APPLICATION NUMBER:

207356Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)
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<td>2018-673</td>
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<td>Reviewer Name(s)</td>
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<td>September 28, 2018</td>
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<td>Subject</td>
<td>Evaluation of the Need for a REMS</td>
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<tr>
<td>Established Name</td>
<td>Amikacin liposomal inhalation suspension (ALIS)</td>
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<td>Trade Name</td>
<td>Arikayce</td>
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<td>Name of Applicant</td>
<td>Insmed, Inc.</td>
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<td>Therapeutic class</td>
<td>Aminoglycoside</td>
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<td>Formulation</td>
<td>Inhalation</td>
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<tr>
<td>Dosing Regimen</td>
<td>590 mg amikacin administered once daily vial oral inhalation using Lamira™, a product specific nebulizer</td>
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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the Arikayce (amikacin liposomal inhalation suspension (ALIS)) is necessary to ensure the benefits outweigh its risks. Insmed Inc., submitted a New Drug Application (NDA) 207356 for ALIS with the proposed indication for the treatment of nontuberculous mycobacterial (NTM) lung disease caused by Mycobacterium avium complex (MAC) as part of a combination antibacterial drug regimen for adult patients. The FDA approved indication for Arikayce will be indicated in adults who have limited or no alternative treatment options for the treatment of refractory nontuberculous mycobacterial (NTM) lung disease caused by Mycobacterium avium complex (MAC). The serious risks of Arikayce include increased respiratory adverse reactions including allergic alveolitis, hemoptysis, bronchospasm, and exacerbation of underlying pulmonary disease that have led to hospitalizations in some cases. The Sponsor’s proposed labeling initially did not include a Box Warning, and they did not submit a proposed REMS or risk management plan with this application.

Based on the benefit:risk profile of Arikayce, the Division of Anti-infective Products (DAIP) was concerned about risk of increased respiratory adverse reactions (hypersensitivity pneumonitis, bronchospasm, exacerbation of underlying pulmonary disease and hemoptysis) and more frequent hospitalization events and possible broader use of this product in the post-market setting. DRISK was consulted regarding the need for a REMS, in particular, a REMS that could include elements to assure safe use (ETASU) consisting of prescriber education and certification and pharmacy certification to address DAIP concerns.

DRISK and DAIP assessed the need for a REMS and discussed a possible REMS with the REMS Oversight Committee. Ultimately DRISK and DAIP agreed that a REMS was not necessary for approval of this application. The label will be maximized through the use of a Boxed Warning highlighting the risks of respiratory adverse events and the potential for increased hospitalizations, and a Limitations of Use for prescribing the product in patients with refractory NTM lung disease. Additionally, this NDA is being approved under the Limited Population Pathway for Antibacterial and Antifungal Drugs (LPAD) as the benefit: risk profile of Arikayce only supports use in patients with refractory MAC lung disease. In addition, the Sponsor has committed to two postmarketing commitments (PMCs) to communicate the known benefit:risk of Arikayce to healthcare providers and to perform a drug utilization study to assess real world use in the post marketing setting.

1 Background

1.1 PRODUCT INFORMATION AND REGULATORY HISTORY
Lung disease caused by NTM is characterized by progressive, irreversible lung damage and increased mortality rates. Approximately 80% of these cases are caused by MAC, and the disease is more prevalent after 60 years of age. There are currently no FDA-approved therapies specifically for the treatment of NTM lung disease caused by MAC, and current treatment guidelines recommend a
combination of three antibacterial drugs (commonly a macrolide, a rifamycin and ethambutol) for 12 months after sputum cultures have become negative.\textsuperscript{1, a,b}

The active ingredient of Arikayce is amikacin sulfate, which belongs to the aminoglycoside class of antibiotics. The product is a liposomal inhalation suspension of amikacin to be used with a nebulizer system (Lamira\textsuperscript{TM}). The Sponsor’s proposed indication is for the treatment of NTM lung disease caused by MAC as part of a combination antibiotic regimen for adult patients. The FDA approved indication for ALIS will be indicated in adults who have limited or no alternative treatment options for the treatment of refractory nontuberculous mycobacterial (NTM) lung disease caused by \textit{Mycobacterium avium} complex (MAC).\textsuperscript{2} The dose is 590 mg once daily via oral inhalation as part of a combination antibacterial drug regimen for adult patients.\textsuperscript{c}

