NDA 213312

NDA APPROVAL

Aadi Bioscience, Inc.
Attention: Mitch Clark
Senior Vice President, Regulatory Affairs and Quality Assurance
17383 Sunset Blvd., Suite A250
Pacific Palisades, CA 90272

Dear Mr. Clark:

Please refer to your new drug application (NDA) dated May 28, 2021, received May 28, 2021, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Fyarro (sirolimus protein-bound particles for injectable suspension) (albumin-bound), for intravenous use.

This NDA provides for the use of Fyarro (sirolimus protein-bound particles for injectable suspension) (albumin-bound), for intravenous use for the treatment of adult patients with locally advanced unresectable or metastatic malignant perivascular epithelioid cell tumor (PEComa).

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

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 FDA.gov.[1] Content of labeling must be identical to the enclosed labeling text for the Prescribing Information, as well as annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As.*[2]

The SPL will be accessible via publicly available labeling repositories.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling, as soon as they are available, but no more than 30 ays after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 213312**." Approval of this submission by FDA is not required before the labeling is used.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for Fyarro (sirolimus protein-bound particles for injectable suspension) (albumin-bound), for intravenous use shall be 24 months from the date of manufacture when stored at 2°C to 8°C (36°F to 46°F).

ADVISORY COMMITTEE

Your application for Fyarro was not referred to an FDA advisory committee because it did not raise significant safety or efficacy issues in the intended population

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 REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a known serious risk of infusion related reactions and to further characterize the risks of severe adverse reactions including myelosuppression, hypokalemia, hyperglycemia, non-infectious pneumonitis, and hypersensitivity in patients receiving Fyarro.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks. Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following study:

4177-1 Conduct an integrated safety analysis to assess the serious risk of infusion related reactions and to further characterize the risks of severe adverse reactions including myelosuppression, hypokalemia, hyperglycemia, non-infectious pneumonitis, hypersensitivity, and their sequelae in a sufficient number of patients exposed to Fyarro; and to identify risk factors for development of these adverse reactions. The study should include appropriate monitoring and risk mitigation strategies.

The timetable you submitted on November 18, 2021, states that you will conduct this study according to the following schedule:

Draft Analysis Plan Submission:	03/2022
Final Analysis Plan Submission:	06/2022
Study Completion:	03/2025
Final Report Submission:	06/2025

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify an unexpected serious risk of increased toxicities when Fyarro is administered to patients with hepatic impairment and to identify the potential for QT interval prolongation in patients administered Fyarro.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following trial:

4177-2 Conduct a hepatic impairment clinical trial to evaluate the pharmacokinetics and safety of Fyarro in subjects with mild, moderate, and severe hepatic impairment (based on NCI criteria) and determine the magnitude of increase in exposure and appropriate dosage. Design and conduct the trial in accordance with the FDA Guidance for Industry titled: “Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.”

The timetable you submitted on November 18, 2021, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	03/2022
Final Protocol Submission::	06/2022
Trial Completion:	10/2023
Final Report Submission:	03/2024

Provide the datasets with the final report.

4177-3 Conduct a clinical trial to assess the potential risk of QT interval prolongation and the effect of Fyarro on the QT interval. Design and conduct the trial in accordance with the ICH E14 Guidance for Industry titled: "E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs."

The timetable you submitted on November 18, 2021, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	03/2022
Final Protocol Submission:	06/2022
Trial Completion:	03/2025
Final Report Submission:	06/2025

Provide the datasets with the final report.

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit clinical protocols to your IND 125669 with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

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

We remind you of your postmarketing commitment:

4177-4 In Trial PEC-001, adverse reactions of hypersensitivity have occurred with infusion of Fyarro. (b) (4) because of the risk of immunogenicity and hypersensitivity with therapeutic proteins, further information is required to characterize the risk of immunogenicity and hypersensitivity in Fyarro. Submit side by side test results of albumin dimer/oligomer levels for Fyarro and any approved products containing albumin as an excipient with an established safety profile to support the proposed limit of albumin dimer/oligomer levels in Fyarro. A CBE-30 supplement will be submitted to propose an update to the drug product specifications if justified based on the results of this study. (b) (4)

The timetable you submitted on November 1, 2021, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	03/2022
Study Completion:	03/2023
Final Report Submission:	06/2023

Submit datasets and product quality information with the final report.

A final submitted protocol is one that the FDA has reviewed and commented upon, and you have revised as needed to meet the goal of the study or clinical trial.

Submit chemistry, manufacturing, and controls protocols and all postmarketing 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, and any changes in plans since the last annual report. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," **or** "**Postmarketing Commitment Correspondence**."

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PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[4]

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[5] Information and Instructions for completing the form can be found at FDA.gov.[6]

REPORTING REQUIREMENTS

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

If you have any questions, please email Sharon Sickafuse, Senior Regulatory Health Project Manager, at sharon.sickafuse@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Martha Donoghue, M.D.
Deputy Director
Division of Oncology 2
Office of Oncologic Diseases
Office of New Drugs
Center for Drug Evaluation and Research

[4] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

ENCLOSURES:

- Content of Labeling
    - Prescribing Information
- Carton and Container Labeling

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/

MARTHA B DONOGHUE
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