CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761286Orig1s000

OTHER REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency Templates
Version: 2018-01-24

Date:	June 21, 2023
Reviewer:	Catherine Callahan, PhD, MA Division of Epidemiology I
Team Leader:	Kira Leishear, PhD, MS Division of Epidemiology I
Division Director:	CAPT Sukhminder K. Sandhu PhD, MPH, MS Division of Epidemiology I
Subject:	ARIA sufficiency memo for study of safety of rozanolixizumab exposure during pregnancy and lactation.
Drug Name:	Rozanolixizumab-noli (RYSTIGGO)
Application Type/Number:	BLA 761286/IND 132407
Applicant/Sponsor:	UCB, Inc
TTT #:	2023-4504

1. BACKGROUND INFORMATION

1.1. Medical Product

Rozanolixizumab-noli is currently under review by the Division of Neurology 1 (DN1) for the proposed indication of treatment of adult patients with generalized myasthenia gravis who are anti-AchR or anti-MuSK antibody positive. Rozanolixizumab is a neonatal Fc receptor blocker. Rozanolixizumab decreases serum IgG concentration by inhibiting the binding of IgG to neonatal Fc receptor (FcRn), a receptor that normally protects IgG from intracellular degradation and recycles IgG back to the cell surface. By the same mechanism, rozanolixizumab decreases the concentration of pathogenic IgG autoantibodies associated with gMG. Clinical data with rozanolixizumab have not identified any clinically relevant impact on levels of albumin, which binds at a different site on FcRn.[1] The recommended dose of rozanolixizumab is administered as a subcutaneous infusion using an infusion pump at a rate of up to 20 mL/hour once weekly for 6 weeks. Subsequent treatment cycles may be administered based on clinical evaluation. The draft label for rozanolixizumab has warnings and precautions for infections. The most common adverse reactions are headache, infections including respiratory tract infection, diarrhea, pyrexia, hypersensitivity reactions, and nausea.[2]

1.2. Describe the Safety Concern

DN1 requested that the Division of Epidemiology (DEPI) assess the sufficiency of ARIA for a broad-based signal detection study of rozanolixizumab exposure during pregnancy and lactation.

Safety during pregnancy due to drug exposure is a concern for women who are pregnant or of childbearing potential. In the U.S. general population, the estimated background risk of major birth defects in clinically recognized pregnancies is 2–4% (Centers for Disease Control and Prevention 2008, Food and Drug Administration 2014). Myasthenia gravis is a serious, life-threatening, chronic autoimmune disease in which antibodies bind to acetylcholine receptors, muscle-specific kinase, or lipoprotein-related peptide 4 in the postsynaptic membrane at the neuromuscular junction (Gilhus 2016, Koneczny and Herbst 2019). Different antibodies can result in different subgroups of myasthenia gravis with variable phenotypes and severity. In most patients, the antibodies bind to acetylcholine receptors (Gilhus 2020). Approximately 15% of patients have a second autoimmune disease, 10% have a thymoma, and although rare, myocarditis occurs with an increased frequency in patients with myasthenia gravis (Gilhus 2016). Myasthenia gravis is a rare disorder, with an estimated prevalence in the general population of 150–250 individuals per million, and with an annual incidence of 8–10 individuals per million

[1] UCB, Inc. Rozanolixizumab Introduction to Summary
[2] RYSTIGGO Proposed U.S. labeling dated June 19, 2023.

(Gilhus 2016).

Myasthenia gravis with onset before age 50 years, thymic hyperplasia, and acetylcholine receptor antibodies is more common in females than in males. Muscle weakness, circulating autoantibodies, hyperplastic thymus, and any autoimmune comorbidity may influence both mother and infant health during pregnancy and during breastfeeding. Preterm rupture of amniotic membranes shows an increased frequency, and especially in those with myasthenia gravis deterioration during the pregnancy. Around 10% of newborns develop neonatal myasthenia during the first few days after birth, which is transient and usually mild. In rare cases, transplacental transfer of acetylcholine receptor antibodies leads to permanent muscle weakness in the child, and arthrogryposis with joint contractures. However, pregnancies among women with myasthenia gravis usually do not have complications (Gilhus 2020).

Pregnancy and breastfeeding were criteria for discontinuation in all rozanolixizumab studies. One pregnancy occurred in clinical studies of rozanolixizumab, in the open-label study MG0004 one subject gave birth to a full-term healthy child after 4-weeks exposure to rozanolixizumab ~7mg/kg dose in the first trimester of pregnancy.[3] In monkey studies there were more early pregnancy losses than controls.[4]

The proposed labeling for rozanolixizumab has the following information regarding pregnancy:[5]

8.1 Pregnancy

Risk Summary

There are limited data on RYSTIGGO use in pregnant women to inform a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. (b) (4) [redacted]

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background rate of major birth defects and miscarriage in the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

Subcutaneous administration of rozanolixizumab-noli to pregnant (b) (4) monkeys every 3 days, (b) (4) [redacted]

[3] U.S. Food and Drug Administration. Division of Neurology 1. Rozanolixizumab-noli (RYSTIGGO, UCB). Draft review dated June 19, 2023.

