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

System Organ Class	Adverse reactions	Frequency category
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
	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

System Organ Class	Adverse reactions	Frequency category
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 Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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

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)

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23/07/2025

10 DATE OF REVISION OF THE TEXT

12/11/2025