CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761371Orig1s000

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 Memorandum

Date:	September 11, 2024
Reviewer(s):	Danielle Abraham, PhD, MPH Division of Epidemiology I
Acting Team Leader:	Catherine Callahan, PhD, MA Division of Epidemiology I
Division Director:	CAPT Sukhminder K. Sandhu, PhD, MPH, MS Division of Epidemiology I
Subject:	ARIA Sufficiency Memorandum
Drug Name(s):	Ocrevus Zunovo (ocrelizumab and hyaluronidase-ocsq)
Application Type/Number:	BLA 761371
Applicant/sponsor:	Genentech, Inc.
TTT #:	2024-10109

Reference ID: 5444818

EXECUTIVE SUMMARY *(place "X" in appropriate boxes)*

Memo type		
-Final	X	
Source of safety concern		
-Peri-approval	X	
-Post-approval		
Is ARIA sufficient to help characterize the safety concern?	Injection-related reactions	All malignancies and breast cancer
-Yes		
-No	X	X
If "No", please identify the area(s) of concern.		
-Surveillance or Study Population		
-Exposure		
-Outcome(s) of Interest	X	X
-Covariate(s) of Interest	X	X
-Surveillance Design/Analytic Tools		

Reference ID: 5444818

A. General ARIA Sufficiency Template

1. BACKGROUND INFORMATION

1.1. Medical Product

OCREVUS ZUNOVO (ocrelizumab and hyaluronidase-ocsq) injection, for subcutaneous use (SC OCR) is a CD20-directed cytolytic antibody with proposed indications for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults as well as primary progressive MS, in adults.[1]

SC OCR is administered subcutaneously by a healthcare professional in the abdomen for a duration of approximately 10 minutes every 6 months. Patients are administered 23 mL of SC OCR (920 mg ocrelizumab and 23,000 units hyaluronidase). The terminal half-life is 20 days.[2]

Ocrelizumab injection, for intravenous use was previously approved on March 28, 2017, under the tradename OCREVUS (IV OCR).[3] IV OCR use is currently approved for the treatment of relapsing forms of MS, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults as well as primary progressive MS, in adults.[4]

1.2. Describe the Safety Concern

The Division of Neurology Products (DNP) identified a safety concern for all malignancies, including all breast cancers, in the clinical development program for IV OCR.[5] The reader is referred to the previous Division of Epidemiology I (DEPI-I) Active Risk Identification and Analysis (ARIA) Sufficiency Memo for a further discussion of these safety concerns.[6] Upon approval of IV OCR, a postmarketing requirement (PMR 3194-2) was issued for a prospective longitudinal observational study to assess the incidence and mortality rates of breast cancer and all malignancies over a five year follow-up period among adult patients with MS exposed to IV OCR.[7] PMR 3194-2 is currently ongoing. The Division of Neurology 2 (DN2) plans to issue the same safety study PMR for SC OCR in order to allow the Sponsor to enroll patients who receive SC OCR in the study.

DN2 expects that the safety profile of SC OCR will be similar to IV OCR for other outcomes, except for injection-related reactions. Local injection site reactions have been reported with other hyaluronidase products in the postmarketing setting. DN2 expects that there will be more injection-related reactions with SC OCR, compared to IV OCR, due to its route of

[1] BLA 761371 DRAFT labeling. September 6, 2024. Silver Spring (MD), U.S. Food and Drug Administration.
[2] Ibid.
[3] BLA 761053 ORIG-1 Approval Letter. March 28, 2017. Silver Spring (MD), U.S. Food and Drug Administration. DARRTS Reference ID: 4076448.
[4] BLA 761053 SUPPL-35 Labeling. June 21, 2024. Silver Spring (MD), U.S. Food and Drug Administration. DARRTS Reference ID: 5401529.
[5] Braver ER, Taylor L, Pinheiro S. ARIA Sufficiency Memo for Ocrelizumab (Ocrevus). November 17, 2016. Silver Spring (MD), U.S. Food and Drug Administration. DARRTS Reference ID: 4014942.
[6] Ibid.
[7] See footnote 3.

administration.[8]

The efficacy and safety of SC OCR was examined in a 96-week, phase 3, randomized, open-label, parallel, group study of subjects with relapsing forms of MS and primary progressive MS that compared the pharmacokinetic non-inferiority of SC OCR to IV OCR (Study CN42097).[9] Supportive safety data was also provided by a 146-week, Phase 1b, randomized, open-label, dose-ranging study that compared SC OCR and IV OCR (Study CN41144).[10]

In Study CN42097, there were no treatment emergent malignancies. In study CN41144 there was one case of basal cell carcinoma in a subject who received ≥1 dose of 1,200 mg SC OCR and one case of papillary thyroid cancer in a subject who received ≥1 dose of 920 mg and ≥1 dose of 1,200 mg SC OCR.[11]

Table 1 displays the FDA analyses of treatment-emergent adverse events (TEAEs)[12] of injection-related reactions in the safety population of Study CN42097. All events were mild (72.4%) or moderate (27.6%) with a median duration of 3 days (interquartile range [IQR]: 2, 5).[13] Signs and symptoms of injection-related reactions after an SC OCR administration were consolidated and reported as a single injection-related reaction adverse event. As a result, there was a possible underestimation of injection-related reaction TEAEs and inadequate characterization of signs and symptoms of injection-related reactions.[14]

Table 1. Rates of local and systemic injection-related reactions within 24 hours after SC OCR injection in the controlled period of Study CN42097

TEAEs	SC OCR (n=118), n (%)	IV OCR (n=118), n (%)	Risk Difference, % (95% confidence interval)
Injection-related reactions (grouped query)	58 (49.2)	0 (0.0)	49.2 (40.3, 58.1)
Injection related reaction	55 (46.6)	0 (0.0)	46.6 (37.8, 55.6)
Injection site erythema	1 (0.8)	0 (0.0)	0.8 (-2.3, 4.7)
Injection site reaction	2 (1.7)	0 (0.0)	1.7 (-1.5, 6.0)
Injection site warmth	1 (0.8)	0 (0.0)	0.8 (-2.3, 4.7)

Source: Table 45 Draft Clinical Review, dated September 10, 2024.
TEAEs, treatment-emergent adverse events; SC OCR, subcutaneous ocrelizumab; IV OCR, intravenous ocrelizumab

In Study CN41144, 66.7% (26/39) of subjects treated with at least one dose of 920 mg SC OCR who were naïve to OCR developed TEAEs of injection site reactions. Among subjects who had been treated with IV OCR for ≥one year prior to study enrollment, the percentage was lower

[8] DRAFT Clinical Safety Review. BLA 761371. September 10, 2024. Silver Spring (MD), U.S. Food and Drug Administration.
[9] DRAFT Interdisciplinary Assessment. BLA 761371. September 10, 2024. Silver Spring (MD), U.S. Food and Drug Administration.
[10] Ibid.
[11] See footnote 8.
[12] Within 24 hours of SC OCR injection
[13] See footnote 8.
[14] Ibid.

