrolide-susceptible MAC pulmonary disease.[2]

Retrospective studies have shown that most MAC patients who will convert do so early in the treatment course.[4-6]

- In one study, 94% of MAC patients who converted on treatment achieved that conversion within 6 months after starting treatment[4]

Culture conversion is a key indicator for therapeutic success or failure. Study data indicate that if a patient remains culture positive, it may be an early sign of future radiographic progression and a decline in lung function (FEV_1 and FVC).[7-9]

12 MONTHS

The 2020 Guidelines recommend continuing MAC‡ treatment for 12 months after culture conversion[2]

IMPORTANT SAFETY INFORMATION (cont'd)

Hypersensitivity Pneumonitis has been reported with the use of ARIKAYCE in the clinical trials. Hypersensitivity pneumonitis (reported as allergic alveolitis, pneumonitis, interstitial lung disease, allergic reaction to ARIKAYCE) was reported at a higher frequency in patients treated with ARIKAYCE plus background regimen (3.1%) compared to patients treated with background regimen alone (0%). Most patients with hypersensitivity pneumonitis discontinued treatment with ARIKAYCE and received treatment with corticosteroids. If hypersensitivity pneumonitis occurs, discontinue ARIKAYCE and manage patients as medically appropriate.

AFB=acid-fast bacilli; FEV_1=forced expiratory volume in the first second; FVC=forced vital capacity.

*See the full Prescribing Information for ARIKAYCE for information about the limited population.

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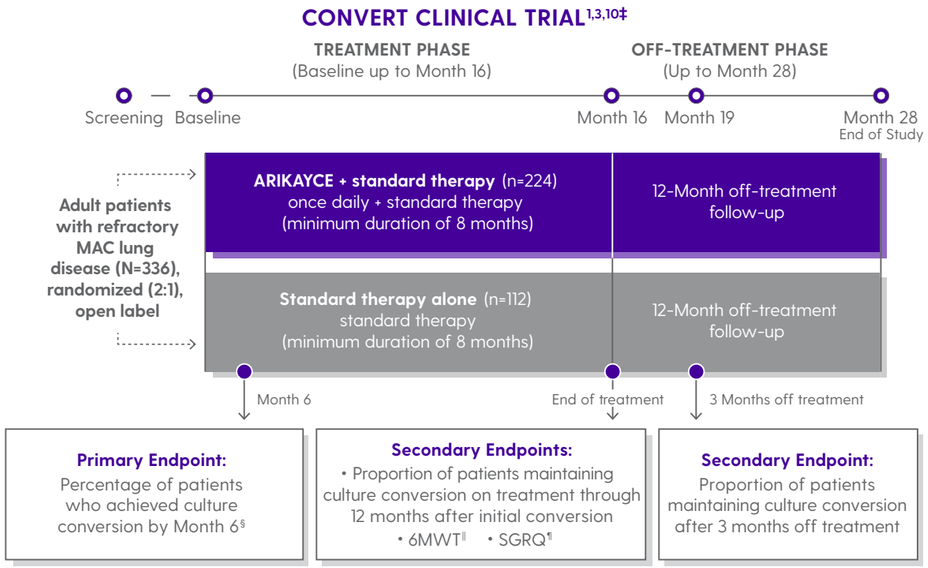
ARIKAYCE® (amikacin liposome inhalation suspension) 590 mg/8.4 mL | Limited Population*

The first and only treatment studied in a Phase 3 trial for patients with refractory MAC lung disease[1]

Patients were considered refractory if they did not convert (achieve negative sputum cultures) after ≥6 months of standard therapy[1,3†]



The efficacy and safety of ARIKAYCE were evaluated in an open-label, randomized (2:1), multicenter, global, Phase 3 trial of 336 adult patients with refractory MAC lung disease.[1,3]

- **The primary endpoint was culture conversion by Month 6. Patients needed to achieve their first negative culture by Month 4 to meet the primary endpoint[1,3]**
- **Culture conversion was defined as 3 consecutive monthly negative sputum cultures.** The study design required 2 or 3 negative sputum samples per month for 3 consecutive months to confirm culture conversion[1,3]
- **Secondary endpoints included assessment of[10]:**
  - Patients who maintained culture conversion on treatment through 12 months after initial conversion
  - Patients who maintained culture conversion after 3 months off treatment (15 months after initial conversion)

In the CONVERT trial, patients continued ARIKAYCE treatment for 12 months after culture conversion[1,3]

†Therapy that was either ongoing or had been stopped no more than 12 months before the screening visit.[1]

‡The CONVERT trial is referred to as "Trial 1" in the ARIKAYCE full Prescribing Information.

§A converter was defined as a patient who had 3 consecutive monthly MAC-negative sputum cultures at any time within the first 6 months of the study. All converters without relapse or recurrence continued randomized treatment for 12 months, starting from the first negative culture that defines culture conversion. "Relapse or recurrence" was defined as having MAC-positive sputum cultures in liquid broth media (agar negative) for 3 or more consecutive months, or having at least 1 MAC-positive sputum culture on solid media (agar positive) after achieving culture conversion.[10]

‖The 6-minute walk test (6MWT) was conducted by using the standard protocol based on the ATS guidelines. After assessments were performed for heart rate, blood pressure, pulse oximetry, dyspnea, and overall fatigue using the Borg scale, patients were instructed to walk on a prescribed course as far as they could in 6 minutes. The maximum distance achieved was compared to the pretest values.[10]

¶The change from baseline (Day 1) to Month 6 in St George's Respiratory Questionnaire (SGRQ) total score was analyzed.[10]

IMPORTANT SAFETY INFORMATION (cont'd)

Hemoptysis has been reported with the use of ARIKAYCE in the clinical trials. Hemoptysis was reported at a higher frequency in patients treated with ARIKAYCE plus background regimen (18.4%) compared to patients treated with background regimen alone (13.4%). If hemoptysis occurs, manage patients as medically appropriate.

Refractory MAC patients studied in CONVERT may have similar characteristics to patients in your practice[3]

KEY BASELINE PATIENT CHARACTERISTICS IN THE CONVERT TRIAL[3,10]

Parameter	ARIKAYCE + standard therapy (n=224) n (%)	Standard therapy alone (n=112) n (%)
Gender		
Female	165 (73.7)	68 (60.7)
Male	59 (26.3)	44 (39.3)
Underlying lung disease		
Bronchiectasis only	146 (65.2)	64 (57.1)
COPD#	29 (12.9)	19 (17.0)
COPD# and bronchiectasis	22 (9.8)	18 (16.1)
Standard therapy prior to enrollment		
On treatment	201 (89.7)	101 (90.2)
Off treatment for at least 3 months	23 (10.3)	11 (9.8)

SUMMARY OF STANDARD THERAPY IN THE CONVERT TRIAL AT BASELINE[11]

- Standard therapy was composed of an antimycobacterial regimen of at least 2 antibiotics based on the 2007 ATS/IDSA Statement or respective local guidelines. Patients in the CONVERT trial continued with the same standard therapeutic regimen for the duration of the study[3,7,10,11]

Parameter	ARIKAYCE + standard therapy (n=223)** n (%)	Standard therapy alone (n=112)** n (%)
Number of drugs in regimen		
≤2	41 (18.4)	17 (15.2)
≥3	182 (81.6)	95 (84.8)
Drug combination††		
Ethambutol/Macrolide/Rifamycin/Other‡‡	30 (13.5)	8 (7.1)
Ethambutol/Macrolide/Rifamycin	123 (55.2)	61 (54.5)
Ethambutol/Macrolide +/- Other‡‡	19 (8.5)	9 (8.0)
Macrolide/Rifamycin +/- Other‡‡	26 (11.7)	17 (15.2)
Ethambutol/Rifamycin +/- Other‡‡	11 (4.9)	7 (6.3)
Macrolide/Other‡‡	9 (4.0)	6 (5.4)

#COPD was derived from the medical history data.[3]

**Safety population.[11]

††This list contains the most common drug regimens used in CONVERT.[11]

‡‡Other may include medications such as fluoroquinolones, linezolid, clofazimine, or agents deemed to be a component of the standard therapy by the investigator, excluding parenteral amikacin and/or streptomycin as defined in the protocol.[11]

ATS=American Thoracic Society; IDSA=Infectious Diseases Society of America.

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ARIKAYCE® (amikacin liposome inhalation suspension) 590 mg/8.4 mL | Limited Population*

In adult patients with refractory MAC lung disease,

Over a 3-fold increase in rate of refractory† patients converting on ARIKAYCE + standard therapy‡ by Month 6

AND more than half of those patients stayed converted for 15 months after initial conversion[1,3,10]

The CONVERT trial studied refractory MAC patients

ARIKAYCE + STANDARD THERAPY = 224 PATIENTS

STANDARD THERAPY ALONE = 112 PATIENTS

PRIMARY ENDPOINT

65 patients converted by Month 6

65

Culture conversion: Patients needed to achieve first negative culture by Month 4 to meet the primary endpoint§

10

10 patients converted by Month 6

Patients who did not convert by Month 6 in either arm did not continue in the CONVERT trial and left the study by Month 8

SECONDARY ENDPOINTS

41 patients stayed converted on treatment through 12 months after initial conversion

41

3

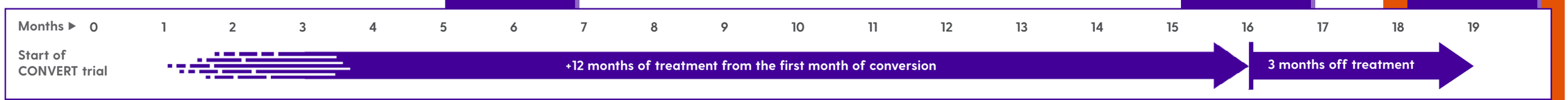
3 patients stayed converted on treatment through 12 months after initial conversion

36 patients continued to stay converted after 3 months off treatment

36

0

0 patients continued to stay converted after 3 months off treatment



- **29%** of patients on ARIKAYCE + standard therapy (n=65/224) **converted** by Month 6[1]
  - **8.9%** of patients on standard therapy alone (n=10/112) **converted** by Month 6

In order to meet this secondary endpoint, patients needed to have 2 to 3 negative sputum samples at several time points throughout the CONVERT trial

- This means that patients who met this secondary endpoint could have had up to 24 to 36 negative sputum cultures

In the CONVERT trial, the endpoints of the change from baseline in 6MWT distance and the SGRQ did not demonstrate clinical benefit at Month 6.[1]

IMPORTANT SAFETY INFORMATION (cont'd)

Bronchospasm has been reported with the use of ARIKAYCE in the clinical trials. Bronchospasm (reported as asthma, bronchial hyperreactivity, bronchospasm, dyspnea, dyspnea exertional, prolonged expiration, throat tightness, wheezing) was reported at a higher frequency in patients treated with ARIKAYCE plus background regimen (28.7%) compared to patients treated with background regimen alone (10.7%). If bronchospasm occurs during the use of ARIKAYCE, treat patients as medically appropriate.

†Refractory MAC lung disease is defined as MAC patients who did not convert after ≥6 months of standard therapy.[1]

‡Standard therapy was composed of an antimycobacterial regimen of at least 2 antibiotics based on the 2007 ATS/IDSA Statement or respective local guidelines. These drugs may have included, but were not limited to, azithromycin, clarithromycin, clofazimine, ethambutol, ethionamide, rifabutin, and rifampicin.[3,7,10,11]

At baseline, the standard therapy included a macrolide (93.3%), a rifamycin (86.3%), or ethambutol (81.4%). Overall, 55.6% of patients were receiving a triple-drug standard therapy consisting of a macrolide, a rifamycin, and ethambutol.[1]

§Culture conversion by Month 6 was a surrogate endpoint.[1] Clinical benefit has not yet been established.

