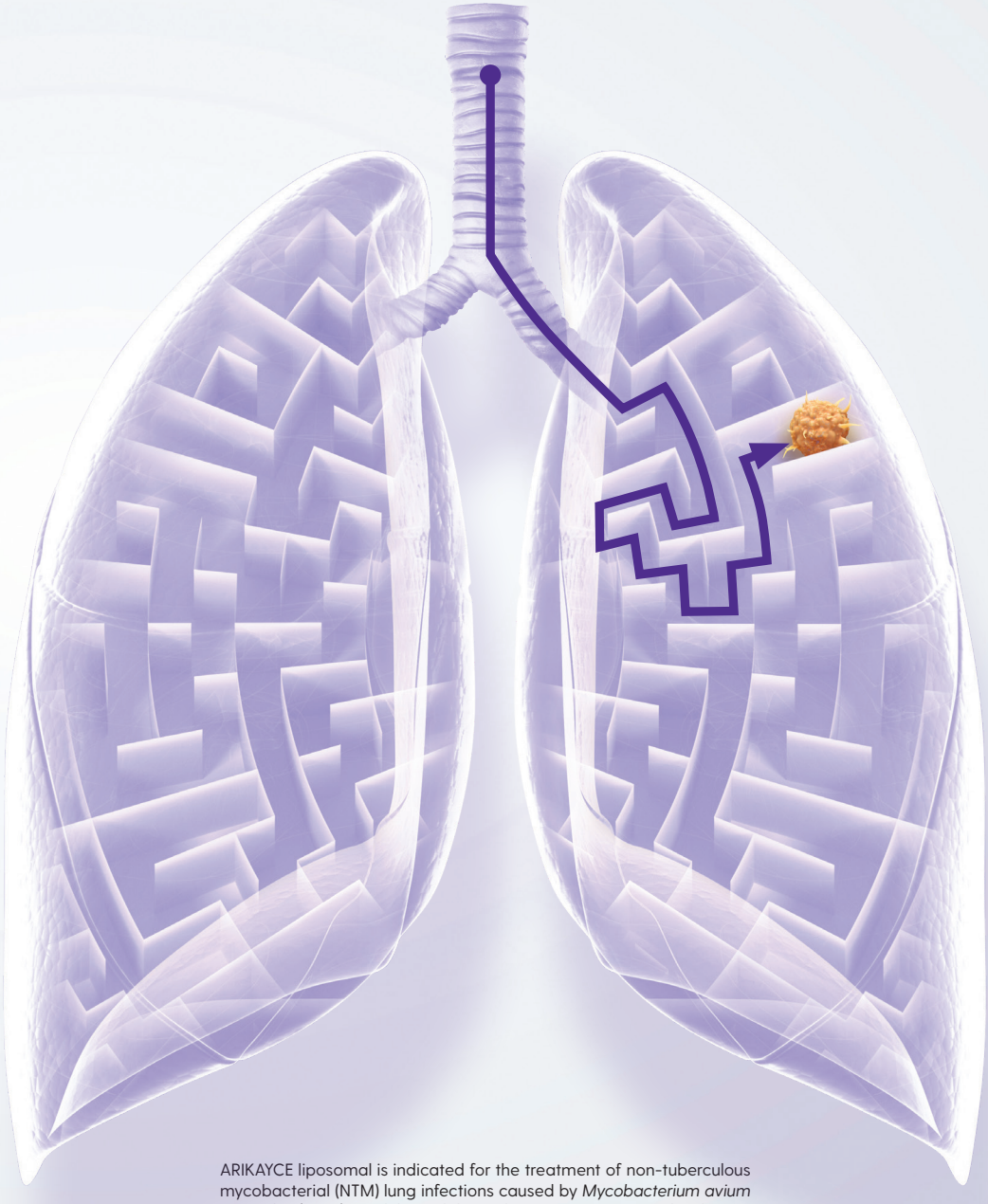
ARIKAYCE® liposomal (amikacin sulphate):

targeting *Mycobacterium avium* complex pulmonary disease (MAC-PD) at the site of infection



