CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

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

Application Type	NDA
Application Number	209569
PDUFA Goal Date	December 29, 2019
OSE RCM #	2019-987
Reviewer Name(s)	Carlisha Gentles, Pharm.D., BCPS, CDE
Team Leader	Laura Zendel, Pharm.D., BCPS
Division Director	Jamie Wilkins, Pharm.D.
Review Completion Date	October 28, 2019
Subject	Evaluation of Need for a REMS
Established Name	Brilliant Blue G Ophthalmic Solution 0.025% (BBG)
Trade Name	TissueBlue
Name of Applicant	Dutch Ophthalmic Research Center (International) B.V.
Therapeutic Class	Ophthalmic dye
Formulation(s)	Ophthalmic solution
Dosing Regimen	Inject BBG 0.025% directly in a BSS-filled vitreous cavity

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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity, TissueBlue (brilliant blue G ophthalmic solution) is necessary to ensure the benefits outweigh its risks. Dutch Ophthalmic Research Center (International) B.V. (DORC), submitted a New Drug Application (NDA) 209569 for brilliant blue G ophthalmic solution with the proposed indication for use as an aid in ophthalmic surgery by selectively staining the (b) (4) internal limiting membrane (ILM) (b) (4) . The risk associated with brilliant blue G ophthalmic solution is excessive staining of the eye. The Applicant did not submit a proposed REMS or risk management plan with this application.

DRISK and the Division of Transplant and Ophthalmology Products (DTOP) agree that a REMS is not necessary to ensure the benefits of brilliant blue G ophthalmic solution outweigh its risks. The risk of excessive staining in the eye can be prevented by removing excess brilliant blue G ophthalmic solution immediately after staining. Reported adverse events were attributed to the surgical procedure and not the staining of the ILM and no safety concerns were identified. Based on the safety profile and efficacy demonstrated in the literature analysis, the benefit-risk profile is acceptable and risk mitigation beyond labeling is not required.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) TissueBlue (brilliant blue G ophthalmic solution, hereinafter referred to as BBG) is necessary to ensure the benefits outweigh its risks. Dutch Ophthalmic Research Center (International) B.V. (DORC) submitted a New Drug Application (NDA) 209569 for BBG with the proposed indication for use as an aid in ophthalmic surgery by selectively staining the (b) (4) internal limiting membrane (ILM) (b) (4) . This application is under review in the Division of Transplant and Ophthalmology Products (DTOP). The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

BBG, a new molecular entity (NME),[a] is a (b) (4) ophthalmic dye proposed for use as an aid in ophthalmic surgery by selectively staining the (b) (4) ILM (b) (4) . BBG nonspecifically binds to multiple types of proteins and has been shown to selectively stain the ILM but not the epiretinal membrane nor the retina, making it easier to visualize for removal. The exact mechanism for this selectivity is not known.

[a] Section 505-1 (a) of the FD&C Act: FDAAA factor (F): Whether the drug is a new molecular entity.

The proposed dosage form is an ophthalmic solution available as 0.025% in 2.25 mL syringes filled to a volume of 0.5 mL. The proposed dosage is 0.025% (0.5 mL) injected into the BSS[b]-filled vitreous cavity prior to surgery. The drug can be administered in an inpatient or outpatient setting. The duration of treatment is short-term during the procedure only, which are primarily outpatient procedures[c].

BBG was first approved in 2010 in the European Union (EU) as ILM Blue ® for use as an aid in ophthalmic surgery for the currently proposed indication. Since approval, the applicant reports that over (b) (4) units of ILM-Blue® have been distributed in the EU for use in surgical procedures. BBG (NDA 209569) was granted orphan drug designation by the Agency on July 31, 2012.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 209569 relevant to this review:

- 07/31/2012: Orphan Drug Designation granted for use an aid in ophthalmic surgery
- 11/02/2018: NDA 209569 submission for use an aid in ophthalmic surgery selectively staining the (b) (4) internal limiting membrane
- 8/20/2019: Midcycle meeting cancelled at the request of Applicant

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Vitreoretinal disorders describe a group of eye diseases that affect the retina at the back of the eye and the vitreous fluid around it. Some examples include macular degeneration, retinal tear or detachment, macular hole, macular pucker, endophthalmitis, severe eye injury and diabetic retinopathy, among others. Because the structures affected in vitreoretinal disorders are integral to vision, a disease in this part of the eye can temporarily or permanently diminish vision and should be evaluated right away.