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Clinical trial safety: Most adverse events were respiratory in nature. Dysphonia and cough were the 2 most common adverse events in the CONVERT trial[1,3]

PATIENTS WHO REPORTED TREATMENT-EMERGENT ADVERSE EVENTS (TEAEs) AND SERIOUS TEAEs IN THE CONVERT TRIAL[1,3†‡]

	ARIKAYCE + standard therapy %	Standard therapy alone %
TEAEs	98.2	91.1
Serious TEAEs	19.7	16.1

†Adverse events (AEs) that occurred from Day 1 to Day 247 (Month 8) were considered TEAEs.[12]

‡Serious TEAEs were defined as any untoward medical occurrence that at any dose resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, or was a congenital anomaly/birth defect.[10]

Dysphonia

In the CONVERT clinical trial, dysphonia was the most commonly reported adverse reaction in the ARIKAYCE + standard therapy arm (48% ARIKAYCE + standard therapy vs 2% standard therapy alone).[1]

Hospitalization rates

In the CONVERT trial, there were 80 hospitalizations in 41 patients (18.4%) treated with ARIKAYCE + standard therapy compared to 29 hospitalizations in 15 patients (13.4%) treated with standard therapy alone. The most common serious adverse reactions and reasons for hospitalization in the ARIKAYCE + standard therapy arm were related to exacerbation of underlying pulmonary disease and lower respiratory tract infections, such as pneumonia.[1]

Discontinuation rates

In the CONVERT trial, there was a higher incidence of premature discontinuation of ARIKAYCE. 34.5% discontinued ARIKAYCE prematurely; most were due to adverse reactions (18.8%) and withdrawal by patient (9.9%). In the comparator arm, 10.7% of patients discontinued their standard therapeutic regimen, 0.9% due to adverse reactions and 5.4% due to withdrawal by patient.[1]

Cough

Cough is a common symptom of MAC lung disease. In the CONVERT trial, cough was a frequently reported adverse reaction and was more common in the ARIKAYCE + standard therapy arm (40% ARIKAYCE + standard therapy vs 17% standard therapy alone). There was a higher rate of cough AE reporting, particularly in the first month of active treatment with ARIKAYCE.[1,3]

Of the patients who experienced cough, most events were episodic and occurred either during or after ARIKAYCE administration. The majority of cough episodes lasted less than 1 minute with most episodes lasting less than 10 minutes.[10]

In the CONVERT trial, investigators were permitted to manage local respiratory AEs (such as dysphonia and cough) with **temporary interruption of ARIKAYCE.** It was recommended in the trial that ARIKAYCE be reintroduced after this short interruption when symptoms subsided.[3,10]

ADVERSE REACTIONS IN ≥5% OF ARIKAYCE-TREATED MAC PATIENTS AND MORE FREQUENT THAN STANDARD THERAPY ALONE IN THE CONVERT TRIAL[1]

Adverse reaction	ARIKAYCE + standard therapy (n=223) n (%)	Standard therapy alone (n=112) n (%)
Dysphonia[a]	106 (48)	2 (2)
Cough[b]	88 (40)	19 (17)
Bronchospasm[c]	64 (29)	12 (11)
Hemoptysis	41 (18)	15 (13)
Musculoskeletal pain[d]	40 (18)	10 (9)
Upper airway irritation[e]	39 (18)	2 (2)
Ototoxicity[f]	38 (17)	11 (10)
Fatigue and asthenia	36 (16)	11 (10)
Exacerbation of underlying pulmonary disease[g]	34 (15)	11 (10)
Diarrhea	28 (13)	5 (5)
Nausea	26 (12)	4 (4)
Headache	22 (10)	5 (5)
Pneumonia[h]	20 (9)	10 (9)
Pyrexia	17 (8)	5 (5)
Weight decreased	16 (7)	1 (1)
Vomiting[i]	15 (7)	4 (4)
Rash[j]	14 (6)	1 (1)
Change in sputum[k]	13 (6)	1 (1)
Chest discomfort	12 (5)	3 (3)

Selected adverse reactions that occurred in <5% of patients and at a higher frequency in ARIKAYCE-treated patients in the CONVERT trial include anxiety[l] (5% vs 0%), oral fungal infection[m] (4% vs 2%), bronchitis (4% vs 3%), dysgeusia (3% vs 0%), hypersensitivity pneumonitis[n] (3% vs 0%), dry mouth (3% vs 0%), epistaxis (3% vs 1%), respiratory failure[o] (3% vs 2%), pneumothorax[p] (2% vs 1%), exercise tolerance decreased (1% vs 0%), balance disorder (1% vs 0%), and neuromuscular disorder[q] (1% vs 0%).[1]

[a]Includes aphonia and dysphonia.

[b]Includes cough, productive cough, and upper airway cough syndrome.

[c]Includes asthma, bronchial hyperreactivity, bronchospasm, dyspnea, dyspnea exertional, prolonged expiration, throat tightness, and wheezing.

[d]Includes back pain, arthralgia, myalgia, pain/body aches, muscle spasm, and musculoskeletal pain.

[e]Includes oropharyngeal pain, oropharyngeal discomfort, throat irritation, pharyngeal erythema, upper airway inflammation, pharyngeal edema, vocal cord inflammation, laryngeal pain, laryngeal erythema, and laryngitis.

[f]Includes deafness, deafness neurosensory, deafness unilateral, dizziness, hypoacusis, presyncope, tinnitus, vertigo, and balance disorders.

[g]Includes COPD, infective exacerbation of COPD, and infective exacerbation of bronchiectasis.

[h]Includes atypical pneumonia, empyema, infection pleural effusion, lower respiratory tract infection, lung infection, lung infection pseudomonas, pneumonia, pneumonia aspiration, pneumonia pseudomonas, pseudomonas infection, and respiratory tract infection.

[i]Includes vomiting and post-tussive vomiting.

[j]Includes rash, rash maculo-papular, drug eruption, and urticaria.

[k]Includes increased sputum, sputum purulent, and sputum discolored.

[l]Includes anxiety and anxiety disorder.

[m]Includes oral candidiasis and oral fungal infection.

[n]Includes allergic alveolitis, interstitial lung disease, and pneumonitis.

[o]Includes acute respiratory failure and respiratory failure.

[p]Includes pneumothorax, pneumothorax spontaneous, and pneumomediastinum.

[q]Includes muscle weakness and neuropathy peripheral.

IMPORTANT SAFETY INFORMATION (cont'd)

Exacerbations of underlying pulmonary disease have been reported with the use of ARIKAYCE in the clinical trials. Exacerbations of underlying pulmonary disease (reported as chronic obstructive pulmonary disease (COPD), infective exacerbation of COPD, infective exacerbation of bronchiectasis) have been reported at a higher frequency in patients treated with ARIKAYCE plus background regimen (15.2%) compared to patients treated with background regimen alone (9.8%). If exacerbations of underlying pulmonary disease occur during the use of ARIKAYCE, treat patients as medically appropriate.

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ARIKAYCE® (amikacin liposome inhalation suspension) 590 mg/8.4 mL | Limited Population*

Dosing and management for ARIKAYCE

Administration

The recommended dose of ARIKAYCE in adults is the **once-daily inhalation** of the contents of **one 590 mg/8.4 mL ARIKAYCE vial** using the Lamira® Nebulizer System.[1]

Pretreatment with a bronchodilator (short-acting selective β_2 agonists) is recommended for patients with a history of hyperreactive airway disease, COPD, asthma, or bronchospasm. Instruct patients to first use the bronchodilator, following the instructions, before using ARIKAYCE.[1]

ARIKAYCE should be administered as part of a multidrug antibacterial regimen[1,10]:

Once daily, around the same time each day

By **oral inhalation** via the Lamira Nebulizer System only

Additional dosing information[13]:

Administered for approximately **14 minutes.** Treatment time may vary and could take up to 20 minutes

Flexibility to administer at home or anywhere with a clean, flat, stable surface

Refer to the Instructions for Use for full administration information.

†In patients with macrolide-susceptible MAC pulmonary disease.[2]

IMPORTANT SAFETY INFORMATION (cont'd)

Anaphylaxis and Hypersensitivity Reactions: Serious and potentially life-threatening hypersensitivity reactions, including anaphylaxis, have been reported in patients taking ARIKAYCE. Signs and symptoms include acute onset of skin and mucosal tissue hypersensitivity reactions (hives, itching, flushing, swollen lips/tongue/uvula), respiratory difficulty (shortness of breath, wheezing, stridor, cough), gastrointestinal symptoms (nausea, vomiting, diarrhea, crampy abdominal pain), and cardiovascular signs and symptoms of anaphylaxis (tachycardia, low blood pressure, syncope, incontinence, dizziness). Before therapy with ARIKAYCE is instituted, evaluate for previous hypersensitivity reactions to aminoglycosides. If anaphylaxis or a hypersensitivity reaction occurs, discontinue ARIKAYCE and institute appropriate supportive measures.

Ototoxicity has been reported with the use of ARIKAYCE in the clinical trials. Ototoxicity (including deafness, dizziness, presyncope, tinnitus, and vertigo) were reported with a higher frequency in patients treated with ARIKAYCE plus background regimen (17%) compared to patients treated with background regimen alone (9.8%). This was primarily driven by tinnitus (8.1% in ARIKAYCE plus background regimen vs 0.9% in the background regimen alone arm) and dizziness (6.3% in ARIKAYCE plus background regimen vs 2.7% in the background regimen alone arm). Closely monitor patients with known or suspected auditory or vestibular dysfunction during treatment with ARIKAYCE. If ototoxicity occurs, manage patients as medically appropriate, including potentially discontinuing ARIKAYCE.

Clinical management strategies for select respiratory adverse events

Ongoing monitoring can help alert physicians to the development of AEs that can be common with multidrug MAC lung disease treatment regimens. One survey reported potential techniques and strategies to help manage upper airway and lower respiratory tract events.[2,14]

Survey limitations and disclosures

- This information is not included in the ARIKAYCE full Prescribing Information
- The data are from a telephone survey of 26 patients prescribed ARIKAYCE conducted during a 2-month period at 2 academic medical centers in the United States[14]
- Writing assistance was provided to the authors through funding from Insmed Incorporated. Insmed was not involved with the conceptualization, development, conduct, or analyses of the survey[14]

Increased coughing

Management strategies included[14]:

- Bronchodilator use
- Changing ARIKAYCE administration to the evening
- Brief interruptions of ARIKAYCE
- Antitussive agents
- Lozenges
- Warm water or glycerin gargle post-dosing
- Soothing fluid intake

Dysphonia

Management strategies included[14]:

- Changing ARIKAYCE administration to the evening
- Brief interruptions of ARIKAYCE
- Antitussive agents
- Lozenges
- Warm water or glycerin gargle post-dosing
- Soothing fluid intake

Dyspnea

Management strategies included[14]:

- Bronchodilator use
- Brief interruptions of ARIKAYCE
- Limiting physical activity
- Increased supplemental oxygen, if already administering

Increased sputum production

Management strategies included[14]:

- Airway clearance (eg, specific breathing techniques, chest percussion, and positive expiratory pressure therapy)

Reminder: It's important to educate patients that increased sputum production may be a form of airway clearance in itself.[14]

Management strategies should be customized to individual patients according to their specific needs. Use your clinical judgment when evaluating which strategy to use, including temporarily interrupting or discontinuing ARIKAYCE treatment, if necessary. Educating both patients and their extended care team may aid in early recognition and management of respiratory AEs that could help contribute to a successful treatment outcome.[2,14]

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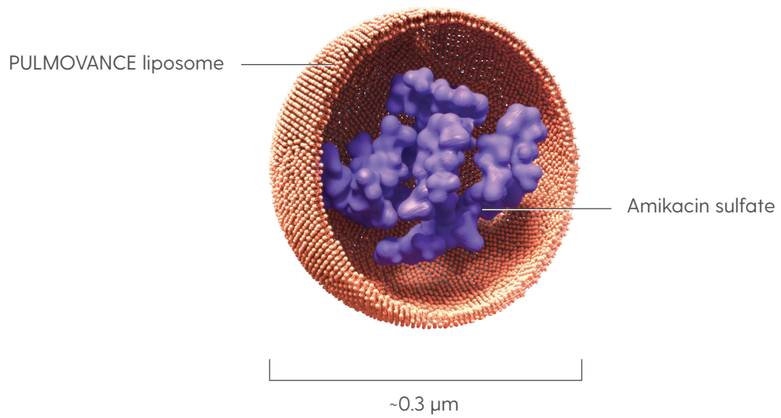
ARIKAYCE was designed to specifically target MAC in the lungs[1,3,10]

- ARIKAYCE utilizes PULMOVANCE™ technology consisting of amikacin sulfate encapsulated in liposomes[1,10]

DEPICTION OF ARIKAYCE[1,10,15]



ARIKAYCE[1,16]:

- Delivers **liposomal and free amikacin** in the lungs through nebulization
- **Delivered 5 to 8 times more amikacin into pulmonary macrophages** compared to inhaled free amikacin in animal studies
- **Penetrated biofilm** in a study of MAC biofilms

The clinical relevance of this is unknown.