ARIKAYCE liposomal is indicated for the treatment of non-tuberculous mycobacterial (NTM) lung infections caused by *Mycobacterium avium* Complex (MAC) in adults with limited treatment options who do not have cystic fibrosis. ARIKAYCE liposomal treatment should be initiated and managed by physicians experienced in the treatment of non-tuberculous lung disease due to *Mycobacterium avium* Complex

Adverse Event reporting information and Prescribing Information can be found at the end of this document

insmed®

ARIKAYCE® LIPOSOMAL amikacin sulphate | 590 mg nebuliser dispersion

Patients, who have failed ≥6 months of oral guideline-based therapy (GBT), need a new treatment approach[1]

International guidelines strongly recommend ARIKAYCE liposomal
in patients in whom oral GBT has failed after ≥6 months[1]

ARIKAYCE liposomal is indicated for the treatment of non-tuberculous mycobacterial (NTM) lung infections caused by *Mycobacterium avium* complex (MAC) in adults with limited treatment options, who do not have cystic fibrosis.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.[2]

ARIKAYCE liposomal should only be initiated and managed by physicians experienced in the treatment of MAC-PD.[2]

Lack of culture conversion after 6 months treatment is a predictor of treatment failure at 12 months.[3]

Despite oral GBT up to 45% of your patients are likely to fail therapy.[4,5]

Patients in whom GBT fails have limited treatment options for their MAC-PD and outcomes are poor.[6]

Active management is key; test on-treatment patients regularly.[7]

Monitor patients every month to be ready to change the treatment strategy if needed

If you have treated your MAC-PD patient with GBT for ≥6 months without success, add ARIKAYCE liposomal[1]

ARIKAYCE liposomal, known as Amikacin Liposomal Inhalation Suspension (ALIS) in clinical trials

ARIKAYCE liposomal is a targeted therapy that has been shown to penetrate macrophages and biofilms where MAC organisms proliferate.[8–10]

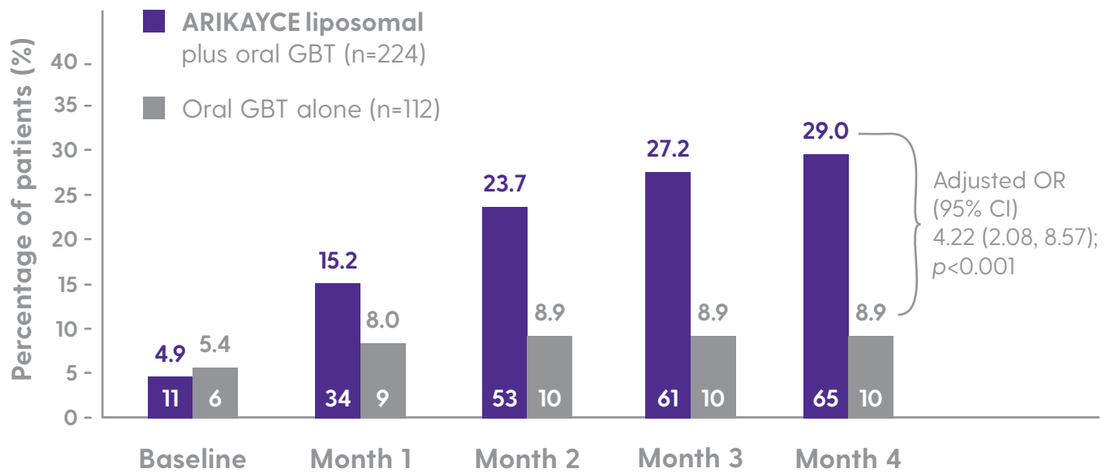
Using unique PULMOVANCE™ liposome technology, ARIKAYCE liposomal is specifically designed for inhalation.[11,2]

