ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ARIKAYCE liposomal 590 mg nebuliser dispersion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Nebuliser dispersion

White, milky, aqueous, nebuliser dispersion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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 (see sections 4.2, 4.4 and 5.1).

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

ARIKAYCE liposomal should be used in conjunction with other antibacterial agents active against *Mycobacterium avium* Complex lung infections.

4.2 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.

Posology

The recommended dose is one vial (590 mg) administered once daily, by oral inhalation.

Duration of treatment
Treatment with inhaled liposomal amikacin, as part of a combination antibacterial regimen, should be continued for 12 months after sputum culture conversion.

Treatment with inhaled liposomal amikacin 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 with inhaled liposomal amikacin should not exceed 18 months.

Missed doses
If a daily dose of amikacin 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.

Elderly
No dose adjustment is required.

Hepatic impairment
Inhaled liposomal amikacin has not been studied in patients with hepatic impairment. No dose adjustments based on hepatic impairment are required since amikacin is not hepatically metabolised.

Renal impairment
Inhaled liposomal amikacin has not been studied in patients with renal impairment. Use is contraindicated in severe renal impairment (see sections 4.3 and 4.4).

Paediatric population
The safety and efficacy of inhaled liposomal amikacin in paediatric patients below 18 years of age have not been established. No data are available.

Method of administration

Inhalation use

Inhaled liposomal amikacin must only be used with the Lamira Nebuliser System (nebuliser handset, aerosol head and controller). For instructions for use, see section 6.6. It must not be administered by any other route or using any other type of inhalation delivery system.

The amount delivered to the lungs will depend upon patient factors. Under recommended *in vitro* testing with the adult breathing pattern (500 mL tidal volume, 15 breaths per minute, and inhalation: exhalation ration of 1:1), the mean delivered dose from the mouthpiece was approximately 312 mg of amikacin (approximately 53% of label claim) with an average drug delivery rate of 22.3 mg/min assuming the nebulisation time of 14 minutes. The average mass median aerodynamic diameter (MMAD) of the nebulised aerosol droplets is about 4.7 µm with D_{10} of 2.4 µm and D_{90} of 9.0 µm as determined using the next generation impactor method.

4.3 Contraindications

Hypersensitivity to the active substance, to any aminoglycoside antibacterial agent, or to any of the excipients listed in section 6.1.

Hypersensitivity to soya.

Co-administration with any aminoglycoside administered via any route of administration.

Severe renal impairment.

4.4 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.

Before therapy with inhaled liposomal amikacin is instituted, an evaluation for previous hypersensitivity reactions to aminoglycosides should take place. If anaphylaxis or a hypersensitivity reaction occurs, inhaled liposomal amikacin should be discontinued and appropriate supportive measures should be instituted.

Allergic alveolitis

Allergic alveolitis and pneumonitis have been reported with the use of inhaled liposomal amikacin in clinical studies (see section 4.8).

If allergic alveolitis occurs, treatment with inhaled liposomal amikacin should be discontinued and patients should be treated as medically appropriate.

Bronchospasm

Bronchospasm has been reported with the use of inhaled liposomal amikacin in clinical studies. In patients with a history of reactive airway disease, asthma or bronchospasm, inhaled liposomal amikacin should be administered after using a short-acting bronchodilator. If there is evidence of bronchospasm due to inhaled liposomal amikacin inhalation, the patient may be pre-treated with bronchodilators (see section 4.8).

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 compared with patients not receiving inhaled liposomal amikacin. Caution should be exercised when initiating inhaled liposomal amikacin in patients presenting with these underlying conditions. Discontinuation of treatment with inhaled liposomal amikacin should be considered if signs of exacerbation are observed.

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 compared with patients not receiving inhaled liposomal amikacin. Tinnitus was the most commonly reported ototoxicity related adverse reaction.

Auditory and vestibular function should be monitored periodically in all patients and frequent monitoring is advised in patients with known or suspected auditory or vestibular dysfunction.

If ototoxicity occurs during treatment, consideration should be given to discontinuing inhaled liposomal amikacin.