Arikayce is not a new molecular entity (NME), and was submitted as a 505(b)(2) application.\textsuperscript{d} ALIS was granted Orphan Drug Designation in March 2013, Fast Track and Qualified Infectious Disease Product (QIDP) designations in June 2013 for the treatment of NTM lung disease, and Breakthrough Therapy Designation in June 2014.\textsuperscript{3} The Breakthrough Therapy Designation was based on preliminary data from a Phase 2 trial that demonstrated sputum culture negativity when ALIS was added to a multidrug antibacterial regimen in adult patients with NTM lung disease who were refractory to treatment. In the Sponsor’s clinical trial, refractory was defined as individuals who remained culture positive after 6 months of a multidrug optimized background regimen. This NDA was submitted, and is being approved under 21 CFR part 314, subpart H (the accelerated approval pathway), in which the determination of efficacy relies on a surrogate endpoint of sputum culture conversion defined as 3 consecutive negative monthly sputum cultures within 6 months of treatment. The Prescription Drug User Fee Act (PDUFA) date for this application is September 28, 2018.

2  Status of the Review

2.1 POST ADVISORY COMMITTEE MEETING DISCUSSION

On August 7, 2018 the Antimicrobial Drugs Advisory Committee convened to discuss whether the data are adequate to support the safety and efficacy of ALIS for the treatment of NTM lung disease caused by MAC in adults as part of a combination antibacterial drug regimen. Specifically, the questions and votes were as follows:

1. Is the surrogate endpoint of sputum culture conversion based on three consecutive negative sputum cultures reasonably likely to predict clinical benefit? \textbf{Vote: 8 yes, 6 no}

\textsuperscript{a} Section 505-1 (a) of the FD&C Act: FDAAA factor (B): \textit{The seriousness of the disease or condition that is to be treated with the drug.}

\textsuperscript{b} Section 505-1 (a) of the FD&C Act: FDAAA factor (A): \textit{The estimated size of the population likely to use the drug involved.}

\textsuperscript{c} Section 505-1 (a) of the FD&C Act: FDAAA factor (D): \textit{The expected or actual duration of treatment with the drug.}

\textsuperscript{d} Section 505-1 (a) of the FD&C Act: FDAAA factor (F): \textit{Whether the drug is a new molecular entity.}
2. Has the applicant provided substantial evidence of the effectiveness and sufficient evidence of the safety of amikacin liposomal inhalation solution (ALIS) for the treatment of nontuberculous mycobacterial lung disease caused by MAC as part of a combination antibacterial drug regimen for adult patients? **Vote: 12 no, 2 yes**

3. Has the applicant provided substantial evidence of the effectiveness and sufficient evidence of the safety of ALIS for the treatment of nontuberculous mycobacterial lung disease caused by *M. avium* complex as part of a combination antibacterial drug regimen for adult patients with limited or no treatment options? **Vote: 12 yes, 2 no**

After the Advisory Committee meeting the Division of Anti-infective Products (DAIP) raised concerns about the benefit-risk of using Arikayce in a broader population of patients without refractory MAC lung disease including those with other pulmonary diseases, and the imbalance of adverse respiratory events, including an increased risk of hospitalizations. DAIP requested advice from DRISK on whether a REMS consisting of prescriber education that informed prescribers of: 1) the benefit for Arikayce relies on a surrogate endpoint, and that clinical benefit has not yet been determined and, 2) the risks of serious pulmonary events and increased number of hospitalization with Arikayce, could help limit the use of the product to the intended population. The REMS DAIP was requesting would have been a REMS with elements to assure safe use (ETASU) consisting of prescriber education and certification, as well as pharmacy certification to ensure that the prescribers are trained and certified to prescribe Arikayce prior to dispensing. The division had also made the decision to include a Boxed Warning for the increased risks of respiratory events, as well as to include a limitation of use, indicating the product only in a refractory population.