In the Phase III CONVERT trial, ARIKAYCE liposomal (known as Amikacin Liposomal Inhalation Suspension [ALIS]) combined with oral GBT, achieved a more **sustained and durable culture conversion** than oral GBT alone.[2,12,13]

Three times more patients treated with ARIKAYCE liposomal plus oral GBT for 6 months achieved culture conversion than those given oral GBT alone (29% vs 9%; $p<0.001$).*[2,12]

Culture conversion rates in the CONVERT study[12]

Secondary endpoint: Cumulative proportion of patients achieving culture conversion



Month 4 was the last month, in which patients could achieve culture conversion and be considered a converter at month 6[12]

Adapted from Griffith et al.[12] Numbers within the bars are numbers of patients in each group.*The study endpoint was culture conversion, defined as three consecutive negative sputum cultures. Month 4 was the last month for which patients could achieve culture conversion and be considered a converter at month 6. CI, confidence interval; GBT, guideline-based therapy; OR, odds ratio

ARIKAYCE liposomal:

strongly recommended by the current guidelines,[1] with clinical efficacy demonstrated in the Phase III CONVERT study[2,12]

ARIKAYCE liposomal must only be administered with **PARI's Lamira® Nebuliser System.**[2]

The Lamira Nebuliser System has been developed to optimise the delivery of ARIKAYCE liposomal deep into the lungs.[14]

ARIKAYCE liposomal is convenient to use: once-daily administration at home or anywhere with a clean, flat surface.[2]

Administration takes about 14 minutes but could take up to 20 minutes.[14]

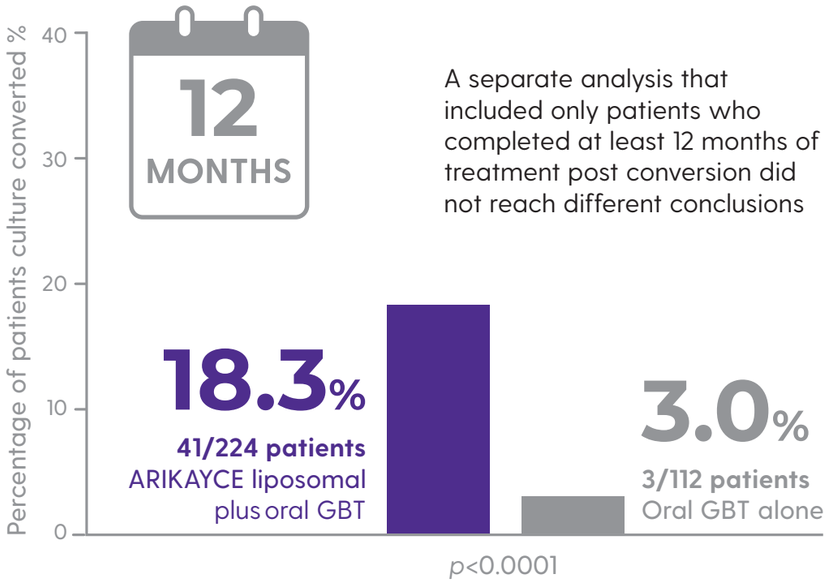
ARIKAYCE liposomal plus oral GBT: numerically more patients had a sustained culture conversion than GBT alone and significantly more experienced a durable conversion when all antibiotic treatments were discontinued.*[2,13]

*In the CONVERT study in patients who failed to convert after >6 months oral GBT, 29.0% (65/224) patients on ARIKAYCE liposomal + oral GBT vs 8.9% (10/112) patients treated with oral GBT alone achieved culture conversion (p<0.0001).[2] Sustained culture conversion for those on ARIKAYCE liposomal + oral GBT was seen 18.3% (41/224) patients vs 2.7% (3/112) on oral GBT alone.[13] Durable conversion when all therapy had been discontinued was observed in 16.1% (36/224) ARIKAYCE liposomal + oral GBT patients vs 0% oral GBT alone after 3 months.[2]

Sustained culture conversion with ARIKAYCE liposomal was defined as maintenance of culture conversion in patients receiving ongoing treatment with ARIKAYCE liposomal.