AMIKACIN SERUM LEVELS WERE LOWER WITH ARIKAYCE VS IV AMIKACIN[1†]

	ARIKAYCE	IV amikacin sulfate
Mean serum $AUC_{0\text{-}24}$	23.5 mcg* hr/mL‡	154 mcg* hr/mL
Mean serum C_{max}	2.8 mcg/mL§	76 mcg/mL

The clinical relevance of this is unknown.

†The maximum C_{max} and $AUC_{0\text{-}24}$ were below the mean C_{max} of approximately 76 mcg/mL and $AUC_{0\text{-}24}$ of 154 mcg*hr/mL observed for IV administration of amikacin sulfate for injection at the approved dosage of 15 mg/kg once daily in healthy adults.[1]

‡Range: 8.0 to 46.5 mcg† hr/mL; n=12.[1]

§Range: 1.0 to 4.4 µg/mL; n=12.[1]

IMPORTANT SAFETY INFORMATION (cont'd)

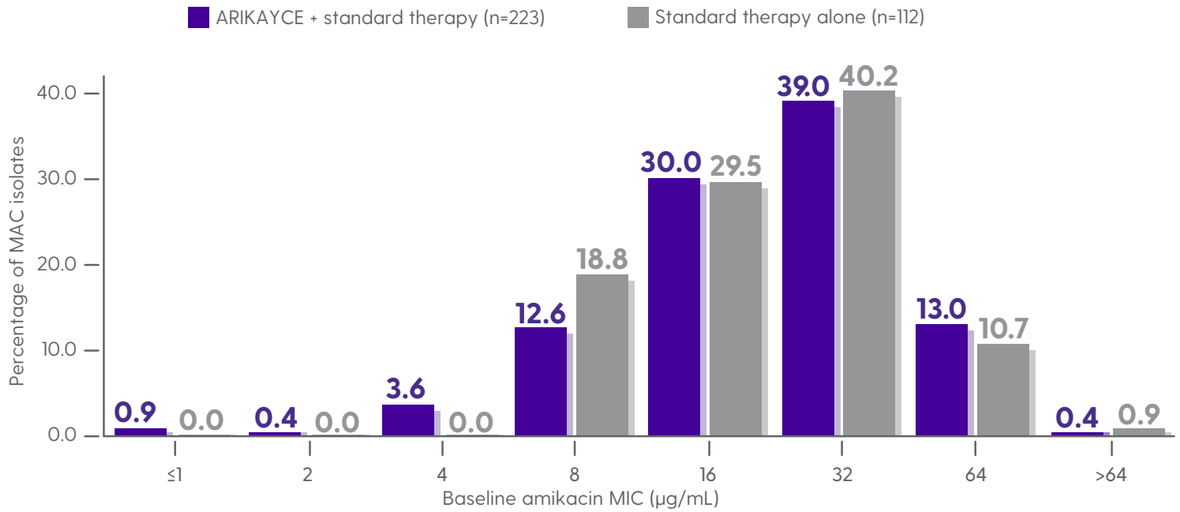
Nephrotoxicity was observed during the clinical trials of ARIKAYCE in patients with MAC lung disease but not at a higher frequency than background regimen alone. Nephrotoxicity has been associated with the aminoglycosides. Close monitoring of patients with known or suspected renal dysfunction may be needed when prescribing ARIKAYCE.

Neuromuscular Blockade: Patients with neuromuscular disorders were not enrolled in ARIKAYCE clinical trials. Aminoglycosides may aggravate muscle weakness by blocking the release of acetylcholine at neuromuscular junctions. Closely monitor patients with known or suspected neuromuscular disorders, such as myasthenia gravis. If neuromuscular blockade occurs, it may be reversed by the administration of calcium salts but mechanical respiratory assistance may be necessary.

CONVERT included patients with baseline amikacin MIC up to 64 µg/mL[11]

- CONVERT investigators determined the *in vitro* susceptibility of MAC isolates to inhibition prior to treatment initiation‖

AMIKACIN MIC DISTRIBUTION AT BASELINE, INTENT-TO-TREAT POPULATION[11¶]



The clinical relevance of this is unknown.

In the 2018 CLSI guidelines, the breakpoint for resistance is ≥128 µg/mL for ARIKAYCE[17]

- An amikacin MIC of ≤64 µg/mL is considered susceptible for ARIKAYCE

‖The screening window allowed for up to 10 weeks for sputum culture results, susceptibility by MIC determination, and scheduling of screening assessments. Results were not available to investigators until Month 8.[10]

¶Sputum culture results were made available to the site after the Month 6 sputum result was known, in time for the Month 8 visit. Prior to the Month 8 visit, the culture results from baseline to Month 6 were blinded to the site and sponsor.[10]

AUC=area under the curve; CLSI=Clinical and Laboratory Standards Institute; IV=intravenous; MIC=minimum inhibitory concentration.

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Please see full Important Safety Information, including Boxed Warning, on pages 21-22 and enclosed full Prescribing Information.

ARIKAYCE® (amikacin liposome inhalation suspension) 590 mg/8.4 mL | Limited Population*

Which of your MAC patients may be appropriate for ARIKAYCE + standard therapy?

Diane, 67 years old

Initial patient visit

Clinical presentation (>6 months)

- Chronic cough
- Sputum production
- Fatigue

Medical history

- Bronchiectasis
- Hyperlipidemia
- Osteoporosis
- Sinusitis
- Hemoptysis
- Weight loss

Diagnostic results

Imaging

Microbiologic results

- 2 AFB stains and 2 cultures positive for MAC
- Macrolide susceptible: MIC 2.5 µg/mL
- Amikacin (IV) susceptible

Diagnosis is MAC lung disease based on

- Symptomatic presentation
- CT scan showing nodular bronchiectatic disease
- Sputum cultures positive for MAC

Diane's journey to ARIKAYCE treatment

Close monitoring
If treatment is not initiated, patients should be **closely monitored** to identify any clinical and/or radiographic progression[2]

Initiated airway clearance and active monitoring

Month 1
Month 2

3-month follow-up visit

- 3 months after initiation of airway clearance:
  - Cultures remain positive for MAC
  - Patient requested another treatment option

Began standard therapy according to guidelines

Month 4
Month 5
Month 6
Month 7
Month 8

May need more
Although some patients can achieve culture conversion on initial guideline-recommended therapy, **20% to 40% experience treatment failure**[18]

9-month follow-up visit

- 6 months after initiation of multidrug regimen:
  - Monthly sputum cultures are still positive for MAC

Add guideline-recommended ARIKAYCE for patients who remain culture positive after 6 months or more of standard therapy[2]

Jan, 74 years old

Initial patient visit

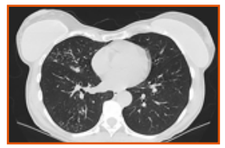
Clinical presentation (1 year)

- Fatigue
- Weight loss

Medical history

- Asthma
- Osteopenia
- GERD

Diagnostic results



Imaging

Microbiologic results

- 2 induced sputum cultures positive for MAC
- Macrolide susceptible: MIC 2.5 µg/mL
- Amikacin (IV) susceptible

Diagnosis is MAC lung disease based on

- Symptomatic presentation
- CT scan showing nodular bronchiectatic disease
- Induced sputum cultures positive for MAC

Jan's journey to ARIKAYCE treatment

Personalized care
Literature suggests **personalizing clearance techniques** for each patient, depending on the comprehensive care needed and taking into account other lung comorbidities and disease severity[19]

Initiated airway clearance and active monitoring

Month 1

2-month follow-up visit

- Requested another treatment option:
  - Cultures remain positive for MAC

Began standard therapy according to guidelines

Month 3
Month 4
Month 5
Month 6
Month 7
Month 8
Month 9

May need more
Although some patients can achieve culture conversion on initial guideline-recommended therapy, **20% to 40% experience treatment failure**[18]

10-month follow-up visit

- 8 months after initiation of multidrug regimen:
  - CT scans show additional areas of nodular bronchiectasis
  - Sputum cultures are persistently positive for MAC

Add guideline-recommended ARIKAYCE for patients who remain culture positive after 6 months or more of standard therapy[2]

CT=computerized tomography; GERD=gastroesophageal reflux disease.

IMPORTANT SAFETY INFORMATION (cont'd)

Embryo-Fetal Toxicity: Aminoglycosides can cause fetal harm when administered to a pregnant woman. Aminoglycosides, including ARIKAYCE, may be associated with total, irreversible, bilateral congenital deafness in pediatric patients exposed *in utero*. Patients who use ARIKAYCE during pregnancy, or become pregnant while taking ARIKAYCE should be apprised of the potential hazard to the fetus.

*See the full Prescribing Information for ARIKAYCE for information about the limited population.

Please see full Important Safety Information, including Boxed Warning, on pages 21-22 and enclosed full Prescribing Information.

