CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761140Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

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:	December 17, 2020
Requesting Office or Division:	Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number:	BLA 761140
Product Name and Strength:	Riabni (rituximab-arrx)* Injection, 100 mg/10 mL, 500 mg/50 mL
Applicant/Sponsor Name:	Amgen Inc.
OSE RCM #:	2019-2613-3
DMEPA Safety Evaluator:	Nicole Iverson, PharmD, BCPS
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on December 11, 2020, December 15, 2020, and December 16, 2020 for Riabni. We reviewed the revised container labels and carton labeling for Riabni (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to a recommendation from the Agency to revise name of the manufacturer from "Amgen Inc." on the proposed labeling and labeling to be consistent with the name on the license, which is "Amgen, Inc.". The revisions were also in response to an information request dated December 15, 2020[a] requesting the Applicant to place adequate space between the numerical dose and unit of measure for the 500 mg/50 mL strength and reorient the linear barcode on the 500 mg/50 mL container label for the ABR packaging site to a vertical position to improve the scannability of the barcode.

* The proposed proprietary name (Riabni) and proposed nonproprietary name (rituximab-arrx) are only conditionally accepted for this product until the application is approved.

[a] Wall L. FDA Communication: Information Request for Riabni (BLA 761140). Silver Spring (MD): FDA, CDER, OOD, DHM2 (US); 2020 DEC 15.

2 CONCLUSION

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

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

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Division of Pediatric and Maternal Health
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M E M O R A N D U M

From:	Ndidi Nwokorie, MD, Medical Officer Division of Pediatric and Maternal Health (DPMH) Office of Rare Diseases, Pediatrics, Urologic & Reproductive Medicine (ORPURM) Office of New Drugs (OND)
Through:	Erica Radden, MD, Lead Medical Officer John J. Alexander, MD, MPH, Deputy Director DPMH, ORPURM, OND
To:	Division of Hematologic Malignancies II (DHM2) Office of Oncologic Diseases (OOD)
Subject:	Labeling Review for Pediatric Use
Drug:	ABP 798 (Proposed Biosimilar to US-licensed Rituximab)
Proprietary Name:	RIABNI (rituximab-arrx)
Application Number:	BLA 761140 (IND 118281)
Applicant:	Amgen, Inc

Proposed Indications: Treatment of:

- non-Hodgkin's lymphoma (NHL);
- chronic lymphocytic leukemia (CLL); and
- granulomatosis with polyangiitis (GPA) (Wegener's granulomatosis) and microscopic polyangiitis (MPA) in adult patients in combination with glucocorticoids.

Proposed Dosage Form & Strength: Injection: 100 mg/10 mL (10 mg/mL) and 500 mg/50 mL (10 mg/mL) solution in single-dose vials

Route of Administration: Intravenous Infusion

Proposed Dosing Regimen:

- The dose for NHL is 375 mg/m^2
- The dose for CLL is 375 mg/m^2 in the first cycle and 500 mg/m^2 in cycles 2-6, in combination with fludarabine and cyclophosphamide, administered every 28 days
- The induction dose for adult patients with active GPA and MPA in combination with glucocorticoids is 375 mg/m2 once weekly for 4 weeks. The follow up dose for adult patients with GPA and MPA who have achieved disease control with induction treatment, in combination with glucocorticoids is two 500 mg intravenous infusions separated by two weeks, followed by a 500 mg intravenous infusion every 6 months thereafter based on clinical evaluation

Consult Request:
DHM2 consulted DPMH to provide assistance with labeling language for subsection 8.4, Pediatric Use.

Materials Reviewed:
Documents tracked under BLA 761140, ABP 798, in DARRTS

- Agreed Initial Pediatric Study Plan, 12/19/2019
- Amended Pediatric Study Plan, 12/19/2019
- DPMH Consult Request for ABP 798
- PeRC Minutes, 04/11/18
- Applicant's Draft Labeling for ABP 798, 12/19/2019

Documents tracked under BLA 761088, Truxima (rituximab-abbs) in DARRTS

- Cover Letter (Sequence 0070), 10/18/2019

Accessed from Drugs@FDA

- Rituxan Label (rituximab) BLA #103705 accessed on 01/31/2020
- Ruxience Final Label (rituximab-pvvr) BLA 761103 accessed on 06/12/2020
- Truxima Final Label (rituximab-abbs) BLA 761088 accessed on 06/12/2020
- Inflectra Final Label (infliximab-dyyb) BLA 125544 accessed on 10/6/2020
- Renflexis Final Label (infliximab-abda) BLA 761054 accessed on 10/6/2020

I. Regulatory Background:

On December 19, 2019, Amgen, Inc. submitted a BLA for ABP 798 under the 351(k) pathway as a proposed biosimilar to U.S.-licensed Rituxan (rituximab) (hereinafter Rituxan). Rituxan is licensed by Genentech USA, Inc. and was first approved by FDA in 1997. Rituximab is a genetically engineered chimeric murine/human monoclonal antibody that acts through binding to CD20 antigen expressed on the surface of pre-B and mature B-lymphocytes. Upon binding to CD20, rituximab mediates B-cell lysis. Possible mechanisms of cell lysis include complement dependent cytotoxicity (CDC) and antibody dependent cell mediated cytotoxicity (ADCC).[1]

Rituxan is approved for the following indications:

- Adult patients with Non-Hodgkin's Lymphoma (NHL);
- Adult patients with Chronic Lymphocytic Leukemia (CLL);
- Rheumatoid arthritis (RA) in combination with methotrexate in adult patients with moderately- to severely-active RA who have inadequate response to one or more tumor necrosis factor (TNF) antagonist therapies
- Granulomatosis with Polyangiitis (GPA) (Wegener's granulomatosis) and Microscopic Polyangiitis (MPA) in adult **and pediatric patients 2 years of age and older in combination with glucocorticoids**; and
- Moderate to severe Pemphigus Vulgaris (PV) in adult patients.