Durable conversion with ARIKAYCE liposomal was defined as culture conversion maintained when patients were off all antibiotic treatment.

Culture conversion in the CONVERT study after 12 month on treatment (secondary endpoint)[13]

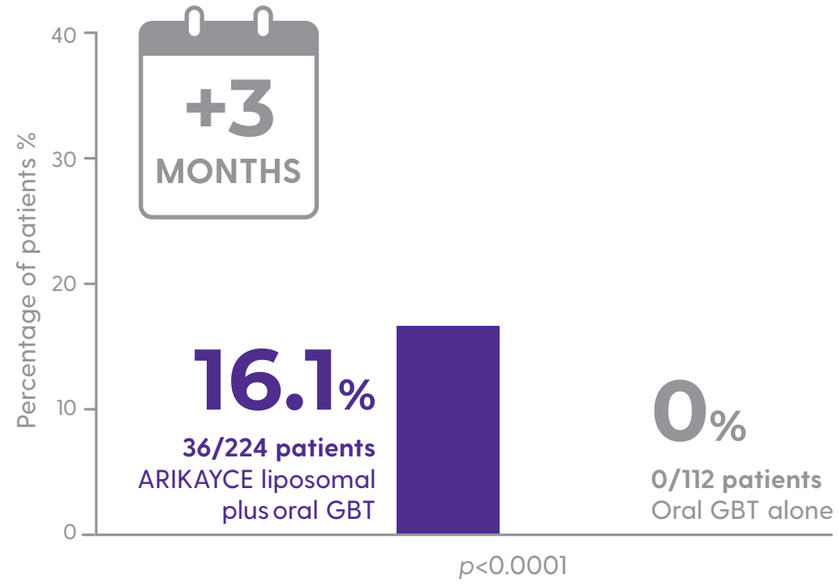


A separate analysis that included only patients who completed at least 12 months of treatment post conversion did not reach different conclusions

Culture conversion was sustained at 12 months in 18.3% (41/224 patients) of those receiving ARIKAYCE liposomal plus oral GBT compared with 2.7% (3/112 patients) of those receiving oral GBT alone ($p<0.0001$).[13]

ARIKAYCE liposomal: durable conversion even when patients are off all treatment for 3 months[2]

Culture conversion in the CONVERT study: maintained at 3 months off treatment (primary endpoint)[2]



At 3 months after stopping antibiotic therapy, significantly more patients given ARIKAYCE liposomal plus oral GBT **maintained their converted status than** those **given oral GBT alone (16.1%** [36/224 patients] vs **0%;** $p<0.0001$).[2]

This equated to 55.4% (36/65 patients) of ARIKAYCE liposomal plus oral GBT treated patients who converted at 6 months and remained converted in the absence of all antibiotic therapy compared with no patients treated with oral GBT alone ($p<0.0017$).[2]

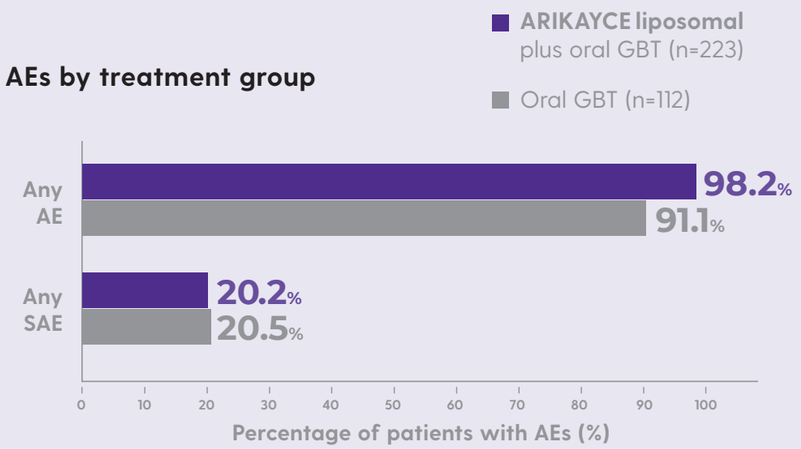
When oral GBT fails add ARIKAYCE liposomal to your oral GBT regimen[1]

