TissueBlue™

Brilliant Blue G Ophthalmic Solution, 0.025%

DRUG PRODUCT INFORMATION MONOGRAPH

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Revised: 01/2020

1 PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Ingredients
intraocular Ophthalmic Injection	Solution 0.25 mg/mL	Active: Brilliant Blue G Inactive: Polyethylene glycol, Sodium chloride, Sodium phosphate dibasic dodecahydrate, Sodium phosphate monobasic dihydrate, Water for injection

1.1 NDA number and date of FDA approval

NDA 209569 was approved by FDA December 20, 2019

1.2 Indication

TissueBlue™ (brilliant blue G 0.25 mg/mL) solution for injection is indicated to selectively stain the internal limiting membrane (ILM)

1.3 Pediatrics

Pediatrics: Safety and effectiveness of TissueBlue™ 0.025% in children have not been established.

1.4 Geriatrics

Geriatrics (> 65 years of age): No overall differences in safety or effectiveness were observed between elderly and younger adult patients.

1.5 Contraindications

None.

1.6 Dosage and administration

Recommended Dose and Dosage Adjustment

TissueBlue™ 0.025% is carefully injected into the Balanced Salt Solution (BSS)-filled vitreous cavity using a blunt cannula attached to the pre-filled syringe, without allowing the cannula to contact the retina or allowing TissueBlue™ to get under the retina.

Administration

Sufficient staining is expected within a few seconds. Following staining, all excess dye should be removed from the vitreous cavity.

Overdosage

Not applicable.

1.7 Dosage forms, strengths, composition and packaging

TissueBlue™ (Brilliant Blue G Ophthalmic Solution) 0.025% is a clear, bright blue, single-dose ophthalmic solution supplied in 2.25 mL syringes pre-filled to a volume of 0.5 mL.

Each mL of TissueBlue™ contains 0.25 mg brilliant blue G in a vehicle consisting of Polyethylene glycol, Sodium chloride, Sodium phosphate dibasic dodecahydrate, Sodium phosphate monobasic dihydrate and Water for injection.

1.8 Warnings and precautions

General

- Excessive Staining - Excess TissueBlue™ 0.025% should be removed from the eye immediately after staining.
- Priming of the Syringe - Make sure the plunger moves smoothly before injecting the solution. Do not use the product if the plunger does not move smoothly to prime the cannula.

Carcinogenesis and Mutagenesis

See NON-CLINICAL TOXICOLOGY

1.9 Special populations

Pregnant Women

There are no available data on the use of TissueBlue™ in pregnant women to inform a drug associated risk. Systemic absorption of TissueBlue™ in humans is negligible following intravitreal injection followed by removal of the drug at the completion of surgical procedures. Due to the negligible systemic exposure, it is not expected that maternal use of TissueBlue™ will result in fetal exposure to the drug. Animal reproduction studies were not conducted with TissueBlue™.

Breastfeeding Women

No data are available regarding the presence of BBG in human milk, and the effects of BBG on the breastfed infant or on milk production. However, breastfeeding is not expected to result in exposure of the child to BBG due to the negligible systemic availability of BBG in humans following intravitreal injection followed by removal of the drug at the completion of surgical procedures.

Pediatrics

Pediatrics: The safety and effectiveness of TissueBlue™ in pediatric patients has not been established.

Geriatrics

Geriatrics (> 65 years of age): No overall differences in safety or effectiveness were observed between elderly and younger adult patients.

1.10 Adverse reactions

Adverse Reaction Overview

Adverse reactions that have been reported in procedures that included the use of Brilliant Blue G Ophthalmic Solution have often been associated with the surgical procedure. These complications include retinal (retinal break, tear, hemorrhage, and detachment) and cataracts.

Post-Market Adverse Reactions

No adverse reactions have been reported for TissueBlue™ marketed outside of the United States

1.11 Drug interactions

Overview

No drug-drug interactions are expected when using TissueBlue™.

1.12 Action and clinical pharmacology

Mechanism of Action

TissueBlue™ has been shown to selectively stain the ILM but not the epiretinal membrane nor the retina, making it an easier to visualize for removal, although the exact mechanism of this selectivity is not elucidated.

Pharmacodynamics

BBG has been shown to selectively stain the ILM but not the epiretinal membrane nor the retina, making it an easier to visualize for removal. There are no known secondary pharmacodynamic effects of BBG.

Pharmacokinetics

TissueBlue™ not intended to be administered systemically and therefore pharmacokinetic studies related to absorption, distribution, metabolism and excretion have not been conducted.

Special Populations and Conditions:

Pharmacokinetic studies have not been conducted in subjects with special conditions which might interfere with the absorption, distribution, metabolism, or excretion of TissueBlue™.

1.13 Storage, stability and disposal

TissueBlue™ should be stored at 15-25°C (59-77°F). Protect from light, frost and moisture.

1.14 Special handling instructions

There are no special handling instructions for TissueBlue™.

