CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761165Orig1s000

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)

Date of This Memorandum:	July 25, 2022
Requesting Office or Division:	Division of Ophthalmology (DO)
Application Type and Number:	BLA 761165
Product Name and Strength:	Cimerli (ranibizumab-eqrn) injection, 0.3 mg; 0.5 mg
Applicant/Sponsor Name:	Bioeq GmbH
OSE RCM #:	2020-116-2
DMEPA 1 Safety Evaluator:	Damon Birkemeier, PharmD
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on July 22, 2022 for Cimerli. The Division of Ophthalmology (DO) requested that we review the revised container labels and carton labeling for Cimerli (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations. Additionally, the Applicant revised the container label for the 0.5 mg strength so that the text "0.5 mg" appears in white instead of (b) (4), which we find acceptable. We have no additional recommendations at this time.

[a] Birkemeier D. Label and Labeling Review for Cimerli (BLA 761165). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 JUL 14. RCM No.: 2020-116-1.

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DAMON A BIRKEMEIER
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VALERIE S VAUGHAN
07/25/2022 04:19:03 PM

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)

Date of This Memorandum:	July 14, 2022
Requesting Office or Division:	Division of Ophthalmology (DO)
Application Type and Number:	BLA 761165
Product Name and Strength:	Cimerli (ranibizumab-eqrn) injection, 0.3 mg; 0.5 mg
Applicant/Sponsor Name:	Bioeq GmbH
OSE RCM #:	2020-116-1
DMEPA 1 Safety Evaluator:	Damon Birkemeier, PharmD
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised prescribing information (PI), container labels, and carton labeling received on July 11, 2022 for Cimerli. The Division of Ophthalmology (DO) requested that we review the revised PI, container labels, and carton labeling for Cimerli (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised container labels are unacceptable from a medication error perspective. We note the Applicant included a linear barcode on the revised container labels. However, the Applicant also stated that the container labels are (b) (4) (see Figure 1).

[a] Birkemeier D. Label and Labeling Review for Cimerli (BLA 761165). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 JAN 10. RCM No.: 2020-116.

Figure 1. Cimerli Vial and Container Label

We are aware of linear barcode scanning issues (b) (4) Thus, the container label may be improved to promote safe use of this product from a medication error perspective. As such, we provide a recommendation in Section 3 for the Applicant.

3 RECOMMENDATIONS FOR BIOEQ GMBH

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

A. You indicate that the proposed container labels (b) (4). We are aware of linear barcode scanning issues (b) (4) Revise the space around the linear barcode to ensure there is adequate contrast between the background color and the barcode to allow for proper scanning (e.g., print the barcode in dark ink on a white background). See our Guidance for Industry: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* for further information.[b]

[b] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. 2022. Available from: https://www.fda.gov/media/158522/download.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON JULY 11, 2022

Prescribing Information: (Image not shown) available from \\CDSESUB1\evsprod\bla761165\0027\m1\us\114-labeling\draft\labeling\cimerli-prescribing-information-redline.pdf

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VALERIE S VAUGHAN
07/14/2022 02:45:59 PM

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

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

Memorandum

Date: June 16, 2022

To: Michael Puglisi, Regulatory Project Manager
Office of Regulatory Operations, Division of Regulatory Operations for Specialty Medicine

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

CC: Jim Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for CIMERLI™ (ranibizumab-eqrn) injection, for intravitreal use

BLA: 761165

In response to the Division of Regulatory Operations for Specialty Medicine (DROSM) consult request dated June 15, 2022, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the BLA submission for CIMERLI™ (ranibizumab-eqrn) injection, for intravitreal use.

Labeling: OPDP has reviewed the attached proposed product labeling (PI) received by electronic mail from DROSM (Michael Puglisi) on June 15, 2022, and we have no additional comments at this time.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling received by electronic mail from DROSM (Michael Puglisi) on June 15, 2022, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Carrie Newcomer at (301) 796-1233 or Carrie.Newcomer@fda.hhs.gov.

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CARRIE A NEWCOMER
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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)

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

Date of This Review:	January 10, 2022
Requesting Office or Division:	Division of Ophthalmology (DO)
Application Type and Number:	BLA 761165
Product Name and Strength:	Cimerli (ranibizumab-xxxx)[a] injection, 0.3 mg; 0.5 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Bioeq GmbH
FDA Received Date:	August 2, 2021
OSE RCM #:	2020-116
DMEPA 1 Safety Evaluator:	Damon Birkemeier, PharmD
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

[a] The nonproprietary name suffix for this BLA has not yet been determined, therefore, the placeholder "ranibizumab-xxxx" is used throughout this review to refer to the non-proprietary name for this product and is not intended to be included in the final labels and labeling.