Adverse events with ARIKAYCE liposomal plus oral GBT were comparable to oral GBT alone[12]

The safety and tolerability of ARIKAYCE liposomal has been evaluated in more than 800 patients across a series of multiple studies.[16]

In the CONVERT study the rate of adverse events with ARIKAYCE liposomal plus oral GBT was similar to that observed with oral GBT alone, 98.2% vs 91.1%.[12]

Treatment emergent adverse events (TEAEs) in the CONVERT study[12]



Adapted from Griffiths et al. 2018
AE, adverse event; SAE, serious adverse event

The incidence of typical amikacin adverse events of ototoxicity was higher in patients treated with ARIKAYCE liposomal plus oral GBT than those treated with GBT alone. The most common ototoxicity-related adverse event was tinnitus.[12] One half of all reported audiological adverse events resolved by month 6 with continued treatment with ARIKAYCE liposomal plus oral GBT.[12]

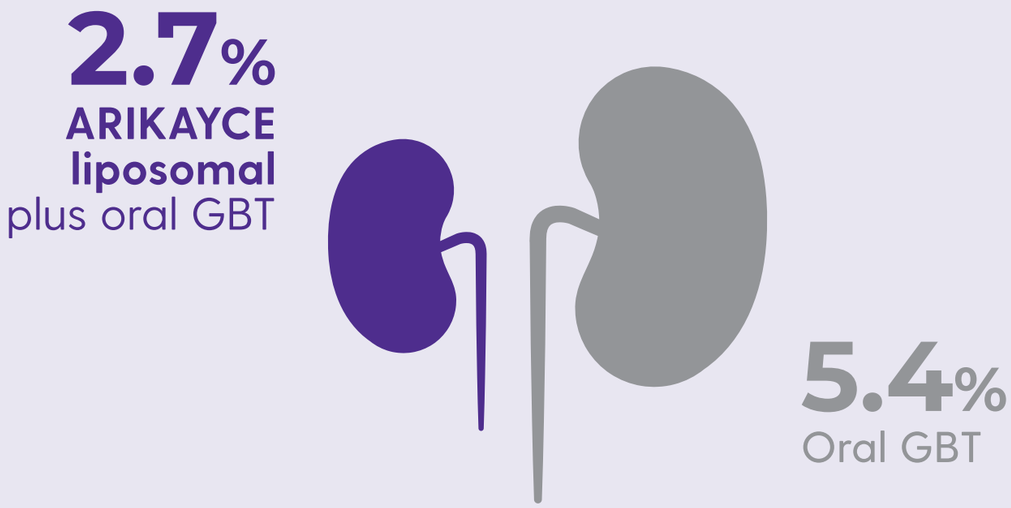
Incidence of adverse events: ototoxicity (safety population)[15]

Adverse event	ARIKAYCE liposomal plus oral GBT (n=223)	Oral GBT alone (n=112)
Tinnitus	17 (7.6)	1 (0.9)
Hearing loss	10 (4.5)	7 (6.3)
Hypoacusis	5 (2.2)	6 (5.4)
Dizziness	14 (6.3)	3 (2.7)
Vertigo	2 (0.9)	0
Presyncope	1 (0.4)	0