(45.6%, 36/79 subjects).[15]

Proposed, draft labeling for SC OCR includes Warnings & Precautions for both injection reactions and malignancies. The relevant Warnings & Precautions subsections are provided below:[16]

5 WARNINGS AND PRECAUTIONS

5.1 Injection Reactions

OCREVUS ZUNOVO can cause injection reactions, which can be local or systemic. Common symptoms of local injection reactions reported by patients treated with OCREVUS ZUNOVO in multiple sclerosis (MS) clinical trials included erythema, pain, swelling, and pruritus. Common symptoms of systemic injection reactions reported by patients included headache and nausea. In an open-label, active-controlled trial, injection reactions were more frequently reported with the first injection; 49% of patients experienced an injection reaction with the first injection [see Adverse Reactions (6.1)].

In MS clinical trials where ocrelizumab was administered intravenously, the incidence of infusion reactions in patients [who received methylprednisolone (or an equivalent steroid) and possibly other premedication to reduce the risk of infusion reactions prior to infusion] was 34% to 40%, with the highest incidence with the first infusion. There were no fatal infusion reactions, but 0.3% of intravenous ocrelizumab-treated MS patients experienced infusion reactions that were serious, some requiring hospitalization. Symptoms of infusion reactions can include pruritus, rash, urticaria, erythema, bronchospasm, throat irritation, oropharyngeal pain, dyspnea, pharyngeal or laryngeal edema, flushing, hypotension, pyrexia, fatigue, headache, dizziness, nausea, tachycardia, and anaphylaxis.

Monitor patients during and after injections [see Dosage and Administration (2.4)]. Inform patients that injection reactions can occur during or within 24 hours of the injection.

Reducing the Risk of Injection Reactions and Managing Injection Reactions

Administer oral premedication (e.g., dexamethasone or an equivalent corticosteroid, and an antihistamine) at least 30 minutes prior to each OCREVUS ZUNOVO injection to reduce the risk of injection reactions. The addition of an antipyretic (e.g., acetaminophen) may also be considered [see Dosage and Administration (2.3)].

Management recommendations for injection reactions depend on the type and severity of the reaction. For life-threatening injection reactions, immediately and permanently stop OCREVUS ZUNOVO and administer appropriate supportive treatment. For less severe injection reactions, the injection should be interrupted immediately, and the patient should receive symptomatic treatment. The injection should be completed at the healthcare provider's discretion and only after all symptoms have resolved.

…

[15] DRAFT Clinical Safety Review. BLA 761371. September 10, 2024. Silver Spring (MD), U.S. Food and Drug Administration.

[16] BLA 761371 DRAFT labeling. September 6, 2024. Silver Spring (MD), U.S. Food and Drug Administration.

Reference ID: 5444818

5.5 Malignancies

An increased risk of malignancy with OCREVUS ZUNOVO may exist. In controlled trials, malignancies, including breast cancer, occurred more frequently in patients treated with intravenous ocrelizumab. Breast cancer occurred in 6 of 781 females treated with intravenous ocrelizumab and none of 668 females treated with REBIF or placebo. Patients should follow standard breast cancer screening guidelines.

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

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

[a]Injection-related reactions
[b]All malignancies, breast cancer

1.4. Statement of Purpose

DN2 requested that DEPI-I conduct an assessment to determine whether Sentinel ARIA would be sufficient to assess the incidence, clinical features, and severity of injection-related reactions in patients with MS treated with SC OCR. Per an email safety assessment meeting (SAM) held July 11, 2023, DN2 determined that the FDAAA purpose was assessment of a known serious risk (see Section 1.3 of this memo), and the regulatory goal for injection-related reactions is signal refinement.

On July 17, 2024, DN2 also requested that DEPI-I conduct an assessment to determine whether ARIA would be sufficient to assess the risk of malignancy, including the risk of breast cancer, in patients with MS treated with SC OCR. During a pre-SAM on July 18, 2024, it was determined that the FDAAA purpose (see Section 1.3 of this memo) and the regulatory goal (signal evaluation) for malignancy has not changed since the prior DEPI-I ARIA sufficiency assessment was conducted for IV OCR.[17]

Additional data on malignancy risk and injection-related reactions in patients treated with SC OCR could further inform labeling and determine whether further regulatory measures are needed.

1.5. Effect Size of Interest or Estimated Sample Size Desired

Malignancy

The estimated sample size for a proposed PMR for malignancy is not specified; however, the agreed upon, target sample size for PMR 3194-2 issued for IV OCR, was 4,000 IV OCR exposed MS patients and 1,133 MS patients in the comparator group.[18] The target follow-up time for

[17] Braver ER, Taylor L, Pinheiro S. ARIA Sufficiency Memo for Ocrelizumab (Ocrevus). November 17, 2016. Silver Spring (MD), U.S. Food and Drug Administration. DARRTS Reference ID: 4014942.
[18] Zhang D, Pennap D. Integrated Statistical Review Memo. Ocrevus (ocrelizumab). October 25, 2021. Silver Spring (MD), U.S. Food and Drug Administration. DARRTS Reference ID: 4877038.

PMR 3194-2 has not been met,[19] and PMR enrollment could be expanded to include patients exposed to SC OCR.

Injection-Related Reactions
The estimated, required sample size for a proposed PMR for injection-related reactions is at least 150 subjects followed for at least two years after SC OCR initiation.

2. SURVEILLANCE OR DESIRED STUDY POPULATION

2.1 Population

Malignancy
The study population is patients with MS.

Injection-Related Reactions
The study population is patients with MS.

2.2 Is ARIA sufficient to assess the intended population?

Malignancy
ARIA is sufficient to identify MS patients. MS patients can be identified with claims-based algorithms that include encounters with MS International Classification of Diseases (ICD) codes and prescription claims for MS therapies (1).

Injection-Related Reactions
ARIA is sufficient to identify patients with MS using claims-based algorithms (1).

3 EXPOSURES

3.1 Treatment Exposure(s)

Malignancy
The exposure of interest is SC OCR.

Injection-Related Reactions
The exposure of interest is SC OCR.

3.2 Comparator Exposure(s)

Malignancy
Other MS therapies.

Injection-Related Reactions
Not applicable because the desired study is a single-arm safety study.

[19] DRAFT Clinical Safety Review. BLA 761371. September 10, 2024. Silver Spring (MD), U.S. Food and Drug Administration.

