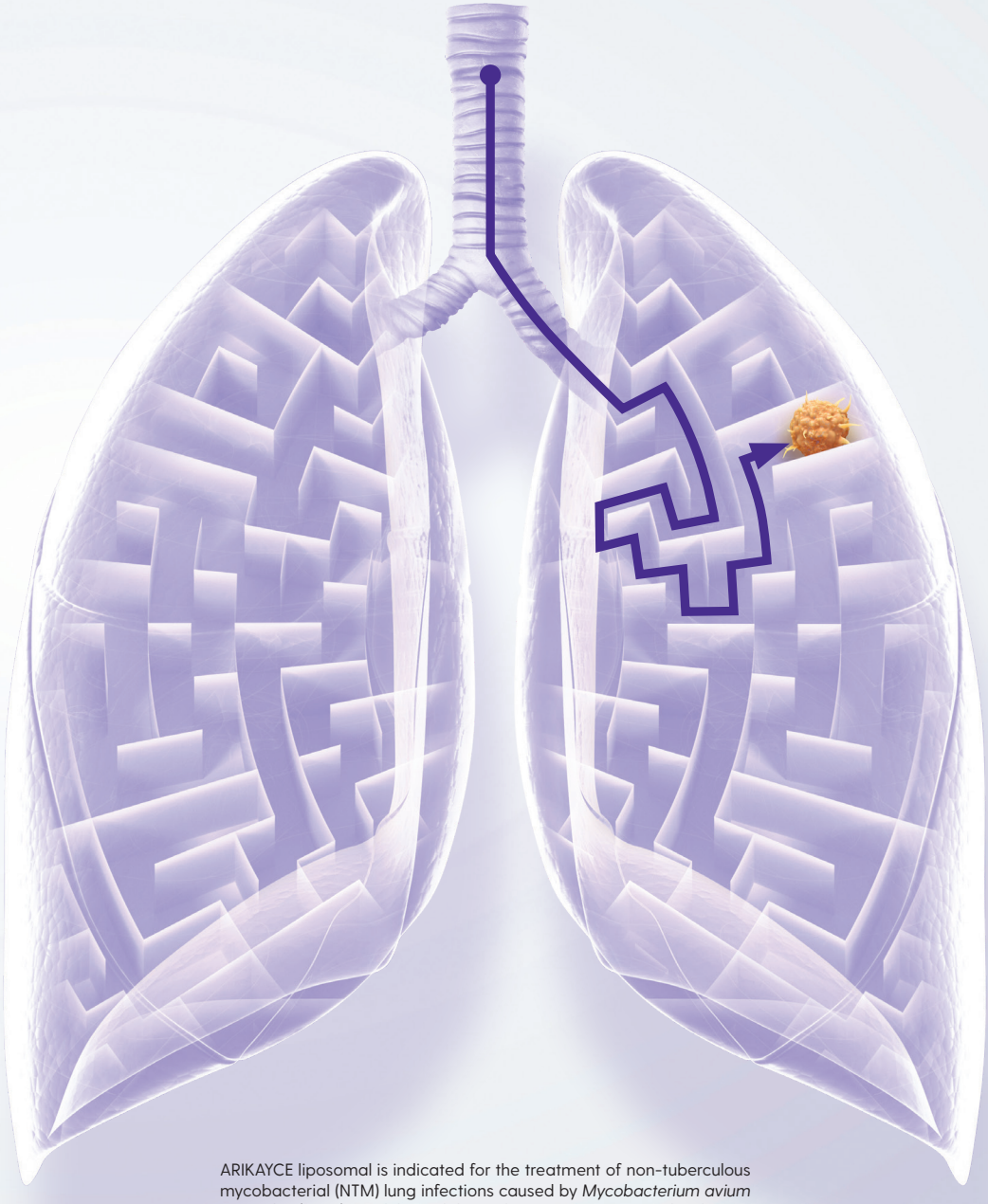
Your patient with *Mycobacterium avium* complex pulmonary disease (MAC-PD):

identification and management



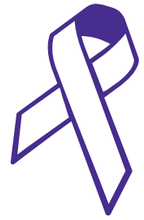
ARIKAYCE liposomal is indicated for the treatment of non-tuberculous mycobacterial (NTM) lung infections caused by *Mycobacterium avium* Complex (MAC) in adults with limited treatment options who do not have cystic fibrosis. ARIKAYCE liposomal treatment should be initiated and managed by physicians experienced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