Data are n (%) of patients experiencing the adverse event

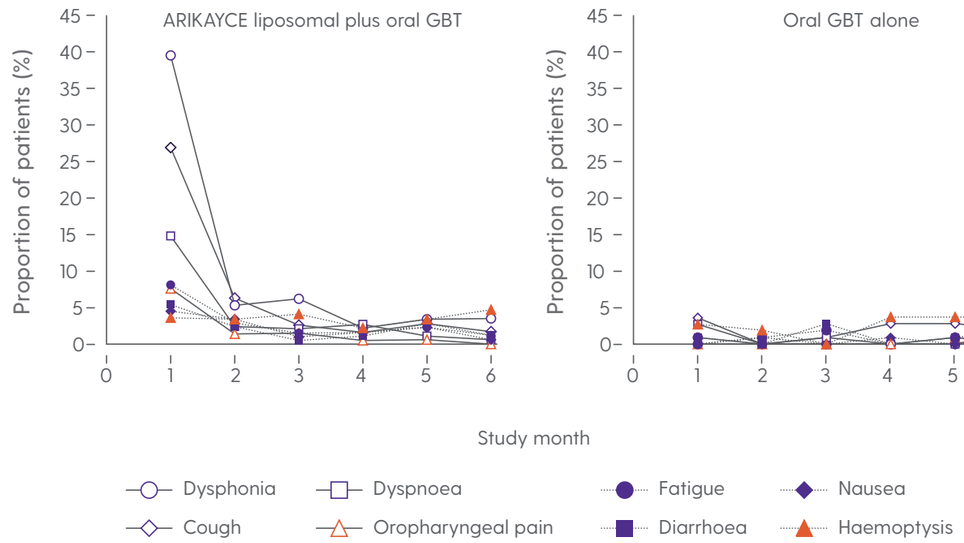
The incidence of nephrotoxicity was comparable in the two treatment arms (ARIKAYCE liposomal plus oral GBT 2.7% vs oral GBT alone 5.4%).[12]

Incidence of nephrotoxicity in the CONVERT study[12]



As expected with an inhaled therapy, most adverse events with ARIKAYCE liposomal were respiratory in nature. The onset of respiratory adverse events typically occurred early in treatment.[12]

Occurrence of adverse events over time[12]



Reproduced with permission from Griffiths et al. 20182
ALIS, Amikacin Liposomal Inhalation Solution; GBT, guideline-based therapy

Most adverse events were respiratory in nature.
Very common adverse events included:[2]

- **Dysphonia**
- **Cough**
- **Dyspnoea**
- **Haemoptysis**

Most common serious adverse events include COPD, haemoptysis and infective exacerbations of bronchiectasis.[2]

Other common adverse events included:[2]

- **Oropharyngeal pain**
- **Bronchospasm**
- **Allergic alveolitis**
- **Wheezing**
- **Increased sputum**
- **Pneumonitis**
- **Vocal cord inflammation**
- **Throat irritation**
- **Headache**
- **Dizziness**
- **Dysguesia**
- **Aphonia**
- **Balance disorder**
- **Diarrhoea**
- **Nausea**
- **Vomiting**
- **Dry mouth**
- **Decreased appetite**
- **Rash**
- **Pruritus**
- **Myalgia**
- **Arthralgia**
- **Renal impairment**
- **Fatigue**
- **Pyrexia**
- **Chest discomfort**
- **Weight decrease**

Anxiety is reported as an uncommon adverse event.[2]

Allergic alveolitis. Allergic alveolitis has been reported with the use of ARIKAYCE liposomal in clinical studies. If allergic alveolitis occurs, treatment with inhaled ARIKAYCE liposomal should be discontinued and the patients treated as medically appropriate.[2]

All patients prescribed ARIKAYCE liposomal will receive a patient alert card for allergic alveolitis with instructions to contact their doctor immediately if they experience fever, cough, worsening breathlessness, weight loss, a worsening in their lung condition affecting their breathing or overall health.