Rituxan has no outstanding pediatric postmarketing requirements or commitments. Genentech, Inc. received a full waiver of the requirement to provide a pediatric assessment under the Pediatric Research Equity Act (PREA) for the RA indication (and the pediatric equivalent condition, juvenile idiopathic arthritis [JIA]) "due to concerns regarding the potential for prolonged immunosuppression as a result of B-cell depletion in the developing juvenile immune system."[1]. FDA granted Genentech, Inc. orphan designation for Rituxan for the NHL, CLL, GPA/MPA, and

[1] Rituxan Label (rituximab) BLA 103705 accessed on 01/31/2020

PV indications, therefore PREA did not apply to these indications. The orphan exclusivity FDA granted for the original approval of the MPA/GPA indication in adults expired April 19, 2018; however, upon approval of Rituxan for MPA/GPA in patients 2 years of age and older in September 2019, FDA granted orphan exclusivity for this indication that expires in September 2026. Of note, FDA approved the PV indication on June 7, 2018, and also granted Rituxan exclusivity for this indication until June 7, 2025. Amgen is not seeking approval for these indications. DHM2 requested DPMH-Pediatrics team to assist in providing labeling recommendations for pediatric use.

II. Pediatric Study Plan

Under PREA, all applications for new active ingredients, 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. Section 505B(l) of the FD&C Act provides that a biosimilar product that has not been determined to be interchangeable with the reference product is considered to have a new "active ingredient" for purposes of PREA. A pediatric assessment is required unless waived, deferred, or inapplicable. The Agency confirmed agreement with the Agreed initial Pediatric Study Plan (iPSP) on June 22, 2018 which Amgen included with their BLA submission. In the Agreed iPSP, Amgen outlined a plan to request full waivers for the NHL, CLL, RA and GPA/MPA indications, summarized in Table 1 below.

Table 1. Agreed Planned Waiver Requests for ABP 798[2]

Indication	Age	Waiver Type	Criteria
Non-Hodgkin lymphoma	Birth to 17 years	Full	Necessary studies are impossible or highly impracticable
Chronic Lymphocytic leukemia	Birth to 17 years	Full	Necessary studies are impossible or highly impracticable
Rheumatoid arthritis (juvenile idiopathic arthritis)	Birth to 17 years	Full	Evidence strongly suggest that this product would be unsafe in this age group
Granulomatosis with polyangiitis (Wegener's granulomatosis) and microscopic polyangiitis	Birth to 17 years	Full	Necessary studies are impossible or highly impracticable

[2] Agreed iPSP, IND 118281, dated 6-22-2018 in DARRTS

Subsequently, FDA published draft guidance for industry *New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 2)* on December 12, 2018 which provides recommendations on fulfilling PREA requirements for biosimilars. The draft guidance states in the answer to Q.I.16, "If the labeling for the reference product does not contain adequate pediatric information for one or more pediatric age groups for an indication for which a biosimilar applicant seeks licensure in adults, and PREA requirements were waived for, or inapplicable to, the reference product for those pediatric age groups, a biosimilar applicant should note this information in its initial pediatric study plan (iPSP), if any, but does not need to request a waiver of PREA requirements for those age groups." Additionally, subsequent to this iPSP agreement, FDA approved Rituxan for the pediatric indication for GPA/MPA. Accordingly, Amgen submitted an Amended PSP with its BLA submission to amend its proposal for satisfying PREA requirements for the adult GPA/MPA indication and to reflect the updated advice in the draft guidance. Because the Amended PSP was not submitted prior to the BLA submission, the division plans to review the proposed amendment during the review cycle. FDA conveyed this decision to the Applicant in a 74 Day Letter sent to the Applicant on February 27, 2020.

In this Amended PSP, Amgen proposed providing a pediatric assessment with its original BLA for GPA/MPA for patients 2 years and older. To support the assessment, Amgen proposes to demonstrate biosimilarity to Rituxan and to provide an adequate justification under the Biologics Price Competition and Innovation Act of 2009 (BPCI Act) to support extrapolation of data and information to support licensure for GPA/MPA. Nevertheless, due to Rituxan's existing orphan exclusivity for this indication, Amgen cannot obtain approval for the pediatric GPA/MPA indication until the associated exclusivity expires. In accordance with the draft guidance, Amgen also noted the waivers and exemptions granted to the reference product, Rituxan, which are summarized in Table 2.

Table 2. PREA Waivers/Exemptions for Rituxan[3]

Indication	Age	Waiver Type or Exemption	Criteria
NHL	Birth to 17 years	Exempt	Indication is orphan drug designated and exempt from PREA requirements
CLL	Birth to 17 years	Exempt	Indication is orphan drug designated and exempt from PREA requirements
RA (JIA)	Birth to 17 years	Full	Evidence strongly suggests that this product would be unsafe in this age group
GPA/MPA	Birth to < 2 years	Exempt	Indication is orphan drug designated and exempt from PREA requirements

Accordingly, because Rituxan does not have adequate pediatric information in its labeling, and PREA requirements were either waived for, or inapplicable to, these indications and subpopulations, Amgen will not be required to provide a pediatric assessment for these indications and subpopulations.

During the review of this BLA, Amgen has decided not to seek approval for the RA indication. Therefore, Amgen is only seeking approval for the NHL, CLL and adult GPA/MPA indications. Of note, the proposed dosage form and strengths of 100 mg/10 mL 500 mg/50 mL single vial solution for injection are age-appropriate for the pediatric GPA/MPA population.