Reference ID: 5444818

3.3 Is ARIA sufficient to identify the exposure of interest?

Malignancy
ARIA is sufficient to identify SC OCR based on National Drug Codes (NDC) codes and Healthcare Common Procedure Coding System (HCPCS) codes. Comparator MS therapies can be similarly identified. DEPI-I's current, assessment of ARIA sufficiency is in line with DEPI-I's previous assessment.[20]

Injection-Related Reactions
ARIA is sufficient to identify SC OCR based on NDC codes and HCPCS codes.

4 OUTCOME(S)

4.1 Outcomes of Interest

Malignancy
In alignment with the previous DEPI-I ARIA sufficiency memo,[21] the outcomes of interest are all malignancies, breast cancer, and all malignancies excluding non-melanoma skin cancers. A minimum of five years of patient follow-up is necessary for assessment of these outcomes.

Injection-Related Reactions
The outcomes of interest are injection-related reactions, including severity, clinical signs, and clinical symptoms. A minimum of two years of patient follow-up is necessary for assessment of these outcomes.

4.2 Is ARIA sufficient to assess the outcome of interest?

Malignancy
ARIA is insufficient for malignancy outcomes.

As noted in the previous DEPI-I ARIA sufficiency memo,[22] ARIA is insufficient due to a lack of information on histology, stage, grade, and other relevant tumor characteristics (e.g., estrogen receptors, progesterone receptors, human epidermal growth factor receptor 2 [HER2]).

Cumulative enrollment in the Sentinel Distributed Database has improved since DEPI-I's previous memo; however, as of April 2024, only 25.4% of members have at least 5 years of cumulative enrollment.[23] As a result, there may be a lack of adequate (≥5 years) follow-up time for a substantial proportion of MS patients treated with ocrelizumab.

Injection-related reactions
ARIA is insufficient to identify injection-related reactions. There is an ICD, Tenth Revision, Clinical Modification (ICD-10-CM) diagnosis code for "other complications following infusion, transfusion and therapeutic injection" (T80.89). However, this code is non-specific and has not

[20] Braver ER, Taylor L, Pinheiro S. ARIA Sufficiency Memo for Ocrelizumab (Ocrevus). November 17, 2016. Silver Spring (MD), U.S. Food and Drug Administration. DARRTS Reference ID: 4014942.
[21] Ibid.
[22] Ibid.
[23] Sentinel. Key Database Statistics. April 23, 2024. Silver Spring (MD), U.S. Food and Drug Administration. Accessed August 5, 2024, at: https://www.sentinelinitiative.org/about/key-database-statistics

been validated in claims. ARIA would also not capture the details required to characterize injection-related reactions with respect to severity and clinical signs/symptoms. As of April 2024, over half (57.4%) of members have at least 2 years of cumulative enrollment.[24]

5 COVARIATES

5.1 Covariates of Interest

Malignancy
As noted in the prior DEPI-I ARIA sufficiency memo,[25] key covariates include patient characteristics such as duration of MS, MS severity, prior MS treatments, and demographics. Additionally, risk factors for malignancy, and specifically breast cancer, such as body mass index, alcohol use, smoking, family history, postmenopausal hormone treatment, and reproductive history are also important covariates.

Injection-Related Reactions
Key covariates include MS phenotype, duration of MS, number of SC ORC injections, treatment duration, prior exposure to IV OCR, demographics, and body mass index.

5.2 Is ARIA sufficient to assess the covariates of interest?

Malignancy
ARIA is insufficient. As noted by DEPI-I,[26] claims would not contain detailed information on covariates such as MS severity or risk factors for malignancy. Additionally, many risk factors such as smoking, alcohol use, body mass index, family history of breast cancer, postmenopausal hormone treatment, and reproductive history are inconsistently captured or would need to be captured in a historical period that would extend prior to the study's designated lookback period.[27]

Injection-related reactions
ARIA is insufficient to identify MS phenotype (e.g., relapsing-remitting MS, primary progressive MS) because MS ICD codes do not distinguish between MS phenotypes. ARIA would be sufficient to identify other key covariates such as demographics; number of SC OCR injections; treatment duration; prior exposure to IV OCR; and possibly body mass index categories.

6 SURVEILLANCE DESIGN / ANALYTIC TOOLS

6.1 Surveillance or Study Design

Malignancy

[24] Sentinel. Key Database Statistics. April 23, 2024. Silver Spring (MD), U.S. Food and Drug Administration. Accessed August 5, 2024, at: https://www.sentinelinitiative.org/about/key-database-statistics
[25] Braver ER, Taylor L, Pinheiro S. ARIA Sufficiency Memo for Ocrelizumab (Ocrevus). November 17, 2016. Silver Spring (MD), U.S. Food and Drug Administration. DARRTS Reference ID: 4014942.
[26] Ibid.
[27] Ibid.

To account for differences in prescribing, statistical analyses would likely need to use propensity scores or other pharmacoepidemiologic methods.[28]

Injection-Related Reactions
Analyses would require descriptive analysis.

6.2 Is ARIA sufficient with respect to the design/analytic tools available to assess the question of interest?

Malignancy
Yes, as noted previously by DEPI-I,[29] ARIA has appropriate study design and statistical methods capabilities.

Injection-related reactions
Yes, ARIA is sufficient to conduct descriptive analysis.

7 NEXT STEPS

Based on DEPI-I's assessment, ARIA is insufficient to assess the risk of all malignancy and breast cancer as well as injection-related reactions in MS patients treated with SC OCR. DN2 concurred with DEPI-I's assessment via the email SAMs held July 18, 2024, for the malignancy safety concern and July 11, 2024, for the injection-related reactions safety concern. Upon approval, DN2 will issue two FDAAA PMRs with the following draft language:

PMR 1: Conduct an observational, single-arm safety study to assess the risk of injection-related reactions in patients treated with subcutaneously-administered ocrelizumab. The study should evaluate the incidence, clinical features, and severity of injection-related reactions to enable a detailed characterization of local and systemic injection-related reactions that can occur with subcutaneously-administered ocrelizumab. The study should involve monitoring subjects for at least 2 years following subcutaneously-administered ocrelizumab treatment initiation.

PMR 2: Conduct a prospective longitudinal observational study in adult patients with relapsing multiple sclerosis and primary progressive multiple sclerosis exposed to ocrelizumab to determine the incidence and mortality rates of breast cancer and all malignancies. All patients enrolled in the study should be followed for a minimum of 5 years or until death following their first exposure to ocrelizumab. The protocol must specify two appropriate populations to which the observed incidence and mortality rates will be compared.

For potential fulfillment of this PMR, patients treated with ocrelizumab and hyaluronidase can be enrolled in the ongoing Study BA39731, intended to fulfill PMR 3194-2 for Ocrevus (ocrelizumab).