ARIKAYCE® (amikacin liposome inhalation suspension) 590 mg/8.4 mL | Limited Population*

Which of your MAC patients may be appropriate for ARIKAYCE + standard therapy? (cont'd)

Eric, 59 years old

Initial patient visit

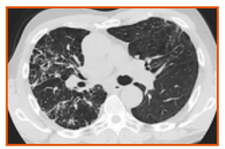
Clinical presentation (>2 years)

- Chronic cough
- Excessive sputum production
- Dyspnea
- Fatigue
- Hemoptysis
- Emphysema

Medical history

- COPD
- Bronchiectasis
- Cardiovascular disease

Diagnostic results



Imaging

Microbiologic results

- 1 AFB stain and 2 cultures positive for MAC
- Macrolide susceptible: MIC 3 µg/mL
- Amikacin (IV) susceptible: MIC 16 µg/mL

Diagnosis is MAC lung disease based on

- Symptomatic presentation
- CT scan showing nodular bronchiectatic disease
- Sputum cultures positive for MAC

Eric's journey to ARIKAYCE treatment

Initiated standard therapy + airway clearance

Month 1
Month 2

Ongoing monitoring
Guidelines recommend **carefully monitoring toxicity** and **assessing sputum cultures every 1 to 2 months** during therapy[2]

Month 3
Month 4
Month 5

6-month follow-up visit

- 6 months after initiation of multidrug regimen:
  - Achieved conversion of 1 sputum culture for MAC

Month 7
Month 8
Month 9
Month 10
Month 11

May need more
Although some patients can achieve culture conversion on initial guideline-recommended therapy, **20% to 40% experience treatment failure**[18]

12-month follow-up visit

- 12 months after initiation of multidrug regimen:
  - Monthly MAC sputum cultures became positive again for the past 6 consecutive months
  - CT scans showed radiographic progression

Add guideline-recommended ARIKAYCE for patients who remain culture positive after 6 months or more of standard therapy[2]

ARIKAYCE is covered for 76% of insured patients†

- Most plans require the completion of a prior authorization. Some plans may require further medical justification
- To learn more about what insurance providers require, contact an *Arikares Patient Access Lead (PAL)*. *PALs* have the reimbursement and payer expertise that may help minimize delays during the authorization and reimbursement process. By understanding payer-specific reauthorization requirements, *Arikares PALs* can provide information that may help patients maintain access to treatment
- Insmed is committed to providing access to ARIKAYCE. The *Arikares Support Program* can be reached at 1-833-ARIKARE (1-833-274-5273) or 1-973-437-2376

†Source: Managed Markets Insights & Technology, LLC, database as of April 2020. All information provided is as of 4/16/2020. The information includes applicable public and private payers. The information available here is compiled from a source believed to be accurate, but Insmed makes no representation that it is accurate. This information is subject to change. Payer requirements may vary or change over time, so it is important to regularly check with each payer as to payer-specific requirements. The use of this information does not guarantee payment or that any payment received will cover your costs.

IMPORTANT SAFETY INFORMATION (cont'd)

Contraindications: ARIKAYCE is contraindicated in patients with known hypersensitivity to any aminoglycoside.

Most Common Adverse Reactions: The most common adverse reactions in Trial 1 at an incidence ≥5% for patients using ARIKAYCE plus background regimen compared to patients treated with background regimen alone were dysphonia (48% vs 2%), cough (40% vs 17%), bronchospasm (29% vs 11%), hemoptysis (18% vs 13%), musculoskeletal pain (18% vs 9%), upper airway irritation (18% vs 2%), ototoxicity (17% vs 10%), fatigue and asthenia (16% vs 10%), exacerbation of underlying pulmonary disease (15% vs 10%), diarrhea (13% vs 5%), nausea (12% vs 4%), headache (10% vs 5%), pneumonia (9% vs 9%), pyrexia (8% vs 5%), decreased weight (7% vs 1%), vomiting (7% vs 4%), rash (6% vs 1%), change in sputum (6% vs 1%), and chest discomfort (5% vs 3%).

*See the full Prescribing Information for ARIKAYCE for information about the limited population.

Please see full Important Safety Information, including Boxed Warning, on pages 21-22 and enclosed full Prescribing Information.

ARIKAYCE® (amikacin liposome inhalation suspension) 590 mg/8.4 mL | Limited Population*

Getting started with the *Arikares Support Program*

Supporting ARIKAYCE patients throughout their journey

Arikares®

Prescribe ARIKAYCE and Enroll Patients in *Arikares*

To prescribe ARIKAYCE and enroll your patients in *Arikares*, complete the *Arikares* Enrollment Form. Submit via fax **(1-800-604-6027)** or e-mail **(enrollment@arikares.com)**

After enrolling patients in the *Arikares Support Program*, they will receive a Welcome Pack in the mail and a call from their *Arikares Coordinator*

Arikares Coordinators

An *Arikares Coordinator* can assist patients with their specialty pharmacy to verify insurance coverage

They can help answer device-related treatment questions

Arikares Patient Access Lead (PAL)

Provides information on the reimbursement process, payer requirements, and the prior authorization and appeals processes

Provides answers to questions that may arise during the reimbursement process

Provides access information, including the most recent publicly available payer-specific forms and procedures

Starting ARIKAYCE

An *Arikares Coordinator* and the specialty pharmacy will work with patients to coordinate the shipment of ARIKAYCE to their home

Arikares Trainers

An *Arikares Trainer* (nurses and respiratory therapists) may provide voluntary in-home or virtual device training for patients and caregivers at treatment initiation

Ongoing Support

Arikares can provide patients with ongoing support during their course of care

IMPORTANT SAFETY INFORMATION (cont'd)

Drug Interactions: Avoid concomitant use of ARIKAYCE with medications associated with neurotoxicity, nephrotoxicity, and ototoxicity. 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.

Overdosage: Adverse reactions specifically associated with overdose of ARIKAYCE have not been identified. Acute toxicity should be treated with immediate withdrawal of ARIKAYCE, and baseline tests of renal function should be undertaken. Hemodialysis may be helpful in removing amikacin from the body. In all cases of suspected overdosage, physicians should contact the Regional Poison Control Center for information about effective treatment.

After I prescribe ARIKAYCE, what will my patient receive?

1. A Welcome Pack and a call from their ***Arikares Coordinator*** to discuss questions and next steps
2. Their first shipment of ARIKAYCE, arriving in 2 packages: the first containing the 28-day supply of medicine and the second delivering the Lamira Nebulizer System and Getting Started Kit

Patients can receive voluntary device training that can be scheduled with an ***Arikares Trainer*** after the ARIKAYCE delivery date is confirmed.

Welcome Pack

Your patients will be sent a Welcome Pack in the mail after enrollment into *Arikares* that includes important and helpful information about getting started with ARIKAYCE.

28-day ARIKAYCE Medication Kit

The first shipment of ARIKAYCE will include a 28-day supply of medicine from a specialty pharmacy. After this initial shipment, patients will continue to receive a 28-day supply of ARIKAYCE each month.

Lamira Nebulizer System and Getting Started Kit

The second shipment will include the Lamira Nebulizer System and Getting Started Kit, and will be sent from the same pharmacy as the first box. Patients will only receive this shipment once.

Lamira Nebulizer System

Getting Started Kit

*See the full Prescribing Information for ARIKAYCE for information about the limited population.

Please see full Important Safety Information on pages 21-22 including Boxed Warning, and enclosed full Prescribing Information.

ARIKAYCE®
(amikacin liposome inhalation suspension)
590 mg/8.4 mL

Limited Population*

As part of a multidrug antibacterial regimen,

The 2020 Guidelines **strongly recommend adding ARIKAYCE** to standard therapy for patients with MAC lung disease who remain culture positive after 6 months of treatment[2]

- **Patients on ARIKAYCE + standard therapy achieved over a 3-fold increase in rates of culture conversion by Month 6[1]**
  - **In the CONVERT trial, the endpoints of the change from baseline in 6MWT distance and the SGRQ did not demonstrate clinical benefit at Month 6**
- **More than half of the patients who converted on ARIKAYCE + standard therapy remained converted through 15 months after initial conversion (remained culture negative after 3 months off treatment)[1]**
- **The most common adverse events (≥10%) experienced in the ARIKAYCE + standard therapy arm were dysphonia, cough, bronchospasm, hemoptysis, exacerbation of underlying pulmonary disease, musculoskeletal pain, ototoxicity, fatigue/asthenia, upper airway irritation, diarrhea, nausea, and headache[1]**
- **The 2020 Guidelines recommend continuing MAC treatment for 12 months after culture conversion[2]**
- **Insmed offers the *Arikares Support Program* to help patients throughout their treatment journey**
- **ARIKAYCE is covered for 76% of insured patients†**

Visit PrescribeARIKAYCE.com to learn more.

†Source: Managed Markets Insights & Technology, LLC, database as of April 2020. All information provided is as of 4/16/2020. The information includes applicable public and private payers. The information available here is compiled from a source believed to be accurate, but Insmed makes no representation that it is accurate. This information is subject to change. Payer requirements may vary or change over time, so it is important to regularly check with each payer as to payer-specific requirements. The use of this information does not guarantee payment or that any payment received will cover your costs.

INDICATION

LIMITED POPULATION: ARIKAYCE® is 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. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

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.

IMPORTANT SAFETY INFORMATION

Hypersensitivity Pneumonitis has been reported with the use of ARIKAYCE in the clinical trials. Hypersensitivity pneumonitis (reported as allergic alveolitis, pneumonitis, interstitial lung disease, allergic reaction to ARIKAYCE) was reported at a higher frequency in patients treated with ARIKAYCE plus background regimen (3.1%) compared to patients treated with background regimen alone (0%). Most patients with hypersensitivity pneumonitis discontinued treatment with ARIKAYCE and received treatment with corticosteroids. If hypersensitivity pneumonitis occurs, discontinue ARIKAYCE and manage patients as medically appropriate.

Hemoptysis has been reported with the use of ARIKAYCE in the clinical trials. Hemoptysis was reported at a higher frequency in patients treated with ARIKAYCE plus background regimen (18.4%) compared to patients treated with background regimen alone (13.4%). If hemoptysis occurs, manage patients as medically appropriate.

Bronchospasm has been reported with the use of ARIKAYCE in the clinical trials. Bronchospasm (reported as asthma, bronchial hyperreactivity, bronchospasm, dyspnea, dyspnea exertional, prolonged expiration, throat tightness, wheezing) was reported at a higher frequency in patients treated with ARIKAYCE plus background regimen (28.7%) compared to patients treated with background regimen alone (10.7%). If bronchospasm occurs during the use of ARIKAYCE, treat patients as medically appropriate.

Exacerbations of underlying pulmonary disease have been reported with the use of ARIKAYCE in the clinical trials. Exacerbations of underlying pulmonary disease (reported as chronic obstructive pulmonary disease (COPD), infective exacerbation of COPD, infective exacerbation of bronchiectasis) have been reported at a higher frequency in patients treated with ARIKAYCE plus background regimen (15.2%) compared to patients treated with background regimen alone (9.8%). If exacerbations of underlying pulmonary disease occur during the use of ARIKAYCE, treat patients as medically appropriate.

Anaphylaxis and Hypersensitivity Reactions: Serious and potentially life-threatening hypersensitivity reactions, including anaphylaxis, have been reported in patients taking ARIKAYCE. Signs and symptoms include acute onset of skin and mucosal tissue hypersensitivity reactions (hives, itching, flushing, swollen lips/tongue/uvula), respiratory difficulty (shortness of breath, wheezing, stridor, cough), gastrointestinal symptoms (nausea, vomiting, diarrhea, crampy abdominal pain), and cardiovascular signs and symptoms of anaphylaxis (tachycardia, low blood pressure, syncope, incontinence, dizziness). Before therapy with ARIKAYCE is instituted, evaluate for previous hypersensitivity reactions to aminoglycosides. If anaphylaxis or a hypersensitivity reaction occurs, discontinue ARIKAYCE and institute appropriate supportive measures.

Ototoxicity has been reported with the use of ARIKAYCE in the clinical trials. Ototoxicity (including deafness, dizziness, presyncope, tinnitus, and vertigo) were reported with a higher frequency in patients treated with ARIKAYCE plus background regimen (17%) compared to patients treated with background regimen alone (9.8%). This was primarily driven by tinnitus (8.1% in ARIKAYCE plus background regimen vs 0.9% in the background regimen alone arm) and dizziness (6.3% in ARIKAYCE plus background regimen vs 2.7% in the background regimen alone arm). Closely monitor patients with known or suspected auditory or vestibular dysfunction during treatment with ARIKAYCE. If ototoxicity occurs, manage patients as medically appropriate, including potentially discontinuing ARIKAYCE.