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Treatment methods are developed based on the type of retinal damage and severity of the condition. In some cases, such as diabetic retinopathy, retinal detachment, macular holes, macular pucker, endophthalmitis, severe eye injury, and cataract surgeries, ophthalmologists recommend surgical

(b) (4)

[c] Section 505-1 (a) of the FD&C Act: FDAAA factor (D): The expected or actual duration of treatment with the drug.

procedures including vitrectomies. Approximately 225,000 vitrectomies are performed annually in the United States and indications for use continue to expand.[1, d]

"Chromovitrectomy" is a term used for describing the use of vital dyes during vitreoretinal surgery to assist in the identification of preretinal tissues and membranes. These transparent tissues include vitreous, epiretinal membrane, and the internal limiting membrane (ILM). Chromovitrectomy assists in highlighting these difficult to detect, very thin and semitransparent preretinal membranes and tissues.[2] ILM peeling is the surgical procedure used for macular hole repair and epiretinal membrane removal. While it is possible to remove all of these tissues without staining, the process is significantly easier and more complete after staining. This is especially true in certain cases, such as ILM peeling in highly myopic eyes or in cases of severe diabetic macular edema.[3,e]

Currently, although compounded forms may be available, no FDA approved ophthalmic dyes for the selective staining of the ILM are available. When ophthalmologists need to perform an ILM peeling or vitrectomy to aid in the treatment of macular hole, retinal detachment or macular edema, compounded BBG or other non-selective vital dyes are used such as include Indocyanine green (ICG) and Tryphan Blue (Membrane Blue). ICG provides a contrast between the stained and unstained ILM but causes toxic effects to both the neuroretina and pigmented epithelium which can impact the success of the surgery, in addition to causing phototoxicity. Also, ICG can remain on the inner retina for months after surgery causing the phototoxic effect to last longer. Tryphan Blue stains the inner retinal surface to provide a contrast but it is not specific for the ILM.[4] Triamcinolone acetonide (TA) can also be used to distinguish the ILM from other retinal layers during vitrectomies. TA is a nonselective dye that can dirty the tip of instruments, limiting its use.[5]

Due to the lack of ophthalmic solution dyes with selective staining properties for the ILM, surgeons in the United States have turned to compounding pharmacies for BBG. Recently, problems due to contamination in compounded BBG, including development of fungal endophthalmitis have been reported. In March 2012, several cases of probable and laboratory-confirmed fungal endophthalmitis occurring after invasive ocular procedures were reported nationwide. Of the confirmed fungal endophthalmitis cases, 21 patients had been exposed to compounded BBG during retinal surgery.[6] The Applicant is proposing BBG to fulfil the unmet medical need for a safe and effective ophthalmic dye with selectivity for the ILM to be used during these surgeries.

[d] Section 505-1 (a) of the FD&C Act: FDAAA factor (A): *The estimated size of the population likely to use the drug involved.*

[e] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

4 Benefit Assessment

Published clinical trials, a meta-analysis of prior literature studies, and a clinical example were used for the benefit-risk assessment of BBG. Specifically, the efficacy data set is derived from 19 treatment groups extracted from 13 peer-reviewed articles. Appendix I details the specific articles, treatment types, number of eyes and rate of visualization success in the efficacy data set. A total of 514 eyes were treated with either ILM-Blue®, BBG, ICG, Tryphan Blue, or Membrane Blue-Dual. Efficacy statistics were reported as the total number of eyes treated per treatment type divided by the number of eyes where treatment was deemed effective by the surgeon (i.e. the internal limiting membrane was visualized). Surgeons performing vitrectomy procedures documented their ability to distinguish and visualize the ILM. Efficacy was based on classifying the surgeons' response as a "yes" or "no" regarding their ability to distinguish and visualize the ILM.

All treatment types analyzed were considered effective in ILM visualization with a total visualization percentage of 96.8% or better. Surgeons reported that BBG treatment allowed ILM visualization of 98.7% of eyes treated and a 98.1% visualization rate with the ILM-Blue® treatment. The literature review and analyses for BBG and ILM-Blue® highlight the effectiveness of both products in aiding surgeons with visualization of the ILM during vitrectomy procedures such as ILM staining.[7]

4.1 TABLE 1. REPORTED SUCCESSFUL VISUALIZATION BY TREATMENT TYPE

	Total	ILM-Blue®	BBG*	ICG	TB	Membrane Blue-Dual
Number of treatment groups with reported visualization	19	2	12	2	2	1
Number of eyes with visualization reported	514	162	223	36	30	63
Number of Eyes in which treatment was assessed as effective	506	159	220	36	30	61
% Effective	98.4	98.1	98.7	100	100	96.8

*BBG group includes all concentrations of BBG (0.25-0.5 mg/mL) not otherwise specified as ILM-Blue®

DTOP states these findings demonstrate the efficacy of BBG in staining the ILM.[f]

5 Risk Assessment & Safe-Use Conditions

The safety profile of BBG was derived from the safety data in the literature review and post-marketing experience of ILM-Blue®. The safety analysis set includes 2,645 eyes undergoing vitreous and membrane visualization and received one of the 5 major treatment types: ILM-Blue ®, BBG, ICG,

[f] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

Tryphan Blue, or "Other[g]" (Bromophenol Blue, Chicago Blue, Membrane Blue-Dual, Retiblue, Vision Blue, Triamcinolone and unstained); the safety analysis set is larger than the efficacy population as certain of the data included in the literature review focused on safety only. There were no serious adverse events (SAEs) or deaths reported in the literature review.