III. DPMH Review of Pediatric Use Labeling:

Discussion on Pediatric Labeling Recommendations:

DPMH met with DHM2, along with Office of Therapeutic Biologics and Biosimilars (OTBB), Office of Chief Council (OCC), Division of Gastroenterology (DG) and Division of Rheumatology and Transplant Medicine (DRTM) to discuss a path forward regarding pediatric labeling for this product and other biosimilars that are seeking approval for adult indications in which the reference product has unexpired orphan exclusivity for the pediatric population (or a pediatric age range). Such biosimilar applicants may choose to submit the pediatric assessment (*e.g.*, by satisfying the statutory requirements for demonstrating biosimilarity and providing an adequate justification under the BPCI Act to support extrapolation of data and information to support licensure in the pediatric indication) with the original BLA submission rather than request a deferral of the required pediatric assessment until the orphan exclusivity for the pediatric indication (or pediatric age range) expires. However, the Agency could not license the proposed product for the pediatric

[3] Amended PSP, BLA 761140, submitted 12-19-2019

indication (or pediatric age range). The Agency would review the pediatric assessment during the pendency of the submission but would not license the proposed product for the orphan-protected indication. As noted above, Amgen submitted its pediatric assessment for pediatric GPA/MPA in pediatric patients two years of age and older with the original BLA submission. Under Sections 505A(j) and 505B(g)(2) of the Federal Food, Drug, and Cosmetic Act, pediatric assessments must be described in labeling whether findings are positive, negative, or inconclusive. However, due to existing orphan exclusivity for the reference product, Riabni cannot be approved for the pediatric GPA/MPA indication until that exclusivity expires. Therefore, if the Agency determines that the pediatric assessment is adequate, the labeling should include the following statement: "A pediatric assessment for RIABNI demonstrated that RIABNI is safe and effective for an indication for which Rituxan (rituximab) is approved. However, RIABNI is not approved for such indication due to marketing exclusivity for Rituxan (rituximab)." DPMH recommends that the Agency advise Amgen to update its labeling once relevant exclusivity expires. Furthermore, if the pediatric assessment is found to be adequate, we would not issue any pediatric postmarketing requirement for that indication.

Note, the Applicant's proposed tradename for ABP 798 is RIABNI.

DPMH Recommended Labeling

This DPMH labeling review of ABP 798 (RIABNI) will focus primarily on subsection 8.4. DPMH proposes the following recommendations based on labeling discussions between DHM2, OTBB, DRTM, and DPMH in which underlined text represents our proposed additions and strikethroughs represent our proposed deletions to the Applicant's proposed labeling.

Applicant's Proposed Labeling

8 Use in Specific Populations

8.4 Pediatric Use

A pediatric assessment for RIABNI demonstrates that RIABNI is safe and effective for pediatric patients in an indication for which Rituxan (rituximab) is approved. However, RIABNI is not approved for such indication due to marketing exclusivity for Rituxan (rituximab). The safety and effectiveness of rituximab products, including RIABNI, have not been established in pediatric patients less than 2 years of age for GPA and MPA.

The safety and effectiveness of rituximab products, including RIABNI have not been established in pediatric patients ~~with~~ for NHL or CLL.

Reviewer Comment:
Rituxan labeling that is specific to pediatric GPA/MPA does not provide any safety information that is not adequately captured in the labeling for the other approved indications, which would preclude safe use if excluded. Therefore, information specific to the pediatric GPA/MPA indication from the Rituxan labeling should be excluded at this time. DPMH added the proposed labeling disclaimer based on the templated language agreed upon with OCC/ORP and the approach taken in Inflectra (infliximab-dyyb) labeling dated 4/5/2016 and Renflexis (infliximab-abda) labeling dated 4/21/2017 (see above).[4,5] *We also added limitation of use language, consistent with the principles in the March 2019 Final Pediatric Labeling Guidance,*[6] *and aligned with the Rituxan (rituximab) labeling which included the language, "RITUXAN is not indicated in pediatric patients less than 2 years of age with GPA or MPA.*[1] *"*

While policy decisions regarding section 8.4 remain ongoing, the proposed approach here was agreed upon by DPMH, OTBB, and DHM2 at this time.

IV. Conclusion:

DPMH reviewed the applicant's draft labeling and participated in the team meetings held during July through October 2020. The Pediatric Review Committee reviewed and concurred with the proposed pediatric plan on October 27, 2020. DPMH provided recommended labeling for the pediatric population based on labeling discussions between DHM2, DRTM, OTBB, and DPMH and in accordance with 21 CFR 201.57(c)(9)(iv). The final labeling and approval letter will reflect DPMH's input. The final labeling will be agreed upon with the applicant and may not fully reflect changes suggested here.

[4] Inflectra Final Label (infliximab-dyyb) BLA 125544 accessed on 10/6/2020
[5] Renflexis Final Label (infliximab-abda) BLA 761054 accessed on 10/6/2020
[6] March 2019 Final Guidance for Industry: Pediatric Information Incorporated into Human Prescription Drug and Biological Product Labeling

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

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:	November 16, 2020
Requesting Office or Division:	Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number:	BLA 761140
Product Name and Strength:	Riabni (rituximab-arrx)* Injection, 100 mg/10 mL, 500 mg/50 mL
Applicant/Sponsor Name:	Amgen Inc.
OSE RCM #:	2019-2613-2
DMEPA Safety Evaluator:	Nicole Iverson, PharmD, BCPS
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised carton labeling received on November 3, 2020 for Riabni. We reviewed the revised carton labeling for Riabni (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to a proposal from the Applicant to remove the pH adjuster, hydrochloric acid from Section 11 *Description* of the proposed Prescribing Information. The Agency recommended for the Applicant to include the pH adjuster, hydrochloric acid in Section 11 *Description* of the proposed Prescribing Information to be to be in accordance with 21 CFR 201.100(b)(5). Subsequently, the proposed carton labeling was revised to reflect the revision and list the pH adjuster, hydrochloric acid.

