The Limited Population Pathway for Antibacterial and Antifungal Drugs

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FDA Panel Members

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Housekeeping

- Lunch
- Meeting webpage - https://www.fda.gov/news-events/fda-meetings-conferences-and-workshops/fda-public-meeting-limited-population-pathway-antibacterial-and-antifungal-drugs-07122019-07122019
  - Slides, recording of the meeting, transcripts will be uploaded after the meeting.

Agenda for the Day

- Nature of the meeting
- Overview of the LPAD Pathway and FDA's experience with the pathway
- Public comments – 10 minutes per person for pre-registered speakers with time for follow up questions from the panel
- Audience comment period – 15 minutes
  - Sign up to speak at the check-in desk by 10 am or send questions through webcast

Public Law 114–255
114th Congress

An Act

To accelerate the discovery, development, and delivery of 21st century cures, and for other purposes.

Dec. 13, 2016
[H.R. 34]

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

21st Century Cures Act.
42 USC 201 note.

SECTION 1. SHORT TITLE; TABLE OF CONTENTS.

(a) SHORT TITLE.—This Act may be cited as the "21st Century Cures Act".

(b) TABLE OF CONTENTS.—The table of contents for this Act is as follows:

SEC. 3042. LIMITED POPULATION PATHWAY.

Section 506 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 356), as amended by section 3033, is further amended by adding at the end the following:

"(h) LIMITED POPULATION PATHWAY FOR ANTIBACTERIAL AND ANTIFUNGAL DRUGS.—

"(1) IN GENERAL.—The Secretary may approve an antibacterial or antifungal drug alone or in combination with one

Limited Population Pathway for Antibacterial and Antifungal Drugs

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Sarah Walinsky at 240-402-4075 or (CBER) the Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-8010.

Issued June 2018

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM610498.pdf

https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM631810

LPAD Pathway: Requirements

- The drug is intended to treat a *serious or life-threatening infection* in a *limited population* of patients with *unmet needs*
  - *Serious or life-threatening* and *unmet needs* defined in Expedited Programs guidance
- Standards for approval under 505(c) and (d) or standards for licensure under 351 of Public Health Service Act are met
- Written request from the Sponsor that the drug be approved as a limited population drug

Limited Population

- A group of patients that is limited in such a way that is clinically relevant to health care providers.
- May be a defined subset of a broader population of patients for whom the drug could potentially be effective or, in some cases, may be the only population of patients for whom the drug may be effective because of its narrow spectrum of activity

Standards for Approval

- Acceptance of greater uncertainty or higher risk in patients with serious diseases and with an unmet need is an appropriate approach to the risk-benefit assessment
- LPAD pathway is based on a benefit-risk assessment that more flexibly takes into account the *severity, rarity, or prevalence* of the infection the drug is intended to treat and the lack of alternatives available for the patient population.

21 CFR 312 subpart E

LPAD Pathway: Conditions for Approval

- Labeling: To indicate that safety and effectiveness has only been demonstrated with respect to a limited population
  - All advertising and labeling will include “Limited Population” in a prominent manner, and
  - The prescribing information will contain the statement “This drug is indicated for use in a limited and specific population of patients”
- Promotional Materials:
  - Pre-submission of promotional materials at least 30 days prior to dissemination of such materials

Examples of Development Programs

- May follow streamlined approaches as described in the guidance *Antibacterial Therapies for Patients with an Unmet Medical Need for the Treatment of Serious Bacterial Diseases* such as:
  - Clinical trials using noninferiority designs, including a single noninferiority trial at a body site of infection or use of wider noninferiority margins than used in traditional development programs
  - Clinical trials using a superiority design
  - Nested noninferiority/superiority clinical trials

FDA's Experience with the LPAD Pathway

- We have approved one drug, Arikayce, using the LPAD pathway – discussed in next slides
- Currently receiving inquiries on ways to utilize the LPAD pathway for NDAs
- Main issues we have seen with sponsors seeking approval under the LPAD pathway:
  - Standards for approval do not change
    - Subsection 506(h)(1)(B) (the LPAD pathway provision) states, "the standards for approval under section 505(c) and (d), or the standards for licensure under section 351 of the Public Health Service Act, as applicable, are met"