There is an increased risk of ototoxicity in patients with mitochondrial DNA mutations (particularly the nucleotide 1555 A to G substitution in the 12S rRNA gene), even if aminoglycoside serum levels are within the recommended range during treatment. Alternative treatment options should be considered in such patients.

In patients with a maternal history of relevant mutations or aminoglycoside induced deafness, alternative treatments or genetic testing prior to administration should be considered.

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.
Consideration should be given to stopping inhaled liposomal amikacin in patients who develop evidence of nephrotoxicity on treatment.

Use in patients with severe renal impairment is contraindicated (see section 4.3).

Neuromuscular blockade

In clinical trials, neuromuscular disorders (reported as muscle weakness, neuropathy peripheral and balance disorder) have been reported with inhaled liposomal amikacin. Aminoglycosides may

aggravate muscle weakness because of a curare-like effect at the neuromuscular junction. Use of inhaled liposomal amikacin in patients with *myasthenia gravis* is not recommended. Patients with any known or suspected neuromuscular disorders should be closely monitored.

Co-administration with other medicinal products

Co-administration of inhaled liposomal amikacin with other aminoglycosides is contraindicated (see section 4.3).

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

4.5 Interaction with other medicinal products and other forms of interaction

No clinical drug interaction studies have been conducted with inhaled liposomal amikacin.

Pharmacodynamic interactions

Use of inhaled liposomal amikacin with any aminoglycoside administered by any route is contraindicated (see section 4.3).

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) (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of inhaled liposomal amikacin in pregnant women. Systemic exposure to amikacin following inhalation of inhaled liposomal amikacin is expected to be low compared to parenteral administration of amikacin.

There are limited data from the use of aminoglycosides in pregnant women. Aminoglycosides can cause foetal harm. Aminoglycosides cross the placenta, and there have been reports of total, irreversible, bilateral congenital deafness in children, whose mothers received streptomycin during pregnancy. Although adverse reactions on the foetus or newborns have not been reported in pregnant women treated with other aminoglycosides, the potential for harm exists. Animal reproductive toxicity studies have not been conducted with inhaled amikacin. In reproductive toxicity studies in mice, rats and rabbits with amikacin administered parenterally, no foetal malformations were reported.

As a precautionary measure, it is preferable to avoid the use of inhaled liposomal amikacin during pregnancy.

Breast-feeding

There is no information regarding the presence of amikacin in human milk. However, systemic exposure to inhaled liposomal amikacin following inhalation is expected to be low compared to parenteral administration of amikacin.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from inhaled liposomal amikacin therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

No fertility studies were conducted with inhaled liposomal amikacin.

4.7 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 (see section 4.8). Patients should be advised not to drive or operate machinery while using inhaled liposomal amikacin.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported respiratory adverse reactions were dysphonia (42.6%), cough (30.9%), dyspnoea (14.4%), haemoptysis (10.9%), oropharyngeal pain (9.2%), and bronchospasm (2.2%). Other commonly reported non-respiratory adverse reactions included fatigue (7.2%), diarrhoea (6.4%), infective exacerbation of bronchiectasis (6.2%), and nausea (5.9%).

Most common serious adverse reactions included Chronic Obstructive Pulmonary Disease (COPD) (1.5%), haemoptysis (1.2%), and infective exacerbation of bronchiectasis (1.0%).

Tabulated list of adverse reactions

Adverse drug reactions in Table 1 are listed according to system organ classes in MedDRA based on clinical trials and post marketing data. Within each system organ class, the following definitions apply to the frequency terminology used hereafter: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known: (cannot be estimated from the available data).