[28] Braver ER, Taylor L, Pinheiro S. ARIA Sufficiency Memo for Ocrelizumab (Ocrevus). November 17, 2016. Silver Spring (MD), U.S. Food and Drug Administration. DARRTS Reference ID: 4014942.
[29] Ibid.

REFERENCES

1. Culpepper WJ, Marrie RA, Langer-Gould A, Wallin MT, Campbell JD, Nelson LM, et al. Validation of an algorithm for identifying MS cases in administrative health claims datasets. Neurology. 2019;92(10):e1016-e28.

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/s/

DANIELLE S ABRAHAM
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SARAH K DUTCHER
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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)

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

Date of This Review:	September 4, 2024
Requesting Office or Division:	Division of Neurology 2 (DN 2)
Application Type and Number:	BLA 761371
Product Name, Dosage Form, and Strength:	Ocrevus Zunovo (ocrelizumab and hyaluronidase-ocsq) injection, 920 mg and 23,000 units/23 mL (40 mg and 1,000 units/mL)
Applicant Name:	Genentech, Inc.
FDA Received Date:	August 19, 2024, September 3, 2024
TTT ID #:	2023-7110-2
DMEPA 2 Safety Evaluator:	Rina Patel, PharmD
DMEPA 2 Team Leader:	Stephanie DeGraw, PharmD

Reference ID: 5440917

1 PURPOSE OF MEMORANDUM

Genentech, Inc. submitted a revised container label on August 19, 2024 and revised carton labeling on September 3, 2024 for Ocrevus Zunovo. The Division of Neurology 2 (DN 2) requested that we review the revised container label and carton labeling for Ocrevus Zunovo (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 memorandum[a], Nonproprietary Name Suffix Advice Letter[b], and an Information Request sent to the Applicant on August 29, 2024 (see Appendix A).

2 CONCLUSION

Genentech, Inc. implemented all of our recommendations and we have no additional recommendations at this time.

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

[a] Patel, R. Label and Labeling Review for Ocrevus Zunovo (BLA 761371). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 JUN 26. TTT ID: 2023-7110-1.

[b] Nonproprietary Name Suffix Advice Letter (Ocrevus Zunovo BLA 761371). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 JUL 19.

Reference ID: 5440917

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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 4th, 2024

TO: Paul Lee, Ph.D.
Director
Division of Neurology II (DNII)
Office of Neuroscience (ON)
Office of New Drugs (OND)

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

THROUGH: Seongeun (Julia) Cho, Ph.D.
Director
DGDSI
OSIS

SUBJECT: Review of Clinical Inspection of Johns Hopkins Hospital Department of Neurology and Neurosurgery, Baltimore, MD, and Charles University Faculty of Medicine, Department of Neurology, Hradec Králové, Czech Republic.

1. Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) arranged a clinical inspection of study CN42097 (BLA 761371) conducted at Johns Hopkins Hospital Department of Neurology and Neurosurgery, Baltimore, MD, and Charles University Faculty of Medicine, Department of Neurology, Hradec Králové, Czech Republic.

A Form FDA 483 was not issued at the inspection close-out at Johns Hopkins Hospital Department of Neurology and Neurosurgery, Baltimore, MD. However, there was one discussion item regarding to contemporaneous record keeping practices. Based on the inspection findings, there are no identified concerns for Johns Hopkins Hospital Department of Neurology and Neurosurgery regarding reliability of the data or human subject protection for inspected study CN42097 for the review division consideration.

A Form FDA 483 was not issued at the inspection close-out at Charles University Faculty of Medicine, Department of Neurology, Hradec Králové, Czech Republic. However, there was one

discussion item regarding documentation of PK sample processing steps. Based on the inspection findings, there are no identified concerns for Charles University Faculty of Medicine, Department of Neurology regarding reliability of the data or human subject protection for inspected study CN42097 for the review division consideration.

2. Inspected Study:

BLA 761371

Study Number: CN42097
Study Title: "A Phase III, Non-Inferiority, Randomized, Open-Label, Parallel Group, Multicenter Study to Investigate the Pharmacokinetics, Pharmacodynamics, Safety and Radiological and Clinical Effects of Subcutaneous Ocrelizumab Versus Intravenous Ocrelizumab in Patients with Multiple Sclerosis"
Dates of study conduct: May 3, 2022 – March 10, 2023

Clinical site 1: John Hopkins University School of Medicine
Department of Neurology and Neurosurgery
600 North Wolfe Street
Baltimore, MD 21287
United States

Clinical site 2: Charles University Faculty of Medicine,
Department of Neurology
Sokolská 581, 500 05 Hradec Králové
Hradec Králové, Czech Republic

3. Inspectional Findings at Johns Hopkins Hospital Department of Neurology and Neurosurgery, Baltimore, MD

ORA investigator Roberto A. Dookhan inspected John Hopkins University School of Medicine Department of Neurology and Neurosurgery located at 600 North Wolfe Street Baltimore, MD 21287 United States from July 08 to 10, 2024.

3.1 Previous Inspection(s)

Reference ID: 5441006

This was the first OSIS inspection of John Hopkins University School of Medicine Department of Neurology and Neurosurgery under the BA/BE program.

3.2 Current Inspection

The current inspection included auditing the following items:

-Case report forms (CRFs)
-Informed consent process
-Protocol deviations
-Monitoring Records
-Institutional review board approvals
-Test article accountability and storage
-Randomization
-Adverse events

3.3 Inspection finding(s)

At the conclusion of the inspection, investigator Roberto A. Dookhan did not issue Form FDA 483 to the clinical site. However, there was one discussion item verbally presented to the site's management. The discussion item and my evaluation are provided below.

3.3.1. Discussion Item

Discussion item 1: The entries of the Expanded Disability Status Scale (EDSS) questionnaire were not captured electronically in real time in eCRFs.

OSIS Evaluation: The study protocol (Version 2, page 56 of 274, section 4.5.9) states that total EDSS scores will be captured electronically and completed in real-time. ORA investigator identified that the site captured EDSS scores in a paper-based questionnaire format and then transferred the scores to eCRF for each subject. This is a protocol violation. However, ORA investigator did not identify any discrepancy between the EDSS scores captured in paper-based questionnaire and the scores provided in subject eCRFs. Thus, this discussion item does not impact the data.

Reference ID: 5441006

4. Charles University Faculty of Medicine, Department of Neurology, Hradec Králové, Czech Republic.

ORA investigator Anna M Brannen inspected Charles University Faculty of Medicine, Department of Neurology located at Sokolská 581, 500 05 Hradec Králové Hradec Králové, Czech Republic from June 17 to 21, 2024.