2 CONCLUSION

The proposed carton labeling is acceptable from a mediation error perspective. We have no additional recommendations at this time.

* The proposed proprietary name (Riabni) and proposed nonproprietary name (rituximab-arrx) are only conditionally accepted for this product until the application is approved.

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	October 28, 2020
To:	Laura Wall, MS, APHN-BC Senior Regulatory Project Manager **Division of Hematologic Malignancies II (DHM2)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Susan Redwood, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Nisha Patel, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	RIABNI (rituximab-arrx)
Dosage Form and Route:	injection, for intravenous use
Application Type/Number:	BLA 761140
Applicant:	Amgen Inc.

1 INTRODUCTION

On December 19, 2019, Amgen Inc., submitted for the Agency's review an original Biologics License Application (BLA) 761140 for RIABNI (rituximab-arrx) injection, for intravenous use. The Applicant seeks approval for RIABNI (rituximab-arrx), a genetically engineered chimeric mouse/human immunoglobulin isotype class G subclass 1 (IgG1) monoclonal antibody, as a biosimilar to the reference product Rituxan (rituximab) BLA 103705.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Hematologic Malignancies II (DHM2) on January 27, 2020, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for RIABNI (rituximab-arrx) injection, for intravenous use.

2 MATERIAL REVIEWED

- Draft RIABNI (rituximab-arrx) injection MG received on December 19, 2019, revised by the Review Division throughout the review cycle and received by DMPP and OPDP on September 8, 2020.
- Draft RIABNI (rituximab-arrx) injection Prescribing Information (PI) received on December 19, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 8, 2020.
- Approved RITUXAN (rituximab) injection reference product labeling dated August 28, 2020.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved referenced product labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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CLINICAL INSPECTION SUMMARY

Date	October 14, 2020
From	Anthony Orencia M.D., F.A.C.P., Medical Officer Min Lu, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Pamela Seam, M.D., Medical Officer Nicholas Richardson, D.O., Medical Team Leader Nicole Gormley, M.D., Acting Director Beatrice Kallungal, Regulatory Health Project Manager Division of Hematology Malignancy II (DHM2)
BLA	761140
Applicant	Amgen, Inc.
Drug	ABP 798, proposed biosimilar to rituximab (Rituxan®)
NME	No
Division Classification	Monoclonal antibody
Proposed Indication	Treatment of adult patients with non-Hodgkin's lymphoma, chronic lymphocytic leukemia, rheumatoid arthritis, granulomatous polyangiitis and microscopic polyangiitis
CDER Memo Issuance Date	February 19, 2019
Summary Goal Date	October 19, 2020
Action Goal Date	December 19, 2020
BsUFA Date	December 19, 2020

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The contract research organization (CRO) (b) (4) was inspected to evaluate the CRO's practices and procedures to determine compliance with applicable regulations, for Study 20130109 in support of BLA 761140, as part of FDA's review of this application for the drug ABP 798 (Riabni), proposed biosimilar to rituximab (Rituxan®).

The inspections of Site 10925009 (Vincent Delwail, M.D., in Poitou-Charentes, France) and Site 10933001 (Alessandra Tucci, M.D., in Brescia, Italy) were cancelled due to COVID-19 pandemic travel restrictions following a discussion between OSI and DHM2.

The inspection of (b) (4) did not find regulatory deficiencies with oversight and monitoring of the trial. Data from Study 20130109, based on the inspection, appear reliable in support of the proposed drug indication.

II. BACKGROUND

Amgen, Inc. has submitted a biologics license application (BLA) for the rituximab biosimilar product ABP 798, indicated for the treatment of adult patients with: (1) non-Hodgkin's lymphoma (NHL), (2) chronic lymphocytic leukemia (CLL), (3) rheumatoid arthritis (RA) in combination with methotrexate in adult patients with moderately-to severely-active RA who have inadequate response to one or more tumor necrosis factor (TNF) antagonist therapies, and (4) granulomatosis with polyangiitis (GPA; formerly called Wegener's granulomatosis) and microscopic polyangiitis (MPA) in adult patients in combination with glucocorticoids.

The signaling effect of rituximab on B cells, independent of immune effector mechanisms, could contribute, in part, to its anti-tumor drug activity. The combination of rituximab and cytotoxic chemotherapy, for instance, is effective in various B cell malignancies (e.g., lymphoma and lymphocytic leukemias). Treatment with the chimerical monoclonal antibody rituximab results in CD20-directed B cell depletion. For autoimmune diseases, including rheumatoid arthritis, this chimerical monoclonal antibody may have an impact on stimulation of T cells, cytokine production, antigen presentation, and production of autoantibodies.

Studies in rheumatoid arthritis patients have shown a rapid decrease in numbers of B cells in the synovial tissue, significant B cell depletion observed in the peripheral blood, a quantitative incomplete depletion of B cells in the synovium, or a low quantity of persistent B cells in the bone marrow after rituximab treatment. B cells are the precursors of short-lived, immunoglobulin-producing plasma cells, which are thought to be the primary source of autoantibodies, including antinuclear cytoplasmic autoantibodies. B cells may contribute to other aspects of the pathogenesis of granulomatous and microscopic polyangiitis (GPA and MPA), including co-stimulation of T cells, cytokine production, and antigen presentation.