Table 1 – Summary of adverse reactions

System Organ Class	Adverse reactions	Frequency category
Infections and infestations	Infective exacerbation of bronchiectasis	Common
	Laryngitis	Common
	Oral candidiasis	Common
Immune system disorders	Anaphylactic reactions	Not known
	Hypersensitivity reactions	Not known
Psychiatric disorders	Anxiety	Uncommon
Nervous system disorders	Headache	Common
	Dizziness	Common
	Dysgeusia	Common
	Aphonia	Common
	Balance disorder	Common
Ear and labyrinth disorders	Tinnitus	Common
	Deafness	Common
Respiratory, thoracic and mediastinal disorders	Dysphonia	Very common
	Dyspnoea	Very common
	Cough	Very common
	Haemoptysis	Very common

System Organ Class	Adverse reactions	Frequency category
	Oropharyngeal pain	Common
	Allergic alveolitis	Common
	Chronic Obstructive Pulmonary Disease	Common
	Wheezing	Common
	Productive cough	Common
	Sputum increased	Common
	Bronchospasm	Common
	Pneumonitis	Common
	Vocal cord inflammation	Common
	Throat irritation	Common
	Pharyngeal swelling	Not known
	Nasal dryness	Not known
	Epistaxis	Not known
	Rhinorrhoea	Not known
	Sneezing	Not known
	Nasal Congestion	Not known
Gastrointestinal disorders	Diarrhoea	Common
	Nausea	Common
	Vomiting	Common
	Dry mouth	Common
	Decrease of appetite	Common
	Dysphagia	Not known
	Glossitis	Not known
	Glossodynia	Not known
	Salivary hypersecretion	Not known
	Stomatitis	Not known
	Abdominal pain	Not known
	Abdominal pain upper	Not known
	Abdominal discomfort	Not known
	Abdominal distension	Not known
Skin and subcutaneous tissue disorders	Rash	Common
	Pruritus	Common
Musculoskeletal and connective tissue disorders	Myalgia	Common
	Arthralgia	Common
Renal and urinary disorders	Renal impairment	Common
General disorders and administration site conditions	Fatigue	Common
	Pyrexia	Common
	Chest discomfort	Common
Investigations	Weight decreased	Common

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 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.

In the event of an overdose inhaled liposomal amikacin should be stopped immediately. Where rapid removal of amikacin is indicated to prevent target organ damage, for example in subjects with renal impairment, peritoneal dialysis or haemodialysis will accelerate the extraction of amikacin from blood.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, other aminoglycosides. ATC code: J01GB06

Mechanism of action

Amikacin binds to a specific receptor protein on the 30S subunit of bacterial ribosomes and interferes with an initiation complex between mRNA (messenger RNA) and the 30S subunit resulting in inhibition of protein synthesis.

Resistance

The mechanism of resistance to amikacin in mycobacteria has been linked to mutations in the rrs gene of the 16S rRNA.

Clinical experience

The efficacy of inhaled liposomal amikacin was evaluated in study INS-212, a randomised, open-label study in adult patients with non-tuberculous mycobacterial lung infections caused by MAC.

Patients who had not achieved sputum culture conversion (SCC) while being treated with Multiple Drug Regimen(s) (MDR) for at least 6 months before study entry were randomised to receive ARIKAYCE in addition to their MDR treatment or to continue with MDR alone. Patients achieving SCC, defined as 3 consecutive negative MAC sputum cultures by month 6 on treatment continued therapy for up to 12 months after achieving SCC. Those not achieving SCC by month 6 were discontinued from the study at month 8.

A total of 335 patients were randomised and dosed (ARIKAYCE liposomal + MDR n = 223; MDR alone n = 112) (Safety population). Median duration of prior MDR treatment was 2.6 years and 2.4 years in the ARIKAYCE liposomal + MDR and MDR alone group, respectively. Patients were stratified per smoking status (current smoker or not) and MDR use at screening (on treatment or off treatment for at least 3 months prior to screening). The primary endpoint was durable SCC defined as the proportion of randomised patients that had achieved SCC by month 6 on treatment and had no positive solid media culture or no more than two broth media cultures by 3 months off treatment.

Sixty-five (29.0%) and 10 (8.9%) patients achieved SCC by month 6 on treatment in the ARIKAYCE liposomal + MDR and the MDR group, respectively ($p< 0.0001$). Of these, based on the primary analysis durable SCC at 3 months off treatment was achieved by 16.1% [36/224] vs. 0% [0/112]; p-value <0.0001.

In a post-hoc analysis that eliminated patients with negative cultures (solid media or broth) at study baseline and which counted any post-treatment positive culture (solid media or broth) as positive, 30/224 (13.4%) in the ARIKAYCE liposomal + MDR group and 0/112 (0%) in the MDR group achieved durable SCC at 3 months off treatment. Respective rates at 12 months off treatment were 25/224 (11%) vs. 0/112 (0%).