[4] U.S. Food and Drug Administration. Division of Pharm/Tox. Rozanolixizumab-noli (RYSTIGGO, UCB). Draft review dated June 19, 2023.

[5] RYSTIGGO Proposed U.S. labeling dated June 19, 2023.

8.2 Lactation

Risk Summary

There are no data on the presence of rozanolixizumab-noli in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for RYSTIGGO and any potential adverse effects on the breastfed child from RYSTIGGO or from the underlying maternal condition.

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

- Please ensure that the selected purpose is consistent with the other PMR documents in DARRTS

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)	
Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X

2. REVIEW QUESTIONS

2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

☐ Specific FDA-approved indication in pregnant women exists and exposure is expected

☐ No approved indication, but practitioners may use product off-label in pregnant women

☒ No approved indication, but there is the potential for inadvertent exposure before a pregnancy is recognized

☒ No approved indication, but use in women of child bearing age is a general concern

2.2. Regulatory Goal

☒ *Signal detection* – Nonspecific safety concern with no prerequisite level of statistical precision and certainty

☐ *Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty. †

☐ *Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review). †

† *If checked, please complete General ARIA Sufficiency Template.*

2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

☐ Pregnancy registry with internal comparison group
☐ Pregnancy registry with external comparison group
☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)
☐ Electronic database study with chart review
☐ Electronic database study without chart review
☒ Other, please specify: Descriptive pregnancy safety study, which enrolls exposed pregnancies into a protocol-driven observational cohort study for descriptive analyses and collects follow-up data, including detailed case narratives. These studies do not have the sample size required for inferential analyses. A single-arm pregnancy safety study is appropriate because this drug is indicated for a rare disease.

2.4. Which are the major areas where ARIA not sufficient, and what would be needed to make ARIA sufficient?

☒ Study Population
☐ Exposures
☒ Outcomes
☒ Covariates
☒ Analytical Tools

For any checked boxes above, please describe briefly:

Study Population: ARIA lacks the capacity to identify lactating women.

Outcomes: ARIA lacks access to detailed narratives. Given that the study for broad-based surveillance being considered is descriptive and without a comparison group, having detailed narratives are deemed necessary to identify and validate outcomes, assess exposure-outcome temporality, and to conduct causality assessments.

Covariates: ARIA does not have detailed information on potential confounders. The descriptive pregnancy safety study being considered would collect detailed narratives with information on potential covariates, such as lifestyle factors and prenatal supplement use.

Analytical tools: ARIA analytic tools are not sufficient to assess the regulatory question of interest because data mining methods have not been fully tested and implemented in postmarketing surveillance of maternal and fetal outcomes. The ARIA analytic tools that assess drug use in pregnancy (and maternal and neonatal outcomes) currently include only women with a live-birth delivery.

2.5. Please include the proposed PMR language in the approval letter.

Conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to rozanolixizumab 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.

3. References

Centers for Disease Control and Prevention (2008). "Update on overall prevalence of major birth defects--Atlanta, Georgia, 1978-2005." MMWR Morb Mortal Wkly Rep 57(1): 1-5.

Food and Drug Administration. (2014). "Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products — Content and Format. Draft Guidance." Guidance for Industry Retrieved May 8, 2023, from https://www.fda.gov/media/90160/download.

Gilhus, N. E. (2016). "Myasthenia Gravis." N Engl J Med 375(26): 2570-2581.

Gilhus, N. E. (2020). "Myasthenia Gravis Can Have Consequences for Pregnancy and the Developing Child." Front Neurol 11: 554.

Koneczny, I. and R. Herbst (2019). "Myasthenia Gravis: Pathogenic Effects of Autoantibodies on Neuromuscular Architecture." Cells 8(7).

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/s/

CATHERINE L CALLAHAN
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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: June 14, 2023

To: Roshell J. Weatherless-Stroble, Regulatory Project Manager, Division of Neurology 1 (DN1)

Tracy Peters, Associate Director for Labeling, DN1

From: Annette Egbonim, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, Team Leader, OPDP

Subject: OPDP Labeling Comments for RYSTIGGO (rozanolixizumab-noli) injection, for subcutaneous use

BLA: 761286

Background:
In response to DN1's consult request dated December 9, 2022, OPDP has reviewed the proposed Prescribing Information (PI), and carton and container labeling for the original BLA submission for RYSTIGGO (rozanolixizumab-noli) injection, for subcutaneous use.

