

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**22-278**

**MEDICAL REVIEW(S)**

Medical Officer Review #2  
 Martin P. Nevitt, M.D., M.P.H.  
 NDA 22-278 Review #2  
 MembraneBlue 0.15 % (trypan blue ophthalmic solution)

## Medical Officer Review #2

<b>Date</b>	February 17, 2009
<b>From</b>	Martin P. Nevitt, M.D., M.P.H.
<b>Subject</b>	Medical Officer Review
<b>NDA#</b>	22-278
<b>Applicant</b>	Dutch Ophthalmic Research Center
<b>Date of Submission</b>	August 18, 2008, January 30, 2009, February 17, 2009
<b>PDUFA Goal Date</b>	February 21, 2009
<b>Proprietary Name / Established (USAN) names</b>	MembraneBlue 0.15 % (trypan blue ophthalmic solution)
<b>Dosage forms / Strength</b>	ophthalmic solution
<b>Proposed Indication(s)</b>	for use as an aid in ophthalmic surgery by staining the epiretinal membranes during ophthalmic surgical vitrectomy procedures, facilitating removal of the tissue
<b>Recommended:</b>	Approval

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### • Background

#### ESTABLISHMENT EVALUATION REQUEST

An Establishment Evaluation Request was made via EES, and an inspection was performed from \_\_\_\_\_ This inspection revealed multiple GMP deficiencies, and a 483 was issued.

b(4)

The observations cited in the 483 included:

- Failure to qualify the maximum amount of \_\_\_\_\_ cycles for which the \_\_\_\_\_ can be reused without being replaced
- Failure to conduct integrity test (pre and post \_\_\_\_\_ ) to the \_\_\_\_\_ used during the sterilization of all batches of Vision Blue 0.06% trypan blue ophthalmic solution syringes produced at the site and distributed to the U.S.
- Manufacture and distribution to the U.S. batches of Vision Blue 0.06% trypan blue ophthalmic solution syringes without having a validation of the sterilization process for VisionBlue using biological indicators
- Failure to have an \_\_\_\_\_ conducted during filing and prior to sterilization of Vision Blue 0.06% trypan blue ophthalmic solution syringes

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Medical Officer Review #2  
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- Failure to establish the manufacturing time for the different critical operations performed during the production of the Vision Blue 0.06% trypan blue ophthalmic solution product.

The applicant has addressed these issues. Upon re-inspection of \_\_\_\_\_ the facilities were found acceptable on \_\_\_\_\_ **b(4)**

- **Labeling**

NDA 22-278 is recommended for approval for use as an aid in ophthalmic surgery by staining the epiretinal membranes during ophthalmic surgical vitrectomy procedures, facilitating removal of the tissue.

The labeling submitted by Dutch Ophthalmic Research Center on January 30, 2009, and February 17, 2009, and found in this Medical Officer Review (see Appendix 1) is acceptable.

- **Recommendations/Risk Benefit Assessment**

**RECOMMENDED REGULATORY ACTION:**

NDA 22-278 is recommended for approval for use as an aid in ophthalmic surgery by staining the epiretinal membranes during ophthalmic surgical vitrectomy procedures, facilitating removal of the tissue.

The labeling submitted by Dutch Ophthalmic Research Center on January 30, 2009, and February 17, 2009, and found in this Medical Officer Review (see Appendix 1) is acceptable.

## **Appendix 1**

The labeling submitted by Dutch Ophthalmic Research Center on January 30, 2009, and February 17, 2009, is acceptable.

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use MembraneBlue™ 0.15% safely and effectively. See full prescribing information for MembraneBlue™ 0.15%.

MembraneBlue™ 0.15% (trypan blue ophthalmic solution)

Initial U.S. Approval: 2004

### Indications and Usage

- For use as an aid in ophthalmic posterior surgery;
- Facilitating removal of epiretinal tissue. (1)

### Dosage and Administration

- Prior to injection of MembraneBlue™ 0.15% perform a 'fluid-air exchange'; Carefully apply MembraneBlue™ 0.15% to epiretinal membranes using a blunt cannula; Remove all excess dye  
Or
- Inject MembraneBlue™ 0.15% directly in a BSS filled - vitreous cavity; Wait 30 seconds; Remove all excess dye. (2)

### Dosage Forms and Strength

- MembraneBlue™ 0.15% (trypan blue ophthalmic solution) in a volume of 0.5 mL. (3)

### Contraindications

- Insertion of a non-hydrated (dry state), hydrophilic acrylic intraocular lens (IOL). (4)

### Warnings and Precautions

- Excessive staining: Excess MembraneBlue™ 0.15% should be removed from the eye immediately after staining. (5)

### Adverse Reactions

- Discoloration of high water content hydrogen intraocular lenses;
- Inadvertent staining of the posterior lens capsule and vitreous face. (6)

To report SUSPECTED ADVERSE REACTIONS contact Dutch Ophthalmic, USA at 1-800-75-DUTCH or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch)

### Use in Specific Populations

- Trypan blue should not be given to a pregnant woman. (8)

Revised 1/2009

## FULL PRESCRIBING INFORMATION: CONTENTS\*

1. Indications and Usage
2. Dosage and Administration
3. Dosage Forms and Strength
4. Contraindications
5. Warnings and Precautions
6. Adverse Reactions
8. Use in Specific Populations
  - 8.1 Pregnancy
  - 8.3 Nursing mothers

- 8.4 Pediatric use
- 8.5 Geriatric use
11. Description
12. Clinical Pharmacology
  - 12.1 Mechanism of Action
13. Nonclinical Toxicology
  - 13.1 Carcinogenesis, mutagenesis, impairment of fertility
16. How Supplied/Storage and Handling

\*Sections or subsections omitted from the Full Prescribing Information are not listed.

