PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrTISSUEBLUE™

Brilliant Blue G Injection

Solution 0.25 mg/mL, Intravitreal

Ophthalmic Dye

D.O.R.C. International B.V.
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Zuidland, The Netherlands
3214 VN

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

TISSUEBLUE (Brilliant Blue G Injection) is indicated for:

- Use as an aid in ophthalmic surgery by selectively staining the internal limiting membrane (ILM)

1.1 Pediatrics

Pediatrics (< 9 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

2 CONTRAINDICATIONS

TISSUEBLUE is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see Dosage Forms, Strengths, Composition and Packaging.

3 DOSAGE AND ADMINISTRATION

3.1 Recommended Dose and Dosage Adjustment

A sufficient volume of TISSUEBLUE is provided (net contents 0.5 mL) in each syringe to stain the ILM.

3.2 Administration

- TISSUEBLUE is carefully injected into the BSS-filled vitreous cavity using a blunt cannula attached to the syringe, without allowing the cannula to contact or damage the retina or allowing TissueBlue to get under the retina.
- Sufficient staining is expected within a few seconds. Following staining, all excess dye should be removed from the vitreous cavity.
- Do not use product if solution shows haziness, particulate matter, discolouration, or leakage.

4 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging.

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients

Intravitreal	Solution 0.25 mg/mL Brilliant Blue G	Polyethylene glycol, Sodium chloride, Sodium phosphate dibasic dodecahydrate, Sodium phosphate monobasic dihydrate, Water for injection

TISSUEBLUE is supplied sterile in a single-use glass syringe filled to 0.5 mL with a grey rubber plunger stopper and tip cap and polypropylene plunger rod packed in a blister sealed with a Tyvek® lid.

5 WARNINGS AND PRECAUTIONS

General

- Excessive Staining - Excess TISSUEBLUE should be removed from the eye immediately after staining
- Priming of the Syringe - Make sure the plunger moves smoothly before use: first retract the plunger or twist the plunger in a clockwise motion before injecting the solution. Do not use the product if the plunger does not move smoothly after priming.

5.1 Special Populations

5.1.1 Pregnant Women

There are no available data on the use of TISSUEBLUE in pregnant women to inform about 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.

5.1.2 Breast-feeding

It is unknown if the drug is excreted in human milk. Because many drugs are excreted in human milk, precaution should be exercised.

5.1.3 Pediatrics

Pediatrics (< 9 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

6 ADVERSE REACTIONS

6.1 Adverse Reaction Overview

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adverse reactions that have been reported in procedures that included the use of TISSUEBLUE have been associated with the surgical procedure and not the drug. These complications include retinal (retinal break, tear, hemorrhage, and detachment) events, cataract complications, cystoid macular edema and transient ocular hypertension.

6.2 Post-Market Adverse Reactions

No adverse reactions have been reported for TISSUEBLUE marketed outside of Canada.

7 DRUG INTERACTIONS

7.1 Overview

No drug interactions are expected when using TISSUEBLUE.

7.2 Drug-Drug Interactions

Interactions with other drugs have not been established.

7.3 Drug-Food Interactions

Interactions of TISSUEBLUE with food products have not been established.

7.4 Drug-Herb Interactions

Interactions of TISSUEBLUE with herbal products have not been established.

7.5 Drug-Laboratory Test Interactions

Interactions of TISSUEBLUE with laboratory tests have not been established.

7.6 Drug-Lifestyle Interactions

Interactions of TISSUEBLUE with lifestyle activities have not been established.

8 ACTION AND CLINICAL PHARMACOLOGY

8.1 Mechanism of Action

A solution of Brilliant Blue G (BBG) and 4% PEG, as contained in 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.

9 STORAGE, STABILITY AND DISPOSAL

TISSUEBLUE should be stored at room temperature (15°C to 25°C). Protect from light, heat, freezing and moisture. Leave in original package until use. Single use. Discard unused portion.

10 SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions for TISSUEBLUE.

PART II: SCIENTIFIC INFORMATION

11 PHARMACEUTICAL INFORMATION

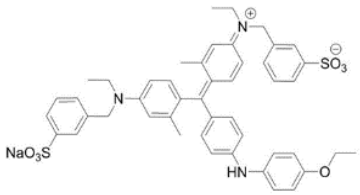
Drug Substance

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:

Physicochemical properties: 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 dehydrate and water for injection.

12 CLINICAL TRIALS

Mohr *et al* 2013 reported a prospective multicentre cohort study in patients undergoing epiretinal membrane removal. Mean patient age was 68 years ± 1.3 years. A solution of BBG 0.25 mg/mL and 4% PEG, as contained in TissueBlue, was used in 64 eyes while a solution containing Trypan Blue 0.15%, BBG 0.25 mg/mL and 4% PEG was used in 63 eyes The staining was reported to support visualization of the membranes in 61 of 64 eyes (95%) when a solution of BBG 0.25 mg/mL and 4% PEG, as contained

in TissueBlue, was used compared to 61 out of 63 eyes (97%) when the other staining solution was used.