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with inhaled liposomal amikacin in one or more subsets of the paediatric population in NTM lung infection (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Sputum concentrations
Following once daily inhalation of 590 mg inhaled liposomal amikacin in MAC patients, sputum concentrations at 1 to 4 hours post-inhalation were 1720, 884, and 1300 µg/g at 1, 3, and 6 months, respectively. High variability in amikacin concentrations was 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 daily inhalation of 590 mg ARIKAYCE in MAC patients, at steady state, the median serum AUC_{0-24} was 16.7 µg *hr/mL (range: 4.31 to 55.6 µg *hr/mL; n = 53) and the median serum C_{max} was 1.81 µg/mL (range: 0.482 to 6.87 µg/mL; n = 53).

Distribution

Amikacin is ≤ 10% bound to serum proteins. The mean total apparent volume of distribution has been estimated to be approximately 5.0 L/kg.

Biotransformation

Amikacin is not metabolised.

Elimination

Amikacin is excreted in the urine unchanged, primarily by glomerular filtration. The median apparent terminal serum half-life of amikacin after inhalation of ARIKAYCE liposomal ranged from approximately 3.29 to 14.0 hrs.

A population pharmacokinetic analysis for ARIKAYCE liposomal in 53 subjects with NTM lung disease aged 20 to 84 years indicated that amikacin clearance is 34 L/h. The only clinical covariate identified to be predictive of amikacin clearance was body weight.

5.3 Preclinical safety data

Carcinogenicity

In a 2-year inhalation carcinogenicity study with inhaled liposomal amikacin in rats at doses of 5, 15, and 45 mg/kg/day, squamous cell carcinoma was observed in the lungs of 2 of 120 rats (0/60 males and 2/60 females) administered the highest dose tested (45 mg/kg/day). This ARIKAYCE dose was 6-fold greater than the clinical dose when normalised on a lung weight basis. No squamous cell carcinoma was observed at the mid-dose of 15 mg/kg/day, which was 2-fold greater than the clinical

dose when normalised on a lung weight basis. The squamous cell carcinomas may be the result of a high lung burden of particulates from inhaled liposomal amikacin in the rat lung. The relevance of the lung tumour findings with regards to humans receiving inhaled liposomal amikacin is unknown. In dogs administered inhaled liposomal amikacin daily by inhalation for 9 months at doses up to 30 mg/kg/day, no preneoplastic or neoplastic changes were observed in the lungs (approximately 3 to 11 times the recommended human dose based on lung weight).

Genotoxicity

No evidence of mutagenicity or genotoxicity was observed in a battery of *in vitro* and *in vivo* genotoxicity studies with liposomal amikacin formulations (*in vitro* microbial mutagenesis test, *in vitro* mouse lymphoma mutation assay, *in vitro* chromosomal aberration study, and an *in vivo* micronucleus study in rats).

Reproductive and development toxicity

Animal reproductive toxicology studies have not been conducted with inhaled amikacin. In non-GLP reproduction toxicology studies in mice and rats with parenterally administered amikacin, no effect of fertility or foetal toxicity was reported.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cholesterol
Dipalmitoylphosphatidylcholine (DPPC)
Sodium chloride
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).

Do not freeze.

ARIKAYCE can be stored at room temperature below 25 °C for up to 4 weeks.

6.5 Nature and contents of container

Glass vial with bromobutyl rubber stopper and aluminium seal with plastic flip-off cap.

Pack-size of 28 vials. The carton also contains the Lamira Nebuliser Handset and 4 aerosol heads.

6.6 Special precautions for disposal and other handling

Discard any vial that has been frozen.

Once at room temperature, any unused medicine must be discarded at the end of 4 weeks.