PI:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP by DN1 on May 31, 2023, and our comments are provided below.

Carton and Container Labeling:
OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on April 14, 2023, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Annette Egbonim at Annette.Egbonim@fda.hhs.gov.

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/s/

ANNETTE O EGBONIM
06/14/2023 10:49:45 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	April 28, 2023
Requesting Office or Division:	Division of Neurology 1 (DN 1)
Application Type and Number:	BLA 761286
Product Name, Dosage Form, and Strength:	Rystiggo (rozanolixizumab-noli) injection, 280 mg/2 mL (140 mg/mL)
Applicant/Sponsor Name:	UCB, Inc.
TTT ID #:	2022-2501-1
DMEPA 2 Safety Evaluator:	Chad Morris, PharmD, MPH
DMEPA 2 Acting Team Leader:	Stephanie DeGraw, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on April 14, 2023 for Rystiggo. The Division of Neurology 1 (DN 1) requested that we review the revised container label and carton labeling for Rystiggo (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Morris, C. Label and Labeling Review for Rystiggo (BLA 761286). Silver Spring (MD): FDA, CDER, OSE, DMEPA2 (US); 2023 MAR 01. TTT ID No.: 2022-2501.

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04/28/2023 04:22:22 PM

Clinical Inspection Summary

Date	4/14/2023
From	Cara Alfaro, Pharm.D., Clinical Analyst Phillip Kronstein, M.D., Team Leader Jenn Sellers, M.D., Ph.D. Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Anhtu (Annie) Nguyen, Regulatory Project Manager Ami Mankodi, M.D., Medical Officer Laura Jawidzik, M.D., Team Leader Division of Neurology 1 Office of Neuroscience
NDA #/BLA #	BLA #761286
Applicant	UCB, Inc.
Drug	Rozanolixizumab
NME	Yes
Proposed Indication	Treatment of generalized myasthenia gravis in adult patients who are anti-acetylcholine receptor or anti-muscle-specific tyrosine kinase antibody positive
Consultation Request Date	12/1/2022
Clinical Inspection Summary Goal Date	4/23/2023
Priority/Standard Review	Priority
Action Goal Date	6/23/2023
PDUFA Date	6/23/2023

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Drs. Bril, Druzdz, Pascuzzi, and the sponsor, UCB Inc., were inspected in support of this BLA, covering Protocol MG0003. The study appears to have been conducted adequately, and the data generated by these sites and submitted by the sponsor appear acceptable in support of the respective indication.

Primary efficacy data, Myasthenia Gravis-Activities of Daily Living (MG-ADL), and secondary efficacy data, Quantitative Myasthenia Gravis (QMG), were verified; no discrepancies were identified for the double-blind treatment phase of the study. Additionally, there was no evidence of under-reporting of adverse events.

II. BACKGROUND

Rozanolixizumab injection for subcutaneous use is being developed under IND #132407 for the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) or anti-muscle-specific kinase (MuSK) antibody positive. The sponsor has submitted BLA #761286, which includes the results of a Phase 3 study (Protocol MG0003), to support the efficacy and safety of rozanolixizumab for this indication.

Protocol MG0003

Title: "A Phase 3, randomized, double-blind, placebo-controlled study evaluating efficacy and safety of rozanolixizumab in adult patients with generalized myasthenia gravis"

Subjects: 200

Sites: 93 sites; Western Europe (31), North America (28; United States [23]), Eastern Europe (15), Asia/Pacific (14), Middle East/Central Asia (5)

Study Initiation and Completion Dates: 6/18/2019 – 9/17/2021

Database Lock Date: 11/12/2021

This was a randomized, double-blind, placebo-controlled study evaluating rozanolixizumab in subjects with generalized myasthenia gravis (gMG). Main eligibility criteria included males or females, ≥18 years of age; documented diagnosis of generalized MG; confirmed positive record of autoantibodies against anti-acetylcholine receptor (AChR) or anti-muscle-specific kinase (MuSK) at screening; Myasthenia Gravis Foundation of America (MGFA) Class II to IVa; Myasthenia Gravis-Activities of Daily Living (MG-ADL) score ≥3 (with ≥3 points from non-ocular symptoms) AND a Quantitative Myasthenia Gravis (QMG) score of ≥11 at screening and baseline.

The study was comprised of three periods: a screening period, a treatment period, and an observation period.

Screening Period (Day -28 to -1/Visit 1)
During this period, study eligibility was determined. Study procedures included, but were not limited to, medical history, physical examination, ECG, labs, MGFA classification, MG-ADL, and QMG.