13 NON-CLINICAL TOXICOLOGY

Single-Dose Toxicity

The ocular toxicity of BBG was assessed in rabbits following a single bilateral intravitreal injection or a single bilateral subretinal injection on Day 1 followed by a 14-day recovery period. BBG was dosed by a single bilateral intravitreal injection of 25 or 50 µg/eye or a single bilateral subretinal injection of 12.5 or 25 µg/eye. After a 14-days follow-up period, BBG was considered well-tolerated based on the in-life observations and the histopathology. There were no macroscopic or microscopic treatment-related findings following a single intravitreal injection of Brilliant Blue G in the controls or BBG-treated groups.

Electroretinogram (ERG) changes, including reductions in scotopic a-wave and/or b-wave amplitude, were noted at both doses following intravitreal administration and in the high dose group following subretinal administration. It is likely that blue color in the vitreous played a role in the ERG changes that were seen at both dose levels in the intravitreal eyes but only the high dose in the subretinal eyes, where reflux into the vitreous was more probable; however, a direct effect of the test article cannot be ruled out.

In eyes treated by subretinal administration, anterior segment inflammation, vitreous opacity, presence of vitreal hemorrhage, and minimal to marked microscopic retinal changes (detachment and degeneration), were noted in control as well as BBG-treated groups. However, due to the route of dose administration (subretinal), it could be considered that histopathology observations may in fact show a retinal re-attachment, as there was no proliferation of detachment around the injection site. Therefore, the changes noted in animals dosed by subretinal administration may have been procedure-related, but a contribution by the test-article could not be ruled out based on the increased incidence and/or severity in BBG-treated groups.

Repeat-Dose Toxicity, Carcinogenesis and Impairment of Fertility

Studies to evaluate the potential for repeat-dose toxicity, and carcinogenicity have not been conducted as TISSUEBLUE is intended for a single-dose ophthalmic use, with subsequent removal of most of the dye. Reproductive and developmental toxicity are also not considered relevant given that systemic absorption is expected to be negligible. In a review of literature, no studies were found that determined fertility, embryofetal, or developmental toxicity of BBG.

Mutagenesis

Brilliant Blue G was not mutagenic in the Ames assay, the *in vitro* mouse lymphoma assay, or the *in vivo* rat micronucleus assay.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

TISSUEBLUE™
Brilliant Blue G Injection

Read this carefully before **TISSUEBLUE** is used on your eye(s). This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **TISSUEBLUE.**

What is TISSUEBLUE used for?

- TISSUEBLUE is used as an aid in eye surgery.
- It is used to stain a part of your eye called the internal limiting membrane (ILM).

How does TISSUEBLUE work?

TISSUEBLUE contains a dye that stains a part of your eye called the internal limiting membrane (ILM). TISSUEBLUE works by making this part of your eye more visible to doctors during eye surgery.

What are the ingredients in TISSUEBLUE?

Medicinal ingredients: Brilliant Blue G.

Non-medicinal ingredients: Polyethylene glycol, Sodium chloride, Sodium phosphate dibasic dodecahydrate, Sodium phosphate monobasic dihydrate, Water for injection

TISSUEBLUE comes in the following dosage forms:

As a 0.25 mg / mL solution.

Do not use TISSUEBLUE if you:

- Are allergic to Brilliant Blue G**.**
- Are allergic to any of the other ingredients in TISSUEBLUE.
- Are allergic to any part of the TISSUEBLUE container.

To help avoid side effects and ensure proper use, talk to your healthcare

professional before you take TISSUEBLUE. Talk about any health conditions or problems you may have, including if you:

- Are allergic to certain ingredients or package components to make sure you can receive TISSUEBLUE
- Are pregnant. TISSUEBLUE has not been tested in pregnant women.
- Are breastfeeding. It is not known if TISSUBLUE is released in human breast milk.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take TISSUEBLUE:

- TISSUEBLUE will be injected into your eye by your doctor during eye surgery.
- It will then be washed out of your eye by your doctor.

Usual dose:

Your doctor will decide how much TISSUEBLUE you will receive.

What are possible side effects from using TISSUEBLUE?
The following side effects can happen with the surgery you get after receiving TISSUEBLUE:

- Problems with a part of your eye called the retina. These include retinal break, tear, bleeding or detachment.

- New or worsening of your cataract symptoms. Cataract is a clouding of a part of your eye called the lens. Symptoms include blurry vision, clouding of your eye, difficulty reading, loss of vision and seeing halos around lights.

- A condition called cystoid macular edema where a part of your retina called the macula is swollen.

- A condition called transient ocular hypertension where the pressure inside your eye is increased.

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- TISSUEBLUE will be stored by your healthcare professional.
- It is stored at room temperature (15°C to 25°C).
- It must be protected from light, heat, freezing and moisture.
- It is kept in the original package until use.
- TISSUEBLUE is for single use only. The unused portion must be discarded.

If you want more information about TISSUEBLUE:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (http://hc-sc.gc.ca/index-eng.php); the manufacturer's website (http://www.dorcglobal.com), or by calling 1-800-467-2081.

This leaflet was prepared by Dutch Ophthalmic Research Center.

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