CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209569Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 209569
Review # 1
Oct 4, 2019

Drug Name/Dosage Form	***TissueBlue (Brilliant Blue G Ophthalmic Solution)***
Strength	*0.025%*
Route of Administration	*Intraocular Injection*
Rx/OTC Dispensed	*Rx*
Applicant	*Dutch Ophthalmic Research Center (International) B.V.*
US agent, if applicable	*Matthew Carignan*

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Original	*4/29/2019*
Amendment	*6/19/2019*
Amendment	*6/28/2019*
Amendment	*7/23/2019*
Amendment	*7/25/2019*
Amendment	*8/7/2019*
Amendment	*8/27/2019*
Amendment	*9/4/2019*
Amendment	*9/9/2019*
Amendment	*9/16/2019*
Amendment	*9/20/2019*
Amendment	*9/26/2019*
Amendment	*10/2/2019*
Amendment	*10/3/2019*

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Application Technical Lead	Chunchun Zhang	NA
Drug Substance	Sharon Kelly	Su (Suong) Tran
Drug Product	Milton Sloan	Chunchun Zhang
Microbiology	Jianli Xue	Neal Sweeny
Biopharmaceutics	Zhuojun Zhao	Elsbeth Chikhale
Process	Feiyan Jin	Steve Rhieu
Facility	Feiyan Jin	Steve Rhieu

Regulatory Business Process Manager	Kristine Leahy	NA
ORA Lead	Caryn McNabb	NA
Laboratory (OTR)	NA	NA
Environmental Assessment (EA)	Milton Sloan	Chunchun Zhang

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status[1]	Date Review Completed	Comments
(b) (4)	Type III		(b) (4)	NA		LoA: 4/9/2018
	Type III			NA		LoA: 12/11/2015

[1]NA (There is enough data in the application, therefore the DMF did not need to be reviewed).

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NA		

2. CONSULTS

NA

Executive Summary

I. Recommendations and Conclusion on Approvability

OPQ recommends APPROVAL of NDA 209569 for commercialization of TissueBlue (Brilliant Blue G Ophthalmic Solution), 0.025%. The applicant has provided adequate product quality information to assure the identity, strength, purity, and quality of the proposed drug product. All information requests and review issues have been addressed. The Office of Process and Facilities has issued an overall acceptable recommendation for all the facilities on 9/9/2019. Labeling recommendations from the Product Quality perspective will be provided to the OND PM for consideration during final labeling discussion.

The following PMCs have been concurred by the applicant on Oct 3, 2019. Additionally, the expiration date of 12 months is granted when stored at 15 °C- 25 °C. Both PMCs and the expiration date should be included in the Action Letter:

1. Post Marketing Commitment # 3724-1: Provide 12-month stability update for Batch 14218 and 6-month stability data for Batch 21618. Final protocol submission date: Dec 15, 2019; study completion: March 15, 2020; and final report submission: April 15, 2020.

2. Post Marketing Commitment # 3724-2: Any further extension of the expiration date post-approval will need to be submitted for review as a PAS supplement. Final protocol submission date: May 15, 2020; study completion: April 15, 2021; and final report submission: May 15, 2021.

3. Post Marketing Commitment # 3724-3: A leachable study on at least one stability Batch 14618 should be conducted through its expiration date. Final protocol submission date: Dec 15, 2019; study completion: March 15, 2020; and final report submission: April 15, 2020.

