CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761378Orig1s000

OTHER REVIEW(S)

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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 3, 2024
Requesting Office or Division:	Division of Ophthalmology (DO)
Application Type and Number:	BLA 761378
Product Name, Dosage Form, and Strength:	Ahzantive (aflibercept-mrbb) injection, 2 mg/0.05 mL
Applicant Name:	Formycon AG
FDA Received Date:	May 23, 2024
TTT ID #:	2023-5353-1
DMEPA 1 Safety Evaluator:	Sofanit Getahun, PharmD, BCPS
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

Formycon AG submitted revised container label and carton labeling received on May 23, 2024 for Ahzantive. The Division of Ophthalmology (DO) requested that we review the revised container label and carton labeling for Ahzantive (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

Formycon AG implemented all of our recommendations. In addition to our recommendations, the Applicant removed the statement, (b) (4) of the carton labeling stating the removal was due to "*technical space constraints*." We note the statement, "single-dose vial," is retained on the principal display panel. The Applicant also increased the prominence of the units of measurements "mg" and "mL" on the container label noting this revision was *"for consistency with the revised carton labeling."*

We find the Applicant's revisions acceptable, and we have no additional recommendations at this time.

[a] Getahun, S. Label and Labeling Review for FYB203 (aflibercept-xxxx) (BLA 761378). Silver Spring (MD): FDA, CDER, OSE, DMEPA1 (US); 2023 DEC 12. TTT ID: 2023-5353.

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SOFANIT N GETAHUN
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VALERIE S VAUGHAN
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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: May 29, 2024

To: Kidist Berhanu, Regulatory Project Manager
Office of Regulatory Operations
Division of Regulatory Operations for Specialty Medicine (DROSM)

From: Carrie Newcomer, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: James Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for AHZANTIVE™ (aflibercept-mrbb) injection, for intravitreal use

BLA: 761378

Background:
In response to DROSM's consult request dated August 24, 2023, OPDP has reviewed the proposed Prescribing Information (PI) and carton and container labeling for the original BLA submission for AHZANTIVE™ (aflibercept-mrbb) injection, for intravitreal use.

PI:
OPDP's review was completed for the proposed PI and comments were sent under separate cover on April 15, 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 May 23, 2024, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Carrie Newcomer at carrie.newcomer@fda.hhs.gov.

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CARRIE A NEWCOMER
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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: April 15, 2024

To: Kidist Berhanu, Regulatory Project Manager
Office of Regulatory Operations
Division of Regulatory Operations for Specialty Medicine (DROSM)

From: Carrie Newcomer, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: James Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for AHZANTIVE™ (aflibercept-mrbb) injection, for intravitreal use

BLA: 761378

Background:
In response to DROSM's consult request dated August 24, 2023, OPDP has reviewed the proposed Prescribing Information (PI) for the original BLA submission for AHZANTIVE™ (aflibercept-mrbb) injection, for intravitreal use.

PI:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on April 1, 2024, and we do not have any comments at this time.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling will be provided under separate cover.

Thank you for your consult. If you have any questions, please contact Carrie Newcomer at carrie.newcomer@fda.hhs.gov.

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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:	December 12, 2023
Requesting Office or Division:	Division of Ophthalmology (DO)
Application Type and Number:	BLA 761378
Product Name, Dosage Form, and Strength:	FYB203[a] (aflibercept-xxxx[b]) injection, 2 mg/0.05 mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Formycon AG
FDA Received Date:	June 28, 2023, July 28, 2023, and November 14, 2023
TTT ID #:	2023-5353
DMEPA 1 Safety Evaluator:	Sofanit Getahun, PharmD, BCPS
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

[a] FYB203 has been developed as a proposed (b) (4) biosimilar to US-licensed Eylea (aflibercept) (hereafter, called Eylea). At the time this review was written, a proprietary name has not yet been found conditionally acceptable, the proprietary name placeholder, FYB203, is used throughout the review.

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

1 REASON FOR REVIEW

As part of the approval process for FYB203 (aflibercept-xxxx) injection, the Division of Ophthalmology (DO) requested that we review the proposed FYB203 prescribing information (PI), container label, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND

BLA 761378 is a 351(k) BLA [redacted] (b) (4) biosimilar to the reference product, US-licensed Eylea, BLA 125387.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

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

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

3 CONCLUSION AND RECOMMENDATIONS

The proposed prescribing information (PI), 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 Formycon AG.

4 RECOMMEDATIONS FOR DIVISION OF OPHTHALMOLOGY (DO)

Table 2. Identified Issues and Recommendations for Division of Ophthalmology (DO)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	As currently presented, the appropriate information to facilitate identification of the dosage form is not included.	A description of the identifying characteristics can be used to help identify the product and is required by 21 CFR 201.57(c)(17)(iii).	Include a description of identifying characteristics of the dosage form, such as color and clarity of the solution in accordance with 21 CFR 201.57(c)(17)(iii).

5 RECOMMENDATIONS FOR FORMYCON AG

Table 3. Identified Issues and Recommendations for Formycon AG (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Carton Labeling			
1.	As currently presented, the principal display panel (PDP) includes the following graphic with product strength in which the units of measurements “mg” and “mL” appear smaller in size in comparison to the numbers “2” and “0.05.” (b) (4)	This presentation can be improved for readability.	We recommend increasing the prominence of the units of measurements “mg” and “mL” to commensurate with the font size of the numeric portions.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

Table presents relevant product information for FYB203 that Formycon AG submitted on June 28, 2023, and the US-licensed Eylea.