## **FULL PRESCRIBING INFORMATION: CONTENTS\***

### **1. Indications and Usage**

MembraneBlue™ 0.15% is indicated for use as an aid in ophthalmic surgery by staining the epiretinal membranes during ophthalmic surgical vitrectomy procedures, facilitating removal of the tissue.

### **2. Dosage and Administration**

Before injection of MembraneBlue™ 0.15% perform a 'fluid-air exchange', i.e. filling the entire vitreous cavity with air, to prevent aqueous dilution of MembraneBlue™ 0.15%. MembraneBlue™ 0.15% is carefully applied to the retinal membrane using a blunt cannula attached to the MembraneBlue™ 0.15% syringe, without allowing the cannula to contact or damage the retina. Sufficient staining is expected on contact with the membrane. All excess dye should be removed from the vitreous cavity before performing an air-fluid exchange, to prevent unnecessary spreading of the dye.

MembraneBlue™ 0.15% can also be injected directly in a BSS filled vitreous cavity (instead of injecting under air). Clinical use demonstrated that, after complete vitreous and posterior hyaloid removal, sufficient staining is achieved after 30 seconds of application under BSS.

MembraneBlue™ 0.15% is intended to be applied directly on the areas where membranes could be present, staining any portion of the membrane which comes in contact with the dye. The dye does not penetrate the membrane.

### **3. Dosage Forms and Strength**

MembraneBlue™ 0.15% (trypan blue ophthalmic solution) is supplied in 2.25 mL syringes filled to a volume of 0.5 mL.

### **4. Contraindications**

MembraneBlue™ 0.15% is contraindicated when a non-hydrated (dry state), hydrophilic acrylic intraocular lens (IOL) is planned to be inserted into the eye. The dye may be absorbed by the IOL and stain it.

### **5. Warnings and Precautions**

#### **Excessive staining**

It is recommended that after injection all excess MembraneBlue™ 0.15% be immediately removed from the eye.

### **6. Adverse Reactions**

Adverse reactions reported following use of MembraneBlue™ 0.15% include discoloration of high water content hydrogen intraocular lenses (see Contraindications) and inadvertent staining of the posterior lens capsule and vitreous face. Staining of the posterior lens capsule or staining of the vitreous face is generally self limited, lasting up to one week.

### **8. Use in Specific Populations**

#### **8.1 Pregnancy**

Teratogenic Effects: Pregnancy Category C. Trypan blue is teratogenic in rats, mice, rabbits, hamsters, dogs, guinea pigs, pigs, and chickens. The majority of teratogenicity studies performed involve intravenous, intraperitoneal, or subcutaneous administration in the rat. The teratogenic dose is 50 mg/kg as a single dose or 25 mg/kg/day during embryogenesis in the rat. These doses are approximately 4,000- and 2,000-fold the maximum recommended human dose of 0.75 mg per injection based in a 60 kg person, assuming that the whole dose is completely absorbed. Characteristic anomalies included neural tube, cardiovascular, vertebral, tail, and eye defects. Trypan blue also caused an increase in post-implantation mortality, and decreased fetal weight. In the monkey, trypan blue caused abortions with single or two daily doses of 50 mg/kg between 20th to 25th days of pregnancy, but no apparent increase in birth defects (approximately 4,000-fold maximum recommended human dose of 0.75 mg per injection, assuming total absorption). There are no adequate and well-controlled studies in pregnant women. Trypan blue should be given to a pregnant woman only if the potential benefit justifies the potential risk to the fetus.

### 8.3 Nursing mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when trypan blue is administered to a nursing woman.

### 8.4 Pediatric use

The safety and effectiveness of trypan blue have been established in pediatric patients. Use of trypan blue is supported by evidence from an adequate and well-controlled study in pediatric patients.

### 8.5 Geriatric use

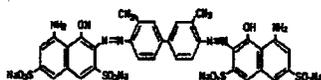
No overall differences in safety and effectiveness have been observed between elderly and younger patients.

## 11. Description

MembraneBlue™ 0.15% (trypan blue ophthalmic solution) is a sterile solution of trypan blue (an acid diazo group dye). MembraneBlue™ 0.15% selectively stains epiretinal membranes during ophthalmic surgical vitrectomy procedures.

Each mL of MembraneBlue™ 0.15% contains: 1.5 mg trypan blue; 1.9 mg sodium mono-hydrogen orthophosphate ( $\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$ ); 0.3 mg sodium di-hydrogen orthophosphate ( $\text{NaH}_2\text{PO}_4 \cdot 2\text{H}_2\text{O}$ ); 8.2 mg sodium chloride ( $\text{NaCl}$ ); and water for injection. The pH is 7.3 - 7.6. The osmolality is 257-314 mOsm/kg.

The drug substance trypan blue has the chemical name 3,3'-[(3,3'-dimethyl-4,4'-biphenylene) bis (azo)] bis(5-amino-4-hydroxy-2,7-naphthalenedisulfonic acid) tetra sodium salt, a molecular weight of 960.8, a molecular formula of  $\text{C}_{34}\text{H}_{24}\text{N}_6\text{Na}_4\text{O}_{14}\text{S}_4$ , and has the following chemical structure:



## 12. Clinical Pharmacology

### 12.1 Mechanism of Action

MembraneBlue™ 0.15% selectively stains membranes in the human eye during posterior surgery, such as epiretinal membranes (ERM) and Internal Limiting Membranes (ILM).

## 13. Nonclinical Toxicology

### 13.1 Carcinogenesis, mutagenesis, impairment of fertility

Trypan blue is carcinogenic in rats. Wistar/Lewis rats developed lymphomas after receiving subcutaneous injections of 1% trypan blue dosed at 50 mg/kg every other week for 52 weeks (total dose approximately 100,000-fold the maximum recommended human dose of 0.75 mg per injection in a 60 kg person, assuming total absorption).