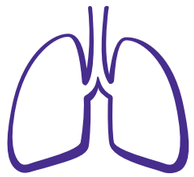
Insmed®

ARIKAYCE® LIPOSOMAL
amikacin sulphate
590 mg nebuliser dispersion

Non-tuberculous mycobacteria pulmonary disease (NTM-PD) is a chronic and potentially debilitating disease[3–5]



Mycobacterium avium complex (MAC) is the most common disease-causing species of non-tuberculous mycobacteria (NTM).[1] A systematic review of 17 studies indicated that MAC-PD has an overall estimated **5-year all-cause mortality of 27%.**[2]



MAC-PD is associated with to **reduced lung function, increased mortality and morbidity** and **reduced health-related quality of life.**[3–10]

A study has shown that, when untreated, nodular bronchiectatic NTM-PD may show radiological progression over 6 years in 97.5% of patients.[11*]

MAC-PD is associated with morbidity

+ **Exacerbations**[7]
+ Risk of **lung cancer**[12,13]
+ Risk of other **lung infections**[9]
+ Risk of **atrial fibrillation**[14]

*Single centre study of 40 patients with nodular bronchiectatic MAC-PD

Which patients are at risk of NTM-PD/MAC-PD?

Factors increasing susceptibility to NTM-PD/MAC-PD	Risk*
Bronchiectasis[15, 16]	**44.0–187.5**
Low BMI[15]	9.1
Cystic fibrosis[17, 18]	6.6–13.0
COPD[15]	2.0–10.0
Thoracic skeletal abnormalities[15]	5.4
Asthma[19]	2.0
Steroid use[15]	1.6–8.0
GORD[15]	1.5–5.3
Immunomodulatory/ immunosuppressant therapies[15]	1.3–2.2

*Relative risk, odds ratio or relative prevalence
BMI, body mass index; COPD, chronic obstructive pulmonary disease; GORD, gastroesophageal reflux disease; MAC-PD, Mycobacterium avium complex pulmonary disease; NTM-PD, non-tuberculous mycobacteria pulmonary disease

Patients with bronchiectasis are at greatest risk[15]. Elderly women with a low body mass index (BMI) who may be taller than average should also be considered at risk of NTM infection.[20]

Patients with bronchiectasis or underlying lung disease are at high risk of developing NTM-PD/MAC-PD.[15,16]

For many at-risk patients, NTM-PD symptoms are similar to those of coexisting lung disease[21]

When do I rule out NTM?

In patients with underlying structural lung disease who:

+ **Present with worsening symptoms** despite treatment optimisation[21]
+ **Present with new pulmonary and non-specific systemic symptoms** (e.g. chronic cough, fatigue, fever or dyspnoea)[23]

When you consider management strategies for exacerbations in patients with underlying structural lung disease, rule out NTM in patients who:

+ **Are being considered for long-term macrolide therapy** to reduce exacerbations[22]
+ **Are already receiving long-term macrolide therapy[22]**

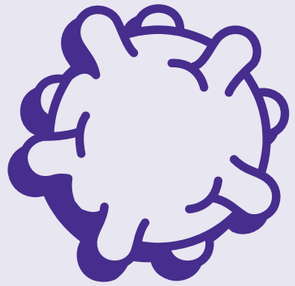
Test at-risk patients with worsening pulmonary symptoms to rule out NTM infection.

International bronchiectasis guidelines recommend that you rule out NTM in patients with bronchiectasis before initiating macrolide therapy.[22]

Think NTM! Test NTM!

Correct early diagnosis and treatment are paramount to prevent disease progression.[24,25]

MAC-PD: the challenge of treatment



MAC organisms evade host defences; MAC accumulation in biofilms and uptake in macrophages gives it a place to hide.[26–28]

Once inside macrophages, MAC limits normal macrophage function and reproduces unhindered, ready to trigger macrophage destruction so MAC can be released to infect the lungs and other new macrophages.[29–31]

Many antibiotics can only **poorly penetrate macrophages** and **biofilms.**[26,32,33]

Diagnosing MAC-PD: focus on symptoms, radiology and microbiology

Clinical symptoms[21]

- Fever
- Malaise
- Dyspnoea
- Haemoptysis
- Weight loss
- Rhonchi, crackles, wheeze

Imagery[34]

- Chest X-ray
- High resolution CT scan

Microbiology[34]

- Two or more consecutive sputum samples

The 2020 international guidelines recommend that **MAC-PD is diagnosed with X-ray or computed tomography scan** and the presence of **MAC-positive sputum** on multiple occasions.[34]

When you find MAC-PD[34]**:**

Follow current guidelines

Speak to an expert colleague

Refer the patient to an expert centre

or initiate treatment – don't wait

When you find MAC-PD, initiate treatment in line with the current international guidelines.[34]

Which patients must be treated?

