Summary of risk management plan for Arikayce (amikacin sulfate)

This is a summary of the Risk Management Plan (RMP) for Arikayce. The RMP details important risks of Arikayce, how these risks can be minimised, and how more information will be obtained about Arikayce's risks and uncertainties (missing information).

Arikayce's Summary of Product Characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Arikayce should be used.

Important new concerns or changes to the current ones will be included in updates of Arikayce's RMP.

I. The medicine and what it is used for

Arikayce is authorised for the treatment of adults with *Mycobacterium Avium* Complex lung infection (see SmPC for the full indication). It contains amikacin sulfate as the active substance and it is given by inhalation.

Further information about the evaluation of Arikayce's benefits can be found in Arikayce's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/arikayce-liposomal.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Arikayce, together with measures to minimise such risks and the proposed studies for learning more about Arikayce 's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Arikayce is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Arikayce are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Arikayce. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	Allergic alveolitis Ototoxicity Nephrotoxicity Impaired neuromuscular transmission
Important potential risks	None
Missing information	None

II.B Summary of important risks

Important identified risk: Allergic alveolitis	
Evidence for linking the risk to the medicine	Allergic alveolitis is a condition in which the air sacs in the lung become inflamed due to breathing in foreign substances including, in some cases, certain medicines. In clinical studies with Arikayce for the treatment of nontuberculous mycobacterial lung disease the percentage of subject in whom allergic alveolitis was reported was 3.2%, which was higher than the percentage in subjects that were not treated with Arikayce in the same studies (1.3%). The evidence is derived from randomised, controlled clinical trials. Evidence from these sources is considered to be a reliable predictor of how subjects will respond to treatment in clinical practice, by convention.
Risk factors and risk groups	Risk factors for the development of allergic alveolitis in response to treatment with inhaled Arikayce have not been identified. In the general population, repeated exposure to inhaled organic materials including inhaled medicines increases the risk of development of allergic alveolitis.
Risk minimisation measures	*Routine risk communication:* • Summary of Product Characteristics (SmPC) section 4.4 and 4.8. • Package Leaflet (PL) section 2 and 4. *Routine risk minimisation activities recommending specific clinical measures to address the risk:* • SmPC section 4.4. Recommending treatment discontinuation and management as medically appropriate. *Other routine risk minimisation measures beyond the Product Information:* Legal status - Medicinal product subject to prescription. Treatment initiated and managed by physicians experienced in the treatment of the targeted population. *Additional risk minimisation measures:* Patient Alert Card

Important identified risk: Ototoxicity	
Evidence for linking the risk to the medicine	Ototoxicity refers to drug or chemical-related damage to the inner ear, resulting in damage to the organs responsible for hearing and balance. Such damage can lead to temporary or permanent hearing loss, and/or loss of balance. In clinical studies with Arikayce for the treatment of nontuberculous mycobacterial lung disease the percentage of subject in whom ototoxicity was reported was 17.8%, which was higher than the percentage in subjects that were not treated with Arikayce in the same studies (10.2%). The evidence is derived from randomised, controlled clinical trials. Evidence from these sources is considered to be a reliable predictor of how subjects will respond to treatment in clinical practice, by convention.
Risk factors and risk groups	Risk factors for the development of ototoxicity in response to treatment with inhaled Arikayce have not been identified. In the general population, the following factors may influence the risk of development of ototoxicity in response to aminoglycoside antibiotics: • dose and duration of treatment; • cumulative lifetime dose; • impaired kidney function; • treatment with another ototoxic drug at the same time; • increasing age; • pre-existing hearing loss; • genetic susceptibility; • family history of ototoxicity.