A total of 284 adverse events (AEs) were reported across all treatment groups with 133 of those events occurring in BBG treated subjects (12% of the total subjects). The most common AEs among the treatment groups include retinal tears/detachment, macular edema, retinal hemorrhage and macular hole re-opening.[h] The Applicant attributes the reported AEs to the vitrectomy procedure and not to the usage of BBG for staining of the ILM. The clinical reviewer agrees that the reported AEs are common to the ophthalmic procedures and unlikely to be caused by the dye itself.

In addition to the evaluation of the common AEs, other key aspects were assessed as part of the clinical laboratory evaluations to determine if these aspects would be negatively impacted. These key safety aspects were visual acuity (VA), macular thickness, and intraocular pressure (IOP)[8]. A general improvement in VA was seen in subjects in the ILM-Blue® and BBG groups. Reduced macular thickness from baseline was noted among all treatment groups which is common after ILM peeling with or without ILM staining. Overall, a negative impact was not seen among these measurements in the treatment groups. The analysis of the safety data in the literature review and post-marketing experience of ILM-Blue® shows that there is no major safety risk to patients posed by BBG. The clinical reviewer agrees that the AEs were minimal and BBG has a relatively safe profile.

6 Expected Postmarket Use

BBG, like other ophthalmic dyes, is likely to be utilized by ophthalmologists during ophthalmic procedures in the outpatient setting and inpatient setting for complex conditions. The proposed dose is 0.025% (0.5 mL) injected in the BSS-filled vitreous cavity prior to surgery.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for BBG beyond routine pharmacovigilance and labeling.

[g] Treatment types defined as other were considered minor treatment types due to having lower percentage of eyes treated.

[h] The Applicant notes that due to inconsistent reporting in the literature, all potential event described are classified as AEs with no attempts at further evaluation or classification by severity.

8 Discussion of Need for a REMS

The clinical reviewer recommends approval of BBG based on the data in the submission and an adequately favorable benefit-risk profile.

The use of vital dyes during vitrectomies to assist in the identification of preretinal tissues and membranes is a common occurrence in the field of ophthalmology. The usage of vitrectomies for the surgical treatment of certain macular conditions, such as surgery for macular holes, can be aided by peeling of the internal limiting membrane. An estimated 225,000 vitrectomies are performed annually in the United States and with indications for use continuing to expand. The usage of BBG to stain the ILM offers a safe and effective alternative option for providers looking for a dye with selectivity for the ILM, and also avoids use of compounded products.

There were no serious adverse events associated with BBG. The risk of excessive staining, which can be prevented by removing excess BBG immediately after administration, will be communicated in the warnings and precautions section of the labeling.

Therefore, based on the data available, and the favorable benefit-risk profile associated with BBG, DRISK is not recommending a REMS for the management of the risks of BBG therapy.

9 Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for BBG to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

Should the DTOP have any concerns or questions or if new safety information becomes available, please send a consult to DRISK.

Appendix - A

Listing of Treatment Groups Where Visualization Was Reported

Author	Total Eyes by Article	Treatment Type	Subjects	Dye Used for Visualization (# Eyes)	Utility for Visualization to Facilitate Removal of Membrane (# Eyes)	Percent of Eyes in Which Utility for Visualization Occurred
Aboutable, 2006	10	Trypan Blue	10	10	10	100%
Carpentier, 2013	98	ILM Blue	92	98	98	100%
Enaida, 2006	20	BBG	20	20	20	100%
Henrich, 2009	17	BBG	17	17	17	100%
Kadonosono, 2013	40	BBG	19	19	19	100%
		ICG	21	21	21	100%
Koehrer, 2014	30	BBG	15	15	15	100%
		BBG	15	15	15	100%
Mohr, 2013	127	MB-Dual	63	63	61	97%
		ILM Blue	64	64	61	95%
Remy, 2008	18	BBG	18	18	15	83%
Rey, 2014	16	BBG	14	16	16	100%
Shukla, 2011	50	BBG	15	15	15	100%
		ICG	15	15	15	100%
		Trypan Blue	20	20	20	100%
Shukla, 2012	20	BBG	19	20	20	100%
Totan, 2015	25	BBG	25	25	25	100%
Wirbeluer, 2011	43	BBG	20	20	20	100%
		BBG	23	23	23	100%

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