Trypan blue was mutagenic in the Ames test and caused DNA strand breaks in vitro.

## 16. How Supplied/Storage and Handling

MembraneBlue™ 0.15% is supplied as follows:

0.5 mL of MembraneBlue™ 0.15% 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 peel pouch. Five pouched products are packed in one distribution box.

MembraneBlue™ 0.15% is stored at 15-25°C (59-77°F). Protect from direct sunlight.

**Rx ONLY**

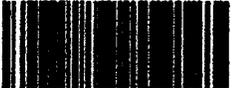
***Manufactured by***  
D.O.R.C. International b.v.  
Scheijdelveweg 2  
3214 VN Zuidland  
The Netherlands

***Distributed in the United States by***  
Dutch Ophthalmic, USA  
10 Continental Drive, Bldg 1  
Exeter, NH 03833, USA  
Phone: 800-75-DUTCH or 603-778-6929.

**5 Pouch Distribution Box Label (to be placed on rear of carton)**

<b>DORC</b>	<b>STERILE!</b>	D672b-1
<b>MembraneBlue™ 0.15%</b>		
<b>(trypan blue ophthalmic solution)</b>		
<b>5 Luer Lok Syringes 2.25mL of 0.5mL</b>		
	Store at 15° to 25°C (59°F to 77°F). Leave in pouch until use.	Rx Only
	<b>LOT</b>	12345
<b>Expiration Date</b>	YYYY-MM	
6 8 8 0 3 - 6 7 2	Protect from direct sunlight. Single use only.	
<i>Manufactured by:</i> D.O.R.C. International b.v. Scheijdelweg 2; 3214 VN Zuidland - The Netherlands	<i>Distributed in US by:</i> Dutch Ophthalmic, USA Exeter, NH 03833 800-753-8824 or 603-778-6929	

**Peel Pouch Label**

<b>DORC</b>	<b>STERILE!</b>	D672g-1
<b>MembraneBlue™ 0.15%</b>		
<b>(trypan blue ophthalmic solution)</b>		
<b>1 Luer Lok Syringe 2.25mL of 0.5mL</b>		
	Store at 15° to 25°C (59°F to 77°F). Leave in pouch until use.	Rx Only
	<b>LOT</b>	12345
<b>Expiration Date</b>	YYYY-MM	
6 8 8 0 3 - 6 7 2	Protect from direct sunlight. Single use only.	
<i>Manufactured by:</i> D.O.R.C. International b.v. Scheijdelweg 2; 3214 VN Zuidland - The Netherlands	<i>Distributed in US by:</i> Dutch Ophthalmic, USA Exeter, NH 03833 800-753-8824 or 603-778-6929	

**Syringe Label**

<b>DORC</b>	68803-672	D672b-1
<b>MembraneBlue™ 0.15%</b>		
<b>(trypan blue ophthalmic solution)</b>		
Single use only	0.5 mL Syringe	
<b>STERILE!</b>	Rx Only	<b>LOT</b> 12345
See package insert for dosing information. Protect from direct sunlight.	<b>Expiration Date</b>	YYYY-MM
<i>Manufactured by:</i> D.O.R.C. International b.v. Scheijdelweg 2 3214 VN Zuidland; The Netherlands		
<i>Distributed in US by:</i> Dutch Ophthalmic USA, Exeter NH 03833 800-753-8824 or 603-778-6929		



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/s/  
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Martin Nevitt  
2/19/2009 10:35:30 AM  
MEDICAL OFFICER

William Boyd  
2/19/2009 11:22:01 AM  
MEDICAL OFFICER

## **CLINICAL REVIEW**

**Application Type** NDA  
**Submission Number** 22-278  
**Submission Code** N-000

**Letter Date** January 30, 2008  
**Stamp Date** February 4, 2008  
**PDUFA Goal Date** August 4, 2008

**Reviewer Name** Martin P. Nevitt, MD, MPH  
**Review Completion Date** July 15, 2008

**Established Name** Trypan Blue Ophthalmic Solution

**(Proposed) Trade Name** MembraneBlue  
**Therapeutic Class** Ophthalmic Dye  
**Applicant** Dutch Ophthalmic Research  
Center, International  
Scheijdelveweg 2  
3214 VN Zuidland, The  
Netherlands

Dutch Ophthalmic, USA  
One Little River Road  
PO Box 968  
Kingston, NH 03848  
603-642-8468

**Priority Designation** P  
**Formulation** Ophthalmic Solution

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## **1 Recommendations/Risk Benefit Assessment**

### **1.1 Recommendation on Regulatory Action**

NDA 22-278 is not recommended for approval for use as an aid in ophthalmic surgery by staining the epiretinal membranes during ophthalmic surgical vitrectomy procedures, facilitating removal of the tissue pending the resolution of an unacceptable site inspection at \_\_\_\_\_

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\_\_\_\_\_ This inspection revealed multiple GMP deficiencies with issuance of a 483.

### **1.2 Risk Benefit Assessment**

Based on the following four adequate and well controlled clinical trials from the literature (reviewed in Section 6.1.4):

1. C Haritoglou, et al. Retina 2004; 24(4):582-90,
2. C Haritoglou, et al. Am J Ophthalmol 2004;138(1):1-5,
3. KL Lee, et al. Br J Ophthalmol 2005; 89:420-4, and
4. J Beutel, et al. Arch Ophthalmol 2007; 125:326-332,

and the other literature studies listed in Section 5.1, this application for Trypan Blue has demonstrated safety and efficacy in selectively staining the epiretinal membranes during ophthalmic surgical vitrectomy procedures, facilitating removal of the tissue.

There are no known safety or effectiveness concerns that have arisen with other members of this pharmacologic class.

