BLA 761262

CORRECTED BLA APPROVAL

AbbVie, Inc
Attention: Tony Freeney, MBA, BSC, PMP
Sr. Manager, Regulatory Affairs
Global Regulatory Strategy, US & Canada
1 North Waukegan Road
Department PA72, Building AP30-4
North Chicago, IL 60064

Dear Mr. Freeney:

Please refer to your biologics license application (BLA) dated and received on September 16, 2021, and your amendments, submitted under section 351(a) of the Public Health Service Act for Skyrizi (risankizumab-rzaa) injection.

We also refer to our approval letter dated June 16, 2022, which contained the following errors:

1. The final formulated drug product labeling and packaging locations
2. The final protocol submission date for Postmarketing Requirement (PMR) 4294-3

This corrected action letter incorporates the corrections of the errors. The effective action date will remain June 16, 2022, the date of the original letter.

We acknowledge receipt of your major amendment dated January 13, 2022, which extended the goal date by three months.

LICENSING

We are issuing Department of Health and Human Services U.S. License No. 1889 to AbbVie, Inc., North Chicago, IL, under the provisions of section 351(a) of the Public Health Service Act controlling the manufacture and sale of biological products. The license authorizes you to introduce or deliver for introduction into interstate commerce, those products for which your company has demonstrated compliance with establishment and product standards.

Under this license, you are authorized to manufacture the product Skyrizi (risankizumab-rzaa). Skyrizi is indicated for the treatment of moderately to severely active Crohn’s disease in adults.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture risankizumab-rzaa drug substance at AbbVie Bioresearch Center, Inc. in Worcester, Massachusetts. The final formulated drug product will be manufactured and filled at (b) (4). The final formulated drug product will be labeled and packaged at AbbVie Inc., North Chicago, IL or AbbVie S.r.l., Campoverde di Aprilia, Italy. You may label your product with the proprietary name, Skyrizi, and market it in 600 mg single-dose vials.

DATING PERIOD

The dating period for Skyrizi shall be 12 months from the date of manufacture when stored at 2-8°C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The dating period for your drug substance shall be (b) (4) months from the date of manufacture when stored at (b) (4)

We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Skyrizi to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

Any changes in the manufacturing, testing, packaging, or labeling of Skyrizi, or in the manufacturing facilities, will require the submission of information to your BLA for our review and written approval, consistent with 21 CFR 601.12.

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.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information,

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

Instructions for Use, and Medication Guide). 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 (October 2009)*.[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 container labeling submitted on January 11, 2022, and carton labeling submitted on March 18, 2022, 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 761262**." Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for Skyrizi was not referred to an FDA advisory committee because this biologic is not the first in its class and outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

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.

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 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.

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

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 of hepatotoxicity. In addition, studies are needed to assess potential adverse pregnancy and infant outcomes in women exposed to risankizumab-containing products 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 unexpected serious risks.

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

4294-1 Conduct an observational study to assess the incidence of severe acute liver injury in adults with moderately to severely active Crohn's disease who are exposed to Skyrizi (risankizumab-rzaa), relative to other therapies used to treat Crohn's disease. 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 timetable you submitted on June 2, 2022, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	12/2022
Final Protocol Submission:	06/2023
Interim/Other:	06/2028
Study Completion:	06/2033
Final Report Submission:	12/2033

4294-2 A prospective, registry-based, observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to risankizumab-containing products regardless of indication 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 births, preterm births, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, neonatal deaths, and infections, will be assessed through at least the first year of life.

The timetable you submitted on May 23, 2022, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	12/2022
Final Protocol Submission:	06/2023
Study Completion:	06/2033
Final Report Submission:	06/2034

4294-3 Conduct an additional pregnancy study that uses a different design from the prospective pregnancy registry established to fulfil postmarketing requirement study 2 (for example a retrospective cohort study using claims or electronic medical record data with outcome validation or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age and preterm births in women exposed to risankizumab-containing products regardless of indication during pregnancy compared to an unexposed control population.

The timetable you submitted on May 23, 2022, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	12/2022
Final Protocol Submission:	12/2023
Study Completion:	06/2032
Final Report Submission:	06/2033

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a identify an unexpected serious risk of the potential safety outcomes from Skyrizi (risankizumab-rzaa) exposure in the breastfed infant have not been characterized.

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

4294-4 Perform a lactation trial (milk only) in lactating women who have received Skyrizi (risankizumab-rzaa) to assess concentrations of Skyrizi (risankizumab-rzaa) in breast milk using a validated assay and to assess the effects on the breastfed infant.

The timetable you submitted on May 23, 2022, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	06/2023
Final Protocol Submission:	12/2023
Study Completion:	06/2025
Final Report Submission:	06/2026

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]

REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)

Submit the protocol(s) to your IND 118701, with a cross-reference letter to this NDA/BLA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final report(s) to your NDA/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 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 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.

[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 COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4294-5 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 Crohn's disease.

The timetable you submitted on June 14, 2022, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	10/2022
Final Protocol Submission:	03/2023
Study/Trial Completion:	03/2029
Final Report Submission:	12/2029

4294-6 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 Crohn's disease who participated in postmarketing commitment study 4294-5. This study can be conducted as part of postmarketing commitment study 4294-5.

The timetable you submitted on May 23, 2022, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	12/2022
Final Protocol Submission:	03/2023
Study Completion:	03/2033
Final Report Submission:	09/2033

4294-7 Conduct a clinical trial to assess whether Skyrizi (risankizumab-rzaa) alters the metabolism or pharmacokinetics of cytochrome P450 (CYP) substrates in patients with Crohn's disease treated with Skyrizi (risankizumab-rzaa) (e.g., using a cocktail of relevant CYP probe drugs).

The timetable you submitted on June 14, 2022, states that you will conduct this study according to the following schedule:

Study Completion:	08/2022
Final Report Submission:	02/2023

Request for Enhanced Pharmacovigilance

In addition to the above studies, we request that you expedite reports of liver injury (for any indication). We recommend that you develop and utilize a detailed questionnaire for follow-up for these reports (you can submit a proposal for our review and comment). Additionally, you should include interim and cumulative summaries of liver injury in periodic safety reports, 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*.[4]

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

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements at 21 CFR 600.80.

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements at 21 CFR 600.81.

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA 3486 to:

[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

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4207
Silver Spring, MD 20903

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

Sincerely,

{See appended electronic signature page}

Jessica J. Lee, MD, MMSc
Director
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
- 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/

JESSICA J LEE
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