Patients with specific characteristics are likely to have potentially progressive MAC-PD **– don't wait to treat patients with risk factors.**

Characteristics that put patients diagnosed with NTM-PD at high risk of disease progression are shown below.[8,34,35]

Infecting organism
Virulence among NTM species differs,[34,36] so treat those of high clinical relevance (e.g. MAC species: *M. avium, M. intracellulare*)[8,35]

Acid-fast bacilli test
Positive[34]

Radiological features
Presence of lung cavities[34]

Rationale for treating MAC-PD

The decision to treat MAC-PD is influenced by the:[21]

- Severity of MAC-PD
- Risk of disease progression
- Presence of comorbidity
- Goals of treatment

The primary goals of therapy for MAC-PD are:[21]

- Sustained culture conversion of sputum on treatment
- Improved symptoms
- Potential radiological improvements

Before treating MAC-PD, establish the goals of therapy for your patient

When you and your patient decide to proceed with MAC-PD treatment, follow the new joint international guidelines from the American Thoracic Society/European Respiratory Society/European Society of Clinical Microbiology and Infectious Diseases/Infectious Diseases Society of America.[34]

Guideline-led management of MAC-PD

Once the decision to treat MAC-PD has been made, the next step is to establish the susceptibility of MAC to antibiotics.[34]

For MAC, test for antimicrobial susceptibility to:
+ macrolides
+ amikacin

Susceptibility-based treatment with macrolides and amikacin is preferred over empirical therapy.[34]

When susceptibility has been established, guidelines recommend the use of at least three oral antibiotics to treat MAC-PD.[34]

Macrolide sensitive	Macrolide insensitive or advanced bronchiectatic/cavitary disease
Oral ethambutol	Oral ethambutol
Oral azithromycin (or clarithromycin) (strong recommendation)	Oral azithromycin (or clarithromycin)
Oral rifampicin	Oral rifampicin
	Parenteral amikacin or streptomycin (conditional recommendation)

Don't wait to treat patients with risk factors!

Once treatment is started, monitoring is key

For successful MAC-PD treatment the following are required:[21]

- frequent sputum cultures
- clinical improvement within 3–6 months
- culture conversion within 12 months of appropriate antibiotic therapy
- sustained culture conversion from positive to negative

Active management is key:
test on-treatment patients regularly so you know if, and when, sputum conversion occurs[37]

Monitor sputum every month
If culture conversion occurs, treat with oral guideline-based therapy (GBT) for a further 12 months beyond the point of culture conversion[34]

Treating MAC-PD: key points

- Implement **combination therapy** of three antibiotics[34]
- Include a **macrolide** in your treatment regimen[34]
- **Azithromycin** is preferred over clarithromycin[34]
- In patients with **severe disease** or macrolide resistance, **add in parenteral amikacin or streptomycin** for 2–3 months[32]
- Adjust treatment frequency by severity of disease – for **severe disease treat daily**[34]
- **Monitor** for treatment response[34,37]

Data indicate that oral guideline-based therapy (GBT) fails in up to 45% of patients with MAC-PD[38,39]

New treatment options are required for patients in whom GBT has failed at 6 months.

Treatment options for patients in whom oral GBT fails

For patients in whom oral GBT has failed after ≥6 months, the 2020 guidelines strongly recommend adding ARIKAYCE® liposomal[34]

ARIKAYCE liposomal is:

inhaled – delivered with the optimised Lamira® Nebuliser System it reaches infection deep in the lungs[40]

innovative – using PULMOVANCE® technology amikacin is encapsulated in liposomes to reach infection where it resides in the lungs, the macrophages and the biofilms[4]

ARIKACYE liposomal can only be administered with PARI's Lamira Nebuliser System[42]

ARIKAYCE liposomal clinical evidence:
more effective in achieving culture conversion than oral GBT alone

- By month 6, **three times as many** patients treated with **ARIKAYCE liposomal** and oral GBT achieved **culture conversion than with oral GBT alone** (29% vs 9%; *p*<0.0001).[42,43]
- Primary endpoint data: Culture conversion was durable when all antibiotics were stopped; at 3 months of no antibiotics 16.1% [36/224 patients] treated with ARIKAYCE liposomal plus oral GBTremained converted compared with no patients on oral GBT alone.[42]
- **Culture conversion was sustained for 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).[44]
- Durable conversion was maintained even at 12 months of no antibiotics: post hoc analysis; (13.4% [30/224 patients] for ARIKAYCE liposomal plus oral GBT vs 0% [0/112 patients] for oral GBT alone) remained converted (*p*<0.0001).[45]