NDA 22-278 is not recommended for approval pending resolution of an unacceptable site inspection at \_\_\_\_\_

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### **1.3 Recommendations for Postmarketing Risk Management Activities**

No additional Phase 4 studies are recommended.

### **1.4 Recommendations for other Post Marketing Study Commitments**

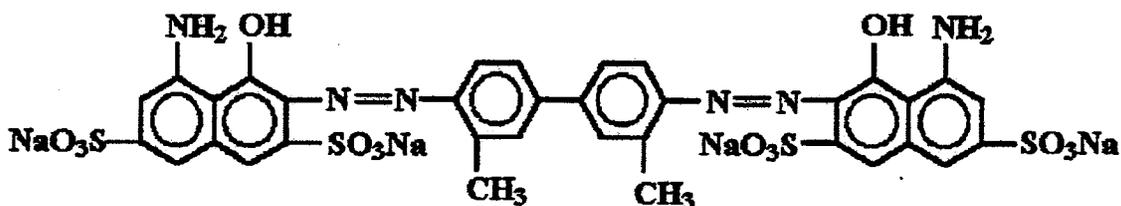
No additional Phase 4 studies are recommended.

## 2 Introduction and Regulatory Background

### 2.1 Product Information

MembraneBlue (trypan blue ophthalmic solution) is a sterile solution of trypan blue. MembraneBlue selectively stains membranes of the inner surface of the retina that can lead to visual disturbances from mild distortions and blurred vision due to the presence of metamorphopsia, micropsia and ultimately to reduced vision. These membranes include epiretinal membranes (ERM) and Internal Limiting Membranes (ILM) that can be removed during ophthalmic surgical vitrectomy procedures.

Identification of the membranes can be difficult, as they are transparent or mildly opaque. These membranes are hypocellular, collagenous proliferations (essentially scar tissue) occurring on the inner surface of the retina. Trypan blue, the active drug substance, is a stain widely used to selectively stain dead tissues or cells. Trypan blue is not absorbed in a viable cell, but traverses the membrane in a dead cell. Therefore, only the membranes are stained in contrast to the retina and excess trypan blue is washed out of the eye during the vitrectomy procedure. Staining the membranes improves the contrast between the membranes and the retina and can facilitate their removal; staining also reduces the chance of incomplete peeling of the membranes, which could lead to persistent metamorphopsia.



MembraneBlue is a blue di-azo group dye. It is a symmetrical molecule with three parts connected by two azo bonds. The molecular weight is 960.8. The empirical formula is: C<sub>34</sub>H<sub>24</sub>N<sub>6</sub>Na<sub>4</sub>O<sub>14</sub>S<sub>4</sub>. It is water soluble. During vitrectomy surgery a few drops (0.3 -0.5 mL) are applied directly onto the areas where membranes could be present. Prior to injecting MembraneBlue a "fluid-air exchange," i.e., a filling of the entire vitreous cavity with air, is performed to prevent dilution of the MembraneBlue. Excess dye can be washed out of the posterior chamber.

MembraneBlue can also be injected directly into a BSS filled vitreous cavity instead of injecting under air. Sufficient staining is usually achieved after 30 seconds of application under BSS.

The proposed indication is for selective staining of epiretinal membranes during ophthalmic surgical vitrectomy procedures. The application is supported by numerous literature studies. A representative sample of the literature studies has been included in this review. This reviewer was unable to find any studies which dispute the efficacy of the product or which identify any safety issues which are not already listed in this review.

Trypan blue has been marketed as MembraneBlue™ (trypan blue ophthalmic solution, 0.15%) in Europe since 2002 as a medical device Class IIa for the same proposed indication. The applicant reports over \_\_\_\_\_ units have been used during ophthalmic surgical vitrectomy procedures. No complaints or any other information concerning adverse events have been received during this period. Trypan blue has also been marketed as VisionBlue™ (0.06% trypan blue ophthalmic solution) in Europe since 1999 and was approved in the US April 12, 2004 (NDA 21-670) for the indication of staining of the anterior capsule during cataract surgery. The applicant reports over \_\_\_\_\_ units have been used during cataract surgery.

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MembraneBlue™ was withdrawn from marketing in Brazil in 2007 due to \_\_\_\_\_

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From clinical studies in the ophthalmic literature during the past five years of using MembraneBlue™ for posterior ophthalmic membrane staining, the dye has been found to be safe and effective. No ocular or systemic side effects or adverse events have been described in any clinical report.

## 2.2 Tables of Currently Available Treatments for Proposed Indications

There are currently no products approved for staining epiretinal membranes during ophthalmic surgical vitrectomy procedures. Indocyanine green (ICG) has been used "off-label" to stain epiretinal membranes.

Triamcinolone acetonide injectable suspension, 40 mg/ml, (NDA 22-048 / 22-223), has been approved for visualization of the vitreous and of pathologic membranes during vitrectomy. Unlike MembraneBlue™, triamcinolone acetonide does not involve the staining of pathologic membranes but rather assists in their visualization during vitrectomy.

## 2.3 Availability of Proposed Active Ingredient in the United States

Trypan blue as been used as a chemical agent for *in vivo* and *in vitro* testing and has been approved in the US for the staining of the anterior capsule during cataract surgery (NDA 21-670). There are no reported safety issues.

## 2.4 Important Safety Issues With Consideration to Related Drugs

There are no known safety or effectiveness concerns that have arisen with other members of this pharmacologic class.

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

Trypan blue was classified as a drug in a letter dated July 19, 2000, from the FDA Ombudsman, (this decision was reconfirmed in a letter from the FDA Ombudsman in 2003).

