NDA 215309

CORRECTED NDA APPROVAL

Incyte Corporation
Attention: Deb McGill, PhD
Director, Global Regulatory Affairs
1801 Augustine Cut-Off
Wilmington, DE 19803

Dear Dr. McGill:

Please refer to your new drug application (NDA) dated and received December 21, 2020, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for OPZELURA (ruxolitinib) cream, 1.5%.

We also refer to our approval letter dated September 21, 2021, which contained the following error: The statement noting the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess the serious risks was omitted from the section identifying postmarketing requirements under 505(o).

This corrected action letter incorporates the correction of the error. The effective action date will remain September 21, 2021, the date of the original letter.

We acknowledge receipt of your major amendment dated June 4, 2021, which extended the goal date by three months.

This NDA provides for the use of OPZELURA (ruxolitinib) cream for the short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised patients 12 years of age and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

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 with minor editorial revisions reflected in the enclosed 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 and Medication Guide) 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.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling and carton and container labeling submitted on August 27, 2021, 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 215309**." 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 OPZELURA (ruxolitinib) cream shall be 24 months from the date of manufacture when stored at 20°C to 25°C.

ADVISORY COMMITTEE

Your application for OPZELURA (ruxolitinib) cream was not referred to an FDA advisory committee because this drug is not the first in its class.

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.

[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.

We are waiving the pediatric study requirement for ages 0 to less than 3 months because necessary studies are impossible or highly impracticable. This is because disease chronicity is a criterion for the diagnosis of atopic dermatitis (AD) and cannot be established in infants < 3 months of age.

We are deferring submission of your pediatric studies for ages 3 months to 11 years 11 months for this application because this product is ready for approval for use in adults and adolescents and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the FDCA 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 FDCA. These required studies are listed below.

4147-1 Conduct a randomized, double-blind, 8-week trial of ruxolitinib 1.5%, ruxolitinib 0.75%, and vehicle, followed by a 44-week long-term safety extension where vehicle subjects are randomized to either ruxolitinib 1.5% or ruxolitinib 0.75%. The trial should enroll 250 subjects ages ≥ 2 to < 12 years with atopic dermatitis of at least 3 months duration, a baseline Investigator's Global Assessment (IGA) score of 2 to 3, and % body surface area (BSA) involvement (excluding scalp) of 3% to 20% (Study INCB 18424-305).

Final Protocol Submission: Submitted 05/2021
Trial Completion: 08/2023
Final Report Submission: 02/2024

4147-2 Conduct a maximal use pharmacokinetic (PK) study in pediatric subjects with atopic dermatitis ages ≥ 2 years to < 12 and target at least 16 completers.

Final Protocol Submission: 06/2021
Study Completion: 06/2023
Final Report Submission: 12/2023

4147-3 Conduct an open-label safety study in 100 subjects ages ≥ 3 months to < 24 months with atopic dermatitis with ruxolitinib cream applied twice daily (BID) for 4 weeks with a 48-week extension treatment period and assess PK under maximal use conditions in a subset of at least 16 subjects.

Draft Protocol Submission: 10/2026
Final Protocol Submission: 02/2027
Study Completion: 08/2029
Final Report Submission: 01/2030

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 077101, with a cross-reference letter to this NDA. Reports of these required pediatric postmarketing studies must be submitted as an 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 studies. 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 unexpected serious risks in the adolescent patient population and will not be sufficient to identify an unexpected serious risk for adverse pregnancy, fetal, or infant outcomes from the use of OPZELURA (ruxolitinib) cream during pregnancy.

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 studies:

4147-4 Conduct a one-year, open-label safety study in subjects with atopic dermatitis ages ≥ 12 years to < 18 years.

The timetable you submitted on September 16, 2021, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	12/2021
Final Protocol Submission:	02/2022
Study Completion:	12/2024
Final Report Submission:	06/2025

[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.

4147-5 Conduct a Pregnancy Exposure Registry, a prospective, registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes in the female population with atopic dermatitis exposed to ruxolitinib cream during pregnancy to an unexposed control population. The registry should be designed to detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, preterm birth, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life. For more information, see the May 2019 FDA draft Guidance for Industry *Postapproval Pregnancy Safety Studies*.

The timetable you submitted on August 27, 2021, states that you will conduct this study according to the following schedule:

Draft Protocol Sumbission: 02/2022
Final Protocol Submission: 08/2022
Study Completion: 08/2032
Final Report Submission: 08/2033

4147-6 Conduct an additional pregnancy study that uses a different design from the Pregnancy Registry (for example a retrospective cohort study using claims or electronic medical record data or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age and preterm birth in the female population with atopic dermatitis exposed to ruxolitinib cream during pregnancy compared to an unexposed control population.

The timetable you submitted on August 27, 2021, states that you will conduct this study according to the following schedule:

Draft Protocol Sumbission: 02/2022
Final Protocol Submission: 08/2022
Study Completion: 08/2027
Final Report Submission: 08/2028

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 077101 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final

[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.

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).**

Submission of the protocol(s) for required postmarketing observational studies to your IND is for purposes of administrative tracking only. These studies do not constitute clinical investigations pursuant to 21 CFR 312.3(b) and therefore are not subject to the IND requirements under 21 CFR part 312 or FDA's regulations under 21 CFR parts 50 (Protection of Human Subjects) and 56 (Institutional Review Boards).

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.

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]

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]

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

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, call Matthew White, Senior Regulatory Project Manager, at 301-796-4997.

Sincerely,

{See appended electronic signature page}

Shari L. Targum, MD, MPH, FACP, FACC
Deputy Director
Division of Dermatology and Dentistry
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide
- 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/

SHARI L TARGUM
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