Treatment Period (Day 1 [baseline] to Day 43/Visits 2 to 10)
Subjects were randomized (1:1:1) to one of the following study arms:

- Rozanolixizumab equivalent to approximately 7 mg/kg subcutaneous (SC) infusion once per week for 6 weeks
- Rozanolixizumab equivalent to approximately 10 mg/kg SC infusion once per week for 6 weeks
- Placebo SC infusion once per week for 6 weeks

Investigational product (IP) dosing was weight-based as shown in the table below.

Weight	Rozanolixizumab ~7 mg/kg	Rozanolixizumab ~10 mg/kg
<50 kg	280 mg	420 mg
≥50 to <70 kg	420 mg	560 mg
≥70 to <100 kg	560 mg	840 mg
≥100 kg	840 mg	1120 mg

Subjects were to be observed for at least 4 hours following the first 2 infusions. For all subsequent infusions, the observation period was 2 hours.

Subjects who experienced disease worsening, defined as an increase of 2 points on the MG-ADL or 3 points on the QMG scale between two consecutive visits, could receive rescue therapy with intravenous immunoglobulin (IVIg) or plasma exchange (PEX) and complete all study visits in this treatment period. If rescue therapy was administered, IP was to be discontinued. These subjects could continue into the Observation Period.

Observation Period (Day 57 to Day 99/Visits 11 to 14)
The observation period was an 8-week blinded period; no IP was administered during this period. If subjects experienced disease worsening during this period, they could receive rescue therapy (IVIg or PEX) or complete the end of study visit and roll over into a separate open-label extension protocol. Subjects who received rescue therapy were to complete all remaining visits in this observation period but could not enroll in the open-label extension protocol.

The *primary efficacy endpoint* was the change from baseline (Day 1) to Day 43 in MG-ADL score. A *secondary efficacy measure* was the QMG score.

Rationale for Site Selection
Clinical sites were chosen based on risk ranking in the Clinical Investigator Site Selection Tool (CISST), enrollment, and prior inspection history.

III. RESULTS

1. **Vera Bril, M.D.**
   Site #50069
   University Health Network (UHN)
   Toronto General Hospital
   200 Elizabeth St
   5EC Toronto, Ontario
   M5G 2C4 CAN
   Inspection Dates: 1/23/2023 – 1/27/2023

   At this site for Protocol MG0003, 18 subjects were screened, 12 subjects were randomized, all of whom completed the study.

   Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records for all randomized subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, and primary (Myasthenia Gravis-Activities of Daily Living [MG-ADL]) and secondary (Quantitative Myasthenia Gravis [QMG]) efficacy endpoint data.

   The primary efficacy variable, MG-ADL, was completed on paper by subjects. The secondary efficacy variable, QMG, was completed on paper by trained raters. Scores recorded on paper source were verified against sponsor data line listings; no discrepancies were identified for the 6-week double-blind treatment period. Two discrepancies were identified in two subjects for the 8-week blinded observation period, the period in which no investigational product (IP) was administered. These errors were due to incorrect scores entered into the eCRF for some individual MG-ADL items.

   - Subject #50069-(b) (6), randomized to rozanolixizumab 7 mg/kg, had a Visit 12 MG-ADL score on paper source of 8 compared to the sponsor data line listing score of 10
   - Subject #50069(b) (6), randomized to rozanolixizumab 7 mg/kg, had a Visit 14 QMG score on paper source of 24 compared to the sponsor data line listing score of 20

   There was no evidence of underreporting of adverse events.

   Reviewer comments: Two efficacy endpoint data discrepancies were identified for two subjects for the observation period of the study. The 6-week double-blind period was the timepoint of interest for the primary and secondary efficacy endpoints; therefore, discrepancies occurring during the observation period should not impact the overall efficacy analyses.

2. Robert Pascuzzi, M.D.
Site #50114
Indiana University Health Neuroscience Center
355 West 16th Street
Suite 4700
Indianapolis, IN 46202
Inspection Dates: 1/23/2023 – 1/27/2023

At this site for Protocol MG0003, 5 subjects were screened, 5 subjects were randomized, and 3 subjects completed the study. Two subjects, randomized to placebo, discontinued the study due to lack of efficacy.

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records for all randomized subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, and primary (MG-ADL) and secondary (QMG) efficacy endpoint data.

The primary efficacy variable, MG-ADL, was completed on paper by subjects. The secondary efficacy variable, QMG, was completed on paper by trained raters. Scores recorded on paper source were verified against sponsor data line listings; no discrepancies were identified. Additionally, there was no evidence of underreporting of adverse events.