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In an amendment to the NDA dated December 17, 2007 the application was changed to a 505(b)(2) application. The sponsor, Dutch Ophthalmic Research Center International B.V., is claiming exclusivity. This claim is supported by the drug product containing an active moiety, trypan blue, that was first approved in NDA 21-670 being intended for a different use and whose claims are supported by reports from new clinical investigations.

NDA 22-278 has been accepted for priority review based on its orphan drug status.

## 2.6 Other Relevant Background Information

MembraneBlue™ obtained CE approval as a medical device Class IIa in 2002. The US will be the first country to obtain market approval of MembraneBlue™ as a drug product.

## 3 Ethics and Good Clinical Practices

### 3.1 Submission Quality and Integrity

No issues related to data quality or data integrity have been identified. Numerous papers have been published and the data is consistent across all papers.

### 3.2 Compliance with Good Clinical Practices

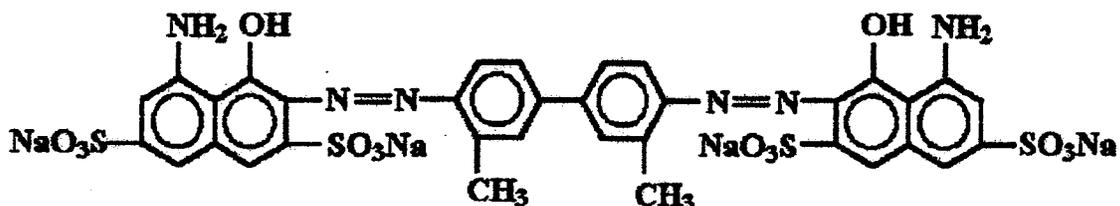
There is no evidence to suggest that the clinical trials were not conducted in compliance with good clinical practices.

### 3.3 Financial Disclosures

The sponsor has certified that no financial arrangements have been made with the investigators.

## 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

### 4.1 Chemistry Manufacturing and Controls



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Martin P Nevitt, M.D., M.P.H.  
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MembraneBlue™ 0.15% (trypan blue ophthalmic solution)

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**Composition and dosage form:** 0.5 milliliter of MembraneBlue (0.15% trypan blue ophthalmic solution) is composed of:

- 0.75 mg trypan blue
- balance \_\_\_\_\_

The \_\_\_\_\_ is composed of the following inactive ingredients:

- 4.1 mg sodium chloride
- 0.95 mg sodium phosphate dibasic dihydrate
- 0.15 mg sodium phosphate monobasic dihydrate
- balance water for injection

b(4)

The dosage form of MembraneBlue™ is an ophthalmic solution.

#### 4.2 Clinical Microbiology

Not applicable because the product is not claiming an indication as an anti-infective agent.

#### 4.3 Preclinical Pharmacology/Toxicology

Trypan blue is widely used to assess the viability of eukaryotic cells. Nonviable cells will exhibit a concentration of the dye in the nuclei. Viable cells will not take up the dye. Studies have also demonstrated trypan blue to inhibit measles and herpes simplex viruses.

#### 4.4 Clinical Pharmacology

##### 4.4.1 Mechanism of Action

Trypan blue, the active drug substance, is a stain widely used to selectively stain dead tissues or cells. Trypan blue is not absorbed in a viable cell, but traverses the membrane in a dead cell.

##### 4.4.2 Pharmacodynamics

The drug product is topically applied to the site of action. The drug product should qualify for a waiver of pharmacodynamic studies.

##### 4.4.3 Pharmacokinetics

Not applicable. The drug product is topically applied to the site of action. The drug product should qualify for a waiver of pharmacokinetic studies.

## 5 Sources of Clinical Data

### 5.1 Tables of Clinical Studies

Clinical studies have been conducted and published in the literature. The applicant has not submitted any additional unpublished clinical studies.

The following clinical studies with MembraneBlue for selective staining of epiretinal membranes during ophthalmic surgical vitrectomy procedures have been conducted. The following abbreviations are used in the following tables: Trypan Blue (TB), Indocyanine green (ICG).

First Author	Journal	Number of patients treated with Test Product	Controls	Results
EJ Feron	Arch Ophthalmol 2002; 120:141-144.	10 TB 0.06%	None	Epiretinal membranes not identified prior to use, identified after supposed complete removal. Pathology confirmation that removed tissues were only epiretinal membranes.
K Li	Br J Ophthalmol 2003; 87:216-9.	14 TB 0.06%	None	Membranes were stained satisfactorily and removed successfully.
M Perrier	Am J Ophthalmol 2003;135(6): 903-5.	18 TB 0.06%	None	Visualization and dissection of the membranes was facilitated by trypan blue staining.
M Perrier	Am J Ophthalmol 2003;135(6): 909-11.	23 TB 0.06%	None	Visualization and dissection of the membranes was facilitated by trypan blue staining without any signs of toxicity.
Francisco A Teba	Ophthalmology 2003; 110: 2409-2412	50 TB 0.2%	None	Epiretinal membranes can be identified.
C Haritoglou	Retina 2004; 24(4):582-90.	10 TB 0.15 %	15: surgery performed without staining	Epiretinal membranes had better visualization after staining with TB.
C Haritoglou	Am J Ophthalmol 2004;138(1):1-5.	22 TB 0.06 %	21: surgery performed without staining	Epiretinal membranes had better visualization after staining with TB.
BJ Vote	Retina 2004;24(5):736-8.	26 TB 0.15%	None	TB staining of epiretinal membranes is a useful adjunct in vitreoretinal surgery and improves the safety and efficiency of membrane identification and removal.
SY Lesnik Oberstein	Br J Ophthalmol 2007; 91:955-7.	29 TB 0.15%	None	Staining of membranes is a safe method.