4.1 Previous Inspection(s)

This was the first OSIS inspection of Charles University Faculty of Medicine, Department of Neurology under the BA/BE program.

4.2 Current Inspection

The current inspection included auditing the following items:

-Case report forms (CRFs)
-Informed consent process
-Protocol deviations
-Institutional review board approvals
-Test article accountability and storage
-Randomization
-Adverse events

4.3 Inspection finding(s)

At the conclusion of the inspection, investigator Anna M Brannen did not issue Form FDA 483 to the clinical site. However, there was one discussion item verbally presented to the site's management. The discussion item and my evaluation are provided below.

4.3.1. Discussion Item

Discussion item 1: The site did not document the PK sample serum processing steps outlined in the laboratory manual for study CN 42097 for all PK samples collected for the 17 enrolled subjects during the clinical trial.

OSIS Evaluation: Per study protocol, the serum samples were collected to determine ocrelizumab concentration for PK analysis. The appendix 4 of the study protocol provides a schedule of PK sample collection at dosing visit, but the protocol does not require that the process for sample collection to be documented in detail. ORA investigator did not identify

Reference ID: 5441006

any issues regarding the sample correction process performed at the site. Thus, this discussion item has no impact on data.

Attachment(s)
No Attachments

Hasan A. Irier, Ph.D.

Draft: HAI 09/03/2024
Edit: MO 09/04/2024; JC 09/04/2024

OSIS File #: BE 10149

eNSpect Assignment ID: 241582
eNSpect OpID: 282231 (Johns Hopkins Hospital)
eNSpect OpID: 282230 (Charles University-Faculty of Medicine)

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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: August 27, 2024

To: Elaine Gettelman, Regulatory Project Manager, Division of Neurology 2 (DN2)

Daniela A. Pimentel Maldonado, DN2

Tracy Peters, Associate Director for Labeling, (DN1)

From: Samuel Fasanmi, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, Team Leader, OPDP

Subject: OPDP Labeling Comments for Ocrevus Zunovo (ocrelizumab and hyaluronidase-ocsq) injection, for subcutaneous use

BLA: 761371

Background: In response to DN2's consult request dated January 12, 2024, OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide and carton and container labeling for the original BLA submission for Ocrevus Zunovo.

PI:
OPDP's review of the proposed PI is based on the draft labeling received by electronic mail from DN2 on August 14, 2024, and our comments are provided below.

Medication Guide:
A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed Medication Guide, and comments were sent under separate cover on August 20, 2024.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the sponsor to the electronic document room on August 19, 2024, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Samuel Fasanmi at (301) 796-5188 or samuel.fasanmi@fda.hhs.gov.

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

Reference ID: 5436674

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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 Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	August 20, 2024
To:	Elaine Gettelman, PhD, PharmD Regulatory Project Manager **Division of Neurology II (DN2)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD, LCSW, BCD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Nyedra W. Booker, PharmD, MPH Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Samuel Fasanmi, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	OCREVUS ZUNOVO (ocrelizumab and hyaluronidase-ocsq)
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Number:	BLA 761371
Applicant:	Genentech, Inc.

1 INTRODUCTION

On November 10, 2023, Genentech, Inc. submitted for the Agency's review an Original Biologics License Application (BLA) for OCREVUS ZUNOVO (ocrelizumab and hyaluronidase-ocsq) injection, for subcutaneous use. The proposed indication for OCREVUS ZUNOVO (ocrelizumab and hyaluronidase-ocsq) is for the treatment of:

- Relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.
- Primary progressive MS, in adults.

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 Neurology II (DN2) on January 12, 2024, for DMPP and OPDP to review the Applicant's proposed Medication Guide for OCREVUS ZUNOVO (ocrelizumab and hyaluronidase-ocsq) injection, for subcutaneous use.

On March 14, 2024, DN2 and DMPP made the agreement that DMPP will retain the current track changes as appropriate to the OCREVUS ZUNOVO patient labeling review so that all proposed edits to the MG are maintained in one version of the patient labeling.

2 MATERIAL REVIEWED

- Draft OCREVUS ZUNOVO (ocrelizumab and hyaluronidase-ocsq) injection, for subcutaneous use MG received on November 10, 2023, revised by the Review Division throughout the review cycle, and received by DMPP on August 14, 2024.
- Draft OCREVUS ZUNOVO (ocrelizumab and hyaluronidase-ocsq) injection, for subcutaneous use MG received on November 10, 2023, revised by the Review Division throughout the review cycle, and received by OPDP on August 14, 2024.
- Draft OCREVUS ZUNOVO (ocrelizumab and hyaluronidase-ocsq) injection, for subcutaneous use Prescribing Information (PI) received on November 10, 2023, revised by the Review Division throughout the review cycle, and received by DMPP on August 14, 2024.
- Draft OCREVUS ZUNOVO (ocrelizumab and hyaluronidase-ocsq) injection, for subcutaneous use Prescribing Information (PI) received on November 10, 2023, revised by the Review Division throughout the review cycle, and received by OPDP on August 14, 2024.

3 REVIEW METHODS

In our collaborative review of the MG, we have:

- 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)

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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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)

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

Date of This Review:	June 26, 2024
Requesting Office or Division:	Division of Neurology 2 (DN 2)
Application Type and Number:	BLA 761371
Product Name, Dosage Form, and Strength:	Ocrevus Zunovo (ocrelizumab and hyaluronidase-xxxx)[a] injection, 920 mg and 23,000 units/23 mL (40 mg and 1,000 units/mL)
Applicant Name:	Genentech, Inc.
FDA Received Date:	June 13, 2024
TTT ID #:	2023-7110-1
DMEPA 2 Safety Evaluator:	Rina Patel, PharmD
DMEPA 2 Team Leader:	Stephanie DeGraw, PharmD

[a] The non-proprietary name suffix for this product has not yet been determined; therefore, the placeholder -xxxx is used throughout this review to refer to the suffix for this product.