According to the protocol, oral corticosteroids were allowed if the dose was stable for 4 weeks prior to baseline and throughout the study. Subject #50114-(b) (6) was receiving prednisone 17.5 mg prior to the study, was randomized to rozanolixizumab 10 mg/kg on (b) (6) and had an increase in prednisone dose to 20 mg/day on (b) (6). This protocol deviation was included in the sponsor data line listing.

Reviewer comments: This subject completed the 6-week double-blind treatment period on (b) (6). The increase in prednisone dose occurred during the observation period. The 6-week double-blind period was the timepoint of interest for the primary and secondary efficacy endpoints; therefore, an increase in concomitant prednisone dose occurring during the observation period should not impact the overall efficacy analyses.

3. **Artur Druzdz, M.D**
Site #40153
Clinical Research Center Sp. ZO.O.
Medic-R Sp. K., Ul. Feliksa
Poznan, Wielkopolskie, 61-731
Poland
Inspection Dates: 2/20/2023 – 2/24/2023

At this site for Protocol MG0003, 15 subjects were screened, 11 subjects were randomized, all of whom completed the study.

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records for 10 of 11 (90.9%) randomized subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, and primary (MG-ADL) and secondary (QMG) efficacy endpoint data.

The primary efficacy variable, MG-ADL, was completed on paper by subjects. The secondary efficacy variable, QMG, was completed on paper by trained raters. Scores recorded on paper source were verified against sponsor data line listing; no discrepancies were identified. Additionally, there was no evidence of underreporting of adverse events.

4. **UCB, Inc.**
4000 Paramount Pkwy
Suite 200
Morrisville, NC 27560-8484
Inspection Dates: 3/20/2023 – 3/24/2023

This inspection covered sponsor practices related to Protocol MG0003 and focused on the three clinical investigator sites chosen for inspection.

Records reviewed during the inspection included, but were not limited to, SOPs, organizational charts, monitoring plan and reports, site selection/qualification, monitor qualification, vendor list, contracts, investigator agreements and 1572s, investigator compliance/corrective actions, IRB approvals, eCRFs, data management, financial disclosure forms, pharmacovigilance procedures and documentation, protocol deviations, and IP accountability.

UCB contracted with the CRO, (b) (4), to perform many of the sponsor responsibilities including, but not limited to: clinical investigator selection, site qualification/initiation/training, trial management, electronic trial master file (eTMF) management, medical oversight, data management, clinical monitor selection and clinical site monitoring, and risk management/data

surveillance. UCB retained oversight for many of the responsibilities contracted to (b) (4) UCB has been in a partnering collaboration with (b) (4) since (b) (4). UCB audits (b) (4) annually, which includes reviewing their SOPs and policies.

Clinical monitoring was conducted by (b) (4) and was consistent with the monitoring plan. According to the sponsor, no sites were terminated, and there were no issues regarding clinical investigator noncompliance. Through their quality assurance (QA) activities, UCB also conducts audits of clinical sites as well as vendors. No deficiencies in QA activities were identified during the inspection.

The process for safety and adverse event reporting was reviewed; no issues were identified. UCB appointed an independent data monitoring committee (IDMC) composed of four external members who were immunologists or statisticians and not employees of the sponsor or CRO. The IDMC met with representatives of UCB and (b) (4) monthly in open meetings. Only IDMC members participated in closed meetings.

According to the sponsor, there was one incident of accidental unblinding caused by a UCB employee. When investigating a suspected unexpected serious adverse reaction (SUSAR) of gastritis occurring in Subject #50121-(b) (6), randomized to rozanolixizumab 7 mg/kg, an UCB employee used an incorrect access function in the computerized system that automatically sent emails containing unblinding information for the subject to several blinded members within (b) (4), including the blinded clinical monitor as well as the clinical site. At the time of this unblinding, the subject had completed the double-blind treatment phase of the study and was in the observation period of the study. A corrective and preventive action (CAPA) was prepared to prevent future occurrences.

Reviewer comments: The unblinding for this subject occurred after the subject had completed the double-blind treatment period; therefore, it is unlikely to have impacted efficacy analyses.

Rozanolixizumab was visibly different from placebo (normal saline) in color (yellowish as described by the sponsor) and viscosity. Due to these differences, the "IP Instructions for Handling" manual originally required that unblinded site personnel prime the infusion line prior to administration of IP in order to maintain the study blind. As a result of staff shortages at some clinical sites due to COVID-19, the IP manual was revised (Version 7, 6/29/2020), allowing blinded staff to perform the priming provided that measures were taken to prevent potential unblinding by making the primed volume visible. If blinded staff were to be used, the site had to make this request and it had to be approved by the local (b) (4) clinical site manager. The sponsor provided a list of 26 of 93 (27.9%) sites that used blinded staff to prime the infusion line.