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First Author	Journal	Number of patients treated with Test Product	Controls	Results
F Uno	Retina2006;26(2):237-9.	1 TB 0.15%	None	Case report: Subretinal migration of TB due to either direct trauma due to accidental subretinal injection, direct (chemical) toxicity of TB or solution osmolality; and photodynamic effect of TB, which may absorb wavelengths of light from the endoilluminator.

**Studies using Double Staining Technique - TB and ICG:**

First Author	Journal	Number of patients treated with Test Product	Controls	Results
P Stalmans	Br J Ophthalmol 2003; 87:713-6.	30 TB 0.15% and ICG	None	Double staining technique using TB and ICG aided in visualization of membranes during vitreoretinal surgery.
AK Kwok	EYE 2004;18(9):882-8.	16 TB 0.15% and ICG	None	Double staining technique using TB and ICG aided in visualization of membranes during vitreoretinal surgery

**Comparable studies of trypan blue to alternatives:**

First Author	Journal	Number of patients treated with Test Product	Controls	Results
KL Lee	Br J Ophthalmol 2005; 89:420-4.	5 TB 0.3% 13 TB 0.15%	5 ICG 0.5% 14 ICG 0.05%	The anatomical and visual results in the two groups were comparable.
J Beutel	Arch Ophthalmol 2007; 125:326-332.	20 TB 0.15%	20 ICG 0.05%	No statistical difference was detected between the two groups; though the TB group had better visual recovery.

**5.2 Review Strategy**

The applicant did not conduct any clinical studies. The studies published in the literature and submitted by the applicant were reviewed. In addition, a Medline search of the literature for ocular studies using trypan blue in epirerinal surgery was conducted. Articles which could be identified as relevant for the proposed indication were reviewed.

### **5.3 Discussion of Individual Studies**

From the articles referenced in Section 5.1 nearly 300 eyes used Trypan Blue (TB) at concentrations of 0.06% and 0.15% or greater for selective staining of epiretinal membranes during ophthalmic surgical vitrectomy procedures. Of these 300 eyes enrolled, 200 eyes were enrolled using a concentration of TB of 0.15% or greater.

#### **Reviewer's comments:**

*To support the approval of a drug product, safety and efficacy is recommended to be demonstrated in at least two adequate and well-controlled trials. At least two replicated trials are recommended to demonstrate robustness of results for the indication. Studies are recommended to be parallel, randomized by person, double masked trials in which the test product group demonstrates superiority over the control group.*

*Of the clinical studies referenced in Section 5.1, the following four studies used a control during surgery compared with the trypan blue (TB) group; the control group included no staining of the epiretinal membrane or staining of the epiretinal membrane with Indocyanine green (ICG). Refer to Section 6.1.4 for the Analysis of Primary endpoints.*

## **6 Review of Efficacy**

### **Efficacy Summary**

#### **6.1 Indication**

##### **6.1.1 Methods**

Published study results were used to establish the efficacy of the drug product.

##### **6.1.2 Demographics**

There are no known differences between any segments of the population for selectively staining retinal membranes. The population at risk for developing epiretinal membranes is the adult population (age 50 plus).

##### **6.1.3 Patient Disposition**

The patients tolerated the use of TB and no safety events were reported in the studies.

#### **Reviewer's comment:**

*F. Uno (Retina 2006;26(2); 237-9), was a case report of subretinal migration of Trypan Blue (TB). This event was thought to be related to surgical technique where TB was inadvertently injected subretinally.*

#### 6.1.4 Analysis of Primary Endpoint(s)

Trypan blue is well known as a vital stain. It differentially stains different tissues in the body. It is used *in vivo* and *in vitro* as a standard to distinguish between living and dead cells. Living cells do not stain; dead cells stain. Epiretinal membranes stain. Trypan blue 0.15% selectively stains epiretinal membranes. Dose ranging studies demonstrate that a concentration of 0.06% or higher is effective in selectively staining epiretinal membranes.

#### **Reviewer's comment:**

*Nearly 300 eyes using Trypan Blue (TB) at concentrations of 0.06% and 0.15% or greater for selective staining of epiretinal membranes during ophthalmic surgical vitrectomy procedures were reviewed, of 300 eyes enrolled, 200 eyes used a concentration of TB of 0.15% or greater.*

*To support the approval of a drug, safety and efficacy is recommended to be demonstrated in at least two adequate and well-controlled trials.*

*Of the clinical studies referenced in Section 5.1, the following four studies used a control during surgery compared with the TB group; the control group included no staining of the epiretinal membrane or staining of the epiretinal membrane with ICG.*

#### **Studies comparing TB to a Control (No staining)**

First Author	Journal	Number of patients treated with Test Product	Controls	Results
C Haritoglou	Retina 2004; 24(4):582-90.	10 TB 0.15 %	15: surgery performed without staining	Epiretinal membranes had better visualization after staining with TB.
C Haritoglou	Am J Ophthalmol 2004;138(1):1-5.	22 TB 0.06 %	21: surgery performed without staining	Epiretinal membranes had better visualization after staining with TB.

#### **Studies comparing TB to a Control (ICG):**

First Author	Journal	Number of patients treated with Test Product	Controls	Results
KL Lee	Br J Ophthalmol	5 TB 0.3%	5 ICG 0.5%	The anatomical and visual

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First Author	Journal	Number of patients treated with Test Product	Controls	Results
	2005; 89:420-4.	13 TB 0.15%	14 ICG 0.05%	results in the two groups were comparable.
J Beutel	Arch Ophthalmol 2007; 125:326-332.	20 TB 0.15%	20 ICG 0.05%	No statistical difference was detected between the two groups; though the TB group had better visual recovery.