If the current dose is refrigerated, the vial of ARIKAYCE liposomal should be removed from the refrigerator and be allowed to come to room temperature. Prepare ARIKAYCE liposomal by shaking the vial vigorously until the contents appear uniform and well mixed. Open the vial of ARIKAYCE liposomal by flipping up the plastic top of the vial, then pulling downward to loosen the metal ring. Carefully remove the metal ring and remove the rubber stopper. Pour the content of the ARIKAYCE liposomal vial into the medicine reservoir of the Lamira Nebuliser Handset.

ARIKAYCE liposomal is administered by oral inhalation via nebulisation using the Lamira Nebuliser System. ARIKAYCE liposomal should only be used with the Lamira Nebuliser System (nebuliser handset, aerosol head, and controller). ARIKAYCE should not be used with any other type of inhalation delivery system. Do not put other medicinal products in the Lamira Nebuliser Handset.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Insmed Netherlands B.V.
Stadsplateau 7
3521 AZ Utrecht
Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1469/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27 October 2020
Date of latest renewal: 02 June 2025

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Almac Pharma Services (Ireland) Ltd.
Finnabair Industrial Estate,
Dundalk, Co. Louth, A91 P9KD,
Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The MAH has developed a patient alert card which will be included in the outer carton. The wording of the alert card is part of the labelling - please see Annex III, A. LABELLING.

The purpose of the alert card is to inform patients that the use of ARIKAYCE liposomal may be associated with the development of allergic alveolitis.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR 28 VIALS CONTAINED IN 4 INNER CARTONS

1. NAME OF THE MEDICINAL PRODUCT

ARIKAYCE liposomal 590 mg nebuliser dispersion
amikacin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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.

3. LIST OF EXCIPIENTS

Excipients: cholesterol, dipalmitoylphosphatidylcholine (DPPC), sodium chloride, sodium hydroxide and water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Nebuliser dispersion

28 vials
4 Lamira aerosol heads
1 Lamira Nebuliser Handset

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Inhalation use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Unopened vials can be stored at room temperature below 25 °C for up to 4 weeks.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Insmed Netherlands B.V.
Stadsplateau 7
3521 AZ Utrecht
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1469/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Arikayce

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INNER CARTON WITH TRAY FOR 7 VIALS AND 1 LAMIRA AEROSOL HEAD

1. NAME OF THE MEDICINAL PRODUCT

ARIKAYCE liposomal 590 mg nebuliser dispersion
amikacin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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.

3. LIST OF EXCIPIENTS

Excipients: cholesterol, dipalmitoylphosphatidylcholine (DPPC), sodium chloride, sodium hydroxide and water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Nebuliser dispersion

7 vials
1 Lamira aerosol head

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Inhalation use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

See vial for batch number and expiry date

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Unopened vials can be stored at room temperature below 25 °C for up to 4 weeks.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Insmed Netherlands B.V.
Stadsplateau 7
3521 AZ Utrecht
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1469/001

13. BATCH NUMBER

See vial for batch number and expiry date

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

ARIKAYCE liposomal 590 mg nebuliser dispersion
amikacin
Inhalation use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

8.9 mL

6. OTHER

PARTICULARS TO APPEAR ON THE PATIENT ALERT CARD

1. OTHER

Front side

PATIENT ALERT CARD

Important safety information

ARIKAYCE liposomal 590 mg (amikacin) may cause serious side effects.
These may happen any time during treatment.
You may experience more than one side effect at the same time.

ARIKAYCE liposomal may be associated with the development of an allergic lung condition (allergic alveolitis)

CONTACT YOUR DOCTOR IMMEDIATELY if you develop any signs or symptoms such as:
- Fever, cough, worsening breathlessness, weight loss
- Lung condition gets worse, affecting your breathing or overall health

Reverse side

Your doctor may give you other medicines to prevent more severe complications and reduce your symptoms. Your doctor may decide to stop treatment.

Important
- Do not attempt to diagnose or treat side effects yourself.
- **Please keep this card with you at all times**, especially when you travel, whenever you go to the Emergency department, or when you must see another doctor.
- Be sure to notify any health care professional you see that you are being treated with ARIKAYCE liposomal and show them this card.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed on this card.