Table 4. Relevant Product Information for Listed Drug and FYB203		
Product Name	Eylea[c]	FYB203
Initial Approval Date	November 18, 2011	N/A
Active Ingredient	Aflibercept	Aflibercept-xxxx
Indication	• Neovascular (Wet) Age-Related Macular Degeneration (AMD) • Macular Edema Following Retinal Vein Occlusion (RVO) • Diabetic Macular Edema (DME) • Diabetic Retinopathy (DR) • Retinopathy of Prematurity (ROP) – Eylea	
Route of Administration	Intravitreal injection	
Dosage Form	Injection	
Strength	2 mg/0.05 mL	
Dose and Frequency	Neovascular (Wet) Age-Related Macular Degeneration (AMD) The recommended dose is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 3 months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Although may be dosed as frequently as 2 mg every 4 weeks (approximately every 25 days, monthly), additional efficacy was not demonstrated in most patients when SB15 was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4 week (monthly) dosing after the first 12 weeks (3 months). Although not as effective as the recommended every 8 week dosing regimen, patients may also be treated with one dose every 12 weeks after one year of effective therapy. Patients should be assessed regularly. Macular Edema Following Retinal Vein Occlusion (RVO) The recommended dose is 2 mg (0.05 mL) administered by intravitreal injection once every 4 weeks (approximately every 25 days, monthly).	

[c] Eylea [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. Feb 2023. [cited 2023 OCT 14]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/125387s075lbl.pdf

<table>
<tr><td></td><td>Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR)
The recommended dose is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months)

Retinopathy of Prematurity (ROP) – Eylea
The recommended dose for EYLEA is 0.4 mg (0.01 mL or 10 microliters) administered by intravitreal injection. Treatment may be given bilaterally on the same day. Injections may be repeated in each eye. The treatment interval between doses injected into the same eye should be at least 10 days</td></tr>
<tr><td>How Supplied</td><td><table>
<tr><th>Carton Type</th><th>Carton Contents</th></tr>
<tr><td>Pre-filled syringe</td><td>One blister pack containing one 2 mg/0.05 mL sterile, singe-dose prefilled glass syringe.

One package insert.</td></tr>
<tr><td>Vial kit with injection components</td><td>One 2 mg/0.05 mL single-dose glass vial

One 19-guage x 1½-inch, 5-micron, filter needle for withdrawal of the vial contents

One 30-guage x ½-inch injection</td></tr>
</table></td><td>Carton containing one single-dose glass vial designed to deliver 0.05 mL of 2 mg/0.05 mL aflibercept solution</td></tr>
</table>

		needle for intravitreal injection One 1 mL syringe for administration One package insert.	
Storage	Refrigerate at 2°C to 8ºC (36°F to 46ºF). Do not freeze. Do not use beyond the date stamped on the carton and container label. Store in the original carton until time of use to protect from light. Do not open sealed blister tray until time of use.		Refrigerate at 2°C to 8ºC (36°F to 46ºF). Do not freeze. Do not use beyond the date stamped on the carton and container label. Store in the original carton until time of use to protect from light.
Container Closure	Glass vial Prefilled Syringe		Glass vial

APPENDIX B. PREVIOUS DMEPA REVIEWS

On October 13, 2023, we searched for previous DMEPA reviews relevant to this current review using the terms, aflibercept and BLA 761378. Our search identified eight (8) previous reviews[d,e,f,g,h,i,j,k], and we considered our previous recommendation to see if they area applicable for this current review. We determined that our previous recommendations are not applicable to this current review.

[d] Fava, W. Label and Labeling Review for Eylea (BLA 125387). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2011 AUG 05. RCM No.: 2011-539.

[e] Roosta, N. Label and Labeling Review for Eylea (BLA 125387/S-061). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 DEC 27. RCM No.: 2018-2596.

(b) (4)

[g] Getahun, S. Label and Labeling Review for Eylea (aflibercept) (BLA 125387/S-75). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 DEC 19. RCM No.: 2022-866

[hh] Getahun, S. Memorandum Review of Revised Label and Labeling for Eylea (aflibercept) (BLA 125387/S-80). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 AUG 11. TTT ID.: 2023-5499

[i] Clark, C. Label and Labeling Review for Yesafili (aflibercept-xxxx) (BLA 761274). Silver Spring (MD): FDA, CDER, OSE, DMPEA 1 (US); 2022 APR 21. OSE RCM No.: 2021-2131.

[j] Myers, D. Memorandum Review of Revised Label and Labeling for Yesafili (aflibercept-xxxx) (BLA 761274). Silver Spring (MD): FDA, CDER, OSE, DMPEA 1 (US); 2022 APR 21. TTT ID.: 2022-582.

[k] Getahun, S. Label and Labeling Review for Opuviz (aflibercept-xxxx) (BLA 761350). Silver Spring (MD): FDA, CDER, OSE, DMPEA 1 (US); 2023 JUL 17. TTT ID.: 2022-3737.

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,[1] along with postmarket medication error data, we reviewed the following FYB203 labels and labeling submitted by Formycon AG.

- Container label received on November 14, 2023
- Carton labeling received on November 14, 2023
- Prescribing Information (Image not shown) received on June 28, 2023, available from:
  - Annotate version: \\CDSESUB1\EVSPROD\bla761378\0001\m1\us\114-labeling\draft\labeling\prescribing-information-word-tracked.docx
  - Clean version: \\CDSESUB1\EVSPROD\bla761378\0001\m1\us\114-labeling\draft\labeling\prescribing-information-word-clean.docx

F.2 Label and Labeling Images

Container label

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

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