2 SCIENTIFIC INFORMATION

2.1 Pharmaceutical information

Drug Substance

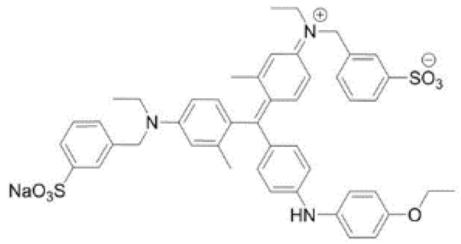
Proper name: Brilliant Blue G

Chemical name:

- ECHA (European Chemicals Agency): Sodium [4-[4-(p-ethoxyanilino)-4'-[ethyl(m-sulphonatobenzyl) amino]-2'-methylbenzhydrylene]-3-methylcyclohexa-2,5-dien-1-ylidene](ethyl)(m-sulphonatobenzyl) ammonium, monosodium salt
- IUPAC (International Union of Pure and Applied Chemistry): Sodium;3-[[4-[(Z)-[4-(4-ethoxyanilino)phenyl]-[4-[ethyl-[(3-sulfonatophenyl)methyl]azaniumylidene]-2-methylcyclohexa-2,5-dien-1-ylidene]methyl]-N-ethyl-3-methylanilino] methyl]benzenesulfonate

Molecular formula and molecular mass: $C_{47}H_{48}N_3NaO_7S_2$, 854.02

Structural formula:



Each mL of TissueBlue™. 0.025% contains 0.25 mg brilliant blue G in a vehicle consisting of Polyethylene glycol, Sodium chloride, Sodium phosphate dibasic dodecahydrate, Sodium phosphate monobasic dihydrate and water for injection.

2.2 Clinical trials

Trial Design and Study Demographics

The safety and efficacy of BBG, the active ingredient in TissueBlue™ 0.025% (marketed as ILM-Blue outside of the United States), for the visualization of ILM in the context of ophthalmic surgical procedures is well known in the

ophthalmic community. A literature review was undertaken to provide an unbiased objective assessment of the safety and efficacy of Brilliant Blue G 0.025% Solution and additionally its active pharmaceutical ingredient (API), BBG. The function of Brilliant Blue G 0.025% Solution and BBG is to stain the internal limiting membrane facilitating the removal during surgical procedures. The literature review was designed to systematically collect available safety and effectiveness data from peer reviewed literature that describes BBG usage for this purpose.
The literature search was conducted in June 2015 and queried published articles from 1980 through June 1, 2015. All identified articles were classified as to whether the authors included information sufficient to include in the efficacy and/or safety analysis. Of the 51 articles, the efficacy data set was derived from 13 of these peer-reviewed articles, and comprised a total of 19 treatment groups and 514 eyes. With respect to the safety analysis, all 51 of the publications, comprising 88 treatment groups and 2,645 eyes treated with various ophthalmic agents for vitreous and membrane visualization during surgical intervention, were identified. The various agents used as reported by the publications included ILM-Blue®, other BBG solutions (referred to herein as BBG), Indocyanine Green (ICG), Trypan Blue (TB), or 'Other' (Bromphenol Blue, Chicago Blue, IfCG, Triamcinolone Acetate, MembraneBlue-Dual or Retiblue). Unstained comparison groups were categorized as 'Other' as well.

BBG and TB were the two most common treatment types analyzed accounting for 38% and 24% of the total treatment groups, respectively, while ICG, "Other", and ILM-Blue® accounted for 17%, 15%, and 7% of total treatment groups, respectively. **Table 1** details the treatment groups including number of subjects and eyes. **Table 2** further breaks down the BBG treatment group to show the ILM-Blue and other BBG subjects that were included in the analysis.

Table 1
Number and Percent of Studies, Treatment Groups, Subjects and Eyes by Treatment Type

Treatment Type	Number of Treatment Groups	Percent of Treatment Groups	Number of Subjects	Percent of Subjects	Number of Eyes	Percent of Eyes
BBG[1]	39	45%	1145	44%	1159	44%
ICG	15	17%	614	23%	614	23%
TB	21	24%	523	20%	527	20%
Other	13	15%	345	13%	345	13%
Total	**88**	**100%**	**2627**	**100%**	**2645**	**100%**

[1] Includes publications where BBG was used at any strength and from any supplier.

Table 2
Number and Percent of Studies, Treatment Groups, Subjects and Eyes by Treatment Type for BBG and ILM-Blue

Treatment Type	Number of Treatment Groups	Percent of Treatment Groups	Number of Subjects	Percent of Subjects	Number of Eyes	Percent of Eyes
ILM-Blue®	6	7%	315	12%	321	12%
BBG[1]	33	38%	830	32%	838	32%

[1] Includes publications where BBG was used but not specifically stated as being "ILM-Blue".

The efficacy data set was derived from 19 treatment groups extracted from 13 peer-reviewed articles. A total of 514 eyes were treated with either ILM-Blue®, BBG, ICG, Trypan Blue, or 'Other' (MembraneBlue-Dual) Efficacy was solely based on classifying data in the form of a "yes" or "no". Surgeons performing vitrectomy procedures documented their ability to distinguish and visualize the internal limiting membrane, directly providing the efficacy data.

Descriptive statistics were used to calculate the number of eyes where ILM visualization occurred from the total

number of eyes. 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. This demonstrates a high success rate of visualization. Based on this analysis, Brilliant Blue G 0.025% Solution (and the active ingredient, BBG) has shown to be effective in aiding surgeons during vitrectomy procedures through ILM staining.

Table 3 details the specific articles, treatment type, number of eyes, and rate of visualization success in the efficacy dataset. ILM-Blue® was 98.1% effective from a total of 162 patients analyzed.

Table 3
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	20	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%

2.3 Non-clinical toxicology

Carcinogenesis, Mutagenesis, Impairment of Fertility:

No carcinogenicity data are available as TissueBlue™ is not intended for systemic exposure and the product is removed following use.

Reproductive toxicology studies have not been conducted by the Applicant as TissueBlue™ is not intended for systemic exposure and the product is removed following use. In addition, systemic uptake is negligible and thus developmental toxicity studies are not considered relevant.

In a review of literature, no studies were found that determined fertility, embryofetal, or developmental toxicity of BBG. Repeat dose studies have not been conducted as TissueBlue™ is not intended for repeat dosing.

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