



BLA 761105/S-029  
BLA 761262/S-007

## SUPPLEMENT APPROVAL

AbbVie Inc  
Attention: Dan Pick  
Associate Director, Global Regulatory Strategy  
1 North Waukegan Road  
Department PA72/Building AP30-4  
North Chicago, IL 60064

Dear Dan Pick:

Please refer to your supplemental biologics license applications (sBLA), dated and received August 18, 2023, and your amendments, submitted under section 351(a) of the Public Health Service Act for Skyrizi (risankizumab-rzaa) injection.

These Prior Approval supplemental biologics license applications provide for the addition of an indication of the treatment of moderately to severely active ulcerative colitis in adults.

### **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, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at FDA.gov,<sup>1</sup> that is identical to the enclosed labeling (text for the Prescribing Information, Instructions for Use, and Medication Guide) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements.

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*.<sup>2</sup>

The SPL will be accessible via publicly available labeling repositories.

<sup>1</sup> <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

<sup>2</sup> 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>.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending “Changes Being Effected” (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] 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 carton and container labeling submitted on June 14, 2024, 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 BLA 761105/S-029 and BLA 761262/S-007.**” 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(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric studies requirement for ages 0 to less than 2 years because necessary studies are impossible or highly impracticable. This is because ulcerative colitis is rarely diagnosed in patients less than 2 years of age.

We are deferring submission of your pediatric studies for ages 2 to 18 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

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 601.28 and section 505B(a)(4)(B) of the Federal Food, Drug, and Cosmetic Act. These required studies are listed below.

- 4656-1 Conduct a one-year, randomized trial to evaluate the safety, efficacy, and pharmacokinetics of Skyrizi (risankizumab-rzaa) in pediatric patients 2 to 17 years of age with moderately to severely active ulcerative colitis.

Final Protocol Submission: 03/2025  
Study Completion: 01/2031  
Final Report Submission: 07/2031

- 4656-2 Conduct a long-term extension study to evaluate the long-term safety of Skyrizi (risankizumab-rzaa) in pediatric patients 2 to 17 years of age with moderately to severely active ulcerative colitis who participated in postmarketing requirement study #1. This study can be conducted as part of postmarketing requirement study #1 or as a basket trial with study PMC 4294-6.

Final Protocol Submission: 03/2025  
Study Completion: 01/2035  
Final Report Submission: 07/2035

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.<sup>3</sup>

Submit the protocol(s) to your IND 133100, with a cross-reference letter to these BLAs. Reports of these required pediatric postmarketing studies must be submitted as a BLA or as a supplement to your approved BLA 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 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

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<sup>3</sup> 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>.

reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of hepatotoxicity.

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 unexpected serious risks.

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

- 4656-3 Conduct an observational study to assess the incidence of severe acute liver injury in adults with moderately to severely active ulcerative colitis who are exposed to Skyrizi (risankizumab-rzaa), relative to other therapies used to treat ulcerative colitis. Compare rates (per person-time) or risks (proportion of patients with a minimum amount of follow-up). Describe and justify the choice of appropriate comparator population(s). Specify concise case definition for severe liver injury and validation of algorithm(s) to identify severe liver injury in the proposed data source. For the Skyrizi (risankizumab-rzaa)-exposed and comparator(s) cohorts, clearly define the study drug initiation period and any exclusion and inclusion criteria. Ensure that the data source allows for average follow-up for at least 1 year. Specify a minimum sample size and justify the precision of the estimate achievable with the proposed study. The ongoing observational study in patients with Crohn's disease (PMR 4294-1) with the same objectives may be amended to also enroll patients with ulcerative colitis.

The timetable you submitted on May 15, 2024, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	06/2025
Study Completion:	06/2033
Final Report Submission:	12/2033

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.<sup>3</sup>

### **REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)**

Submit clinical protocol(s) to your IND 133100 with a cross-reference letter to this NDA/BLA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your BLA. 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.

