CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209569Orig1s000

OTHER REVIEW(S)

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

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

Memorandum

Date: November 19, 2019

To: Michael Puglisi
Regulatory Project Manager
Division of Transplant and Ophthalmology Products (DTOP)

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

Subject: **NDA: 209569**
TissueBlue (Brilliant Blue G Ophthalmic Solution) 0.025%

OPDP has reviewed the proposed prescribing information (PI) and Carton and Container Labeling submitted for consult on November 12, 2019, for TissueBlue (Brilliant Blue G Ophthalmic Solution) 0.025% for Intraocular Ophthalmic Administration. Our review is based on the version of the proposed PI and Carton and Container Labeling that was emailed to OPDP by Michael Puglisi on November 7, 2019. OPDP's comments are provided directly on the attached version of the proposed PI. OPDP's comments on the proposed carton and container labeling (also attached) are provided below.

Carton and Container Label

1. The proposed carton label includes part of the indication for TissueBlue ("Staining Solution for Ophthalmic Surgery") but omits important material facts with respect to consequences that may result from the use of the drug as recommended or suggested on the package labeling. Therefore, we recommend deleting this claim or revising it to include the full complete indication and also providing sufficient disclosure of the most serious and most common risks associated with the drug in depth and in detail to balance this claim.

2. OPDP recommends that the established name be revised to have prominence commensurate with the proprietary name. The established name should be at least half as large as the letters comprising the proprietary name 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 factors, including typography, layout, contrast, and other printing features, according to 21 CFR 201.10 (g)(2). The proprietary name is more than twice the size of the established name. In addition, the bolded dark font of the proprietary name also gives it greater prominence as compared to the light-colored white font used for the established name on the carton label. Please apply this comment to all container and carton labeling.

Thank you for your consult. If you have any questions on our comments for the proposed labeling, please contact Carrie Newcomer at 6-1233, or carrie.newcomer@fda.hhs.gov.

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

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/s/

CARRIE A NEWCOMER
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LABEL AND LABELING REVIEW

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

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

Date of This Review:	October 11, 2019
Requesting Office or Division:	Division of Transplant and Ophthalmology Products (DTOP)
Application Type and Number:	NDA 209569
Product Name and Strength:	TissueBlue (Brilliant Blue G) Ophthalmic Solution, 0.025%
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Dutch Ophthalmic Research Center International BV (D.O.R.C International)
FDA Received Date:	June 5, 2019 and September 23, 2019
OSE RCM #:	2019-988
DMEPA Safety Evaluator:	Maximilian Straka, PharmD, FISMP
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 REASON FOR REVIEW

As part of the approval process for TissueBlue (Brilliant Blue G) Ophthalmic Solution, the Division of Transplant and Ophthalmology Products (DTOP) requested that we review the proposed TissueBlue Prescribing Information (PI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

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

Table 1. Materials Considered for this Label and Labeling Review

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

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

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We note that there is no 2-D barcode on the carton end label and blister label. We also note that there is no linear barcode present on the syringe label.

We also note that the package type term "single (b) (4) only" is used in the PI, the container label and carton labeling. We defer to OPQ to determine the appropriate package type term and to make appropriate changes across all labels and labeling.

4 CONCLUSION & RECOMMENDATIONS

The proposed Tissue Blue prescribing information, container label and carton labeling can be improved to promote the safe use of this product.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

1. Dosage and Administration Section

a. The term (b) (4) should be replaced with "prefilled syringe" throughout the Prescribing Information so that the reader does not think there are two different syringes needed for the procedure.

b. In the Dosage Forms and Strengths section, it states that TissueBlue (Brilliant Blue G Ophthalmic Solution) 0.025% is supplied in 2.25 mL syringes filled to a volume of 0.5 mL. Currently, it is unclear how much of the 0.5 mL contained in the syringe should be injected into the vitreous cavity. We recommend clarifying whether a portion of the volume or the total volume should be injected. We also recommend removing the term "2.25 mL" from the statement "is supplied in 2.25 mL syringes" so that the syringe size is not confused with the fill volume. For example, the statement should read: "TissueBlue (Brilliant Blue G Ophthalmic Solution) 0.025% is supplied in prefilled syringes filled to a volume of 0.5 mL."