As part of the regulatory review of this 351k (biosimilar) proposed approval pathway, the Division of Hematology Malignancy II (DHM2) requested inspection of the contract research organization (CRO) involved in Study 20130109 entitled "A Randomized, Double-blind Study Evaluating the Efficacy, Safety, and Immunogenicity of ABP 798 Compared with Rituximab in Subjects with CD20 Positive B-cell Non-Hodgkin Lymphoma (NHL)".

Study 20130109

Study 20130109 was a randomized, double-blind study in adult subjects with Grade 1, 2, or 3a follicular B-cell NHL and low tumor burden. Subjects were randomized in a 1:1 ratio to receive a 375 mg/m^2 intravenous infusion of either ABP 798 or rituximab once weekly for four weeks followed by dosing at weeks 12 and 20. Tumor assessments were performed at screening (baseline) and weeks 12 and 28. Randomization was stratified by geographic region (Europe, Americas, Japan, Asia Pacific – Other) and age group (over 60 years of age, 60 years of age or less).

Rituximab was sourced from the US (manufactured by Genentech, Inc., South San Francisco, CA), and was supplied as a sterile, clear, preservative-free liquid concentrate for IV infusion at a concentration of 10 mg/mL in either 100 mg/mL or 500 mg/50 mL single-dose vials.

The primary objective of the study was to evaluate the efficacy of rituximab biosimilar (ABP 798) compared with rituximab in subjects with NHL. The primary efficacy endpoint was a risk difference of the overall response rate (ORR) by week 28. Overall response rate was defined as the percentage of subjects with a complete response (CR), unconfirmed complete response (CRu), or partial response (PR) as defined by the International Working Group response criteria for NHL (Cheson et al.).

The first subject enrolled on May 25, 2016. The date of last subject's last visit was June 28, 2019. A total of 380 subjects were screened and 256 subjects were randomized at 91 centers across 20 countries. Of the 256 randomized subjects, 254 were treated with investigational product (128 subjects in the ABP 798 treatment group and 126 subjects in the US-licensed rituximab treatment group).

III. RESULTS

(b) (4)

Inspection dates: (b) (4)

This inspection evaluated compliance with the CRO's responsibilities concerning the conduct of Study 20130109. (b) (4) was responsible for data management, site selection and monitoring, statistical analysis, and safety reporting. The inspection included review of organizational charts, transfer of obligations, investigator agreements, institutional review board (IRB) approvals, training records, monitoring plans, monitoring reports, safety reports, adverse events (AEs) assessment, protocol deviations, standard operating procedures, electronic records and validations, drug accountability records, statistical assessment and data management procedures. A copy of the transfer of regulatory obligations documentation was reviewed and collected.

All records for SAEs and AEs were reviewed for Site 10933001, Alessandra Tucci, M.D., Brescia, Italy and Site 10925009, Vincent Delwail, M.D., Poitou-Charentes, France. Procedures for safety reporting such as SAEs, SUSARS, signal detection, and aggregate safety reporting were also reviewed and found to be adequate. The firm used Medidata RAVE for electronic data capture, Almac for IXRS and ARGUS (maintained by the sponsor applicant) for safety reporting. The audit review found that collected procedures for data collection and handling associated with the electronic data capture (EDC), IXRS® an Interactive Response Technology (IRT) database, and security/validation of data collection systems were unremarkable.

A total of five sites were reviewed for monitoring adequacy under the clinical investigator compliance program. The two sites (Site 10925009, Dr. Vincent Delwail in France and Site 10933001, Dr. Alessandra Tucci in Italy planned for inspection and later cancelled due to COVID-19 pandemic travel restrictions), and three additional sites (two U.S. and one Canadian sites) were reviewed:

1. Site 10916002, Caroline Hamm, M.D., in Windsor, Ontario, Canada
2. Site 10966009, Patrick Cobb, M.D., F.A.C.P., in Billings, MT
3. Site 10966015, Amanda Gillespie-Twardy, M.D., in Roanoke, VA

All blinded and unblinded monitoring visit reports were reviewed for these sites. (b) (4) did not report having any site issues that were closed due to noncompliance. The queries generated in the system included audit trails indicating the users, roles, and signatory. There were no observed objectionable conditions related to audit trails.

In general, no regulatory deficiencies were observed during the inspection. No observations or inspectional findings appeared to have an impact on data integrity or reliability.

{See appended electronic signature page}
Anthony Orencia, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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Min Lu, M.D., M.P.H.
Team Leader
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/s/

ANTHONY J ORENCIA
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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: September 10, 2020

To: Laura Wall, Regulatory Project Manager
Division of Hematologic Malignancies 2 (DHM2)

Stacy Shord, Associate Director for Labeling, DHM2

From: Nisha Patel, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Trung-Hieu (Brian) Tran, Team Leader, OPDP

Subject: OPDP Labeling Comments for RIABNI™ (rituximab-arrx) injection, for intravenous use

BLA: 761140

In response to DHM2's consult request dated January 27, 2020, OPDP has reviewed the proposed product labeling (PI) and Medication Guide for the original BLA submission for RIABNI™ (rituximab-arrx) injection, for intravenous use.

Labeling: OPDP reviewed the proposed PI received by electronic mail from DHM2 on September 8, 2020, and we have no comments at this time.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide will be sent under separate cover.

Thank you for your consult. If you have any questions, please contact Nisha Patel at (301) 796-3715 or nisha.patel@fda.hhs.gov.