DRISK expressed concerns with requiring a REMS with ETASU for the intended goals of preventing off-label use, as well as communicating risks to likely prescribers. The prescribing population would likely be pulmonologists and infectious disease specialists (as per DAIP) and should be aware of the management of respiratory events in the intended population. As proposed, the use of an REMS that relies only on education program to decrease off-label use may not be successful. DRISK recommends that if education is used, it would not be a sole mechanism to prevent use in other populations; additional requirements would be necessary which could impact patient access for the intended population. In addition, it is known in the prescribing community that amikacin is compounded in hospital pharmacies for the treatment of various pulmonary diseases. DRISK brought this up as a consideration, that requiring a restrictive REMS that included ETASU, may inadvertently depress use of Arikayce in the intended population. It is unknown if third parties such as insurance companies will require preauthorization, but such requirements may also impact use.
On September 24, 2018, DAIP’s proposal for a REMS was brought to the REMS Oversight Committee to discuss whether the approvability of ALIS should also include a REMS with ETASU with the intended goal of educating prescribers on the increased pulmonary risks and hospitalizations of Arikayce and the need to limit the prescribing of this drug in patients diagnosed with refractory MAC disease, in addition to maximizing labeling to include a Boxed Warning on the increased risks of pulmonary events, Limitations of Use to specify the intended population, and also using the Limited Population Pathway for Antibacterial and Antifungal Drugs (LPAD). DRISK recommended communicating the risks of Arikayce through maximizing the label as described above, in addition to Sponsor-led safety communications that could be done outside of a REMS such as Dear Healthcare Provider Letters and targeted emails to pulmonary and infectious disease specialists and professional societies.

One ROC member noted that DAIP’s rationale for requiring a REMS for approval of ALIS was a proactive idea as a means to help prevent use in the unintended population, while communicating the benefit:risk of the product to likely prescribers. However, the remaining ROC members commented that the likely prescribers, pulmonologists and infectious diseases specialists, would be those who are likely aware of the adverse events of Arikayce and the management thereof, thus, requiring an education and certification program by way of a REMS would not be necessary, and could delay patient access. The ROC members thought it would be necessary for these risks to be communicated and agreed that these communications could occur outside of a REMS and perhaps under a post-marketing requirement (PMR). This PMR could also include submission of data showing how the product is used in a real-world setting (i.e., drug utilization data, and/or the emergence of new safety events). ROC members also noted that the Limitation of Use may impact off-label use by payers if the drug is prescribed in the unintended population. The members of the ROC noted as with any drug, if additional safety signals arise post approval the need for a REMS can be revisited.

2.2 COMMUNICATIONS WITH THE SPONSOR
Prior to our internal meeting with the ROC, it was communicated to the Sponsor that discussions for a REMS with ETASU were under consideration. The Sponsor disagreed with the need for a REMS and stated that they would be willing to provide a non-REMS communication plan for health care providers highlighting the risks associated with ALIS and the fact that clinical benefit had not been verified. DRISK and DAIP agreed after the ROC that before making a decision on a REMS, additional information from the Sponsor on how they plan to communicate the benefit:risk profile of Arikayce should be considered, as well as possibly requesting this additional information through a post marketing commitment (PMC). On September 25, the Agency sent an information request to the Sponsor with the following questions:

- Details of their communication plan for health care providers, as well as to provide information about the target audience and the methods of communication that they plan to use.

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* As per the 21st Century review process, all REMS with elements to assure safe use (ETASU) are discussed at the REMS Oversight Committee (ROC) which consists of senior level management from the Offices of New Drugs, Surveillance and Epidemiology, and Regulatory Policy.
• Plans for monitoring real world use of ALIS, including use for the broader NTM population and non-NTM population.
• How the Sponsor plans to distribute ALIS; whether through a limited number of pharmacies/specialty pharmacies or if they expect it to be available in retail pharmacies.

On September 26th, the Sponsor provided the following details in response to the Agency’s questions:

SPONSOR RESPONSE 1:

To inform healthcare providers about the risks and safe use of ARIKAYCE, Insmed will voluntarily disseminate communication materials to the target audience of Healthcare Providers, including Pulmonology and Infectious Disease physicians, and associated Physician Assistants, Nurse Practitioners, and Respiratory Therapists. The target audience will also include the Professional Societies: American Thoracic Society (ATS), Infectious Disease Society of America (IDSA), American College of Chest Physicians (ACCP) and the American Association of Respiratory Care (AARC). Clinical Pharmacists who are within Insmed’s limited Specialty Pharmacy network are included. The plan to disseminate the non-REMS communication material includes:

• who will provide the communication outlining the risks associated with ARIKAYCE and the fact that clinical benefit has not yet been verified, ARIKAYCE prescribing information and Medication Guide to the Healthcare Providers described above.
• Direct mailing of the above-mentioned communication materials to Healthcare Providers within 60 days of approval, followed by another mailing 12 months post-approval. The planned mailing will include the above-mentioned Healthcare providers, Professional Societies and the Clinical Pharmacists in the limited network of Specialty Pharmacies.