II. Summary of Quality Assessments

A. Product Overview

Proposed Indication(s) including Intended Patient Population	(b) (4) selectively stain the (b) (4) internal limiting membrane (ILM) (b) (4)
Duration of Treatment	Injected into the BSS-filled vitreous cavity using a blunt cannula attached to the syringe. See package insert for the recommended dosage in patients.
Maximum Daily Dose	As above (see the package insert for details).
Alternative Methods of Administration	NA

B. Quality Assessment Overview

i. Drug Substance Quality Summary

The drug substance, Brilliant Blue G, [redacted] The analytical methods to control the quality of the drug substance are adequately described and validated to ensure quality control.
The primary packaging material consists of [redacted] The primary stability data support the proposed retest period of [redacted] months at [redacted]C.

ii. Drug Product Quality Summary

Brilliant Blue G ophthalmic solution has been marketed by the Applicant outside the United States as a device, and received CE-approval/CE-mark (CE-0344) in 2010. Brilliant Blue G ophthalmic solution, 0.025% is regulated as a drug product in US per 21 CFR 200.50. Brilliant Blue G ophthalmic solution 0.025% is a sterile, stable, single-dose ophthalmic solution packaged in a single-use Luer Lok, 2.25 mL glass syringe, grey rubber plunger stopper and tip cap with polypropylene plunger rod packed in a preformed polypropylene blister sealed with a Tyvek® [redacted] The fill volume is [redacted] mL.

The proposed Brilliant Blue G Ophthalmic Solution, 0.025% and CE-approval ILM-Blue® [redacted]. All excipients used in the formulation are adequately qualified. No novel excipients are used in the formulation. The drug product specification includes tests for appearance, identity, assay, impurities, [redacted], pH, osmolality, sterility, endotoxin, particulate matter. All analytical methods are described in reasonable detail and have been adequately validated.

The applicant has submitted three primary stability batches at the commercial scale [redacted] syringes) using the commercial process and packaging in the commercial container closure system. Stability data for three primary stability batches with twelve months at long term storage of 30°C/65%RH and nine months accelerated condition at 40°C/75% RH are provided. All the quality attributes except the particulate matter remained within the proposed limits. Particulate matter was observed to be out of the specification (OOS) even at

release for all three batches. The applicant, in the root cause analysis report attributes the particulate matter OOS triggered (b) (4) Two additional drug product batches (14218 and 21618) were manufactured with the optimized drug substance batch. Six months stability data at long term and at accelerated conditions for Batch 14218 and one month stability data at long term and at accelerated conditions for Batch 21618 have been submitted. The limited stability data, in itself, does not support the requested (b) (4) shelf life. However, all quality attributes in the initial three stability batches meet the proposed specification and therefore can be considered as supportive batches to establish an expiration period. Photostability study suggests the proposed drug product is sensitive to the direct sunlight. A cautious statement should be included. Since the applicant appears to have established adequate control to address the particulate issue, the expiration date of 12 months is granted when stored at 15 °C- 25 °C with the proposed PMCs. The applicant agreed with the PMCs # 3724-1 and 3724-3, and has proposed the timelines for PMC # 3724-2 which are found acceptable by the Agency on Oct 4, 2019. The granted expiration date of 12-months for the drug product was communicated to the applicant on Oct 4, 2019.

1. *Post Marketing Commitment # 3724-1: Provide 12-month stability update for Batch 14218 and 6-month stability data for Batch 21618. Final protocol submission date: Dec 15, 2019; study completion: March 15, 2020; and final report submission: April 15, 2020.*

2. *Post Marketing Commitment # 3724-2: Any further extension of the expiration date post-approval will need to be submitted for review as a PAS supplement. Final protocol submission date: May 15, 2020; study completion: ~~March 15, 2021~~ April 15, 2021; and final report submission: ~~April 15, 2021~~ May 15, 2021.*

3. *Post Marketing Commitment # 3724-3: A leachable study on at least one stability Batch 14618 should be conducted through its expiration date. Final protocol submission date: Dec 15, 2019; study completion: March 15, 2020; and final report submission: April 15, 2020.*

The storage statement is “Protect from light. Store at 15°C - 25°C (59°F - 77°F).” and will be finalized at the OND’s labeling meeting.

The proposed drug product manufacturing process consists: (b) (4) During the NDA review several information requests regarding to critical process parameters and

executive batch records etc. were conveyed to and addressed by the applicant. The overall information regarding the manufacturing process provided in the NDA submission and subsequent amendments was found acceptable. The drug product [redacted] (b) (4) It is found acceptable from quality micro perspective.