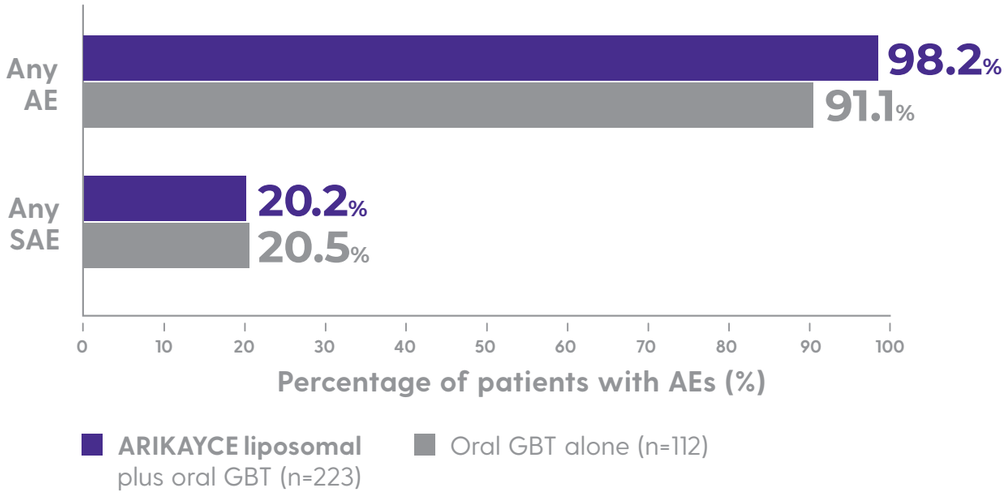
	ARIKAYCE liposomal plus oral GBT, % (n/N)	Oral GBT alone, % (n/N)	*P* value (n/N)
Culture conversion at 6 months	29.0 (65/224)	8.9 (10/112)	<0.0001
Sustained culture conversion at 12 months on treatment	18.3 (41/224)	2.7 (3/112)	<0.0001
Durable conversion off treatment at 3 months	16.1 (36/224)	0 (0/112)	<0.0001
Durable conversion off treatment at 12 months	13.4 (30/224)	0 (0/112)	<0.0001

Intention-to-treat population
ARIKAYCE liposomal: Amikacin Liposomal Inhalation Suspension (ALIS) in clinical studies
GBT, guideline-based therapy

ARIKAYCE liposomal: rate of adverse events comparable to that of oral GBT alone[43]

The safety and tolerability of ARIKAYCE liposomal has been evaluated in more than 800 patients across multiple studies.[45]

In the CONVERT study, the rate of adverse events was similar for ARIKAYCE liposomal plus oral GBT to that seen with oral GBT alone.[43]



Adapted with permission from Griffiths et al. 2018

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.[43] One half of all reported audiological adverse events resolved by month 6 with continued treatment with ARIKAYCE liposomal plus oral GBT.[43]

Incidence of adverse events: ototoxicity (safety population)[46]

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 both treatment arms (ARIKAYCE liposomal plus oral GBT 2.7% vs oral GBT alone 5.4%).[43]

When oral GBT has failed after ≥ 6 months, the new international guidelines strongly recommend adding ARIKAYCE liposomal to the treatment regimen.[34]

MAC-PD and your patients

Your patients with underlying conditions,
including **bronchiectasis** and COPD, are at risk of developing NTM-PD/MAC-PD.[15,16]

You may be considering macrolide monotherapy for these patients for exacerbations, or they may already be receiving macrolides.[22]

Treating macrolide resistant MAC-PD is hard and patient mortality risk is increased.[47]

In patients at risk of MAC-PD, who may be being considered for macrolide treatment, **think NTM and test for NTM!**[22]

Many of your patients may already have a high treatment burden and you may be reluctant to start therapy for MAC-PD. However, if you do not treat, your patient has a high risk of disease progression.

New guidelines recommend early treatment of MAC-PD as the benefits outweigh the risks.[34]

A study has shown that, **without diagnosis and treatment, nodular bronchiectatic MAC-PD may show radiological progression in 97.5% of patients,**[11] with the potential of increased mortality,[2] increased morbidity[3,8] and of reduced health-related quality of life.[10]

Think NTM! Test NTM!

and when NTM-PD or MAC-PD is identified Treat!

Or refer your patients to expert colleagues or expert centres.

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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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