Risk minimisation measures	*Routine risk communication:* • Summary of Product Characteristics (SmPC) section 4.4 and 4.8. • SmPC section 4.5. Interaction potential with other ototoxic medicines • Package Leaflet (PL) section 2 and 4. *Routine risk minimisation activities recommending specific clinical measures to address the risk:* • SmPC section 4.4. Recommending monitoring and potentially treatment discontinuation. *Other routine risk minimisation measures beyond the Product Information:* Legal status - Medicinal product subject to prescription. Treatment initiated and managed by physicians experienced in the treatment of the targeted population. *Additional risk minimisation measures:* None

Important identified risk: Nephrotoxicity	
Evidence for linking the risk to the medicine	Nephrotoxicity refers to damage to kidney function as a result of exposure to certain substances including chemicals and some medicines. In clinical studies with Arikayce for the treatment of nontuberculous mycobacterial lung disease the percentage of subject in whom nephrotoxicity was reported was 4.2%, which was higher than the percentage in subjects that were not treated with Arikayce in the same studies (2.5%). The evidence is derived from randomised, controlled clinical trials. Evidence from these sources is considered to be a reliable predictor of how subjects will respond to treatment in clinical practice, by convention.
Risk factors and risk groups	Risk factors for the development of nephrotoxicity in response to treatment with inhaled Arikayce have not been identified. Pre-existing kidney disease and simultaneous treatment with other drugs that may affect the kidney are the most important risk factors for nephrotoxicity. In the general population, the following factors may influence the risk of development of nephrotoxicity in response to aminoglycoside antibiotics, including Arikayce: The presence of other serious illnesses; low blood volume; liver disease; sepsis ((blood poisoning); low blood level of potassium; low blood level of magnesium; advanced age; prolonged treatment; high frequency of dosing; high blood level of aminoglycoside antibiotic; and the timing of treatment administration.

Risk minimisation measures	*Routine risk communication:* • Summary of Product Characteristics (SmPC) section 4.3, 4.4 and 4.8. • SmPC section 4.5. Interaction potential with other nephrotoxic medicines • Package Leaflet (PL) section 2 and 4. *Routine risk minimisation activities recommending specific clinical measures to address the risk:* • SmPC section 4.3. Contraindicated in severe renal impairment. • SmPC section 4.4. Recommending close monitoring, potentially treatment discontinuation. *Other routine risk minimisation measures beyond the Product Information:* Legal status - Medicinal product subject to prescription. Treatment initiated and managed by physicians experienced in the treatment of the targeted population. *Additional risk minimisation measures:* None

Important identified risk: Impaired neuromuscular transmission	
Evidence for linking the risk to the medicine	Impaired neuromuscular transmission refers to a condition in which nerve impulses cannot be properly transmitted to muscles to make them contract. This may lead to muscle weakness or fluctuating muscle fatigue. In clinical studies with Arikayce for the treatment of nontuberculous mycobacterial lung disease the percentage of subject in whom impaired neuromuscular transmission was reported was 3.0%, which was higher than the percentage in subjects that were not treated with Arikayce in the same studies (0.6%). The evidence is derived from randomised, controlled clinical trials. Evidence from these sources is considered to be a reliable predictor of how subjects will respond to treatment in clinical practice, by convention.
Risk factors and risk groups	Risk factors for the development of impaired neuromuscular transmission in response to treatment with inhaled Arikayce have not been identified. In the general population, the following factors may influence the risk of development of impaired neuromuscular transmission during treatment with aminoglycoside antibiotics including Arikayce: the presence of diseases affecting neuromuscular transmission (e.g., myasthenia gravis, Eaton-Lambert syndrome); simultaneous treatment with other medicines that affect neuromuscular transmission (e.g., muscle relaxants used in anaesthesia); recent exposure to some agricultural insecticides.
Risk minimisation measures	*Routine risk communication:* • Summary of Product Characteristics (SmPC) section 4.4 and 4.8. • SmPC section 4.5. Interaction potential with other medicines • Package Leaflet (PL) section 2 and 4. *Routine risk minimisation activities recommending specific clinical measures to address the risk:* • SmPC section 4.4. Recommending close monitoring. Use in myasthenia gravis not recommended. *Other routine risk minimisation measures beyond the Product Information:* Legal status - Medicinal product subject to prescription. Treatment initiated and managed by physicians experienced in the treatment of the targeted population. *Additional risk minimisation measures:* None.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Arikayce.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Arikayce.