Biopharmaceutics reviewer Dr. Zhuojun Zhao has found acceptable that the applicant has not conducted bioavailability and/or bioequivalence studies per 21 CFR 320.24(b)(6). Additionally, a bridge between the proposed drug product and the CE approved ILM-Blue® is established, which justifies reliance on literature that uses ILM-Blue®.

The facilities related to the drug substance manufacturing and testing as well as the drug product manufacturing and testing are acceptable based on the satisfactory compliance history and review of manufacturing capabilities. OPF has issued an overall acceptable recommendation for all the facilities on 9/9/2019.

C. Special Product Quality Labeling Recommendations (NDA only)

NA

D. Final Risk Assessment (see Attachment)

I. From Initial Risk Identification			Review Assessment		
Attribute/CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Eval.	Lifecycle Considerations Comments
Sterility	Formulation Container closure[1] Process parameters Scale/equipment Site	**H**	[redacted] (b) (4)	**L**	[redacted] (b) (4)
Endotoxin Pyrogen	Formulation Container closure[1] Process parameters Scale/equipment	**L**		**L**	
Assay (API), stability	Formulation Container closure[1] Raw materials	**L**		**L**	

Assay (b) (4)	Formulation Container closure[1] Process parameters Scale/equipment	**L**	(b) (4)	**L**	
Uniformity of Dose (Fill Vol/ Deliverable volume)	Formulation Container closure[1] Process parameters Scale/equipment	**M**		**L**	
pH	Formulation Container closure[1] Process parameters Scale/equipment	**L**		**L**	
Particulate matter	Formulation Container closure[1] Process parameters Scale/equipment	H		L	Two PMCs on the stability update and extension of the assigned expiration date are proposed. The applicant agreed with the proposed PMCs.
Extractable/Leachable	Formulation Container closure[1] Process parameters Scale/equipment	H		L	A PMC is proposed to conduct a leachable study through its expiration date. The applicant agreed with the proposed PMC.

[1]Stability studies demonstrate container closure compatibility with the drug product for all quality attributes.

This NDA is recommended for APPROVAL from the Product Quality Perspective.

On behalf of the OPQ team
Chunchun Zhang, Ph.D. ATL for NDA 209569

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CHAPTER VI: BIOPHARMACEUTICS

Application No: NDA 209569-ORIG-1 [505(b)(2)]
Drug Product Name / Strength: Brilliant Blue G Ophthalmic Solution, 0.025%
Route of Administration: Ophthalmic Solution
Applicant Name: Dutch Ophthalmic Research Center (International) B.V.
Indication: For use as an aid in ophthalmic surgery by selectively staining the (b) (4) internal limiting membrane (b) (4)

Biopharmaceutics Review Team:
Primary Reviewer: Zhuojun Zhao, Ph.D.
Secondary Reviewer: Elsbeth Chikhale, Ph.D. (For Jing Li, Ph.D.)

Review Summary:
NDA 209569 was submitted as a 505(b)(2) NDA under the Federal Food, Drug and Cosmetic Act. The Applicant relies on literature references using ILM-Blue® and Brilliant Blue G containing product to support the safety and efficacy of the proposed drug product. (b) (4)

Table 1: Composition of the proposed drug product (b) (4)

Component	% w/w	Function
Brilliant Blue G (BBG)	0.025	Active Ingredient
Polyethylene Glycol (PEG) 3350	(b) (4)	
Buffered Sodium Chloride solution		

ILM-Blue® has been marketed by the Applicant outside the United States as a device, and received CE-approval/CE-mark (CE-0344) in 2010. The Food Drug and Cosmetic Act classifies the proposed product as a drug product, not a device. The Clinical review relies on published clinical trials of Brilliant Blue G products, including ILM-Blue ®, to support the safety and efficacy of the proposed drug product. In addition, the Clinical review relies in part on post-marketing experience of ILM-Blue ® to support the safety. Some of the publications use ILM-Blue ® specifically, while others refer to Brilliant Blue G.