Nephrotoxicity was observed during the clinical trials of ARIKAYCE in patients with MAC lung disease but not at a higher frequency than background regimen alone. Nephrotoxicity has been associated with the aminoglycosides. Close monitoring of patients with known or suspected renal dysfunction may be needed when prescribing ARIKAYCE.

Neuromuscular Blockade: Patients with neuromuscular disorders were not enrolled in ARIKAYCE clinical trials. Aminoglycosides may aggravate muscle weakness by blocking the release of acetylcholine at neuromuscular junctions. Closely monitor patients with known or suspected neuromuscular disorders, such as myasthenia gravis. If neuromuscular blockade occurs, it may be reversed by the administration of calcium salts but mechanical respiratory assistance may be necessary.

Embryo-Fetal Toxicity: Aminoglycosides can cause fetal harm when administered to a pregnant woman. Aminoglycosides, including ARIKAYCE, may be associated with total, irreversible, bilateral congenital deafness in pediatric patients exposed *in utero*. Patients who use ARIKAYCE during pregnancy, or become pregnant while taking ARIKAYCE should be apprised of the potential hazard to the fetus.

Contraindications: ARIKAYCE is contraindicated in patients with known hypersensitivity to any aminoglycoside.

Please see additional Important Safety Information, including Boxed Warning, on back cover and enclosed full Prescribing Information.

ARIKAYCE®
(amikacin liposome inhalation suspension)
590 mg/8.4 mL

Limited Population

IMPORTANT SAFETY INFORMATION (cont'd)

Most Common Adverse Reactions: The most common adverse reactions in Trial 1 at an incidence ≥5% for patients using ARIKAYCE plus background regimen compared to patients treated with background regimen alone were dysphonia (48% vs 2%), cough (40% vs 17%), bronchospasm (29% vs 11%), hemoptysis (18% vs 13%), musculoskeletal pain (18% vs 9%), upper airway irritation (18% vs 2%), ototoxicity (17% vs 10%), fatigue and asthenia (16% vs 10%), exacerbation of underlying pulmonary disease (15% vs 10%), diarrhea (13% vs 5%), nausea (12% vs 4%), headache (10% vs 5%), pneumonia (9% vs 9%), pyrexia (8% vs 5%), decreased weight (7% vs 1%), vomiting (7% vs 4%), rash (6% vs 1%), change in sputum (6% vs 1%), and chest discomfort (5% vs 3%).

Drug Interactions: Avoid concomitant use of ARIKAYCE with medications associated with neurotoxicity, nephrotoxicity, and ototoxicity. 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.

Overdosage: Adverse reactions specifically associated with overdose of ARIKAYCE have not been identified. Acute toxicity should be treated with immediate withdrawal of ARIKAYCE, and baseline tests of renal function should be undertaken. Hemodialysis may be helpful in removing amikacin from the body. In all cases of suspected overdosage, physicians should contact the Regional Poison Control Center for information about effective treatment.

WARNING: RISK OF INCREASED RESPIRATORY ADVERSE REACTIONS

ARIKAYCE has been associated with an increased risk of respiratory adverse reactions, including hypersensitivity pneumonitis, hemoptysis, bronchospasm, and exacerbation of underlying pulmonary disease that have led to hospitalizations in some cases.

ARIKAYCE®
(amikacin liposome inhalation suspension)
590 mg/8.4 mL

Limited Population*

References: 1. ARIKAYCE [package insert]. Bridgewater, NJ: Insmed Incorporated; 2020. **2.** Daley CL, et al. *Clin Infect Dis*. 2020;71(4):e1-e36. **3.** Griffith DE, et al. *Am J Respir Crit Care Med*. 2018;198(12):1559-1569. **4.** Moon SM, et al. *Eur Respir J*. 2019;53(5). doi:10.1183/13993003.01636-2018. **5.** Furuuchi K, et al. *Chest*. 2020. doi:10.1016/j.chest.2019.12.016. **6.** Koh WJ, et al. *Eur Respir J*. 2017;50(3). doi:10.1183/13993003.02503-2016. **7.** Griffith DE, et al. *Am J Respir Crit Care Med*. 2007;175(4):367-416. **8.** Park HY, et al. *Chest*. 2016;150(6):1222-1232. **9.** Pan SW, et al. *Clin Infect Dis*. 2017;65(6):927-934. **10.** Data on file. Insmed Incorporated. Bridgewater, NJ. **11.** Griffith DE, et al. Online data supplement. *Am J Respir Crit Care Med*. 2018;198(12)(suppl):E1-E28. Accessed October 16, 2020. https://www.atsjournals.org/doi/suppl/10.1164/rccm.201807-1318OC/suppl_file/griffith_data_supplement.pdf. **12.** Center for Drug Evaluation and Research. NDA Multi-Disciplinary Review and Evaluation–NDA 207356. 2018. Accessed October 16, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/207356Orig1s000MultidisciplineR.pdf. **13.** Lamira Nebulizer System instructions for use. Midlothian, VA: PARI Respiratory Equipment, Inc; 2018. **14.** Swenson C, et al. *Open Forum Infect Dis*. 2020:7(4). doi:10.1093/ofid/ofaa079. **15.** Olivier KN, et al. *Am J Respir Crit Care Med*. 2017;195(6):814-823. **16.** Zhang J, et al. *Front Microbiol*. 2018;9(915). doi:10.3389/fmicb.2018.00915. **17.** Woods GL, et al. *Performance Standards for Susceptibility Testing of Mycobacteria, Nocardia spp., and Other Aerobic Actinomycetes*. Clinical and Laboratory Standards Institute. 1st ed. CLSI supplement M62. 2018:38(22). **18.** Koh WJ, et al. *Antimicrob Agents Chemother*. 2013;57(5):2281-2285. **19.** McIlwaine M, et al. *Eur Respir Rev*. 2017;26(143). doi:10.1183/16000617.0086-2016.

*See the full Prescribing Information for ARIKAYCE for information about the limited population.

Please see additional Important Safety Information on page 21 and enclosed full Prescribing Information.

insmed®

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ARIKAYCE safely and effectively. See full prescribing information for ARIKAYCE.

ARIKAYCE® (amikacin liposome inhalation suspension), for oral inhalation use
Initial U.S. Approval: 2018
LIMITED POPULATION

WARNING: RISK OF INCREASED RESPIRATORY ADVERSE REACTIONS
See full prescribing information for complete boxed warning.

ARIKAYCE has been associated with a risk of increased respiratory adverse reactions, including, hypersensitivity pneumonitis, hemoptysis, bronchospasm, and exacerbation of underlying pulmonary disease that have led to hospitalizations in some cases. (5.1, 5.2, 5.3, 5.4)

----------INDICATIONS AND USAGE----------
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. (1)

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. (1)

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.

----------DOSAGE AND ADMINISTRATION----------
- For oral inhalation use only. (2.1)
- Use ARIKAYCE vials only with the Lamira Nebulizer System. (2.1)
- Pre-treatment with inhaled bronchodilator should be considered in patients with a history of hyperreactive airway disease. (2.1)
- The recommended dosage in adults is once daily oral inhalation of the contents of one 590 mg/8.4 mL ARIKAYCE vial. (2.2)

---------- DOSAGE FORMS AND STRENGTHS ----------
ARIKAYCE is supplied as a sterile, aqueous, liposome suspension for oral inhalation in a unit-dose glass vial containing amikacin 590 mg/8.4 mL. (3)

----------CONTRAINDICATIONS----------
ARIKAYCE is contraindicated in patients with a known hypersensitivity to any aminoglycoside. (4)

----------WARNINGS AND PRECAUTIONS----------
- Hypersensitivity Pneumonitis: Reported with ARIKAYCE treatment; if hypersensitivity pneumonitis occurs, discontinue ARIKAYCE and manage patients as medically appropriate. (5.1)
- Hemoptysis: Higher frequency of hemoptysis has been reported with ARIKAYCE treatment. If hemoptysis occurs, manage the patients as medically appropriate. (5.2)
- Bronchospasm: Higher frequency of bronchospasm has been reported with ARIKAYCE treatment. Treat patients as medically appropriate if this occurs during treatment with ARIKAYCE. (5.3)
- 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. (5.4)
- Anaphylaxis and Hypersensitivity Reactions: Serious and potentially life-threatening hypersensitivity reactions, including anaphylaxis, have been reported in patients taking ARIKAYCE. If anaphylaxis or a hypersensitivity reaction occurs, discontinue ARIKAYCE and institute appropriate supportive measures. (5.5)
- 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. (5.6)
- Nephrotoxicity: Nephrotoxicity was observed during the clinical trials of ARIKAYCE in patients with MAC lung disease but not at a higher frequency than the background regimen alone. Aminoglycosides have been associated with nephrotoxicity. Close monitoring of patients with known or suspected renal dysfunction may be needed when prescribing ARIKAYCE. (5.7)
- Neuromuscular Blockade: Aminoglycosides may aggravate muscle weakness by blocking the release of acetylcholine at neuromuscular junctions. Closely monitor patients with known or suspected neuromuscular disorders, such as myasthenia gravis. If neuromuscular blockade occurs, it may be reversed by the administration of calcium salts but mechanical respiratory assistance may be necessary. (5.8)
- Embryo-Fetal Toxicity: Aminoglycosides can cause fetal harm when administered to a pregnant woman. Aminoglycosides, including ARIKAYCE, may be associated with total, irreversible, bilateral congenital deafness in pediatric patients exposed *in utero*. Advise pregnant women of the potential risk to a fetus. (5.9, 8.1)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence ≥10% and higher than control) in the patients with refractory MAC lung disease were: dysphonia, cough, bronchospasm, hemoptysis, musculoskeletal pain, upper airway irritation, ototoxicity, fatigue/asthenia, exacerbation of underlying pulmonary disease, diarrhea, nausea, and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Insmed Incorporated at 1-844-4-INSMED or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: RISK OF INCREASED RESPIRATORY ADVERSE REACTIONS

ARIKAYCE has been associated with an increased risk of respiratory adverse reactions including, hypersensitivity pneumonitis, hemoptysis, bronchospasm, exacerbation of underlying pulmonary *disease* that have led to hospitalizations in some cases *[see Warnings and Precautions (5.1, 5.2, 5.3, 5.4)]*.

1 INDICATIONS AND USAGE

LIMITED POPULATION: ARIKAYCE® is 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 *[see Clinical Studies (14)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

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.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

ARIKAYCE is for oral inhalation use only. Administer by nebulization only with the Lamira® Nebulizer System. Refer to the Instructions for Use for full administration information on use of ARIKAYCE with the Lamira Nebulizer System.

Instruct patients using a bronchodilator (‘reliever’) to first use the bronchodilator following the bronchodilator leaflet for use information before using ARIKAYCE.

Pre-treatment with short-acting selective beta-2 agonists should be considered for patients with known hyperreactive airway disease, chronic obstructive pulmonary disease, asthma, or bronchospasm *[see Warnings and Precautions (5.3)]*.

2.2 Recommended Dosage

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 *[see Clinical Studies (14)]*.

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.

3 DOSAGE FORMS AND STRENGTHS

ARIKAYCE is supplied as a sterile, white, milky, 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).

4 CONTRAINDICATIONS

ARIKAYCE is contraindicated in patients with a known hypersensitivity to any aminoglycoside.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Pneumonitis

Hypersensitivity pneumonitis has been reported with the use of ARIKAYCE in the clinical trials. Hypersensitivity pneumonitis (reported as allergic alveolitis, pneumonitis, interstitial lung disease, allergic reaction to ARIKAYCE) was reported at a higher frequency in patients treated with ARIKAYCE plus a background regimen (3.1%) compared to patients treated with a background regimen alone (0%). Most patients with hypersensitivity pneumonitis discontinued treatment with ARIKAYCE and received treatment with corticosteroids *[see Adverse Reactions (6.1)]*. If hypersensitivity pneumonitis occurs, discontinue ARIKAYCE and manage the patient as medically appropriate.

