CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

761286Orig1s000

Trade Name:	RYSTIGGO injection, for subcutaneous use
Generic or Proper Name:	rozanolixizumab-noli
Sponsor:	UCB, Inc.
Approval Date:	June 26, 2023
Indication:	for the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) or anti-muscle-specific tyrosine kinase (MuSK) antibody positive

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APPROVAL LETTER

BLA 761286

BLA APPROVAL

UCB, Inc.
Attention: Marian L. Saxon, PhD, MS
US Regulatory Lead
4000 Paramount Parkway, Suite 200
Morrisville, NC 27560

Dear Dr. Saxon:

Please refer to your biologics license application (BLA) dated October 24, 2022, received October 24, 2022, and your amendments, submitted under section 351(a) of the Public Health Service Act for Rystiggo (rozanolixizumab-noli) injection, for subcutaneous use.

LICENSING

We have approved your BLA for Rystiggo (rozanolixizumab-noli) injection effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Rystiggo under your existing Department of Health and Human Services U.S. License No. 1736. Rystiggo is indicated for the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) or anti-muscle-specific tyrosine kinase (MuSK) antibody positive.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture rozanolixizumab drug substance at (b) (4) The final formulated drug product will be manufactured and filled at (b) (4) and labeled and packaged at UCB Pharma SA, Braine-l'Alleud, Belgium. You may label your product with the proprietary name, Rystiggo, and market it as 280 mg/2 mL (140 mg/mL) injection in a single-dose vial.

DATING PERIOD

The dating period for Rystiggo shall be 24 months from the date of manufacture when stored at 2°C to 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) °C.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Rystiggo 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 Rystiggo, 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). 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 carton and container labeling submitted on April 14, 2023, 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 *SPL Standard for Content of Labeling Technical Qs & As.* For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved BLA 761286**." Approval of this submission by FDA is not required before the labeling is used.

[1] See 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 at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

ADVISORY COMMITTEE

Your application for Rystiggo was not referred to an FDA advisory committee because this biologic 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(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.

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 adverse maternal, fetal, and infant outcomes resulting from the use of Rystiggo (rozanolixizumab-noli) during pregnancy and an unexpected serious risk of the potential presence of rozanolixizumab-noli in human breast milk resulting in effects on the breastfed infant.

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:

4427-1 Conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to rozanolixizumab-noli 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 June 15, 2023, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	3/2024
Final Protocol Submission:	1/2025
Annual Interim Report Submissions:	1/2026
	1/2027
	1/2028
	1/2029
	1/2030
	1/2031
	1/2032
	1/2033
	1/2034
Study Completion:	1/2035
Final Report Submission:	1/2036

4427-2 Perform a lactation study (milk only) in lactating women who have received therapeutic doses of rozanolixizumab-noli using a validated assay to assess concentrations of rozanolixizumab-noli in breast milk and the effects on the breastfed infant as applicable.

The timetable you submitted on June 15, 2023, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	02/2024
Final Protocol Submission:	09/2024
Study Completion:	02/2026
Final Report Submission:	07/2026

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]

Submit clinical protocol(s) to your IND 132407 with a cross-reference letter to this 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).**

[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.

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 NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4427-3 To develop a two-tiered reference standard system consisting of primary and working reference standards to support the rozanolixizumab-noli product lifecycle. The primary and working reference standard will be created from representative DS batches which have passed all release specifications. The first new reference standards will be qualified against the current reference standard (b) (4) according to a predefined protocol. The results for qualification of new primary and working/secondary reference standards will be submitted in a Prior Approval Supplement. Alternatively, protocols for qualification and requalification of future primary and working/secondary reference standards may be submitted as a Prior Approval Supplement, which may facilitate a reduced reporting category for implementation of new reference standards.

The timetable you submitted on June 09,2023, states that you will conduct this study according to the following schedule:

Final reference standard qualification report submission date: 02/29/2024

4427-4 To perform a shipping validation study under real time shipping conditions (i.e., temperature, mode of transport, shipping duration, and shipping containers and packing representative of the minimum and maximum load) using rozanolixizumab-noli finished product in the final commercial container closure and packaging systems to verify the impact of shipping on the product quality of rozanolixizumab-noli finished product. The shipping validation data will be submitted in accordance with 21 CFR 601.12.

The timetable you submitted on June 09,2023, states that you will conduct this study according to the following schedule:

Final shipping validation report submission date: 04/30/2024 (report covering winter condition) followed by 07/31/2024 (report covering summer condition)

REQUESTED PHARMACOVIGILANCE

We request that you perform postmarketing surveillance for serious events related to malignancy, reactivation of hepatitis B or of latent tuberculosis, and infection, including opportunistic infection. Include analyses of individual events as well as comprehensive summaries and analyses of these events, including incidence, quarterly as part of your required postmarketing safety reports [e.g., periodic safety update reports (PSURs)]. Include analyses of the events by age and sex. In the analysis of each case, provide an assessment of causality, with documentation of risk factors and results of all assessments that support the diagnosis or the causality, including IgG levels if available, along with extent of exposure to Rystiggo and most recent exposure to Rystiggo, concomitant therapies, treatment given for the event, and outcome.

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

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

[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:

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

POST APPROVAL FEEDBACK MEETING

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.

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

If you have any questions, contact Annie Nguyen, Regulatory Project Manager at Anhtu.Nguyen@fda.hhs.gov or at (240) 402-4460.

Sincerely,

{See appended electronic signature page}

Teresa Buracchio, MD
Director (Acting)
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information

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/

EMILY R FREILICH on behalf of TERESA J BURACCHIO
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