Reference ID: 5403626

1 PURPOSE OF MEMORANDUM

Genentech, Inc. submitted revised container label and carton labeling received on June 13, 2024 for Ocrevus Zunovo. The Division of Neurology 2 (DN 2) requested that we review the revised container label and carton labeling for Ocrevus Zunovo (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.[b]

2 DISCUSSION

Genentech, Inc. implemented most of our recommendations except the following:[c]

- The Applicant intends to use the MM YYYY (e.g., 05 2025) expiration date format with numerical characters (b) (4) In this instance, we do not object to the expiration date format from a medication error perspective.
- The Applicant declined to add a statement to the carton labeling instructing users that the product must be administered by a healthcare provider. We acknowledge the Applicant's justification that adding more text could result in a smaller font size on the carton labeling and a busy display which may hinder the readability of the text. We note the requested statement is included in the prescribing information. Further, this statement was not added to the carton labeling for other subcutaneous Genentech products that are administered by healthcare professionals only (e.g., Rituxan Hycela, Phesgo, Herceptin Hylecta), and we are not aware of medication errors associated with patients self-administering these products. Therefore, in this instance, we do not object to Genentech, Inc.'s proposal to omit this statement from the carton labeling.
- The Applicant declined to add a peel-off sticker to the container label for application on the prepared syringe. The Applicant states that the prepared syringe for intravenous use is not stored and should be used immediately, the peel-off sticker may cover markings on the syringe, (b) (4) In this instance, we do not object to Genentech, Inc.'s proposal to not include a peel-off sticker at this time; however, we recommend the Applicant consider this for future development.

Our review of the revised container labels and carton labeling did not identify any new medication error concerns and we have no additional recommendations at this time.

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[b] Patel, R. Label and Labeling Review for Ocrevus Zunovo (BLA 761371). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 MAY 21. TTT ID: 2023-7110.

[c] Response to FDA Request for Information. Ocrevus Zunovo (BLA 761371). San Francisco (CA): Genentech, Inc. 2024 JUN 13. Available from: \\CDSESUB1\EVSPROD\bla761371\0013\m1\us\clinical-information-amendment.pdf

3 CONCLUSION

Genentech, Inc. implemented most of our recommendations, and we have no additional recommendations for the container labels and carton labeling at this time that need to be addressed prior to approval of this application. However, the Applicant will need to submit final revised container label and carton labeling once the non-proprietary name suffix has been approved. Further, we have an additional comment for the Applicant to consider for future product development which does not require resubmission under this application. We provide our comment for the Applicant in Section 4 below.

4 COMMENT FOR GENENTECH, INC.

We acknowledge your rationale and concerns with adding a peel-off sticker to the product's container label for application on the prepared syringe; however, we note that similar Genentech, Inc. subcutaneous products (e.g., Herceptin Hylecta, Phesgo, Rituxan Hycela) include a peel-off sticker on the container label for syringe application. Therefore, we recommend you consider the possibility of future development and implementation of a peel-off sticker for the Ocrevus Zunovo container label.

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/s/

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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)

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Date of This Review:	May 21, 2024
Requesting Office or Division:	Division of Neurology 2 (DN 2)
Application Type and Number:	BLA 761371
Product Name, Dosage Form, and Strength:	Ocrevus Zunovo (ocrelizumab and hyaluronidase-xxxx)[a] injection, 920 mg and 23,000 units/23 mL (40 mg and 1,000 units/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Genentech, Inc.
FDA Received Date:	November 13, 2023
TTT ID #:	2023-7110
DMEPA 2 Safety Evaluator:	Rina Patel, PharmD
DMEPA 2 Team Leader:	Stephanie DeGraw, PharmD

[a] A nonproprietary name suffix has not yet been designated; therefore, -xxxx is used throughout the review as a placeholder.

Reference ID: 5384761

1 REASON FOR REVIEW

As part of the approval process for Ocrevus Zunovo (ocrelizumab and hyaluronidase-xxxx) injection, the Division of Neurology 2 (DN 2) requested that we review the proposed Ocrevus Zunovo prescribing information (PI), medication guide, container label, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND AND REGULATORY HISTORY

BLA 761371 is a 351(a) application referencing IND 100593 and BLA 761053, Ocrevus (ocrelizumab). Ocrevus is an intravenous formulation of ocrelizumab indicated for the treatment of relapsing forms of multiple sclerosis (MS) and primary progressing MS that was approved under BLA 761053 on March 28, 2017. Genentech is now seeking approval for Ocrevus Zunovo, a subcutaneous formulation of ocrelizumab, for the same indications as Ocrevus.

DMEPA previously completed (b) (4) for IND 100593 for subcutaneous administration of ocrelizumab and hyaluronidase (b) (4) [b] We note that (b) (4) this BLA submission is for a subcutaneous formulation supplied in a vial ((b) (4) to be administered via syringe by healthcare professionals only.

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
Proposed Recommendations for Section 2 of the PI	E
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

(b) (4)

Reference ID: 5384761

3 CONCLUSION AND RECOMMENDATIONS

The proposed prescribing information (PI), medication guide, container label, and carton labeling 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 Genentech, Inc.

4 RECOMMEDATIONS FOR DIVISION OF NEUROLOGY 2 (DN 2)

Table 2. Identified Issues and Recommendations for Division of Neurology 2 (DN 2)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Highlights of Prescribing Information (HPI) – Dosage and Administration			
1.	The Dosage and Administration section is missing important administration information.	Failure to clearly state this product is for healthcare professional administration only may lead to patients or caregivers administering the product, especially since this product is for subcutaneous administration.	Consider adding a statement to the HPI which states, "Must be administered by a healthcare professional." or a similar statement.
2.	The warning statement (b) (4) " is expressed as (b) (4) (b) (4)	Post-marketing reports have shown that (b) (4)	We recommend deleting the statement (b) (4) " as the route of administration is already expressed using a (b) (4) statement, "For subcutaneous use in the abdomen only". If the division or Applicant feel strongly about retaining the (b) (4) statement, we recommend moving so it appears immediately after "For subcutaneous use in the abdomen only" in the same bullet point (not in bold font).
3.	The administration instructions lack clarity.	Failure to provide clarity on administration may cause administration errors.	We recommend revising the administration statement, "… subcutaneously in the abdomen *in* approximately 10 *mins*…" to

Table 2. Identified Issues and Recommendations for Division of Neurology 2 (DN 2)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
4.	As currently presented, the administration instructions contain the abbreviation "mins".	Error prone abbreviations may lead to misinterpretation and, in this case, administration errors.	read "…subcutaneously in the abdomen over approximately 10 minutes…". We defer to the clinical team for final determination related to the administration time.
Full Prescribing Information – Section 2 Dosage and Administration			
1.	There is important administration information in subsection (b) (4) (b) (4) that is administration information and is not in presented in a prominent location.	Important administration information should be moved to the beginning of Section 2 to help mitigate wrong route and wrong dose errors.	We recommend moving the first four sentences under subsection (b) (4) to the beginning of Section 2 and creating a new subsection *2.1 Important Administration Information*, or something similar.
2.	The warning statement "(b) (4) " in subsection (b) (4) is expressed as (b) (4) (b) (4)	Post-marketing reports have shown that (b) (4)	We recommend deleting the statement (b) (4) ." as the route of administration is already expressed using a (b) (4) statement, "OCREVUS ZUNOVO is for subcutaneous use in the abdomen only". If the division or Applicant feel strongly about retaining the (b) (4) " statement, we recommend un-bolding the statement and moving it so it appears immediately after "OCREVUS ZUNOVO is for subcutaneous use in the abdomen only".
3.	The statement (b) (4)	It is unclear in this statement that this product is for administration by healthcare professionals only (b) (4)	Revise the statement to read, "OCREVUS ZUNOVO must be administered by a healthcare professional." or a similar statement. Move the statement