5.2 Hemoptysis

Hemoptysis has been reported with the use of ARIKAYCE in the clinical trials. Hemoptysis was reported at a higher frequency in patients treated with ARIKAYCE plus a background regimen (18.4%) compared to patients treated with a background regimen alone (13.4%) *[see Adverse Reactions (6.1)]*. If hemoptysis occurs, manage the patients as medically appropriate.

5.3 Bronchospasm

Bronchospasm has been reported with the use of ARIKAYCE in the clinical trials. Bronchospasm (reported as asthma, bronchial hyperreactivity, bronchospasm, dyspnea, dyspnea exertional, prolonged expiration, throat tightness, wheezing) was reported at a higher frequency in patients treated with ARIKAYCE plus a background regimen (28.7%) compared to patients treated with a background regimen alone (10.7%) *[see Adverse Reactions (6.1)]*. If bronchospasm occurs during the use of ARIKAYCE, treat the patients as medically appropriate.

5.4 Exacerbation of Underlying Pulmonary Disease

Exacerbations of underlying pulmonary disease have been reported with the use of ARIKAYCE in the clinical trials. Exacerbations of underlying pulmonary disease (reported as chronic obstructive pulmonary disease, infective exacerbation of chronic obstructive pulmonary disease, infective exacerbation of bronchiectasis) have been reported at a higher frequency in patients treated with ARIKAYCE plus a background regimen (15.2%) compared to patients treated with background regimen alone (9.8%) *[see Adverse Reactions (6.1)]*. If exacerbations of underlying pulmonary disease occur during the use of ARIKAYCE, treat the patients as medically appropriate.

5.5 Anaphylaxis and Hypersensitivity Reactions

Serious and potentially life-threatening hypersensitivity reactions, including anaphylaxis, have been reported in patients taking ARIKAYCE. Signs and symptoms include acute onset of skin and mucosal tissue hypersensitivity reactions (hives, itching, flushing, swollen lips/tongue/uvula), respiratory difficulty (shortness of breath, wheezing, stridor, cough), gastrointestinal symptoms (nausea, vomiting, diarrhea, crampy abdominal pain), and cardiovascular signs and symptoms of anaphylaxis (tachycardia, low blood pressure, syncope, incontinence, dizziness). Before therapy with ARIKAYCE is instituted, evaluate for previous hypersensitivity reactions to aminoglycosides. If anaphylaxis or a hypersensitivity reaction occurs, discontinue ARIKAYCE and institute appropriate supportive measures.

5.6 Ototoxicity

Ototoxicity has been reported with the use of ARIKAYCE in the clinical trials. Ototoxicity (including deafness, dizziness, presyncope, tinnitus, and vertigo) were reported with a higher frequency in patients treated with ARIKAYCE plus a background regimen (17%) compared to patients treated with background regimen alone (9.8%). This was primarily driven by tinnitus (8.1% in ARIKAYCE plus background regimen vs. 0.9% in the background regimen alone arm) and dizziness (6.3% in ARIKAYCE plus background regimen vs. 2.7% in the background regimen alone arm) *[see Adverse Reactions (6.1)]*.

Closely monitor patients with known or suspected auditory or vestibular dysfunction during treatment with ARIKAYCE. If ototoxicity occurs, manage the patient as medically appropriate, including potentially discontinuing ARIKAYCE.

5.7 Nephrotoxicity

Nephrotoxicity was observed during the clinical trials of ARIKAYCE in patients with MAC lung disease but not at a higher frequency than the background regimen alone *[see Adverse Reactions (6.1)]*. Nephrotoxicity has been associated with the aminoglycosides. Close monitoring of patients with known or suspected renal dysfunction may be needed when prescribing ARIKAYCE.

5.8 Neuromuscular Blockade

Patients with neuromuscular disorders were not enrolled in ARIKAYCE clinical trials. Aminoglycosides may aggravate muscle weakness by blocking the release of acetylcholine at neuromuscular junctions. Closely monitor patients with known or suspected neuromuscular disorders, such as myasthenia gravis. If neuromuscular blockade occurs, it may be reversed by the administration of calcium salts but mechanical respiratory assistance may be necessary.

5.9 Embryo-Fetal Toxicity

Aminoglycosides can cause fetal harm when administered to a pregnant woman. Aminoglycosides, including ARIKAYCE, may be associated with total, irreversible, bilateral congenital deafness in pediatric patients exposed *in utero*. Patients who use ARIKAYCE during pregnancy, or become pregnant while taking ARIKAYCE should be apprised of the potential hazard to the fetus *[see Use in Specific Populations (8.1)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described in greater detail in other sections of labeling:

- Hypersensitivity pneumonitis *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Hemoptysis *[see Boxed Warning and Warnings and Precautions (5.2)]*
- Bronchospasm *[see Boxed Warning and Warnings and Precautions (5.3)]*
- Exacerbation of Underlying Pulmonary Disease *[see Boxed Warning and Warnings and Precautions (5.4)]*
- Anaphylaxis and Hypersensitivity Reactions *[see Warnings and Precautions (5.5)]*
- Ototoxicity *[see Warnings and Precautions (5.6)]*
- Nephrotoxicity *[see Warnings and Precautions (5.7)]*
- Neuromuscular Blockade *[see Warnings and Precautions (5.8)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Overview of Clinical Trials for Safety Evaluation

Within the refractory NTM clinical program, 404 patients that participated in three clinical trials were treated with ARIKAYCE at the dose of 590 mg/day (median duration of exposure to ARIKAYCE was 236.5 days).

Trial 1 (NCT#02344004) was an open-label, randomized (2:1), multi-center Phase 3 trial in patients with refractory *Mycobacterium avium* complex (MAC) lung disease. Patients were randomized to either 8 months of ARIKAYCE plus a background regimen (n=223) or background regimen alone (n=112).

Trial 2 (NCT#02628600) was a single-arm extension of Trial 1 for refractory MAC lung disease patients that failed to achieve negative sputum cultures after 6 months of treatment or had a relapse or recurrence by Month 6 from either study arm of Trial 1. A total of 163 patients (n=90 from the prior background regimen alone arm of Trial 1, and n=73 from the prior ARIKAYCE plus background regimen arm in Trial 1) participated in the trial.

Trial 3 (NCT#01315236) was a double-blind, randomized, placebo-controlled Phase 2 study in patients with refractory nontuberculous mycobacterial (NTM) lung disease caused by MAC and *Mycobacterium*

abscessus. Patients were randomized to either ARIKAYCE plus background regimen (N=44) or an inhaled diluted empty liposome placebo plus background regimen (N=45) for 84 days.

Across all clinical trials of patients with and without refractory NTM lung infection, 818 patients were exposed to multiple doses of ARIKAYCE.

Adverse Reactions Leading to Treatment Discontinuation

In the three NTM studies, there was a higher incidence of premature discontinuation of ARIKAYCE. In Trial 1, 34.5% discontinued ARIKAYCE prematurely; most were due to adverse reactions (18.8%) and withdrawal by subject (9.9%). In the comparator arm, 10.7% of subjects discontinued their background regimen, with 0.9% due to adverse reactions and 5.4% due to withdrawal by subject. In Trial 2 (the single-arm extension of Trial 1), 37.8% of patients starting on ARIKAYCE discontinued prematurely with 24.4% discontinuing due to adverse reactions. In Trial 3, all 9 (20.5%) premature discontinuations occurred in the ARIKAYCE plus background regimen-treated patients and there were no premature discontinuations in the placebo plus background regimen arm.

Serious Adverse Reactions in Trials 1 and 3

In Trial 1, 19.7% of patients treated with ARIKAYCE plus background regimen reported SAR as compared to 16.1% of patients treated with background regimen alone. In addition, in Trial 1 [2 to 1 randomization, ARIKAYCE plus background regimen versus background regimen alone], there were 80 hospitalizations in 41 patients (18.4%) treated with ARIKAYCE plus background regimen compared to 29 hospitalizations in 15 patients (13.4%) treated with background regimen alone. The most common SARs and reasons for hospitalization in the ARIKAYCE plus background regimen arm were related to exacerbation of underlying pulmonary disease and lower respiratory tract infections, such as pneumonia.

In Trial 3, 18.2% of patients treated with ARIKAYCE plus background regimen reported SARs compared to 8.9% of patients treated with background regimen plus inhaled placebo.

Common Adverse Reactions

The incidence of adverse reactions in Trial 1 are displayed in Table 1. Only those adverse reactions with a rate of at least 5% in the ARIKAYCE plus background regimen group and greater than the background regimen alone group, are shown.

Table 1: Adverse Reactions in ≥ 5% of ARIKAYCE-treated MAC Patients and More Frequent than Background Regimen Alone in Trial 1

Adverse Reaction	ARIKAYCE plus Background Regimen (N=223) n (%)	Background Regimen Alone (N=112) n (%)
Dysphonia[a]	106 (48)	2 (2)
Cough[b]	88 (40)	19 (17)
Bronchospasm[c]	64 (29)	12 (11)
Hemoptysis	41 (18)	15 (13)
Musculoskeletal pain[d]	40 (18)	10 (9)
Upper airway irritation[e]	39 (18)	2 (2)
Ototoxicity[f]	38 (17)	11 (10)
Fatigue and asthenia	36 (16)	11 (10)
Exacerbation of underlying pulmonary disease[g]	34 (15)	11 (10)
Diarrhea	28 (13)	5 (5)
Nausea	26 (12)	4 (4)
Headache	22 (10)	5 (5)
Pneumonia[h]	20 (9)	10 (9)
Pyrexia	17 (8)	5 (5)
Weight decreased	16 (7)	1 (1)
Vomiting[i]	15 (7)	4 (4)
Rash[j]	14 (6)	1 (1)
Change in sputum[k]	13 (6)	1 (1)
Chest discomfort	12 (5)	3 (3)

[a]Includes aphonia and dysphonia

[b]Includes cough, productive cough, and upper airway cough syndrome
[c]Includes asthma, bronchial hyperreactivity, bronchospasm, dyspnea, dyspnea exertional, prolonged expiration, throat tightness, and wheezing
[d]Includes back pain, arthralgia, myalgia, pain/body aches, muscle spasm and musculoskeletal pain
[e]Includes oropharyngeal pain, oropharyngeal discomfort, throat irritation, pharyngeal erythema, upper airway inflammation, pharyngeal edema, vocal cord inflammation, laryngeal pain, laryngeal erythema, laryngitis
[f]Includes deafness, deafness neurosensory, deafness unilateral, dizziness, hypoacusis, presyncope, tinnitus, vertigo, balance disorders
[g]Includes COPD, infective exacerbation of COPD, infective exacerbation of bronchiectasis
[h]Includes atypical pneumonia, empyema, infection pleural effusion, lower respiratory tract infection, lung infection, lung infection pseudomonas, pneumonia, pneumonia aspiration, pneumonia pseudomonas, pseudomonas infection, and respiratory tract infection
[i]Includes vomiting and post-tussive vomiting
[j]Includes rash, rash maculo-papular, drug eruption, and urticaria
[k]Includes increased sputum, sputum purulent, and sputum discolored

Selected adverse drug reactions that occurred in <5% of patients and at higher frequency in ARIKAYCE-treated patients in Trial 1 are presented in Table 2.