(b) (4)

Considering that the pharmacokinetic properties including systemic absorption, distribution, metabolism and excretion, are not relevant because Brilliant Blue G 0.025% Solution remains in the eye for a very short period of time (less than one minute) and systemic exposure is not expected following intraocular administration, it is acceptable that the Applicant has not conducted bioavailability and/or bioequivalence studies per 21 CFR 320.24(b)(6).

Since the proposed Brilliant Blue G Ophthalmic Solution, 0.025% (b) (4) (b) (4) (b) (4) a bridge between the proposed drug product and ILM-Blue® is established, which justifies reliance on literature that uses ILM-Blue®. Although the formulation used in the publications using Brilliant Blue G is not always specified, it is likely that ILM-Blue® was in fact used in some of those publications. Therefore, those publications can be used as supportive evidence.

RECOMMENDATION:

From the Biopharmaceutics perspective, NDA 209569 for Brilliant Blue G Ophthalmic Solution, 0.025% is recommended for **APPROVAL**.

Zhuojun Zhao

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Elsbeth Chikhale

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MICROBIOLOGY

IQA Review Guide Reference

Product Background:

NDA: 209569

Drug Product Name / Strength: Brilliant Blue G Ophthalmic Solution, 0.025%

Route of Administration: Ophthalmic injection

Applicant Name: D.O.R.C. International, b.v.

Manufacturing Site: (b) (4)

Method of Sterilization: (b) (4)

Review Recommendation: **Adequate**

Theme (ANDA only): Choose an item.

Justification (ANDA only): Choose an item.

Review Summary:

List Submissions Being Reviewed: 4/29/2019; 6/19/2019; 7/23/2019; 8/7/2019; 9/9/2019; 9/19/2019; 9/26/2019

Highlight Key Outstanding Issues from Last Cycle: N/A

Remarks: N/A

Concise Description Outstanding Issues Remaining: None

Supporting Documents: DMF (b) (4) and microbiology review (b) (4) dated 10/3/2018, (b) (4) dated 2/2/2018, (b) (4) dated 6/13/2017 for (b) (4) for the subject drug product.

List Number of Comparability Protocols (ANDA only): N/A

S Drug Substance

Reviewer's Assessment: ***Adequate***

The drug substance is (b) (4)

P.1 Description of the Composition of the Drug Product

- **Description of drug product –** Sterile ophthalmic solution supplied in a single-use Luer Lok, 2.25 ml glass syringe, grey rubber plunger stopper and tip cap

- **Drug product composition –**

Component	% w/w	Function	Compendial status
Brilliant Blue G (BBG)	0.025	Active ingredient	Noncompendial
Polyethylene glycol (PEG) 3350	(b) (4)		USP/NF
Buffered sodium chloride solution			
Sodium chloride			USP
Sodium phosphate dibasic dodecahydrate			USP
Sodium phosphate monobasic dihydrate			USP
WFI			USP

- **Description of container closure system –**

Component	Color and materials	Material and component suppliers*	Supplier DMF
(b) (4)			

		(b) (4)	

*Alternate component suppliers may be used if appropriately qualified.

Exhibit batches (p41/44 in 2.3.P):

Stability lot no.	Manufacturing batch no.	Fill volume/container size	Batch size (units)	Date of manufacture
Supporting stability batches		(b) (4)	(b) (4)	
1	52115	2.25 ml		
2	62115	2.25 ml		
3	72115	2.25 ml		
Primary stability batches				
1	19217	2.25 ml		
2	19317	2.25 ml		
3	19517	2.25 ml		
Additional supporting batch				
1	14218	2.25 ml		

Proposed commercial batch: minimum (b) (4) units) to maximum (b) (4) units)

Reviewer's Assessment: ***Adequate***

The sponsor provided an adequate description of the drug product composition and the container closure system designed to maintain product sterility.

P.2 Pharmaceutical Development

(b) (4)

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Chunchun Zhang

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