ARIKAYCE liposomal start date
Insmed

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

ARIKAYCE liposomal 590 mg nebuliser dispersion
amikacin

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What ARIKAYCE liposomal is and what it is used for

ARIKAYCE liposomal is an **antibiotic** that contains the active ingredient amikacin. Amikacin belongs to a group of antibiotics called aminoglycosides which stop the growth of certain bacteria that cause infections.

ARIKAYCE liposomal is used by inhalation to treat **lung infection** caused by *Mycobacterium avium* Complex in adults with limited treatment options who do not have cystic fibrosis.

2. What you need to know before you use ARIKAYCE liposomal

Do not use ARIKAYCE liposomal
- if you are allergic to **amikacin** or other **aminoglycosides**, **soya** or **any of the other ingredients** of this medicine (listed in section 6)
- if you are taking any other aminoglycosides (oral or for injection)
- if you have very poor kidney function

Warnings and precautions
Talk to your doctor or pharmacist before using ARIKAYCE liposomal if:
- you use a bronchodilator (“reliever”) for breathing problems, as you will be asked to use that first, before using ARIKAYCE liposomal;
- you have **kidney problems**; you may need to have a kidney test before starting treatment;
- you have **hearing difficulties**, **ringing or buzzing in the ears** (tinnitus) or **balance problems** including spinning sensation, lack of coordinated muscle movements, dizziness or light-headedness. You may have to have a hearing test before starting or during treatment, if you have any hearing problems;
- you suffer from **other lung diseases**;
- you have a disease that causes muscle weakness and fatigue, such as **myasthenia gravis**;
- you have, or have a maternal history of mitochondrial mutation disease (a genetic condition) or loss of hearing due to antibiotic medicines, you are advised to inform your doctor or pharmacist before you take an aminoglycoside; certain mitochondrial mutations may increase your risk of

hearing loss with this product. Your doctor may recommend genetic testing before administration of ARIKAYCE liposomal.

Talk to your doctor immediately if, <u>whilst using</u> ARIKAYCE liposomal you experience any of the below:
- loss of consciousness, skin rash, fever, worsening or new problems with your breathing;
- worsening of kidney problems;
- ear problems like ringing in your ears or loss of hearing.

See section 4.

Children and adolescents
ARIKAYCE liposomal should not be given to children and adolescents less than 18 years old.

Other medicines and ARIKAYCE liposomal
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Special care is needed if you are taking other medicines, as some could interact with ARIKAYCE liposomal, for example:
- diuretics ("water tablets") such as ethacrynic acid, furosemide, or mannitol
- other medicines that can affect your kidneys, hearing, balance or reduce muscle strength.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, the use of ARIKAYCE liposomal should be avoided. Ask your doctor or pharmacist for advice before using this medicine.

If you become pregnant while using ARIKAYCE liposomal, inform your doctor. He will advise whether to stop using ARIKAYCE liposomal.

It is not known if amikacin passes into breast milk in humans. If you are breastfeeding, your doctor will advise you whether to stop breast-feeding or stop treatment with this medicine.

Driving and using machines
ARIKAYCE liposomal can cause dizziness and other vestibular disturbances, such as vertigo and balance disorders. You are advised not to drive or operate machinery while inhaling ARIKAYCE liposomal. If you have questions, please talk to your doctor.

3. How to use ARIKAYCE liposomal

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

The recommended dose is **one vial** of ARIKAYCE liposomal inhaled in your mouth once a day, using the Lamira Nebuliser Handset. After 6 months of treatment your doctor will advise whether to continue or to stop treatment. The maximum duration of treatment is 18 months.

Taking ARIKAYCE liposomal

If you use a bronchodilator ("reliever"), use that first, before using ARIKAYCE liposomal.
Each vial is **for single use only**.
- **Only use** ARIKAYCE liposomal with the Lamira Nebuliser Handset and aerosol head connected to a Lamira Control Unit. See section 7 for how to use the medicine together with the Lamira Nebuliser System.
- **Do not** use ARIKAYCE liposomal with any other type of nebuliser handset or aerosol head.
- **Do not** put other medicines in the Lamira Nebuliser Handset.

- **Do not** drink the liquid in the vial.
- **Read the instructions** for use, which are provided at the end of this leaflet.