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(a)(1) of the FDCA, as well as 21 CFR 601.70 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(a)(1) and 21 CFR 601.70 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 601.70. 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.

### **POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B**

We remind you of your postmarketing commitments:

- 4656-4 Submit postmarketing device reports to evaluate the on-body injector device used to deliver Skyrizi (risankizumab-rzaa) in patients with moderately to severely active Crohn's disease or ulcerative colitis.

For reported device failure or use error events, collect information to allow root-cause analysis and assessment of associated adverse events. Specific information collected should include essential elements to allow for root-cause analysis such as patient narratives of the events and evaluation of returned devices, dosing information including the start of maintenance therapy, and any adverse events associated with the device failure or use error event (i.e., injection site pain/erythema) including disease activity as reported.

Among confirmed device failure or use error events, identify a cohort of patients to prospectively follow for 6 months to assess disease activity (i.e., remission, flare/worsening disease symptoms, escalation of care, hospitalization, procedures).

The timetable you submitted on April 30, 2024, and June 14, 2024, states that you will submit the reports according to the following schedule:

First Report Submission:	02/2025
Interim Report Submission:	08/2025
Interim Report Submission:	02/2026
Interim Report Submission:	08/2026
Final Report Submission:	02/2027

Submit clinical protocols to your IND 133100 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. 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/subjects 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.”**

### **Enhanced Pharmacovigilance Request**

We acknowledge that you have ongoing enhanced pharmacovigilance related to hepatotoxicity following Skyrizi (risankizumab-rzaa) treatment (for any indication) in which you have developed and are utilizing a detailed questionnaire for follow-up for these reports. You confirmed on June 12, 2024, that reports in patients with ulcerative colitis indication will be included in this ongoing enhanced pharmacovigilance.

In addition, we are modifying our previous EPV request included in our June 16, 2022, approval letters for the supplemental BLA 761105/S-016 and BLA 761262, as follows:

1. We request that for SKYRIZI you submit all serious and non-serious domestic and foreign cases of liver injury for any indication as 15-day “Alert reports” (described under 21 CFR 600.80(c)(1)) through March 25, 2028. To identify events related to liver injury for any indication, we recommend using the Preferred Terms proposed previously in addition to the following: *Suspected drug-induced liver injury, Immune-mediated hepatic disorder, Liver transplant, Autoimmune hepatitis, Hepatitis acute, and Immune-mediated hepatitis.*

2. We request that you provide a separate narrative summary and analysis of liver injury, apart from your required analysis of 15-day “Alert reports,” as part of your required periodic safety reports (i.e., periodic adverse experience report (PAER) required under 21 CFR 600.80(c)(2) or the ICH E2C Periodic Benefit-Risk Evaluation Report (PBRER) format), quarterly through the reporting interval ending June 25, 2025, then annually through the reporting interval ending March 25, 2028. Your analysis should include interval and cumulative data relative to June 16, 2022, by indication.

## **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*.<sup>4</sup>

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.<sup>5</sup> Information and Instructions for completing the form can be found at FDA.gov.<sup>6</sup>

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-related information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety-related 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).

## **REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

Your product is a Part 3 combination product (21 CFR 3.2(e)); therefore, you must also comply with postmarketing safety reporting requirements for an approved combination product (21 CFR 4, Subpart B). Additional information on combination product postmarketing safety reporting is available at FDA.gov.

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<sup>4</sup> For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/media/128163/download>.

<sup>5</sup> <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>

<sup>6</sup> <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>

BLA 761105/S-029

BLA 761262/S-007

Page 8

If you have any questions, contact Jay Fajiculay, PharmD, Senior Regulatory Health Project Manager, at (301) 796-9007 or email at [jay.fajiculay@fda.hhs.gov](mailto:jay.fajiculay@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Tara Altepeter, MD  
Associate Director for Therapeutic Review  
Division of Gastroenterology  
Office of Immunology and Inflammation  
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide
  - Instructions for Use

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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.**  
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/s/  
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