1 REASON FOR REVIEW

Under the 351(k) application pathway, Bioeq GmbH submitted BLA 761165 for Cimerli (ranibizumab-xxxx) injection for Agency review as a proposed biosimilar to US-licensed Lucentis. This review evaluates the proposed Cimerli prescribing information (PI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 PRODUCT BACKGROUND

US-licensed Lucentis (ranibizumab) was approved on June 30, 2006, under BLA 125156. Cimerli is being proposed to treat the following five conditions:

- Neovascular (Wet) Age-Related Macular Degeneration (AMD)
- Macular Edema Following Retinal Vein Occlusion (RVO)
- Diabetic Macular Edema (DME)
- Diabetic Retinopathy (DR)
- Myopic Choroidal Neovascularization (mCNV)

Like US-licensed Lucentis, the proposed strengths are 0.3 mg and 0.5 mg. The 0.3 mg dose is contained in a vial designed to deliver 0.05 mL of a 6 mg/mL solution; the 0.5 mg dose is contained in a vial designed to deliver 0.05 mL of a 10 mg/mL solution.

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 – N/A
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 Prescribing Information is acceptable from a medication error perspective; however, the proposed container labels 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 Bioeq GmbH.

4 RECOMMENDATIONS FOR BIOEQ GMBH

Table 2. Identified Issues and Recommendations for Bioeq GmbH (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Labels and Carton Labeling			
1.	As currently presented, the dosage form is located on the same line immediately following the proper name.	Per 21 CFR the proper name for biological products should not include the finished dosage form.	Revise the container and carton labeling so that the finished dosage form, injection, appears on a separate line below the proper name, ranibizumab-xxxx. See the April 2013 Draft Guidance for Industry, *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*, for more information.[b]
Container Labels			
1.	There is no linear barcode present on the immediate container label.	The drug barcode is often used as an additional verification before drug administration in the hospital setting; therefore, it is an important safety feature that should be part of the label whenever possible.	Add the product's linear barcode to each individual package as required per 21 CFR 201.25(c)(2). Orient the linear barcode in a vertical position to improve the scannability of the barcode, as barcodes placed in a horizontal position may not scan due to vial curvature.

[b] Draft Guidance: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-considerations-container-labels-and-carton-labeling-design-minimize-medication-errors

Table 2. Identified Issues and Recommendations for Bioeq GmbH (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Carton Labeling			
1.	As currently presented, the statement "Refrigerate at 2°C to 8°C (36°F to 46°F)" is not prominent on the side panel.	Increasing the prominence of this important storage information minimizes the risk of the storage information being overlooked.	Revise and bold the statement "Refrigerate at 2°C to 8°C (36°F to 46°F)".

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table presents relevant product information for Cimerli that Bioeq GmbH submitted on August 2, 2021, and Lucentis[c].

Table 4. Relevant Product Information for Listed Drug and Cimerli		
Product Name	Lucentis	Cimerli
Initial Approval Date	June 30, 2006	N/A
Active Ingredient	Ranibizumab	Ranibizumab-xxxx
Indication	Treatment of the following five conditions: • Neovascular (Wet) Age-Related Macular Degeneration (AMD) • Macular Edema Following Retinal Vein Occlusion (RVO) • Diabetic Macular Edema (DME) • Diabetic Retinopathy (DR) • Myopic Choroidal Neovascularization (mCNV)	
Route of Administration	Intravitreal	
Dosage Form	Injection	
Strength	0.3 mg/0.05 mL; 0.5 mg/0.05 mL	
Dose and Frequency	<u>Neovascular (Wet) Age-Related Macular Degeneration (AMD)</u> • 0.5 mg once a month (approximately every 28 days) • Although not as effective, may treat with 3 monthly doses followed by less frequent doses. • Although not as effective, may treat with 4 monthly doses followed by one dose every 3 months. <u>Macular Edema Following Retinal Vein Occlusion (RVO)</u> • 0.5 mg once a month (approximately every 28 days) <u>Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR)</u> • 0.3 mg once a month (approximately every 28 days) <u>Myopic Choroidal Neovascularization (mCNV)</u>	

[c] Lucentis [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. Mar 2018. [cited 2021 Dec 12]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125156s117lbl.pdf.

	• 0.5 mg once a month (approximately every 28 days) for up to three months. Patients may be retreated if needed	
How Supplied	• Single use prefilled syringe designed to deliver 0.3 mg (0.05 mL of 6 mg/mL) • Single use prefilled syringe designed to deliver 0.5 mg (0.05 mL of 10 mg/mL) • Single use 2-mL glass vial designed to deliver 0.3 mg (0.05 mL of 6 mg/mL) • Single use 2-mL glass vial designed to deliver 0.5 mg (0.05 mL of 10 mg/mL)	• Single dose 2-mL glass vial designed to deliver 0.3 mg (0.05 mL of 6 mg/mL) • Single dose 2-mL glass vial designed to deliver 0.5 mg (0.05 mL of 10 mg/mL)
Storage	Refrigerate at 2 °C to 8 °C (36 °F to 46 °F). Do not freeze. Protect from light and store in the original carton until time of use.	

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,[d] along with postmarket medication error data, we reviewed the following Cimerli labels and labeling submitted by Bioeq GmbH.

- Container label(s) received on August 2, 2021
- Carton labeling received on August 2, 2021
- Prescribing Information (Image not shown) received on August 2, 2021, available from \\CDSESUB1\evsprod\bla761165\0009\m1\us\114-labeling\draft\labeling\cimerli-vial-prescribing-information.pdf

F.2 Label and Labeling Images

Container labels:

(b) (4)

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

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