How and when do you replace the Lamira Nebuliser Handset?
One Lamira Nebuliser Handset should be used for one 28-day treatment course. The aerosol head should be replaced weekly. There are 4 aerosol heads provided in each ARIKAYCE liposomal carton. Please refer to the manufacturer's instructions for use for cleaning and storage advice.

If you use more ARIKAYCE liposomal than you should
Tell your doctor immediately if you are concerned that you may have used too much of this medicine.

If you forget to use ARIKAYCE liposomal
If you forget to take your medicine, take it as soon as possible on the day of the missed dose. Do not take more than one dose on the same day to make up for a forgotten dose.

If you stop using ARIKAYCE liposomal
You must tell your doctor if you decide to stop using ARIKAYCE liposomal for any reason.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor immediately if:
- you experience any hypersensitivity or severe allergic reactions when taking ARIKAYCE liposomal (e.g. with low blood pressure, loss of consciousness, severe skin rash or severe wheezing and breathlessness). The frequency of these side effects is not known.
- you experience worsening of your usual lung problems or new problems with your breathing (e.g. breathlessness or wheezing). This may be a sign of severe inflammation in the lungs that requires treatment and may mean you should stop taking ARIKAYCE liposomal. The frequency of these severe side effects is common to very common.

Other side effects:
Tell your doctor or pharmacist if you experience any of the following:

Very common side effects (may affect more than 1 in 10 people)
- Difficulty in speaking
- Difficulty in breathing
- Cough
- Coughing up blood

Common side effects (may affect up to 1 in 10 people)
- Infection causing worsening of your lung condition
- Increase in mucus coughed up from lungs
- Chesty cough
- Wheezing
- Throat irritation
- Sore throat
- Loss of voice
- Thrush (a fungal infection) in the mouth
- Pain in the mouth
- Change in your sense of taste
- Lung inflammation
- Headache
- Dizziness

- Feeling unsteady
- Diarrhoea
- Feeling sick (nausea)
- Being sick (vomiting)
- Dry mouth
- Decrease of appetite
- Itching of the skin
- Deafness
- Ringing in your ears
- Kidney problems including poor kidney function
- Joint pain
- Muscle pain
- Rash
- Tiredness
- Discomfort in chest
- Fever
- Loss of weight

Uncommon side effect (may affect up to 1 in 100 people)
- Anxiety

Side effects with Unknown frequency
- Pharyngeal swelling
- Nasal dryness
- Epistaxis
- Rhinorrhoea
- Sneezing
- Nasal Congestion
- Dysphagia
- Glossitis
- Glossodynia
- Salivary hypersecretion
- Stomatitis
- Abdominal pain
- Abdominal pain upper
- Abdominal discomfort
- Abdominal distension

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store ARIKAYCE liposomal

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and vial label after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C – 8 °C). Do not freeze, discard any vial that has been frozen.

Alternatively, ARIKAYCE liposomal can be stored at room temperature below 25 °C, but only for up to 4 weeks. Once at room temperature, any unused medicinal product must be discarded at the end of 4 weeks.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What ARIKAYCE liposomal contains
- The active substance is amikacin. 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.
- The other ingredients are cholesterol, dipalmitoylphosphatidylcholine (DPPC), sodium chloride, sodium hydroxide and water for injections.

What ARIKAYCE liposomal looks like and contents of the pack
ARIKAYCE liposomal is a white to off-white, milky nebuliser dispersion in a glass vial with rubber stopper and metal seal with plastic flip-off cap.

The 28 vials are provided in a carton for a 28-day supply; one vial per day. One ARIKAYCE liposomal carton contains 4 inner cartons, each containing 7 vials and one aerosol head. The 28-day supply pack also contains 1 Lamira Nebuliser Handset.

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

Manufacturer
Almac Pharma Services (Ireland) Ltd.
Finnabair Industrial Estate,
Dundalk, Co. Louth, A91 P9KD,
Ireland

This leaflet was last revised in {month/YYYY}.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

7. Instructions for use

ARIKAYCE liposomal is for oral inhalation use with the Lamira Nebuliser System.
Before using your Lamira Nebuliser System, be sure you read and understand the detailed information in the full Instructions for Use that come with the Lamira Nebuliser System. These will provide more complete information about how to put together (assemble), prepare, use, clean, and disinfect your Lamira Nebuliser System.