Latest international guidelines for treating MAC-PD support your clinical decision making[1]

ARIKAYCE liposomal is indicated for the treatment of non-tuberculous mycobacterial (NTM) lung infections caused by *Mycobacterium avium* complex (MAC) in adults with limited treatment options, who do not have cystic fibrosis. Consideration should be given to official guidance on the appropriate use of antibacterial agents. It should be initiated and managed by physicians experienced in treating MAC-PD.[2]

1. **Patients diagnosed with MAC-PD should receive triple-therapy** including a macrolide, ethambutol and rifampicin[1]

2. Patients treated for **≥6 months** with oral GBT, who have not achieved culture conversion, **need new treatment options**[1]

3. **2020 international guidelines strongly recommend ARIKAYCE liposomal for patients treated for ≥6 months with oral GBT, who have failed to achieve culture conversion**[1]

4. **Continue treatment for 12 months** after culture conversion (defined as three consecutive negative cultures)[1]

Monitor treatment responses early and regularly[7] after starting oral GBT for MAC-PD

References

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4. Fukushima K et al. J Clin Med 2020;9:1315
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14. Pari Pharma GmbH. Lamira® Nebulizer System, Instructions for Use 2020
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16. Insmed Incorporated, Bridgewater, NJ, USA. Data on file. Development Safety Update Report No:9, July 2020.

ARIKAYCE LIPOSOMAL 590 MG NEBULISER DISPERSION (AMIKACIN SULFATE) - ABBREVIATED PRESCRIBING INFORMATION (API)

Prescribers are recommended to consult the summary of product characteristics before prescribing.

Presentations
Each vial contains amikacin sulfate equivalent to 590 mg amikacin in a liposomal formulation. The mean delivered dose per vial is approximately 312 mg of amikacin.

Indication
Arikayce is indicated for the treatment of non-tuberculous mycobacterial (NTM) lung infections caused by Mycobacterium avium Complex (MAC) in adults with limited treatment options who do not have cystic fibrosis.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Posology and method of administration
ARIKAYCE liposomal treatment should be initiated and managed by physicians experienced in the treatment of non-tuberculous lung disease due to Mycobacterium avium Complex. ARIKAYCE liposomal should be used in conjunction with other antibacterial agents active against Mycobacterium avium Complex lung infections.

Arikayce recommended dosage: one vial (590 mg) administered once daily, by oral inhalation.

Duration of treatment: Treatment with Arikayce, as part of a combination antibacterial regimen, should be continued for 12 months after sputum culture conversion. Treatment should not continue beyond a maximum of 6 months if sputum culture conversion (SCC) has not been confirmed by then. The maximum duration of treatment should not exceed 18 months.

Hepatic/renal impairment: Arikayce has not been studied in patients with hepatic or renal impairment. No dose adjustments based on hepatic impairment are required since amikacin is not hepatically metabolised. Use is contraindicated in severe renal impairment.

Paediatrics: The safety and efficacy of Arikayce in paediatric patients below 18 years of age have not been established. No data are available.

Missed doses: If a daily dose of Arikayce is missed, the next dose should be administered the next day. A double dose should not be given to make up for the missed dose.

Method of administration: Arikayce is for inhalation use only. Arikayce must only be used with the Lamira Nebuliser System (nebuliser handset, aerosol head and controller). It must not be administered by any other route or using any other type of inhalation delivery system.

Refer to full SmPC for full information on posology and administration.

Contraindications
- Hypersensitivity to active substance, to any aminoglycoside antibacterial agent, or any excipient.
- Hypersensitivity to soya.
- Co-administration with any aminoglycoside administered via any route of administration.
- Severe renal impairment.

Special warnings and precautions for use
Anaphylaxis and hypersensitivity reactions: Serious and potentially life-threatening hypersensitivity reactions, including anaphylaxis, have been reported in patients taking inhaled liposomal amikacin.

Allergic alveolitis: Allergic alveolitis and pneumonitis have been reported with the use of inhaled liposomal amikacin.

Bronchospasm: Bronchospasm has been reported with the use of inhaled liposomal amikacin.

