NDA 211675/S-004

SUPPLEMENT APPROVAL

AbbVie Inc.
Attention: Viraj Gandhi, MS, MBA, RAC
Associate Director, Regulatory Affairs
1 N. Waukegan Road
Dept. PA72/Bldg. AP30-4
North Chicago, IL 60064

Dear Mr. Gandhi:

Please refer to your supplemental new drug application (sNDA) dated and received October 15, 2020, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Rinvoq (upadacitinib) extended-release tablets.

We acknowledge receipt of your major amendments dated March 26, 2021, which extended the goal date by three months.

This Prior Approval supplemental new drug application provides for the new indication of the treatment of adults and pediatric patients 12 years of age and older with refractory, moderate-to-severe atopic dermatitis whose disease is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies are inadvisable.

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 (Prescribing Information, and Medication Guide), with the addition of any labeling changes in pending “Changes Being Effected” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

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

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 from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

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 June 30, 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 211675/S-004**." Approval of this submission by FDA is not required before the labeling is used.

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 study requirement for patients less than 6 months of age because necessary studies are impossible or highly impracticable. This is because of the diagnostic uncertainty especially in children below 3 months of age.

[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 submission of your pediatric studies for ages 6 months to 11 years for this application because this product is ready for approval for use in adults and adolescents 12 years and older and the pediatric study has not been completed.

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

4212-1 Conduct an active controlled efficacy and safety study (with sparse PK assessment) in patients 6 years to 11 years of age with refractory, moderate to severe atopic dermatitis whose disease is not adequately controlled with other systemic therapies, or when use of these therapies is not advisable. Subjects should initiate treatment with low dose upadacitinib or active control. The study should evaluate the treatment benefit of higher upadacitinib dosage in subjects who had inadequate response to the initial upadacitinib lower dosage. The study should include at least 300 subjects treated with the upadacitinib and exposed for at least 52 weeks. Provide the results of PK Study (Study M16-049) with the protocol for Study A.

Final Protocol Submission:	September 2022
Study Completion:	December 2025
Final Report Submission:	June 2026

Results from PMR 4212-1 for pediatric subjects 6-11 years of age will inform our decision on whether to require a pediatric trial to support the use of upadacitinib for refractory, moderate-to-severe atopic dermatitis in the pediatric population ages 6 months to 5 years and on the type of data that would be required.

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 128180 with a cross-reference letter to this NDA. Reports of this required pediatric postmarketing study 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 this study. 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.

[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.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (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 the unexpected serious risk of long term use of upadacitinib and the effect on women exposed to upadacitinib during pregnancy and /or lactation.

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:

4212-2 Conduct a prospective observational study (analyses conducted in patient cohorts enrolled prospectively and followed actively in accordance with a written protocol) to assess the long-term safety of upadacitinib treatment in U.S. patients with moderate-to-severe atopic dermatitis. Fully ascertain and centrally verify serious adverse events, Major Adverse Cardiovascular Events (myocardial infarction, stroke, cardiovascular death, and sudden death), malignancies (including lymphoma, lung cancer, and other malignancies), serious infections, opportunistic infections (including herpes zoster), retinal detachment, thrombosis (including deep venous thrombosis, pulmonary embolism, and arterial thrombosis), hepatoxicity (including drug induced liver injury), and possibly other adverse events of special interest. For each adverse-event outcome separately, compare incidence in upadacitinib-treated patients against reference rates internally derived from analyses conducted in patients treated with dupilumab or other chronic systemic treatments for moderate to-severe atopic dermatitis. Regardless of treatment discontinuation or switch to a different treatment for atopic dermatitis, continue following patients for malignancy outcomes and possibly other adverse events with delayed onset. Enroll a sufficient number of patients to describe the frequency of the adverse events of special interest in representative U.S. patients who start treatment with upadacitinib for atopic dermatitis in the setting of routine clinical practice. Implement a plan that uses rigorous, transparent, and verifiable methods to ascertain and characterize safety events that occur

during and after treatment with upadacitinib. Enroll patients over a 4-year period and follow each patient for at least 8 years from time of enrollment.

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

Draft Protocol Submission: June 2022
Final Protocol Submission: June 2023
Study/Trial Completion: December 2035
Final Report Submission: December 2036

4212-3 Conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to Rinvoq (upadacitinib), for any indication, during pregnancy and /or lactation to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. Infant outcomes will be assessed through at least the first year of life. The minimum number of patients will be specified in the protocol.

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

Draft Protocol Submission: June 2022
Final Protocol Submission: December 2022
Interim/Other: December 2025
Study/Trial Completion: December 2027
Final Report Submission: June 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 the protocol(s) to your IND 128180 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing 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)"**.

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

[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.

clinical investigations pursuant to 21 CFR 312.3(b) and therefore are not subject to the IND requirements under 21 CFR part 312.

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]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[6] Information and Instructions for completing the form can be found at FDA.gov.[7]

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4).

[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).

As required under 21 CFR 314.80, report each adverse drug experience that is both serious and unexpected within 15 days from initial receipt of the information. You are also required to report cases of drug-induced liver injury (DILI) and retinal detachment regardless of whether it was assessed as serious or non-serious within 15 days from initial receipt of the information. Every effort should be made to obtain thorough and complete follow-up of events related to DILI or retinal detachment, including results from specialist consults (e.g., hepatology, ophthalmology). The clinical information collected in this manner will enhance the quality of adverse event reports submitted to the FDA and facilitate our assessment of these reports.

If you have any questions, call Craig Johnson, Regulatory Project Manager, at 301-796-3921.

Sincerely,

{See appended electronic signature page}

Kendall A. Marcus, MD
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/

KENDALL A MARCUS
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