Table 2: Selected Adverse Reactions in < 5% of ARIKAYCE-treated MAC Patients and More Frequent than Background Regimen Alone in Trial 1

Adverse Reaction	ARIKAYCE plus Background Regimen N=223 n (%)	Background Regimen Alone N=112 n (%)
Anxiety[a]	10 (5)	0 (0)
Oral fungal infection[b]	9 (4)	2 (2)
Bronchitis	8 (4)	3 (3)
Dysgeusia	7 (3)	0 (0)
Hypersensitivity pneumonitis[c]	7 (3)	0 (0)
Dry mouth	6 (3)	0 (0)
Epistaxis	6 (3)	1 (1)
Respiratory failure[d]	6 (3)	2 (2)
Pneumothorax[e]	5 (2)	1 (1)
Exercise tolerance decreased	3 (1)	0 (0)
Balance disorder	3 (1)	0 (0)
Neuromuscular disorder[f]	2 (1)	0 (0)

[a]Includes anxiety and anxiety disorder
[b]Includes oral candidiasis and oral fungal infection
[c]Includes allergic alveolitis, interstitial lung disease, and pneumonitis
[d]Includes acute respiratory failure and respiratory failure
[e]Includes pneumothorax, pneumothorax spontaneous and pneumomediastinum
[f]Includes muscle weakness and neuropathy peripheral

Refer to Table 1 and Table 2 for the incidence rate of hypersensitivity pneumonitis, bronchospasm, cough, dysphonia, exacerbation of underlying disease, hemoptysis, ototoxicity, upper airway irritation, and neuromuscular disorders *[see Warnings and Precautions (5.1, 5.2, 5.3, 5.4, 5.6, 5.7)]*.

6.2 Postmarketing Experience

The following adverse reactions have been identified from postmarketing surveillance. Because these adverse reactions are reported voluntarily from a population of unknown size, precise estimates of frequency cannot be made and a causal relationship to drug exposure cannot be established.

Immune System Disorders: hypersensitivity, anaphylaxis *[see Warnings and Precautions (5.5)]*

7 DRUG INTERACTIONS

7.1 Drugs with Neurotoxic, Nephrotoxic, or Ototoxic Potential

Avoid concomitant use of ARIKAYCE with medications associated with neurotoxicity, nephrotoxicity, and ototoxicity.

7.2 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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no data on ARIKAYCE use in pregnant women to evaluate for any drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Although systemic absorption of amikacin following oral inhalation is expected to be low *[see Clinical Pharmacology (12.3)],* systemic exposure to aminoglycoside antibacterial drugs, including ARIKAYCE, may be associated with total, irreversible, bilateral congenital deafness when administered to pregnant women *[see Warnings and Precautions (5.9)]*. Advise pregnant women of the potential risk to a fetus.

Animal reproductive toxicology studies have not been conducted with inhaled amikacin. Subcutaneous administration of amikacin to pregnant rats (up to 100 mg/kg/day) and mice (up to 400 mg/kg/day) during organogenesis was not associated with fetal malformations. Ototoxicity was not adequately evaluated in offspring in animal studies.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

No animal reproductive toxicology studies have been conducted with ARIKAYCE or non-liposomal amikacin administered by inhalation.

Amikacin was subcutaneously administered to pregnant rats (Gestation Days 8-14) and mice (Gestation Days 7-13) at doses of 25, 100, or 400 mg/kg to assess developmental toxicity. These doses did not cause fetal visceral or skeletal malformations in mice. The high dose was excessively maternally toxic in rats (nephrotoxicity and mortality were observed), precluding the evaluation of offspring at this dose. Fetal malformations were not observed at the low or mid dose in rats. Postnatal development of the rats and mice exposed to these doses of amikacin *in utero* did not differ significantly from control.

Ototoxicity was not adequately evaluated in offspring in animal developmental toxicology studies.

8.2 Lactation

Risk Summary

There is no information regarding the presence of ARIKAYCE in human milk, the effects on the breastfed infant, or the effects on milk production after administration of ARIKAYCE by inhalation. Although limited published data on other routes of administration of amikacin indicate that amikacin is present in human milk, systemic absorption of ARIKAYCE following inhaled administration is expected to be low [*see Clinical Pharmacology (12.3)*]. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ARIKAYCE and any potential adverse effects on the breastfed child from ARIKAYCE or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness of ARIKAYCE in pediatric patients below 18 years of age have not been established.

8.5 Geriatric Use

In the NTM clinical trials, of the total number of patients receiving ARIKAYCE, 208 (51.5%) were ≥ 65 years and 59 (14.6%) were ≥ 75 years. No overall differences in safety and effectiveness were observed between elderly subjects and younger subjects. Because elderly patients are more likely to have decreased renal function, it may be useful to monitor renal function *[see Warnings and Precautions (5.7)]*.

8.6 Hepatic Impairment

ARIKAYCE has not been studied in patients with hepatic impairment. No dose adjustments based on hepatic impairment are required since amikacin is not hepatically metabolized *[see Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

ARIKAYCE has not been studied in patients with renal impairment. Given the low systemic exposure to amikacin following administration of ARIKAYCE, clinically relevant accumulation of amikacin is unlikely to occur in patients with renal impairment. However, renal function should be monitored in patients with known or suspected renal impairment, including elderly patients with potential age-related decreases in renal function *[see Warnings and Precautions (5.7), Use in Specific Populations (8.5)]*.

10 OVERDOSAGE

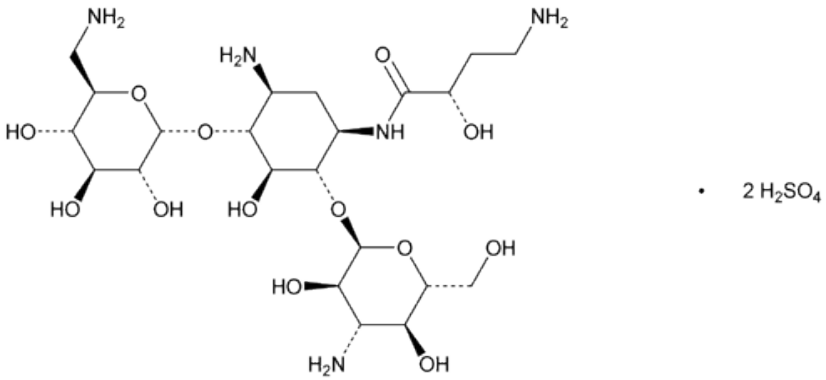
Adverse reactions specifically associated with overdose of ARIKAYCE have not been identified. Acute toxicity should be treated with immediate withdrawal of ARIKAYCE, and baseline tests of renal function should be undertaken.

Hemodialysis may be helpful in removing amikacin from the body.

In all cases of suspected overdosage, physicians should contact the Regional Poison Control Center for information about effective treatment. In the case of any overdosage, the possibility of drug interactions with alterations in drug disposition should be considered.

11 DESCRIPTION

The active ingredient in ARIKAYCE (amikacin liposome inhalation suspension) is amikacin sulfate USP, an aminoglycoside antibacterial. Its chemical name is D-Streptamine, *O*-3-amino-3-deoxy-α-D-glucopyranosyl-(1→6)-*O*-[6-amino-6-deoxy-α-D-glucopyranosyl-(1→4)]-N^1-(4-amino-2-hydroxy-1-oxobutyl)-2-deoxy-, (*S*)-, sulfate (1:2) salt with a chemical formula of $C_{22}H_{43}N_5O_{13}•2H_2SO_4$ with a molecular weight of 781.76. Its structural formula is:



ARIKAYCE is a white milky suspension consisting of amikacin sulfate encapsulated in liposomes and is supplied in a unit-dose 10 mL clear glass vial containing amikacin 590 mg/8.4 mL (equivalent to amikacin sulfate 623 mg/8.4 mL) as a sterile aqueous liposomal suspension for oral inhalation. ARIKAYCE consists of amikacin sulfate encapsulated in liposomes at a targeted concentration of 70 mg amikacin/mL with the pH range of 6.1 to 7.1 and lipid to amikacin weight ratio in the range of 0.60 to 0.79. The inactive ingredients are cholesterol, dipalmitoylphosphatidylcholine (DPPC), sodium chloride, sodium hydroxide (for pH adjustment), and water for injection.

ARIKAYCE is administered only using a Lamira Nebulizer System *[see Dosage and Administration (2.1)]*. Like all other nebulized treatments, the amount delivered to the lungs will depend upon patient factors. Under standardized *in vitro* testing per USP<1601> adult breathing pattern (500 mL tidal volume, 15 breaths per minute, and inhalation: exhalation ratio of 1:1), the mean delivered dose from the mouthpiece was approximately 312 mg of amikacin sulfate (53% of label claim). The mass median aerodynamic diameter (MMAD) of the nebulized aerosol droplets is about 4.7 µm (4.1 – 5.3 µm) as determined using the Next Generation Impactor (NGI) method. A percentage of the amikacin in the liposome is released by the nebulization process, thus nebulized ARIKAYCE delivers a combination of free and liposomal amikacin.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

ARIKAYCE is an antibacterial drug *[see Microbiology (12.4)]*.

12.2 Pharmacodynamics

ARIKAYCE exposure-response relationships and the time course of pharmacodynamic response are unknown.

12.3 Pharmacokinetics

Sputum Concentrations

Following once daily inhalation of 590 mg ARIKAYCE in *Mycobacterium avium* complex (MAC) patients, sputum concentrations at 1 to 4 hours post-inhalation were 1720, 884, and 1300 mcg/g at 1, 3, and 6 months, respectively. High variability in amikacin concentrations were observed (CV% >100%). After 48 to 72 hours post-inhalation, amikacin sputum concentrations decreased to approximately 5% of those at 1 to 4 hours post-inhalation.

Serum Concentrations

Following 3 months of once daily inhalation of 590 mg ARIKAYCE in MAC patients, the mean serum $AUC_{0\text{-}24}$ was 23.5 mcg*hr/mL (range: 8.0 to 46.5 mcg*hr/mL; n=12) and the mean serum C_{max} was 2.8 mcg/mL (range: 1.0 to 4.4 µg/mL; n=12). The maximum C_{max} and $AUC_{0\text{-}24}$ were below the mean C_{max} of approximately 76 mcg/mL and $AUC_{0\text{-}24}$ of 154 mcg*hr/mL observed for intravenous administration of amikacin sulfate for injection at the approved dosage of 15 mg/kg once daily in healthy adults.

Absorption

The bioavailability of ARIKAYCE is expected to vary primarily from individual differences in nebulizer efficiency and airway pathology.

Distribution

The protein binding of amikacin in serum is ≤ 10%.

Elimination

Following inhalation of ARIKAYCE in MAC patients, the apparent serum half-life of amikacin ranged from approximately 5.9 to 19.5 hrs.

Metabolism

Amikacin does not undergo appreciable metabolism.

Excretion

Systemically absorbed amikacin following ARIKAYCE administration is eliminated principally via glomerular filtration. On average, 7.42% (ranging from 0.72 to 22.60%; n=14) of the total ARIKAYCE dose was excreted in urine as unchanged drug compared to 94% following intravenous administration of amikacin sulfate for injection. Unabsorbed amikacin, following ARIKAYCE inhalation, is probably eliminated primarily by cellular turnover and expectoration.

Drug Interaction Studies

No clinical drug interaction studies have been conducted with ARIKAYCE *[see Drug Interactions (7)]*.

12.4 Microbiology

Mechanism of Action

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.

Resistance

The mechanism of resistance to amikacin in mycobacteria has been linked to mutations in the rrs gene of the 16S rRNA. In clinical trials, MAC isolates developing an amikacin MIC of > 64 mcg/mL after baseline were observed in a higher proportion of subjects treated with ARIKAYCE *[see Clinical Studies (14)]*.