Table 2. Identified Issues and Recommendations for Division of Neurology 2 (DN 2)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
	[redacted]" in subsection [redacted] is misleading.	[redacted]	to the new subsection *2.1 Important Administration Information*.
4.	As currently presented, there is monitoring information in subsection [redacted]	Important dosing information should be moved to the beginning of subsection [redacted] to help mitigate wrong dose errors.	We recommend moving the monitoring information [redacted]
5.	The dosing instructions lack clarity in subsection *2.3 Recommended Dosage* and subsection *2.5 Preparation and Administration*.	Failure to provide clarity on administration may cause administration and dosing errors.	We recommend revising the administration statements, "... [redacted] " to read "...subcutaneously in the abdomen ***over*** approximately 10 minutes...". We also recommend re-wording the last sentence in subsection 2.3 to provide better clarity. For example, [redacted] or something similar (see Appendix E).
6.	Subsection 2.5 is not written in active voice.	Passive voice creates ambiguity regarding the correct actions to take.	We recommend revising the language in this section to reflect active voice. For example, "[redacted] should be inspected visually for particulate matter and discoloration prior to administration" could state "Inspect [redacted] visually for particulate matter and discoloration prior to administration". Note, this statement is also presented in active voice in the Ocrevus PI. We provide recommendations for consideration in Appendix E.

Table 2. Identified Issues and Recommendations for Division of Neurology 2 (DN 2)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			See Guidance for Industry: *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products-Content and Format (March 2019).*
7.	There is important preparation information in subsection *2.5 Preparation and Administration* that is not presented prominently.	Important information should be prominent to help mitigate preparation errors. If the statement "…must be prepared by a healthcare professional" is overlooked, it may lead to patients or caregivers preparing (and ultimately administering) the product.	We recommend modifying the statement "OCREVUS ZUNOVO must be prepared by a healthcare professional" to be in bold font.
8.	As currently presented, subsection (b) (4) contains the abbreviation "SC" and the "≤" symbol.	Error prone abbreviations may lead to misinterpretation and, in this case, administration and wrong storage errors.	We recommend replacing the abbreviations and symbols with their intended meanings.
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	The established name for hyaluronidase is incorrect.	The nonproprietary name for a biologic product should include a 4-letter suffix.	We recommend revising the active ingredient from, "hyaluronidase" to include the nonproprietary name suffix placeholder, "hyaluronidase-xxxx".
2.	One of the storage statements includes the "≤" symbol.	Error prone symbols may lead to misinterpretation and, in this case, wrong storage errors.	We recommend replacing symbol with its intended meaning. For example, revise to read "…must not exceed 12 hours at or below 25°C (77°F)."
Medication Guide			
1.	Important administration information is missing.	It may be unclear that this product is for administration by healthcare professionals	We recommend adding a statement which states, "OCREVUS ZUNOVO must be

Table 2. Identified Issues and Recommendations for Division of Neurology 2 (DN 2)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		only and may lead to patients self-administering, especially since this product is for subcutaneous administration.	administered by a healthcare professional" or a similar statement in the "How will I receive OCREVUS ZUNOVO?" section.
2.	The established name for hyaluronidase is incorrect.	The nonproprietary name for a biologic product should include a 4-letter suffix.	We recommend revising the active ingredient from, "hyaluronidase" to include the nonproprietary name suffix placeholder, "hyaluronidase-xxxx".

5 RECOMMENDATIONS FOR GENENTECH, INC.

Table 3. Identified Issues and Recommendations for Genentech, 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.	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

Table 3. Identified Issues and Recommendations for Genentech, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			alphabetical characters are used to represent the month. FDA recommends that a hyphen or forward slash be used to separate the portions of the expiration date.
2.	As currently presented, the proprietary name is denoted by the placeholder "Tradename".	We are unable to assess the prominence and readability of the intended presentation of the proprietary name.	We reference our February 7, 2024 Proprietary Name Request Conditionally Acceptable letter informing you that the proprietary name, Ocrevus Zunovo, was found conditionally acceptable. We recommend replacing the placeholder "Tradename" with the conditionally acceptable proprietary name, Ocrevus Zunovo, and use the intend-to-market presentation of the proprietary name (font, color, etc.) so that we may adequately evaluate your labels and labeling.
3.	The established name as presented does not appear to be at least half the size of the proprietary name.	We refer you to 21 CFR 201.10(g)(2) which states that the established name shall be printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent	Revise or confirm that the established name is at least half the size of the proprietary name in accordance with 21 CFR 201.10(g)(2).

Table 3. Identified Issues and Recommendations for Genentech, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		factors, including typography, layout, contrast, and other printing features.	
4.	The statement, "Store refrigerated" is missing from the storage statement.	Not including the "Store refrigerated" statement may result in risk of the refrigerated storage information being overlooked and lead to deteriorated drug medication errors.	We recommend revising and bolding the storage statement to read "Store refrigerated at 2°C to 8°C (36°F to 46°F)" or "Store refrigerated at 2°C to 8°C (36°F to 46°F)".
Container Label(s)			
1.	The container label does not contain important administration information.	Including the administration time may help mitigate the risk of inadvertent intravenous administration due to the relatively large volume (i.e., 23 mL) not typically seen for subcutaneous injections.	If space allows, consider revising "(b) (4) " to "For subcutaneous injection over 10 minutes" or consider adding the administration time to a peel-off sticker (see recommendation 2).
2.	We note that the volume of drug required for the subcutaneous injection is similar to the volume of undiluted Ocrevus for intravenous use (23 mL vs. 20 mL). The injection volume is also a relatively large volume for a subcutaneous injection.	Post-marketing experience with medications that have both intravenous and subcutaneous formulations illustrates that there is risk for wrong route errors with these types of products.	Consider adding a peel-off sticker on the container that the healthcare provider can affix to the prepared syringe which includes the following information: - Brand and established name - Route of administration - Administration time (i.e., over 10 minutes) - Drug dose (total milligram/total volume) - Area of injection (i.e., abdomen)

Table 3. Identified Issues and Recommendations for Genentech, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			If added, we recommend updating subsection *2.5 Preparation and Administration* of the prescribing information to include instructions to affix the sticker to the prepared syringe.
3.	We note there are two barcodes on the container label.	Since the drug barcode is often used as an additional verification before drug administration in the inpatient setting, the presence of multiple barcodes is confusing to the healthcare providers.	Please clarify the intention of having two barcodes on the container label (i.e., if one is a linear barcode and the other is a data matrix code required by DSCSA). Confirm that one of the barcodes on the container label is a linear barcode for product identification. We recommend you ensure that the barcode that does not contain the NDC number is presented in a size that does not compete with or distract from the presentation of other required or recommended information on the label.
Carton Labeling			
1.	The carton labeling does not contain instructions that this product must be administered by healthcare providers only.	Failure to include instructions on the labeling may result in patients or caregivers administering the product, which may lead to medication errors. The statement will help alert patients, caregivers, and healthcare providers (particularly pharmacies	We recommend adding the statement "Must be administered by a healthcare provider" to the carton labeling. Alternatively, you can include it as part of the route of administration such that it states, "For Subcutaneous Use by a Healthcare Provider Only".