LPAD Pathway Approval: Arikayce

- Amikacin liposome inhalation suspension approved September 2018 in adults who have limited or no alternative treatment options for the treatment of MAC lung disease as part of a combination antibacterial drug regimen in patients refractory to other treatment regimens
  - Well-defined limited population
  - Substantial evidence of effectiveness provided on a surrogate endpoint – approved under the accelerated approval pathway
  - Due to
    - Acceptable level of uncertainty given the seriousness of the condition and the degree of unmet need
    - a significant potential for broad use if the indication is not well described
    - Also considering
      - respiratory adverse events observed in clinical trials
      - relatively limited safety dataset
  - Risk-benefit considered favorable only for a limited population of patients (as described in the indication)
    - Summary basis of approval

LPAD Pathway Labeling: Arikayce

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ARIKAYCE safely and effectively. See full prescribing information for ARIKAYCE.

ARIKAYCE® (amikacin liposome inhalation suspension), for oral inhalation use
Initial U.S. Approval: 2018
LIMITED POPULATION

WARNING: RISK OF INCREASED RESPIRATORY ADVERSE REACTIONS
See full prescribing information for complete boxed warning.

ARIKAYCE has been associated with a risk of increased respiratory adverse reactions, including, hypersensitivity pneumonitis, hemoptysis, bronchospasm, and exacerbation of underlying pulmonary disease that have led to hospitalizations in some cases. (5.1, 5.2, 5.3, 5.4)

----------INDICATIONS AND USAGE----------

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. (1)

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. (1)

Limitation of Use:

----------DOSAGE FORMS AND STRENGTHS----------

ARIKAYCE is supplied as a sterile, aqueous, liposome suspension for oral inhalation in a unit-dose glass vial containing amikacin 590 mg/8.4 mL. (3)

----------CONTRAINDICATIONS----------

ARIKAYCE is contraindicated in patients with a known hypersensitivity to any aminoglycoside. (4)

----------WARNINGS AND PRECAUTIONS----------

- Hypersensitivity Pneumonitis: Reported with ARIKAYCE treatment; if hypersensitivity pneumonitis occurs, discontinue ARIKAYCE and manage patients as medically appropriate. (5.1)
- Hemoptysis: Higher frequency of hemoptysis has been reported with ARIKAYCE treatment. If hemoptysis occurs, manage the patients as medically appropriate. (5.2)
- Bronchospasm: Higher frequency of bronchospasm has been reported with ARIKAYCE treatment. Treat patients as medically appropriate if this occurs during treatment with ARIKAYCE. (5.3)
- Exacerbations of Underlying Pulmonary Disease: Higher frequency of exacerbations of underlying pulmonary disease has been reported with ARIKAYCE treatment. Treat patients as medically appropriate if this occurs during treatment with ARIKAYCE. (5.4)
- Ototoxicity: Higher frequency of ototoxicity has been reported with ARIKAYCE treatment. Closely monitor patients with known or suspected auditory or vestibular dysfunction. If patients develop tinnitus this may be an early symptom of ototoxicity. (5.5)
- Nephrotoxicity: Aminoglycosides can cause nephrotoxicity. Close monitoring of patients with known or suspected renal dysfunction may be needed when prescribing ARIKAYCE. (5.6)
- Neuromuscular Blockade: Aminoglycosides may aggravate muscle weakness because of a potential curare-like effect on neuromuscular function. If neuromuscular blockade occurs, it may be reversed by the administration of calcium salts but mechanical assistance may be necessary .(5.7)
- Embryo-Fetal Toxicity: Aminoglycosides can cause total, irreversible, bilateral congenital deafness in pediatric patients exposed in utero. (5.8, 8.1)

Next steps

- We are currently working on finalizing the LPAD Pathway draft guidance
  - We will utilize feedback from this meeting in our efforts to finalize the guidance
- The docket is reopened for further comments until August 12, 2019
  - https://www.regulations.gov/docket?D=FDA-2018-D-2032

Thank you!


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