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NISHA PATEL
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M E M O R A N D U M DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 4, 2020

TO: Nicole Gormley, MD
Director (Acting)
Division of Hematologic Malignancies 2
Office of Oncologic Diseases

Steven Lemery, MD
Director (Acting)
Division of Oncology 3
Office of Oncologic Diseases

FROM: Kara A. Scheibner, Ph.D.
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

Xiaohan Cai, Ph.D.
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Kimberly Benson, Ph.D.
Deputy Director (Acting)
(DGDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Remote Record Review (RRR) [redacted] (b) (4)

1. RRR Summary

The Office of Study Integrity and Surveillance (OSIS) conducted a remote record review (RRR) of the analytical portion of [redacted] (b) (4) and 20130108 (BLA 761140, ABP 798, a rituximab biosimilar to Rituxan) conducted at [redacted] (b) (4)

We observed objectionable findings that impact the reliability of some study data.

1.1. Recommendation

Based on our review of the RRR findings and the firm's response, we conclude the RRR findings may impact the reliability of data from portions of the audited studies.

(b) (4)

For the analytical portion of study 20130108, we recommend that the PK, ADA, and NAb data be accepted with a few considerations and exceptions. Details are included in section 5 Conclusion section.

2. Reviewed Studies

(b) (4)

Study 20130108 (BLA 761140)
"A Randomized, Double-Blind Study to Compare Pharmacokinetics and Pharmacodynamics, Efficacy and Safety of ABP 798 with Rituximab in Subjects with Moderate to Severe Rheumatoid Arthritis"
Sample Analysis Period: 9/16/2016 – 11/09/2018

3. Scope of RRR

OSIS scientists Kara A. Scheibner, Pharmacologist and Xiaohan Cai, Senior Staff Fellow reviewed the analytical portion of the above studies conducted at [redacted] (b) (4)

The RRR included an examination of relevant SOPs; study records including correspondence, investigations, sample storage-tracking; method validation; and sample analysis. We also conducted interviews with the firm's management and staff.

4. RRR Findings

At the conclusion of the RRR, we observed objectionable findings that may impact reliability of study data. We discussed the following items with the firm's management during the RRR close-out meeting.

Our evaluation of the findings that were discussed, and the firm's response dated 07/21/2020 (**Attachment 1**) are presented below.

4.1. Findings discussed at the close-out of RRR

[redacted] (b) (4)

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MICHAEL F SKELLY
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KIMBERLY A BENSON
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

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:	July 29, 2020
Requesting Office or Division:	Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number:	BLA 761140
Product Name and Strength:	Riabni (ABP 798)* Injection, 100 mg/10 mL, 500 mg/50 mL
Applicant/Sponsor Name:	Amgen Inc.
OSE RCM #:	2019-2613-1
DMEPA Safety Evaluator:	Nicole Iverson, PharmD, BCPS
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on July 23, 2020 for Riabni. We review the revised container labels and carton labeling for Riabni (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] We note the Applicant will implement revisions to the expiration date by June 2021.

2 CONCLUSION

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

* ABP 798 has been developed as a proposed biosimilar to US-licensed Rituxan (rituximab). Since the proper name for ABP 798 has not yet been determined, the developmental code name, ABP 798 or the proposed proprietary name (Riabni), is used throughout this review to refer to this product. The proposed proprietary name (Riabni) and proposed nonproprietary name (rituximab-arrx) are only conditionally accepted for this product until the application is approved.

[a] Iverson N. Label and Labeling Review for Riabni (BLA 761140). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JUL 08. RCM No.: 2019-2613.

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HINA S MEHTA
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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
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:	July 8, 2020
Requesting Office or Division:	Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number:	BLA 761140
Product Name, Dosage Form, and Strength:	Riabni (ABP 798)* Injection, 100 mg/10 mL, 500 mg/50 mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Amgen Inc.
FDA Received Date:	December 19, 2019
OSE RCM #:	2019-2613
DMEPA Safety Evaluator:	Nicole Iverson, PharmD, BCPS
DMEPA Team Leader:	Hina Mehta, PharmD

* ABP 798 has been developed as a proposed biosimilar to US-licensed Rituxan (rituximab). Since the proper name for ABP 798 has not yet been determined, the developmental code name, ABP 798 or the proposed proprietary name (Riabni), is used throughout this review to refer to this product. The proposed proprietary name (Riabni) and proposed nonproprietary name (rituximab-arrx) are only conditionally accepted for this product until the application is approved.

1 REASON FOR REVIEW

As part of the approval process for BLA 761140 Riabni ("ABP 798") Injection, 100 mg/10 mL and 500 mg/50 mL, this review evaluates the proposed container labels, carton labeling, Prescribing Information (PI), and Medication Guide for areas that could lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C- N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F- N/A
Labels and Labeling	G

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 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Amgen submitted a 351(k) application to obtain marketing approval of Riabni ("ABP 798") Injection. Riabni is proposed for the treatment of adult patients with NHL, CLL, RA, GPA and MPA. We note, Riabni has the same dosing, route of administration, strength, dosage form and storage requirements as US-licensed Rituxan (BLA 103705). We note, Amgen is pursuing all indications approved for US-licensed Rituxan except for use in adult patients with PV and pediatric patients with GPA and MPA.

We performed a risk assessment of the proposed container labels, carton labeling, PI, and Medication Guide for Riabni ("ABP 798") Injection to determine whether there are significant concerns in terms of safety, related to preventable medication errors. The Medication Guide is acceptable from a medication error perspective. We have identified areas of the proposed PI,

container labels and carton labeling that could be revised to improve clarity and readability of important information. For the Division, we note the PI has large numbers presented without commas, improper nomenclature used for the diluents, and lack of clarity of the how supplied information. For the Applicant, we recommend changes to the container labels and carton labeling to improve readability and prominence of important information. Specifically, we recommend revisions to the strength, presentation, dosage form, route of administration, package type term, Rx only statement, product identifiers and expiration date. We provide recommendations for the Division in Section 4.1 and the Applicant in Section 4.2 below and advise they be implemented prior to approval of BLA 761140.