The Sponsor is committed to a communication plan that will emphasize the appropriate patient population and safety profile. The Sponsor intends for this plan to be a non-REMS communication program.

SPONSOR RESPONSE 2:

In real world practice, the LPAD labeling and restrictions for use will limit the use of ARIKAYCE in unintended populations. Our survey work indicates that payers will actively limit the use of ARIKAYCE to the intended population.

The methods that Insmed will employ to monitor the real-world use of ARIKAYCE and patient populations being treated:

1. Payer data: Insmed’s expectation, formed through market research and interactions with the payers, is that all prescriptions will require a Prior Authorization to labeled indication. As part of the Prior Authorization, Healthcare Providers will attest to patient’s diagnosis and experience with prior NTM therapy. We expect that payers will limit use of ARIKAYCE to labeled indication.

2. Arikares Patient Support Program: Insmed will collect information on patients who enroll in the Arikares Patient Support Program, including Healthcare Provider’s attested ICD-10 code. As the current ICD-10 code for NTM is not specific to NTM species (i.e. MAC) or status (i.e. front line, refractory), we do not expect to be able to report on patient’s NTM species or patient’s previous treatment status through that data. We will be able to collect data on any patient enrollments who have a documented ICD-10 code for non-NTM populations. Additionally, we will be collecting and
reporting data on patient experience with ARIKAYCE from standard pharmacovigilance monitoring activities.

3. **Specialty Pharmacy network:** As ARIKAYCE will be distributed through a limited network of Specialty Pharmacies, audits could be conducted as needed for additional real-world data.

**SPONSOR RESPONSE 3:**

ARIKAYCE will only be distributed through a limited distribution network of Specialty Pharmacies that have expertise in respiratory and rare disease. The Sponsor plans to utilize Specialty Pharmacies.

### 3 CONCLUSION

DAIP and DRISK reviewed the Sponsor’s submission, and overall agreed with the Sponsor’s proposal but with some recommended changes, along with the outline to make the communication plan as part of PMCs for approval for Arikayce. On September 27th, the Sponsor agreed to PMCs that include their communication plan activities for outlining the risks associated with Arikayce and the fact that clinical benefit has not yet been verified, and a drug utilization study to assess real world use. The PMCs are to be done in concert with their confirmatory trial. The proposed PMCs are noted in Appendix 1 of this review: Postmarketing Commitments Related to Communicating the Benefit:Risks of Arikayce.
4 Appendices

4.1 Postmarketing Commitments Related to Communicating the Benefit: Risks of ARIKAYCE.

PMC - 2: Provide and implement an email, standard mail, and facsimile communication plan to include a Dear Healthcare Provider letter as well as targeted educational materials to clinicians and professional societies.

• Draft submission: 10/2018 (within 2 weeks to 1 month after approval)
• Follow-up issue: 12/2018 (communication to be sent within 60 days of launch)
• Follow-up issue: 03/2019 (communication to be sent within 6 months of launch)
• Follow-up issue: 09/2019 (communication to be sent within 12 months of launch)
• Final report submission: 12/2019

Note to the applicant: the final report should contain the following: 1) Number of letters sent to healthcare providers and professional societies via email, standard mail, and facsimile, and the dates the letters were sent. For letters sent via email, include the number of letters successfully delivered, and number of email letters opened by the recipients; 2) Any actions that targeted professional societies took as a result of the communications. For example, did they post the letter on their website, include this information in a newsletter to their membership or develop a continuing education program that included this information; 3) The sources of the distribution lists; and, 4) Name and date of any scientific meetings where the letter was displayed.

PMC-3: Provide results of a drug utilization assessment including ICD-10 code or other information on the indication and patient demographic/clinical characteristics of users of ARIKAYCE through pharmacies that will be distributing ARIKAYCE, and the results of chart reviews of a random subset of patients who are prescribed ARIKAYCE.

• Interim report: 06/2019
• Interim report: 06/2020
• Interim report: 06/2021
• Interim report: 06/2022
• Interim report: 06/2023
• Final Study report: 06/2024
4.2 REFERENCES

1 Arikayce ROC Slide Presentation, September 24, 2018

2 Draft Prescribing Information, Arikacye, September 17, 2018

3 FDA Briefing Document for Arikayce NDA 207356 August 7, 2018
This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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NAOMI B REDD
09/28/2018

CYNTHIA L LACIVITA
09/28/2018
concur

ELIZABETH E EVERHART
09/28/2018
I concur