Reviewer comments: The "IP Instructions for Handling" manual described procedures for maintaining the blind if blinded staff primed the infusion line. These instructions were also provided to clinical sites in a note to file written by (b) (4) and dated (b) (4); the IP manual

was updated with this information in the version dated (b) (4) *. The procedures used to maintain the blind when blinded staff primed the infusion line appear adequate.*

{See appended electronic signature page}

Cara Alfaro, Pharm.D.
Clinical Analyst
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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Phillip Kronstein, M.D.
Team Leader
Good Clinical Practice Assessment Branch
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CONCURRENCE:

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Jenn Sellers, M.D., Ph.D.
Branch Chief
Good Clinical Practice Assessment Branch
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cc:

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Division of Neurology 1/Division Director/Teresa Buracchio
Division of Neurology 1/Deputy Division Director/Emily Freilich (Acting)
Division of Neurology 1/Medical Team Leader/Laura Jawidzik
Division of Neurology 1/Medical Officer/Ami Mankodi
Division of Neurology 1/Project Manager/Anhtu (Annie) Nguyen

OSI/Office Director/David Burrow
OSI/Office Deputy Director/Laurie Muldowney
OSI/DCCE/Division Director/Kassa Ayalew
OSI/DCCE/GCPAB/Branch Chief/Jenn Sellers
OSI/DCCE/GCPAB/Team Leader/Phillip Kronstein
OSI/DCCE/GCPAB/Clinical Analyst/Cara Alfaro
OSI/DCCE/GCPAB Program Analyst/Yolanda Patague
OSI/DCCE/GCPAB Program Analyst/Loreto-Corazon Lim

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JENN W SELLERS
04/14/2023 02:02:40 PM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	March 1, 2023
Requesting Office or Division:	Division of Neurology 1 (DN 1)
Application Type and Number:	BLA 761286
Product Name and Strength:	Rystiggo (rozanolixizumab-xxxx)[a] injection, 280 mg/2 mL (140 mg/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	UCB, Inc.
FDA Received Date:	October 24, 2022
TTT ID #:	2022-2501
DMEPA 2 Safety Evaluator:	Chad Morris, PharmD, MPH
DMEPA 2 Acting Team Leader:	Stephanie DeGraw, PharmD

[a] The proposed nonproprietary name with suffix "rozanolixizumab-(b)(4)" is used in the labeling submitted under BLA 761286; however, the acceptability of the suffix is still under review by the Agency, and will be denoted as -xxxx in this review.

1 REASON FOR REVIEW

As part of the approval process for Rystiggo (rozanolixizumab-xxxx) injection, the Division of Neurology 1 (DN 1) requested that we review the proposed Rystiggo prescribing information (PI), carton labeling, and container label for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C (N/A)
FDA Adverse Event Reporting System (FAERS)*	D (N/A)
Other	E (N/A)
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 CONCLUSION AND RECOMMENDATIONS

The proposed PI, carton labeling, and container label may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for the Division and in Section 5 for UCB, Inc.

4 RECOMMEDATIONS FOR DIVISION OF NEUROLOGY 1 (DN 1)

See Appendix G for screenshots of our proposed PI revisions.

Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN 1)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			
1.	The symbols ≥ and < are used in the HPI and Section 2 of the full PI.	Symbols may be misinterpreted.	We recommend replacing symbols with their intended

Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN 1)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			meaning, “greater than or equal to” and “less than”.
2.	A unit of measure does not follow each number in the dosing tables used in the HPI and Section 2 of the full PI.	Add for clarity and completeness.	We recommend adding the unit of measure “kg” after each weight.
3.	The dosing tables used in the HPI and Section 2 of the full PI do not contain the dose in mL.	Incomplete dosing information may increase the risk for wrong dose medication errors.	We recommend adding the dose (volume to be infused) in mL as a separate column in the dosing table in HPI and Section 2. Alternatively, if a third column cannot be added, specifically in the HPI section, consider adding the dose volume in parentheses after the dose in mg. For example: 420 mg (3 mL) 560 mg (4 mL)
Full Prescribing Information – Section 2 Dosage and Administration			
1.	General administration information is presented separately in multiple areas.	Can be improved for completeness and clarify.	We recommend combining statements from multiple locations into one recommended dose administration statement in 2.1 appearing after Table 1 to read “Administer the recommended dose as a subcutaneous infusion using an infusion pump at a rate of up to 20 mL/hour once weekly for 6 weeks.”
2.	In Section 2.1, the recommended dose administration statement can be improved for clarity and directness by adding a	This may help reduce the risk for preparation and administration errors.	We recommend adding language referring the user to preparation and administration instructions, such as “See Section 2.3 for detailed

Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN 1)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
	parenthetical reference to Section 2.3.		preparation and administration instructions.
3.	Section 2.2 contains duplicative dosing and packaging information.	Remove for brevity.	We recommend removing the statements (b) (4) and (b) (4) as this information is presented elsewhere in more appropriate locations within Section 2.
Full Prescribing Information – Section 2.3 (b) (4)			
1.	Two vials are always needed to provide one dose, and the words "vial and "vials" are used inconsistently and/or inappropriately.	May increase the risk for selecting the wrong number of vials for use.	We recommend revising use of the word "vial" to "vials" throughout the IFU to indicate the need for more than one vial per dose. Also, we recommend updating use of "carton" in Step 1 to "cartons", and "alcohol wipe" in Step 2 to "alcohol wipes", and other revisions to indicate two vials of the product are required. Additionally, (b) (4)
2.	Some of the (b) (4) are unclear and overall, we find the (b) (4) to be unnecessary for the	Revise for clarity and to be appropriate for HCP preparation and administration.	We recommend removing the (b) (4).

Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN 1)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	intended uses, healthcare providers (HCPs), to successfully perform the steps required to prepare and administer the product.		
3.	(b) (4) contradicts itself by stating to (b) (4) .	Revise for clarity and consistency.	We recommend deleting the statement (b) (4)
4.	(b) (4)	The second option may increase the risk for overdose, especially for patients that only require a 3 mL dose since 4 mL or more will be in the syringe.	We recommend labeling the product to be administered with infusion pumps that allow pre-setting the volume to be infused only.
5.	In Step 10, the recommended infusion rate is missing.	Add for completeness to prevent wrong rate of administration errors.	We recommend adding the statement "Infuse RYSTIGGO at a constant flow rate up to 20 mL/hour.".
6.	(b) (4)	(b) (4)	(b) (4) .
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			

Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN 1)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	The description of the packaging is poorly worded.	This can be improved for clarity.	We recommend revising "RYSTIGGO (rozanolixizumab-(b) (4) injection is a sterile, preservative-free, clear to slightly opalescent, colorless to pale brownish yellow solution. (b) (4) supplied as: 280 mg/2 mL (140 mg/mL) (b) (4) NDC 50474-980-79" to read: "RYSTIGGO (rozanolixizumab-(b) (4) injection is a sterile, preservative-free, clear to slightly opalescent, colorless to pale brownish yellow solution supplied as a: 280 mg/2 mL (140 mg/mL) single-dose glass vial in a carton: NDC 50474-980-79"
2.	The storage statement does not contain a unit of measure after each temperature numerical value.	This may increase the risk for improper storage medication errors.	We recommend revising the storage temperatures to read "36°F to 46°F (2°C to 8°C)."

5 RECOMMENDATIONS FOR UCB, INC.

Table 3. Identified Issues and Recommendations for UCB, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label(s) and Carton Labeling			
1.	The format for expiration date is not defined.	We are unable to assess from a medication error perspective.	To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use.

Table 3. Identified Issues and Recommendations for UCB, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. Please specify whether the month will be represented with numerical or alphabetical characters. FDA recommends that a forward slash or a hyphen be used to separate the portions of the expiration date.
2.	The presentation of the product strength is not expressed consistently.	Consistent presentation of the strength statement will reduce the risk for confusion.	Please ensure the product strength is expressed as total quantity per total volume followed by the concentration per milliliter (mL) in parenthesis. For example: 280 mg/2 mL (140 mg/mL)

Table 3. Identified Issues and Recommendations for UCB, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			or 280 mg/2 mL (140 mg/mL).
Container Label			
1.	The storage statement does not contain reference to refrigeration and does not contain other special storage and handling requirements.	This can be improved for directness and clarity to reduce the risk for improper storage.	We recommend revising the storage statement to read "Store refrigerated at 36°F to 46°F (2°C to 8°C). Protect from light. Do Not Freeze or Shake.".
2.	It is unclear whether the linear barcode on the container labels contains, at a minimum, the appropriate National Drug Code (NDC) number.	The NDC number must be contained within the linear barcode per 21 CFR 201.25.	Ensure the linear barcode on the container labels contains, at a minimum, the NDC number, in accordance with 21 CFR 201.25.
Carton Labeling			
1.	The established name lacks prominence commensurate with the proprietary name, and does not appear to be at least half the size of the proprietary name.	As currently presented, the established name does not appear to satisfy 21 CFR 201.10(g)(2).	Increase the prominence of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).
2.	The product is intended for healthcare provider use only; however, there is not a statement alerting patients, caregivers, or healthcare providers.	The statement will help alert patients and healthcare providers (particularly pharmacies who may dispense the product directly to the patient) that the patient should take the product to	Please add the statement "To be administered by a healthcare provider only" or similar to the principal display panel.

