CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

213716Orig1s000

Trade Name:	Lupkynis
Generic or Proper Name:	Voclosporin capsule
Sponsor:	Aurinia Pharmaceuticals, Inc.
Approval Date:	January 22, 2021
Indication:	For the use of Lupkynis in combination with a background immunosuppressive therapy regimen for the treatment of adult patients with active lupus nephritis.

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APPLICATION NUMBER:

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APPROVAL LETTER

NDA 213716

NDA APPROVAL

Aurinia Pharmaceuticals, Inc.
c/o Aurinia Pharma U.S., Inc.
77 Upper Rock Circle, Suite 700
Rockville, MD 20850

Attention: Sue Evans
Vise President, Regulatory Affairs US

Dear Ms. Evans:

Please refer to your new drug application (NDA) dated and received May 22, 2020, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Lupkynis (voclosporin) capsule.

This new drug application provides for the use of Lupkynis in combination with a background immunosuppressive therapy regimen for the treatment of adult patients with active lupus nephritis.

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.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

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 FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide) as well as annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using eLIST

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

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.

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 days 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 213716**." 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 Lupkynis (voclosporin) capsule shall be 36 months from the date of manufacture when stored at 20 to 25°C (68 to 77ºF) with excursions permitted to 15 to 30ºC (59 to 86ºF).

ADVISORY COMMITTEE

Your application for Lupkyns (voclosporin) was not referred to an FDA advisory committee because this drug is not the first in its class and the application did not warrant a discussion at an advisory committee meeting.

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.

We are waiving the pediatric studies requirement for the lupus nephritis pediatric patients ages 0 to less than 5 years of age because necessary studies are impossible or highly impracticable. This is because the number of patients are too small.

[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.

We are deferring the pediatric studies of pediatric patients for ages 5 to equal or less than 17 years of age. This product is ready for approval for use in adults and the pediatric studies have not been completed.

Deferred Pediatric Studies:

Your deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(4)(C) of the Federal Food, Drug, and Cosmetic Act. These required studies are listed below

4007-1 An adaptive design, double-blind, placebo-controlled, dose escalation, PK/PD, efficacy and safety study of voclosporin in lupus nephritis in addition to standard therapy, in pediatric patients from 12 to ≤17 years with active lupus nephritis.

The timetable you submitted on January 20, 2021, states that you will conduct this study according to the following schedule:

- Final Protocol Submission Date: March 2021
- Study Completion Date: December 2024
- Final Report Submission Date: June 2025

4007-2 A prospective, open-label, 52-week, multi-center efficacy and safety study of voclosporin in addition to background standard of care with mycophenolate mofetil and oral steroids in pediatric patients from 5 to ≤17 years of age with lupus nephritis.

The timetable you submitted on January 20, 2021, states that you will conduct this study according to the following schedule:

- Final Protocol Submission Date: September 2026
- Study Completion Date: December 2030
- Final Report Submission Date: June 2031

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 the protocol(s) to your IND 114577, with a cross-reference letter to this NDA.

[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.

Reports of these required pediatric postmarketing studies must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studyies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

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 identify an unexpected serious risk associated with the presence of voclosporin in human milk.

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 this serious risk.

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

4007-3 Perform a milk only lactation study in lactating women who have received LUPKYNIS (voclosporin) to assess concentrations of voclosporin and its active metabolites in breast milk using a validated assay.

The timetable you submitted on January 20, 2021, states that you will conduct this study according to the following schedule:

- Draft Protocol Submission Date: December 2021
- Final Protocol Submission Date: June 2022
- Interim Report Date: June 2023 and then every year for 3 years
- Study Completion Date: June 2025
- Final Report Submission Date: March 2026

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a known serious risk of nephrotoxicity.

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

4007-4 Submit the final study report for the ongoing clinical trial AUR-VCS-2016-02 (AURORA-2), a 24-month, multi-center, randomized, placebo-controlled, double-blind study in adult patients with active lupus nephritis to evaluate long-term efficacy and safety with voclosporin 23.7 mg twice daily. Safety evaluations include but are not limited to nephrotoxicity.

The timetable you submitted on January 21, 2021, states that you will conduct this study according to the following schedule:

- Trial Completion Date: December 2021
- Final Report Submission Date: March 2022

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.[4]

Submit clinical protocol(s) to your IND 114577 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) 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 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.

[4] 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.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

4007-5 A drug-drug interaction study to evaluate the effect of repeat doses of voclosporin 23.7 mg BID on the pharmacokinetics of a transporter substrate of OATP1B1, assess the magnitude of exposure change, and inform appropriate dosing strategies for coadministration of voclosporin with OATP1B1 substrates.

The timetable you submitted on January 20, 2021, states that you will conduct this study according to the following schedule:

- Draft Protocol Submission Date: July 2021
- Final Protocol Submission Date: October 2021
- Study Completion Date: November 2022
- Final Report Submission Date: May 2023

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 clinical protocols to your IND 114577 for this product. Submit nonclinical and 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, 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

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.*[5]

[5] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.

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.[6] Information and Instructions for completing the form can be found at FDA.gov.[7]

REPORTING REQUIREMENTS

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

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biological products qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Sadaf Nabavian, Regulatory Project Manager, at 301-796-2777.

Sincerely,

{See appended electronic signature page}

Julie Beitz, MD
Director
Office of Immunology and Inflammation (OII)
Center for Drug Evaluation and Research

ENCLOSURE(S):

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

[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[7] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

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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/

JULIE G BEITZ
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