**Reviewer's comments:**

1. C Haritoglou, et al. *Retina* 2004; 24(4):582-90.

*In this clinical study 10 eyes of 10 consecutive patients with intraoperative use of TB (0.15%) were analyzed and compared with the functional outcome in a matched group of patients (15 eyes) who had undergone vitrectomy without TB.*

*The studied demonstrated TB permitted better visualization of the epiretinal membrane which might enable the surgeon to better and more completely remove the epiretinal tissue. No adverse effects of the dye on functional outcome were observed.*

2. C Haritoglou, et al. *Am J Ophthalmol* 2004;138(1):1-5.

*This clinical trial was a prospective, randomized, comparative study. Forty three eyes of 43 consecutive patients were randomized between TB (0.06%) staining or to no staining.*

*The authors concluded the application of TB may be beneficial since it enables the surgeon to better visualize and therefore remove the epiretinal tissue more completely (though there were no statistically significant differences in functional outcome after a follow-up of up to 6 months - the statistical difference in functional outcome between the groups was  $p > 0.5$ ). The study reported that no apparent dye-related adverse events occurred.*

3. KL Lee, et al. *Br J Ophthalmol* 2005; 89:420-4.

*This was a retrospective analysis of 37 eyes from 37 consecutive patients. In 19 patients ICG was used and in 18 patients TB.*

*There was no significant difference between the preoperative visual acuities in the TB and ICG groups but the postoperative visual acuities were better in the TB than in the ICG group ( $p = 0.036$ ). The TB group also had more lines of improvement than the ICG group (2.94 versus 1.79 lines;  $p = 0.046$ ), follow-up ranged from 1 – 30 months and the median follow-up was 5 months. TB appears to be less toxic than ICG when used in dye assisted removal of epiretinal membranes as reflected by the better visual results in the TB group.*

4. J Beutel, et al. *Arch Ophthalmol* 2007; 125:326-332.

*This was a randomized, controlled trial with 20 patients (20 eyes) receiving ICG and 20 patients (20 eyes) receiving TB. Although the primary outcome measurement of visual acuity at 3 months*

*measured by the Early Treatment of Diabetic Retinopathy scale did not demonstrate a significant difference between the TB and ICG study groups, after 6 months the TB group did show significant improvement in visual acuity ( $p = 0.002$ ).*

*These four clinical trials with control groups and the other studies listed in Section 5.1 support the use of TB as an aide to the surgeon in the selective staining of epiretinal membranes during vitrectomy surgery.*

*Based on these four adequate and well controlled clinical trials and the other studies listed in Section 5.1, this application for trypan blue has demonstrated efficacy in selectively staining epiretinal membranes and is not recommended for approval pending resolution of an unacceptable site inspection at \_\_\_\_\_*

b(4)

#### 6.1.5 Analysis of Secondary Endpoints(s)

Not applicable. No secondary endpoints were studied.

#### 6.1.6 Other Endpoints

Not applicable. No other endpoints were studied.

#### 6.1.7 Subpopulations

There are no known differences between any segments of the population for selectively staining retinal membranes. The population at risk for developing epiretinal membranes is the adult population (age 50 plus).

#### 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

A few drops (0.3 to 0.5 mL) of TrypanBlue 0.15% are administered intraocularly during a vitrectomy. Staining of the epiretinal membrane occurs within seconds and the selectively stained epiretinal membrane is removed during the vitrectomy operation.

#### 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The TB stained epiretinal membrane are removed during the vitrectomy operation. There are no other efficacy or tolerance effects.

#### 6.1.10 Additional Efficacy Issues/Analyses

There are no other efficacy analyses required.

## 7 Review of Safety

### Safety Summary

#### 7.1 Methods

##### 7.1.1 Clinical Studies Used to Evaluate Safety

Published literature study results were used to establish the efficacy of the drug product and the patients tolerated the use of TB.

As early as 1967, trypan blue has been used in ophthalmology to achieve vital staining of the cornea and conjunctiva. It has been injected into the anterior chamber since the 1970s to evaluate the corneal endothelium. It is the standard screening agent for organ donor corneas to evaluate the corneal endothelium prior to corneal transplantation. Well over ——— corneas have been screened and transplanted after administration of trypan blue, 0.3%. This dose is approximately 2 times the proposed dose. In donor corneal grafts, there are no documented adverse effects.

b(4)

There are no known safety concerns that have arisen with other members of this pharmacologic class.

#### Reviewer's comment:

*Of the clinical studies referenced in Section 5.1, the following four studies used a control during surgery when compared with the TB group and support the safety of the drug product.*

1. C Haritoglou, et al. *Retina* 2004; 24(4):582-90.

*In this clinical study of 10 eyes of 10 consecutive patients with intraoperative use of TB (0.15%), no adverse effects of the dye on functional outcome were observed.*

2. C Haritoglou, et al. *Am J Ophthalmol* 2004;138(1):1-5.

*Forty three eyes of 43 consecutive patients were randomized between TB (0.06%) staining or to no TB staining. There were no dye-related adverse events reported.*

3. KL Lee, et al. *Br J Ophthalmol* 2005; 89:420-4.

*This was a retrospective analysis of 37 eyes from 37 consecutive patients. The adverse events that were reported were those commonly associated with a vitrectomy procedure. Postoperatively, in the ICG group one retinal detachment occurred and two small retinal detachments occurred intraoperatively that were repaired at the time of the surgery; in the TB group one patient experienced a choroidal / vitreous hemorrhage.*

*4. J Beutel, et al. Arch Ophthalmol 2007; 125:326-332.*

*This was a randomized, controlled trial with 20 patients (20 eyes) receiving ICG and 20 patients (20 eyes) receiving TB. Again, the adverse events that were reported were those commonly associated with a vitrectomy procedure. In both groups there was one post-op retinal detachment and in all phakic eyes the progression of nuclear cataracts were noted.*

*These four clinical trials with control groups and the other studies listed in Section 5.1 supports the safety of using TB as a surgical aide in the selective staining of epiretinal membranes during vitrectomy surgery.*

*Based on these four adequate and well controlled clinical trials and the other studies listed in Section 5.1, this application for trypan blue has demonstrated to be safe in selectively staining epiretinal membranes and is not recommended for approval pending resolution of an unacceptable site inspection at \_\_\_\_\_*

b(4)

#### 7.1.2 Adequacy of Data

No issues related to data quality or data integrity have been identified. Numerous papers have been published and the data is consistent across all papers.