4 CONCLUSION & RECOMMENDATIONS

We have identified areas in the proposed PI, container labels, and carton labeling that can be improved to increase readability and prominence of important information and promote safe use of the product. We provide recommendations in Section 4.1 for the Division and Section 4.2 for Amgen to address our concerns.

4.1 RECOMMENDATIONS FOR DIVISION OF HEMATOLOGIC MALIGNANCIES 2 (DHM 2)

A. Highlights of Prescribing Information

1. Dosage and Administration

a. The dose of Riabni is presented as 1000 mg and appears without comma. Numbers greater than or equal to 1,000 should contain a comma to prevent the reader from misinterpreting thousands “1000” as hundreds “100” or ten-thousands “10000”. Revise the dose of Riabni to include a comma, for example, to read as 1,000 instead of 1000.

B. Prescribing Information

1. Dosage and Administration Section

a. Section 2.5 *Recommended Dose for Rheumatoid Arthritis (RA)*

i. The dose for rheumatoid arthritis of Riabni is presented as 1000 mg and appears without comma. Numbers greater than or equal to 1,000 should contain a comma to prevent the reader from misinterpreting thousands “1000” as hundreds “100” or ten-thousands “10000”. Revise the dose of Riabni to include a comma, for example, to read as 1,000 instead of 1000.

b. Section 2.8 *Administration and Storage*

i. Revise all presentations of the statement, “0.9% Sodium Chloride” using proper nomenclature to appear as “0.9% Sodium Chloride Injection, USP”.

ii. Revise all presentations of the statement, “5% Dextrose” using proper nomenclature to appear as “5% Dextrose Injection, USP”.

2. How Supplied/Storage and Handling Section

a. Revise the statement for clarity, “RIABNI (rituximab-arrx) injection is a sterile, preservative-free clear to slightly opalescent, colorless to slightly yellow solution for intravenous infusion supplied as single-dose vials of 100 mg/10 mL (10 mg/mL) in cartons of one vial (NDC 55513-224-01) and single-dose vials of 500 mg/50 mL (10 mg/mL) in a carton of one vial (NDC 55513-326-01).” to “RIABNI (rituximab-arrx) injection is a sterile, clear to slightly opalescent, colorless to slightly yellow preservative-free solution for intravenous infusion supplied as a carton containing one 100 mg/10 mL (10 mg/mL) single-dose vial (NDC 55513-224-01) and a carton containing one 500 mg/50 mL (10 mg/mL) single-dose vial (NDC 55513-326-01).”

4.2 RECOMMENDATIONS FOR AMGEN INC.

We recommend the following be implemented prior to approval of this BLA:

A. General Comments (Container labels & Carton Labeling)

1. The “Rx only” statement appear more prominent than other critical information (e.g. route of administration, and strength) on the principal display panel. Ensure the “Rx only” statement does not compete in size or prominence with critical information on the principal display panel.

2. The format for the expiration date is not defined. Clearly defining the expiration date will minimize confusion and risk for deteriorated drug medication errors. Identify the expiration date format you intend to use. 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.

FDA recommends that a hyphen or forward be used to separate the portions of the expiration date.

B. Container Labels

1. The strength statement lacks prominence as it appears on the side panel. Lack of prominence of the strength statement may contribute to product selection medication errors. Relocate the strength statement from the side panel to appear beneath the proper name and dosage form in the same visual field so that the expression as strength per total volume is the primary and prominent expression on the principal display panel followed in close proximity by the concentration per mL consistent with USP General Chapter <7>. Take into account all pertinent factors including font size, type, and color; background contrast; and statement location. If necessary, consider relocating the storage information to the side panel to improve readability.
2. The principal display panel is cluttered and does not contain important information including the strength, package type term, and net quantity statement. Relocate the storage statements, "Store refrigerated at 2°C to 8°C (36°F to 46°F). Protect from direct sun-light. Do not freeze or shake." to the side panel.
3. Revise the statements, "Solution in Single-dose Vial. Discard unused portion." to "Single-dose vial. Discard unused portion." as the terminology "solution" is not needed.
4. The recommended dosage statement is missing from the container label. The recommended dosage statement is required per 21 CFR 201.55. If space allows, consider adding the recommended dosage statement, "Dosage: See Prescribing Information." on the side panel of the container label.
5. Consider including the finished dosage form on the principal display panel below the proper name on the container label and carton labeling as follows:

Riabni

(rituximab-arrx)

Injection

6. If space permits, consider revising the statement that reads "For Intravenous Infusion Only" to read "For Intravenous Infusion After Dilution." We recommend this to minimize the risk of administering the drug as an intravenous push.

C. Carton Labeling

1. Revise the statement "See package insert for dosage and Full Prescribing Information." to read, "Dosage: See Prescribing Information." The later statement is more appropriate when referring to labeling in the Physician Labeling Rule format.
2. The dosage form, "Injection" appears less prominent on the carton labeling. Consider increasing the prominence of the dosage form, "Injection" on the carton labeling taking into consideration the size and layout of other important information on the labeling.

3. Revise the statement that reads "For Intravenous Infusion Only" to read "For Intravenous Infusion After Dilution." We recommend this to minimize the risk of administering the drug as an intravenous push.
4. The machine-readable (2D data matrix barcode) product identifier is missing from the carton labeling. In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act.[1] The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling.

   [1]The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf

5. On the side panel, revise the statement, "Solution in Single-dose Vial." to "Single-dose vial. Discard unused portion."