Interaction with Other Antimicrobials

There has been no *in vitro* signal for antagonism between amikacin and other antimicrobials against MAC based on fractional inhibitory concentration (FIC) and macrophage survival assays. In select instances, some degree of synergy between amikacin and other agents has been observed, as for example, synergy between aminoglycosides, including amikacin, and the beta-lactam class has been documented.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year inhalation carcinogenicity study, rats were exposed to ARIKAYCE for 15-25, 50-70, or 155-170 minutes per day for 96-104 weeks. These provided approximate inhaled doses of 5, 15, and 45 mg/kg/day. Squamous cell carcinoma was observed in the lungs of 2 of 120 rats administered the highest dose tested. Maximum serum AUC levels of amikacin in the rats at steady state were approximately 1.3, 2.8, and 7.6 mcg·hr/mL at the low, mid, and high doses, respectively, compared with 23.5 mcg·hr/mL (8.0 to 46.5 mcg·hr/mL) measured in humans. The squamous cell carcinomas may be the result of a high lung burden of particulates from ARIKAYCE in the rat lung. The relevance of the lung tumor findings with regards to humans receiving ARIKAYCE is unknown.

No evidence of mutagenicity or genotoxicity was observed in a battery of *in vitro* and *in vivo* genotoxicity studies with a liposome-encapsulated amikacin formulation similar to ARIKAYCE (*in vitro* microbial mutagenesis test, *in vitro* mouse lymphoma mutation assay, *in vitro* chromosomal aberration study, and an *in vivo* micronucleus study in rats).

No fertility studies were conducted with ARIKAYCE. Intraperitoneal administration of amikacin to male and female rats at doses up to 200 mg/kg/day prior to mating through Day 7 of gestation were not associated with impairment of fertility or adverse effects on early embryonic development.

13.2 Animal Toxicology and/or Pharmacology

To provide information about chronic dosing of ARIKAYCE to another animal species, a 9-month inhalation toxicology study was conducted in dogs. Foamy alveolar macrophages associated with clearance of the inhaled product were present at dose-related incidence and severity, but they were not associated with inflammation, tissue hyperplasia, or the presence of preneoplastic or neoplastic changes. Dogs were exposed to ARIKAYCE for up to 90 minutes per day, providing inhaled amikacin doses of approximately 5, 10, and 30 mg/kg/day.

14 CLINICAL STUDIES

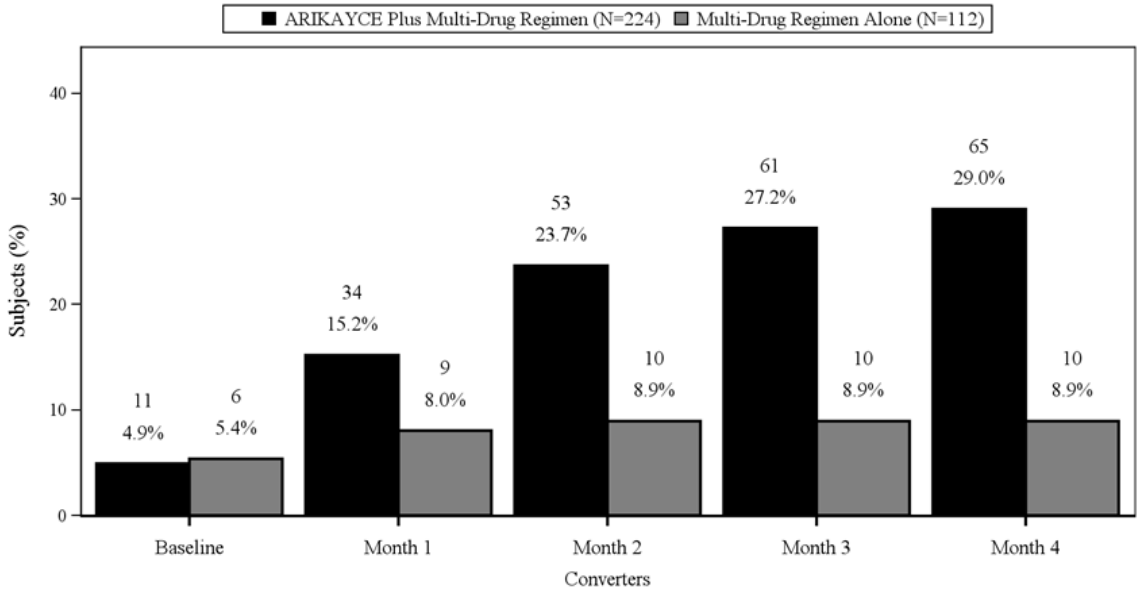
Trial 1 (NCT#02344004) was an open-label, randomized (2:1), multi-center trial in patients with refractory *Mycobacterium avium* complex (MAC) lung disease as confirmed by at least 2 sputum culture results. Patients were considered to have refractory MAC lung disease if they did not achieve negative sputum cultures after a minimum duration of 6 consecutive months of background regimen therapy that was either ongoing or stopped no more than 12 months before the screening visit. Patients were randomized to either ARIKAYCE plus a background regimen or background regimen alone. The surrogate endpoint for assessing efficacy was based on achieving culture conversion (3 consecutive monthly negative sputum cultures) by Month 6. The date of conversion was defined as the date of the first of the 3 negative monthly cultures, which had to be achieved by Month 4 in order to meet the endpoint by Month 6. Patients who achieved culture conversion by Month 6 were continued on study drug (ARIKAYCE plus background regimen or background regimen alone based on their randomization) for a total of 12 months after the first negative sputum culture.

A total of 336 patients were randomized (ARIKAYCE plus background regimen, n=224; background regimen alone, n=112) (ITT population), with a mean age of 64.7 years and there was a higher percentage of females (69.3%) than males (30.7%) in the study. At the time of enrollment, of the 336 subjects in the ITT population, 302 (89.9%) were either on a guideline-based regimen for MAC or off guideline-based therapy for MAC for less than 3 months while 34 (10.1%) were off treatment for 3 to 12 months prior to enrollment. At screening, patients were stratified by smoking status (current smoker or not) and by whether patients were on treatment or off treatment for at least 3 months. Most patients at screening were not current smokers (89.3%) and had underlying bronchiectasis (62.5%). At baseline, 329 patients were on a

multidrug background regimen that included a macrolide (93.3%), a rifamycin (86.3%), or ethambutol (81.4%). Overall, 55.6% of subjects were receiving a triple-drug background regimen consisting of a macrolide, a rifamycin and ethambutol.

The proportion of patients achieving culture conversion (3 consecutive monthly negative sputum cultures) by Month 6 was significantly ($p<0.0001$) greater for ARIKAYCE plus background regimen (65/224, 29.0%) compared to background regimen alone (10/112, 8.9%). Of those receiving ARIKAYCE plus background regimen, 18.3% (41/224) achieved culture conversion by Month 6 and sustained sputum culture conversion (defined as consecutive negative sputum cultures with no positive culture on solid media or no more than 2 consecutive positive cultures on liquid media following culture conversion) for up to 12 months of treatment after the first culture that defined culture conversion, compared to 2.7% (3/112) of patients receiving background regimen alone ($p<0.0001$). At 3 months after the completion of treatment, 16.1% (36/224) of patients who had received ARIKAYCE plus background regimen maintained durable culture conversion, compared to 0% of patients who had received background regimen alone ($p<0.0001$).

Cumulative Proportion of Subjects Achieving Culture Conversion Shown by the First Month of Conversion Intent to Treat (ITT) Population



In Trial 1, 23/224 (10.3%) of patients had MAC isolates that developed MIC of > 64 mcg/mL while receiving treatment with ARIKAYCE. In the background regimen alone arm, 4/112 (3.6%) of patients had MAC isolates that developed amikacin MIC of > 64 mcg/mL.

Additional endpoints to assess the clinical benefit of ARIKAYCE, for example, change from baseline in six-minute walk test distance and the Saint George's Respiratory Questionnaire, did not demonstrate clinical benefit by Month 6.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

ARIKAYCE (amikacin liposome inhalation suspension), 590 mg/8.4 mL, is supplied in a sterile, unit-dose 10-mL glass vial. The product is dispensed as a 28-vial kit.

Each carton contains a 28-day supply of medication (28 vials). In addition to the ARIKAYCE vials in the carton, one Lamira Nebulizer Handset and four Lamira Aerosol Heads are provided.

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The Lamira Nebulizer System contains a controller, a spare Aerosol Head, a spare Handset, Power Cord and accessories.

16.2 Storage and Handling

Store ARIKAYCE vials refrigerated at 2°C to 8°C (36°F to 46°F) until expiration date on vial. *Do not freeze.* Once expired, discard any unused drug.

ARIKAYCE can be stored at room temperature up to 25°C (77°F) for up to 4 weeks. Once at room temperature, any unused drug must be discarded at the end of 4 weeks.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Patient Instructions for Use).

Important Instructions for Administration of ARIKAYCE

Instruct patients to read the *Instructions for Use* before starting ARIKAYCE. Instruct patients to only use the Lamira® Nebulizer System to administer ARIKAYCE. Advise the patient or caregiver not to use the Lamira Nebulizer System with any other medicine.

Hypersensitivity Pneumonitis and Bronchospasm (Difficulty Breathing)

Advise patients to inform their healthcare provider if they experience shortness of breath or wheezing after administration of ARIKAYCE. Advise patients with a history of reactive airway disease, asthma, or bronchospasm, to administer ARIKAYCE after using a short-acting bronchodilator *[see Warnings and Precautions (5.1, 5.3)]*.

Hemoptysis or Cough

Advise patients to inform their healthcare provider if they cough up blood or experience episodic cough either during or after ARIKAYCE administration particularly in the first month after starting ARIKAYCE *[see Warnings and Precautions (5.2) and Adverse Reactions (6.1)]*.

Exacerbations of Underlying Pulmonary Disease

Advise patients to inform their healthcare provider if they experience worsening of their lung disease after starting ARIKAYCE *[see Warnings and Precautions (5.4)]*.

Dysphonia or Difficulty Speaking

Advise patients to inform their healthcare provider if they have difficulty speaking. Difficulty speaking or loss of ability to speak has been reported with ARIKAYCE *[see Adverse Reactions (6.1)]*.

Anaphylaxis and Hypersensitivity Reactions

Advise patients and caregivers that serious and potentially life-threatening hypersensitivity reactions, that require immediate treatment could occur. Advise the patient to discontinue ARIKAYCE and seek immediate medical attention if any signs or symptoms of a hypersensitivity reaction occur [see *Warnings and Precautions (5.5)]*.

Ototoxicity (Ringing in the Ears)

Advise patients to inform their healthcare provider if they experience ringing in the ears, dizziness, or any changes in hearing because ARIKAYCE has been associated with hearing loss *[see Warnings and Precautions (5.6)]*.

Advise the patient not to operate heavy machinery or do dangerous activities while inhaling ARIKAYCE through the Lamira Nebulizer System because ARIKAYCE can cause symptoms such as dizziness or respiratory symptoms.

Nephrotoxicity or Kidney Damage

Advise patients to inform their health care provider if they have kidney problems because kidney damage has been reported with aminoglycosides *[see Warnings and Precautions (5.7)]*.

Neuromuscular Blockade

Advise patients to inform their healthcare provider of known neuromuscular disease (e.g., myasthenia gravis) *[see Warnings and Precautions (5.8)]*.

Embryo-Fetal Toxicity

Advise pregnant women that aminoglycosides, including ARIKAYCE, may cause irreversible congenital deafness when administered during pregnancy *[see Warnings and Precautions (5.9) and Use in Special Populations (8.1)]*.

Manufactured for:

Insmed®, Bridgewater, NJ 08807