There is no evidence to suggest that the clinical trials were not conducted in compliance with good clinical practices.

#### 7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

Not applicable. Refer to section 7.1.1.

### 7.2 Adequacy of Safety Assessments

#### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The submitted studies are adequate with respect to extent of exposures and time to evaluate the potential for adverse events. Complete safety evaluations have been performed in adequate numbers of patients.

#### 7.2.2 Explorations for Dose Response

The doses of trypan studied in the published literature ranged from 0.06% to 0.3%. The majority of eyes enrolled in the published studies were 0.15%.

### **7.2.3 Special Animal and/or In Vitro Testing**

Preclinical testing was adequate to establish a testing pattern for the human studies.

### **7.2.4 Routine Clinical Testing**

Clinical testing was adequate to estimate the safety of the drug product.

### **7.2.5 Metabolic, Clearance, and Interaction Workup**

The drug product is not metabolized. Clearance of the drug product is achieved primarily by irrigation and removal of stained tissue. There are no significant drug-drug interactions.

### **7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class**

In view of the 30 year history of the drug product in a concentration twice the proposed dose, evaluation for potential adverse events is adequate.

## **7.3 Major Safety Results**

### **7.3.1 Deaths**

There were no deaths reported in the published studies.

### **7.3.2 Nonfatal Serious Adverse Events**

There were no serious adverse events related to the drug product reported in the published studies.

### **7.3.3 Dropouts and/or Discontinuations**

There were no dropouts / discontinuations related to the drug product reported in the published studies.

### **7.3.4 Significant Adverse Events**

There were no significant adverse events related to the drug product reported in the published studies.

### **7.3.5 Submission Specific Primary Safety Concerns**

There were no specific safety concerns.

## **7.4 Supportive Safety Results**

### **7.4.1 Common Adverse Events**

There were no common adverse events related to the drug product reported in the published studies.

### **7.4.2 Laboratory Findings**

There are no reported abnormal laboratory findings (chemistry, hematology, and urinalysis).

### **7.4.3 Vital Signs**

There are no reported changes in vital signs following administration of Trypan Blue.

### **7.4.4 Electrocardiograms (ECGs)**

No evaluation of ECG data has been performed. It is not considered necessary for the evaluation of this drug product.

### **7.4.5 Special Safety Studies**

No special safety studies were performed to study this drug product.

### **7.4.6 Immunogenicity**

Trypan blue may have an effect on macrophages causing immunogenicity. The ability of trypan blue to cause immunogenicity requires prolonged contact with living cells. This does not occur with this indication.

## **7.5 Other Safety Explorations**

### **7.5.1 Dose Dependency for Adverse Events**

There were no dose dependency adverse events reported in the published studies.

### **7.5.2 Time Dependency for Adverse Events**

There were no time dependency adverse events reported in the published studies.

### **7.5.3 Drug-Demographic Interactions**

There were no drug-demographic interactions reported in the published studies.

### **7.5.4 Drug-Disease Interactions**

There were no drug-disease interactions reported in the published studies.

### **7.5.5 Drug-Drug Interactions**

There are no known drug-drug interactions.

## **7.6 Additional Safety Explorations**

### **7.6.1 Human Carcinogenicity**

There are no known cases of human carcinogenicity, although trypan blue is known to be carcinogenic in certain strains of rats at doses of 50 mg/kg/week. These effects occur after the accumulation of trypan blue within the Kupfer cells of the liver. The doses necessary to cause carcinogenicity effects in man are below the levels proposed for this product and there are no free molecules available to accumulate in the Kupfer cells.

### **7.6.2 Human Reproduction and Pregnancy Data**

Trypan blue is known to be teratogenic in hamsters, mice, rabbits and rats. These effects occur because there are binding sites on the dye molecule which are recognized by living cells after prolonged contact. The doses expected to be necessary to cause teratogenic effects in man are below the levels proposed for this product. The established teratogenic dose is 100 mg/kg.

### **7.6.3 Pediatrics and Effect on Growth**

The drug would not be expected to be used on pediatric patients. The mean age of the published studies ranged from 60 to 71 years old.

The use of Trypan Blue in lower concentrations in pediatric patients was supported by adequate and well controlled studies in NDA 21-670 which was approved April 12, 2004.

### **7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound**

There is no potential for overdose of this drug product.

## **7.7 Additional Submissions**

No additional submissions are recommended.

## **8 Postmarketing Experience**

No post marketing studies are recommended.

## **9 Appendices**

### **9.1 Literature Review/References**

Specific details of the individual studies are listed in the table in section 5.1.

### **9.2 Labeling Recommendations**

Refer to comments within the line-by-line labeling review which follows.

### **9.3 Advisory Committee Meeting**

No Advisory Committee was necessary or convened for this drug product.

#### **Labeling Recommendations:**

*The applicant has submitted the following label for review.*

*Reviewer's deletions are noted by ~~strikeout~~ and additions by an underline within this review.  
This is a draft label.*

4 Page(s) Withheld

\_\_\_\_\_ § 552(b)(4) Trade Secret / Confidential

√ § 552(b)(4) Draft Labeling

\_\_\_\_\_ § 552(b)(5) Deliberative Process

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/s/

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8/1/2008 02:41:00 PM  
MEDICAL OFFICER

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