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Riabni received on December 19, 2019 from Amgen Inc. , and US-licensed Rituxan.

Table 2. Relevant Product Information for Riabni and the Listed Drug

Product Name	**Riabni**	**US-licensed Rituxan[a]**
Initial Approval Date	N/A	November 26, 1997
Nonproprietary Name	rituximab-arrx	Rituximab
Indication	For the treatment of adult patients with: • Non-Hodgkin's Lymphoma (NHL) • Chronic Lymphocytic Leukemia (CLL) • Rheumatoid Arthritis (RA) in combination with methotrexate in adult patients with moderately-to-severely-active RA who have inadequate response to one or more TNF antagonist therapies • Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA) in adult patients in combination with glucocorticoids	For the treatment of adult patients with: • Non-Hodgkin's Lymphoma (NHL) • Chronic Lymphocytic Leukemia (CLL) • Rheumatoid Arthritis (RA) in combination with methotrexate in adult patients with moderately-to-severely-active RA who have inadequate response to one or more TNF antagonist therapies • Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA) in adult and pediatric patients 2 years of age and older in combination with glucocorticoids • Pemphigus Vulgaris (PV)

[a] Rituxan [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2020 MAR 13. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/103705Orig1s5458lbl.pdf].

Route of Administration	Intravenous infusion
Dosage Form	Injection
Strength	100 mg/10 mL, 500 mg/50 mL (10 mg/mL)

Dose and Frequency	**NHL:** the dose is 375 mg/m^2. Depending on severity and/or stage of disease, administration can range from 4 to 16 doses. The dose as a component of	**NHL:** the dose is 375 mg/m^2. Depending on severity and/or stage of disease, administration can range from 4 to 16 doses. The dose as a

	Zevalin therapeutic regimen is 250 mg/m^2. **CLL:** 375 mg/m^2 in the first cycle and 500 mg/m^2 in cycles 2-6, in combination with FC, administered every 28 days. **RA:** In combination with methotrexate the dose is two-1,000 mg intravenous infusions separated by 2 weeks (one course) every 24 weeks or based on clinical evaluation, but not sooner than every 16 weeks. Methylprednisolone 100 mg intravenous or equivalent glucocorticoid is recommended 30 minutes prior to each infusion. **GPA and MPA in adult patients:** In combination with glucocorticoids, the dose is 375 mg/m^2 once weekly for 4 weeks. The follow up dose for adult patients with GPA and MPA who have achieved disease control with induction treatment, in combination with glucocorticoids is two 500 mg intravenous infusions separated by two weeks, followed by a 500 mg intravenous infusion every 6 months thereafter based on clinical evaluation.	component of Zevalin therapeutic regimen is 250 mg/m^2. **CLL:** 375 mg/m^2 in the first cycle and 500 mg/m^2 in cycles 2-6, in combination with FC, administered every 28 days. **RA:** In combination with methotrexate the dose is two-1,000 mg intravenous infusions separated by 2 weeks (one course) every 24 weeks or based on clinical evaluation, but not sooner than every 16 weeks. Methylprednisolone 100 mg intravenous or equivalent glucocorticoid is recommended 30 minutes prior to each infusion. **GPA and MPA** **Adult:** In combination with glucocorticoids, the dose is 375 mg/m^2 once weekly for 4 weeks. The follow up dose for adult patients with GPA and MPA who have achieved disease control with induction treatment, in combination with glucocorticoids is two 500 mg intravenous infusions separated by two weeks, followed by a 500 mg intravenous infusion every 6 months thereafter based on clinical evaluation.

		Pediatrics: In combination with glucocorticoids, the dose is 375 mg/m^2 once weekly for 4 weeks. The follow up dose for pediatric patients with GPA and MPA who have achieved disease control with induction treatment, in combination with glucocorticoids is two 250 mg/m^2 intravenous infusions separated by 2 weeks followed by a 250 mg/m^2 intravenous every 6 months thereafter or based on clinical evaluation. **PV:** Two-1,000 mg intravenous infusions separated by 2 weeks in combination with a tapering course of glucocorticoids, then a 500 mg intravenous infusion at Month 12 and every 6 months thereafter or based on clinical evaluation. Dose upon relapse is a 1,000 mg intravenous infusion with considerations to resume or increase the glucocorticoid dose based on clinical evaluation. Subsequent infusions may be sooner than 16 weeks after the previous infusion.
How Supplied	Riabni vials are supplied as 100 mg/10 mL and 500 mg/50 mL single-dose vials	Rituxan vials are supplied as 100 mg/10 mL and 500 mg/50 mL single-dose vials
Storage	Store Riabni vials refrigerated at 2°C - 8°C (36°F-46°F). Riabni vials should be protected from direct sunlight. Do not freeze or shake	Rituxan vials are stable at 2°C - 8°C (36°F-46°F). Rituxan vials should be protected from direct sunlight. Do not freeze or shake

APPENDIX B. PREVIOUS DMEPA REVIEWS

On May 19, 2020, we searched for previous DMEPA reviews relevant to this current review using the terms, Riabni and ABP 798. Our search did not identify any previous label and labeling reviews.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Riabni labels and labeling submitted by Amgen Inc. .

- Container labels received on December 19, 2019
- Carton labeling received on December 19, 2019
- Prescribing Information (Image not shown) received on December 19, 2019, available from \\cdsesub1\evsprod\bla761140\0001\m1\us\annotated-draft-labeling-text-uspi.pdf
- Medication Guide received on December 19, 2019, available from \\cdsesub1\evsprod\bla761140\0001\m1\us\annotated-draft-labeling-text-medguide.pdf

G.2 Label and Labeling Images

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