Exacerbation of underlying pulmonary disease: In clinical trials, exacerbation of underlying pulmonary disease (chronic obstructive pulmonary disease, infective exacerbation of chronic obstructive pulmonary disease, infective exacerbation of bronchiectasis) was reported with a higher frequency in patients treated with inhaled liposomal amikacin.

Ototoxicity: In clinical trials, ototoxicity, (including deafness, dizziness, presyncope, tinnitus, and vertigo) was reported with a higher frequency in patients treated with inhaled liposomal amikacin.

Nephrotoxicity: Nephrotoxicity was reported in clinical trials in patients treated with inhaled liposomal amikacin. Renal function should be monitored periodically during treatment in all patients and frequent monitoring is advised in patients with pre-existing renal dysfunction.

Neuromuscular blockade: In clinical trials, neuromuscular disorders (reported as muscle weakness, neuropathy peripheral and balance disorder) have been reported with inhaled liposomal amikacin. Use of inhaled liposomal amikacin in patients with myasthenia gravis is not recommended.

Refer to full SmPC for further information on warnings and precautions.

Interaction with other medicinal products and other forms of interaction
No clinical drug interaction studies have been conducted with inhaled liposomal amikacin.

Co-administration of inhaled liposomal amikacin with any aminoglycoside administered by any route is contraindicated.

Co-administration with any other medicinal product affecting auditory function, vestibular function or renal function (including diuretics) is not recommended.

Concurrent and/or sequential use of inhaled liposomal amikacin is not recommended with other medicinal products with neurotoxic, nephrotoxic or ototoxic potential that can enhance aminoglycoside toxicity (e.g. diuretic compounds such as ethacrynic acid, furosemide or intravenous mannitol).

Refer to full SmPC for further information on interactions.

Fertility, pregnancy and lactation
Human data on use during pregnancy or lactation are not available. No fertility studies were conducted with inhaled liposomal amikacin.

Effects on ability to drive and use machines
Amikacin has minor influence on the ability to drive and use machines. The administration of inhaled liposomal amikacin can cause dizziness and other vestibular disturbances.

Undesirable effects
The most commonly reported respiratory adverse reactions were dysphonia, cough, dyspnoea, haemoptysis, oropharyngeal pain, and bronchospasm.

Other commonly reported non-respiratory adverse reactions included fatigue, diarrhoea, infective exacerbation of bronchiectasis, and nausea.

Most common serious adverse reactions included Chronic Obstructive Pulmonary Disease (COPD), haemoptysis, and infective exacerbation of bronchiectasis.

Refer to full SmPC for further information on undesirable effects.

Overdose
Adverse reactions specifically associated with overdose of inhaled liposomal amikacin have not been identified in clinical trials. Overdose in subjects with pre-existing impaired renal function, deafness or vestibular disturbance, or impaired neuromuscular transmission may develop worsening of the pre-existing disorder.

Refer to full SmPC for further information on overdose.

Legal Category
Prescription only medicine.

Pack quantities and costs
Pack-size of 28 vials. The carton also contains the Lamira Nebuliser Handset and 4 aerosol heads... £9,513 / €10,570 per pack

Marketing Authorisation Holder
Insmed Netherlands B.V., Stadsplateau 7, 3521 AZ Utrecht, Netherlands

Marketing Authorisation Number
EU/1/20/1469/001

Ireland: Adverse events should be reported. Healthcare professionals are asked to report any adverse events involving ARIKAYCE LIPOSOMAL 590 MG via HPRA Pharmacovigilance, website: www.hpra.ie. Adverse events should also be reported via safety@insmed.com

Unted Kingdom: Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in Google play or Apple App store. Adverse events should also be reported via safety@insmed.com

Date of last revision of the API text
May 2021 REF-4139

For more information please contact medicalinformation@insmed.com
Telephone: 0800 031 8440 and ask to contact your local Insmed medical science liaison.

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PP-ARIK-UK-00021