Wash your hands with soap and water and dry them well.

Assemble the Lamira Nebuliser Handset including the connection to the controller as illustrated in the full Instructions for Use.

This medicine is a milky white liquid in a clear vial. Do not use if you notice change in colour or any small lumps floating in the vial.

Preparing the medicine for use:

1. It is recommended that the vial be removed from the refrigerator at least 45 minutes before use to allow it to come to room temperature. Do not use other medicines in the Lamira Nebuliser Handset.

2. Shake the ARIKAYCE liposomal vial vigorously, until the medicine looks the same throughout and well mixed.

3. Lift orange cap from vial and put aside (Figure 1).

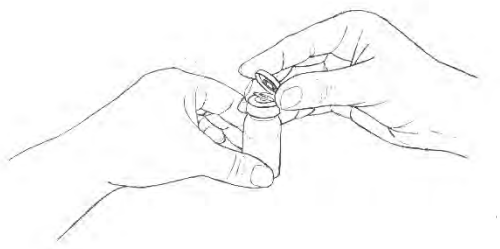

Figure 1

4. Grip the metal ring on top of the vial and pull it down gently until one side breaks away from the vial (Figure 2).

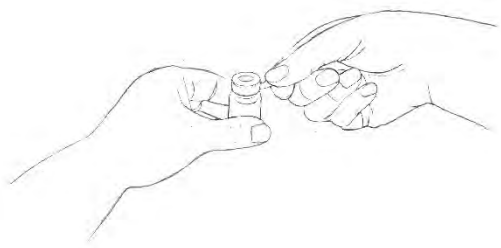

Figure 2

5. Pull the metal band from around the vial top in a circular motion until it comes off completely from the vial (Figure 3).

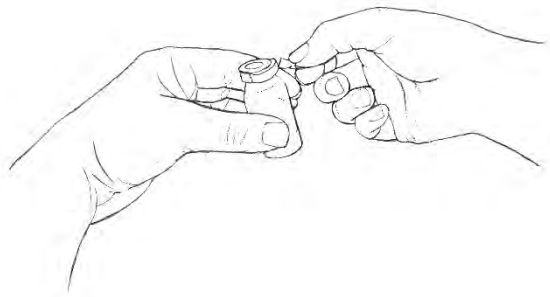

Figure 3

6. Put aside the metal ring after it is detached. Carefully remove the rubber stopper (Figure 4).

Figure 4

7. Pour the contents of the ARIKAYCE liposomal vial into the medicine's reservoir of the Lamira Nebuliser Handset (Figure 5).

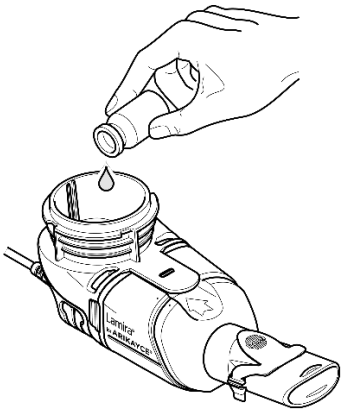

Figure 5

8. Close the medication reservoir (Figure 6).

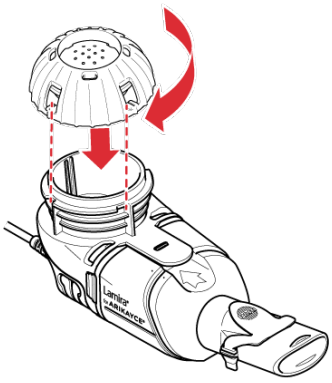

Figure 6

9. Sit in a relaxed, upright position. This makes inhaling easier and helps the medicine get into your lungs.

10. Insert the mouthpiece and take slow, deep breaths. Then, breathe normally in and out through the mouthpiece until your treatment is complete. Treatment should take about 14 minutes but could take up to 20 minutes. Be sure to hold the Lamira Nebuliser Handset level throughout the treatment (Figure 7).

Figure 7