Table 3. Identified Issues and Recommendations for UCB, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		their healthcare provider for administration	
3.	The strength statement on the PDP is placed (b) (4)	The strength statement could get damaged under normal use conditions.	Please move the strength statement, so that it is less likely to become damaged under normal use conditions.
4.	The net quantity statement is disjointed and contains duplicative information.	Unnecessary separation of information and duplicative text may detract the user from other important information.	We recommend removing the vertical line between the number "1" and the package type statement, removing "2 mL", and replacing the number "1" with the word "one" to read: "One single-dose vial".
5.	The package type statement is missing the "discard unused portion" warning.	Incomplete information may increase the risk for deteriorated drug medication errors.	Please revise the package type statement to read "One single-dose vial – Discard unused portion".
6.	The (b) (4) is uninformative and unnecessary from a product identification perspective.	Unnecessary information may detract the user from other important information.	We recommend removing all (b) (4).
7.	There is a placeholder for serialization information, but not for a 2D barcode.	The Drug Supply Chain Security Act (DSCSA) requires certain prescription drugs to have a human-readable and machine-readable (2D data matrix barcode) product identifier on the smallest saleable unit (usually the carton) for tracking and tracing purposes.	Please add a placeholder for the 2D barcode.
8.	The storage statement does not contain a unit of measure after each	This may increase the risk for improper storage medication errors.	We recommend you revise the storage temperatures to read "36°F to 46°F (2°C to 8°C)."

Table 3. Identified Issues and Recommendations for UCB, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	temperature numerical value.		
9.	The recommended dose statement can be improved.	The language is not consistent with the prescribing information (PI).	We recommend revising the statement (b) (4) to read "Recommended Dosage: See prescribing information".

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Rystiggo that UCB, Inc. submitted on October 24, 2022.

Table 4. Relevant Product Information for Rystiggo	
Initial Approval Date	n/a
Active Ingredient	rozanolixizumab
Indication	treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) or anti-muscle-specific tyrosine kinase (MuSK) antibody positive
Route of Administration	Subcutaneous infusion
Dosage Form	Injection
Strength	280 mg/2 mL (140 mg/mL)
Dose and Frequency	420 mg or 560 mg once weekly for 6 weeks
How Supplied	Carton containing one single dose vial
Storage	Store vials refrigerated at 36° to 46°F (2° to 8°C) in the original carton until the time of use. Do not freeze. Vials may be stored at room temperature up to 77°F (25°C) for a single period of up to 30 days in the original carton to protect the vial from light.
Container Closure[b]	(b) (4) clear neutral (b) (4) glass vial with a 6mL ((b) (4) nominal capacity, closed with a (b) (4)

[b] Container closure specifications available from: \\CDSESUB1\EVSPROD\bla761286\0001\m3\32-body-data\32p-drug-prod\rozimab-sol-inj-common\32p7-cont-closure-sys\container-closure-system-dp-rozi-ma-eu.pdf

APPENDIX B. PREVIOUS DMEPA REVIEWS

On January 13, 2023, we searched for previous DMEPA reviews relevant to this current review using the terms, BLA 761286, rozanolixizumab, and UCB7665. Our search did not identify any previous reviews.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

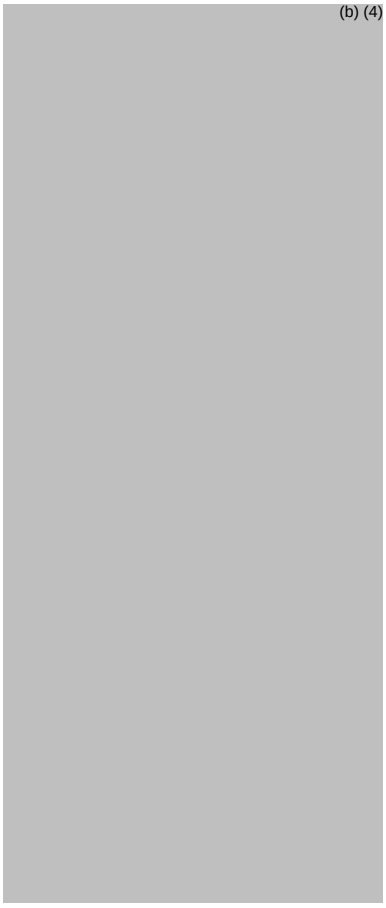
Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Rystiggo labels and labeling submitted by UCB, Inc. on October 24, 2022.

- Container label
- Carton labeling
- Prescribing Information (Image not shown), available from \\CDSESUB1\EVSPROD\bla761286\0001\m1\us\114-labeling\draft\labeling\cir-202209-sub.docx

F.2 Label and Labeling Images

Container label

(b) (4)



[c] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

6 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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