c. The abbreviation "BSS" in the statement "injected into the BSS-filled vitreous cavity" is not defined. We note the abbreviation BSS is commonly used in the ophthalmology field; however, non-ophthalmology professional will have access to the Prescribing Information for this product. Therefore, the abbreviation, BSS, should be defined the first time it is used in the Prescribing Information followed by (BSS) so that the non-ophthalmology professionals can understand the abbreviation.

4.2 RECOMMENDATIONS FOR DUTCH OPHTHALMIC RESEARCH CENTER INTERNATIONAL BV (D.O.R.C INTERNATIONAL)

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

A. General Comments (Container labels & Carton Labeling)

1. The Applicant's logo, presented as "DORC", competes in prominence with the proprietary name on the container labels and carton labeling. Reduce the size of the logo to increase the readability and prominence of the proprietary name.[a]

2. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the 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

[a] Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from: http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf.

if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.[b]

3. In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act. The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling.[b]

B. Container Labels

1. The syringe label may be improved in the following ways:

   a. The NDC on the syringe is the same as the NDC on the Carton. If a carton contains multiple syringes, then the carton labeling should have a different NDC package code (last 2 digits of the NDC) than the syringes within the carton. Assigning different package codes, distinguishes the individual syringe from the carton of 5 preflled syringes.

   b. To ensure consistency with the Prescribing Information, revise the statement, "See package insert for dosing information" to read "Recommended Dosage: See prescribing information."

   c. The linear barcode is not included. 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. Therefore, we request you add the product's linear barcode to each individual syringe as required per 21CFR 201.25(c)(2). The linear barcode should be presented in a vertical position so the barcode can be properly scanned. If the linear barcode is presented in horizontal position, then the barcode may wrap around the curvature of the syringe, and will not be scannable.

[b] Draft Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act Questions and Answers. Food and Drug Administration. 2018. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/product-identifiers-under-drug-supply-chain-security-act-questions-and-answers

C. Carton Labeling

1. In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act.[c] The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling.

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

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for TissueBlue received on June 5, 2019 from Dutch Ophthalmic Research Center International BV (D.O.R.C International).

Table 2. Relevant Product Information for TissueBlue	
Initial Approval Date	N/A
Active Ingredient	Brilliant Blue G
Indication	(b) (4) selectively staining the internal limiting membrane (ILM).
Route of Administration	Injection
Dosage Form	Ophthalmic Solution
Strength	0.025%
Dose and Frequency	0.5 mL injection per treated eye.
How Supplied	In a sterile single-use Luer Lok, 2.25 mL glass syringe, grey rubber plunger stopper and tip cap with polypropylene plunger rod in a (b) (4) NDC 68803-722-05 (5-unit carton)
Storage	Store at 15-25°C (59-77°F). Protect from direct sunlight.
Container Closure	2.25 mL glass syringe, grey rubber plunger stopper and tip cap with polypropylene plunger rod in a (b) (4).

APPENDIX B. PREVIOUS DMEPA REVIEWS

On September 10, 2019, we searched for previous DMEPA reviews relevant to this current review using the terms, TissueBlue and brilliant blue. Our search did not identify any relevant reviews.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[d] along with postmarket medication error data, we reviewed the following TissueBlue labels and labeling submitted by Dutch Ophthalmic Research Center International BV (D.O.R.C International).

- Carton End Label received on September 23, 2019.
- Container labeling received on June 5, 2019.
- Patient Label received on September 23, 2019.
- Syringe Label received on June 5, 2019.
- Unit-Dose Blister label received on September 23, 2019.
- Prescribing Information (Image not shown) received on June 5, 2019.

G.2 Label and Labeling Images

Carton End Label

(b) (4)

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

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