DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207356

ACCELERATED APPROVAL
LPAD PATHWAY APPROVAL

Insmed Incorporated
Attention: Diane C. Fiorenza, BS, RAC
Executive Director, Regulatory Affairs
10 Finderne Avenue, Building 10
Bridgewater, NJ 08807-3365

Dear Ms. Fiorenza:

Please refer to your New Drug Application (NDA) dated March 28, 2018, received March 28, 2018, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ARIKAYCE (amikacin liposome inhalation suspension), 590 mg.

We also refer to your written request dated September 13, 2018, for approval under section 506(h) of the FDCA for the Limited Population Pathway for Antibacterial and Antifungal Drugs (LPAD Pathway).

This new drug application provides for the use of ARIKAYCE (amikacin liposome inhalation suspension), 590 mg, as follows:

LIMITED POPULATION: ARIKAYCE is an aminoglycoside antibacterial indicated in adults who have limited or no alternative treatment options, for the treatment of *Mycobacterium avium* complex (MAC) lung disease as part of a combination antibacterial drug regimen in patients who do not achieve negative sputum cultures after a minimum of 6 consecutive months of a multidrug background regimen therapy. As only limited clinical safety and effectiveness data for ARIKAYCE are currently available, reserve ARIKAYCE for use in adults who have limited or no alternative treatment options. This drug is indicated for use in a limited and specific population of patients.

This indication is approved under accelerated approval based on achieving sputum culture conversion (defined as 3 consecutive negative monthly sputum cultures) by Month 6. Clinical benefit has not yet been established.

Limitation of Use:
ARIKACYE has only been studied in patients with refractory MAC lung disease defined as patients who did not achieve negative sputum cultures after a minimum of 6 consecutive months of a multidrug background regimen therapy. The use of ARIKAYCE is not recommended for patients with non-refractory MAC lung disease.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved under the provisions of accelerated approval regulations (21 CFR 314.500), effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text. Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

LPAD PATHWAY APPROVAL

This application is furthermore approved under section 506(h) of the FDCA and marketing of this drug product is subject to the requirements for labeling and promotional materials described therein.

Under section 506(h)(7), FDA may terminate the limitations associated with the LPAD pathway when FDA has determined that the product is safe and effective for a broader population. The additional data supporting approval for the broader population should demonstrate that the conditions of the LPAD pathway are no longer necessary for the drug product. If you decide to conduct clinical trials to support termination of limitations, submit final reports to this NDA as a supplemental application. For administrative purposes, designate this submission "**LPAD Pathway Termination Request**."

WAIVER OF HIGHLIGHTS SECTION

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the prescribing information, text for the patient package insert, Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical*

Product Applications and Related Submissions Using the eCTD Specifications (May 2015, Revision 3). For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 207356**." Approval of this submission by FDA is not required before the labeling is used.

MARKET PACKAGE

Please submit one market package of the drug product when it is available to the following address:

Deborah Wang, PharmD
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 6349
10903 New Hampshire Avenue
Silver Spring, Maryland
Use zip code **20903** *if shipping via United States Postal Service (USPS).*
Use zip code **20993** *if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled clinical trials to verify and describe clinical benefit. You are required to conduct such a clinical trial with due diligence. If the postmarketing clinical trial fails to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 314.530, withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated September 26, 2018. This requirement, along with required completion dates, is listed below.

3480-1 Conduct a randomized, double-blind, placebo-controlled clinical trial to assess and describe the clinical benefit of ARIKAYCE in patients with nontuberculous mycobacterial (NTM) lung disease caused by MAC. The trial will evaluate the effect of ARIKAYCE on a clinically meaningful endpoint, as compared to an appropriate control in the intended patient population of patients with MAC infection.

The timetable you submitted on September 27, 2018, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	03/2019
Final Protocol Submission:	06/2019
Trial Completion:	06/2023
Final Report Submission:	06/2024

Submit clinical protocols to your **IND 108674** for this product. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each requirement in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial.

Submit final reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated "**Subpart H Postmarketing Requirement(s)**."

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3480-2 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.

The timetable you submitted on September 27, 2018, states that you will conduct this study according to the following schedule:

Draft Submission:	10/2018
First Communication:	12/2018
Second Communication:	03/2019
Third Communication:	09/2019
Final Report Submission:	12/2019

3480-3 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.

The timetable you submitted on September 28, 2018, states that you will conduct this drug utilization assessment according to the following schedule:

Final Protocol Submission:	01/2019
Interim Report Submission:	06/2019
Interim Report Submission:	06/2020
Interim Report Submission:	06/2021
Interim Report Submission:	06/2022
Interim Report Submission:	06/2023
Final Study Report Submission:	06/2024

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

3480-4 Conduct further studies to identify an optimal quality control (QC) in vitro drug release method in which only the drug released from the liposomes (free drug) is sampled and analyzed and propose new acceptance criteria for the drug product.

The timetable you submitted on September 13, 2018, states that you will conduct this study according to the following schedule:

Interim Report Submission:	03/2019
Final Report Submission:	09/2019

Submit clinical protocols to your **IND 108674** for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all post-marketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled **"Postmarketing Commitment Protocol," "Postmarketing Commitment Final Report," or "Postmarketing Commitment Correspondence."**

PROMOTIONAL MATERIALS

Under 21 CFR 314.550, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 314.550, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved prescribing information (PI)/Medication Guide/patient PI (as applicable). We note that meeting the requirements under 21 CFR 314.550 described above will also satisfy the requirements in section 506(h)(3)(B) of the FDCA for the submission of promotional materials for drugs approved under the LPAD pathway.

Send each submission directly to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotions (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit promotional materials for accelerated approval products electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

REPORTING REQUIREMENTS

We remind you that you must comply with the reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Deborah Wang, PharmD, Regulatory Project Manager, at (301) 796-9053.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, MD, MPH
Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

{See appended electronic signature page}

Edward M. Cox, MD, MPH
Director
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURES:
- Content of Labeling
  - Prescribing Information
  - Medication Guide
  - ARIKAYCE Patient Instructions for Use
  - LAMIRA Nebulizer System Instructions for Use
- Carton and Container Labeling
- Quick Start Guide

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/

SUMATHI NAMBIAR
09/28/2018

EDWARD M COX
09/28/2018