Table 3. Identified Issues and Recommendations for Genentech, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		who may dispense the product directly to the patient) that the patient should take the product to their healthcare provider for administration.	
2.	The administration statement on the carton does not include the specific injection site and can be reworded for clarity.	Failure to provide clarity on administration may cause administration errors.	We recommend revising the statements, "(b) (4) " to read "*For* subcutaneous injection in the abdomen *over* approximately 10 minutes".
3.	The product identifier is missing.	In June 2021, FDA finalized the Guidance for Industry on product identifiers required under the Drug Supply Chain Security Act (DSCSA). The Act requires manufacturers and repackagers 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. The product identifier includes the NDC, serial number, lot number, and expiration date in both a human-readable form and machine-readable (2D data matrix barcode) format.	We recommend that you review the guidance to determine if the product identifier requirements apply to your product's labeling. See Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021). If you determine that the product identifier requirements apply to your product's labeling, we request you add a place holder to the carton labeling.

APPEARS THIS WAY ON ORIGINAL

Reference ID: 5384761

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table presents relevant product information for Ocrevus Zunovo that Genentech, Inc. received on November 13, 2023, and the referenced intravenous formulation for ocrelizumab[c].

Table 4. Relevant Product Information for Listed Drug and Ocrevus Zunovo

Product Name	Ocrevus[bd]	Ocrevus Zunovo
Initial Approval Date	03/28/2017	N/A
Active Ingredient(s)	ocrelizumab	ocrelizumab and hyaluronidase-xxxx
Indication	Indicated for the treatment of: • Relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults • Primary progressive MS, in adults	
Route of Administration	intravenous	subcutaneous
Dosage Form	injection	injection
Strength	300 mg/10 mL (30 mg/mL)	920 mg ocrelizumab and 23,000 units hyaluronidase per 23 mL (40 mg and 1,000 units per mL)
Dose and Frequency	• Starting dose: 300 mg intravenous infusion, followed two weeks later by a second 300 mg intravenous infusion • Subsequent doses: 600 mg intravenous infusion every 6 months	Administer 23 mL of OCREVUS ZUNOVO (920 mg ocrelizumab and 23,000 units hyaluronidase) subcutaneously in the abdomen over approximately 10 mins every 6 months.
How Supplied	A preservative-free, sterile, clear or slightly opalescent, and colorless to pale brown solution supplied as a carton containing one 300 mg/10 mL (30 mg/mL) single-dose vial	A preservative-free, sterile, clear to slightly opalescent, and colorless to pale brown solution supplied as a carton containing one 920 mg and 23,000 units/23 mL (40 mg and 1,000 units/mL) single-dose vial

[c] Ocrevus [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. August 2023. [cited 2024 Jan 8]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761053s031lbl.pdf.

[d] Ocrevus [Chemistry Reviews]. Drugs@FDA. U.S. Food and Drug Administration. March 2017. [cited 2024 Jan 10]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/761053Orig1s000ChemR.pdf.

Table 4. Relevant Product Information for Listed Drug and Ocrevus Zunovo		
Product Name	**Ocrevus**[bd]	**Ocrevus Zunovo**
Storage	Store vials at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze or shake.	
		[redacted] (b) (4) OCREVUS ZUNOVO can be removed and placed back into the refrigerator. [redacted] (b) (4)
Container Closure	• 15 mL glass vial • Rubber vial stopper • Aluminum seal with plastic flip-off cap	• 50 mL glass vial • Rubber vial stopper • Aluminum seal with plastic flip-off cap

APPENDIX B. PREVIOUS DMEPA REVIEWS

On December 1, 2023, we searched for previous DMEPA reviews relevant to this current review using the terms, "BLA 761371" and "Ocrevus". Our search identified one previous review[e] since the date of our last search on May 19, 2020. We also searched for previous DMEPA post-market reviews using the term "hyaluronidase" and identified two previous post-market reviews[fg]. We considered our previous recommendations to see if they are applicable for this current review.

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[e] Weitzman, B. Label, Labeling, and Packaging Review for Ocrevus (ocrelizumab) BLA 761053/S-022. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 June 22. OSE RCM#: 2020-359.
[f] Garrison, N. Postmarket Medication Error Review for Rituxan Hycela (rituximab and hyaluronidase) BLA 761064. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 September 2018. OSE RCM#: 2018-414.
[g] Garrison, N. Postmarket Medication Error Review for Rituxan Hycela (rituximab and hyaluronidase) BLA 761064. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 April 2019. OSE RCM#: 2018-2367.

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,[h] along with postmarket medication error experiences with similar products, we reviewed the following Ocrevus Zunovo labels and labeling submitted by Genentech, Inc.

- Container label received on 11/13/2023
- Carton labeling received on 11/13/2023
- Medication Guide (image not shown) received on 11/13/2023, available from \\CDSESUB1\EVSPROD\bla761371\0001\m1\us\draft-labeling-text.pdf
- Prescribing Information (image not shown) received on 11/13/2023, available from \\CDSESUB1\EVSPROD\bla761371\0001\m1\us\draft-labeling-text.pdf

F.2 Label and Labeling Images

Container label

(b) (4)

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

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/s/

RINA N PATEL
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05/21/2024 09:03:20 PM

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: 3/20/2024

TO: Division of Neurology II (DN II)
Office of Neuroscience (ON)

FROM: Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: BLA 761371

The Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not needed for the site listed below. The rationale for this decision is noted below.

Rationale

OSIS conducted a Remote Regulatory Assessment (RRA) for the analytical site in (b) (4). The RRA was conducted under the following submission: NDA non-responsive.

OSIS concluded that the data from the reviewed study was reliable.

Site

Facility Type	Facility Name	Facility Address
Analytical	(b) (4)	(b) (4)

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/s/

FOLAREMI ADEYEMO
03/20/2024 11:31:56 AM