

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-278

SUMMARY REVIEW

Division Director Summary Review
Wiley A. Chambers, MD
NDA 22-278
MembraneBlue 0.15% (trypan blue ophthalmic solution)

Division Director Summary Review

Date	February 20, 2009
From	Wiley A. Chambers, M.D.
NDA#	22-278
Applicant	Dutch Ophthalmic Research Center
Submission date	August 18, 2008
Name	MembraneBlue 0.15% (trypan blue ophthalmic solution)
Dosage forms	ophthalmic solution
Proposed Indication(s)	for use as an aid in ophthalmic surgery by staining the epiretinal membranes during ophthalmic surgical vitrectomy procedures, facilitating removal of the tissue.
Action:	Approval

b(4)

1. Introduction

MembraneBlue 0.15% (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. 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 and not the retina itself are stained 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.

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: $C_{34}H_{24}N_6 Na_4O_{14}S_4$. 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.

2. Background

Trypan blue has been marketed as MembraneBlue™ 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. Trypan blue has also been marketed as VisionBlue™ 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.

b(4)

This is a 505(b)(2) application. The safety and efficacy of MembraneBlue for the proposed indication can be supported from published studies which use the applicant's product. The applicant has marketed the product in Europe without doing any studies on their own. Studies were subsequently done with their product and reported in the literature.

The proposed indication, use as an aid in ophthalmic surgery by staining the epiretinal membranes during ophthalmic surgical vitrectomy procedures, facilitating removal of the tissue and _____ was not supported by the submitted data. A revised indication, for use as an aid in ophthalmic surgery by staining the epiretinal membranes during ophthalmic surgical vitrectomy procedures, facilitating removal of the tissue, is acceptable. Based on the following four adequate and well controlled clinical trials from the literature (reviewed in Section 6.1.4 of the Medical Officer's review): 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 of the Medical Officer's review, 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.

b(4)

3. CMC

DRUG SUBSTANCE:

Trypan blue, the drug substance in MembraneBlue 0.15%, is _____ by _____ DMF _____ is authorized to be referenced for information regarding the _____ trypan blue. Reviews of DMF _____ were completed and the DMF was noted to be adequate to support the current NDA.

b(4)

DRUG PRODUCT:

The formulation of MembraneBlue 0.15% is similar to VisionBlue 0.06%, which was submitted by the same applicant and approved in June 2004. The only difference is an increased trypan blue concentration from 0.06% to 0.15% for MembraneBlue. Each mL of MembraneBlue 0.15% contains 1.5 _____ mg trypan blue, 1.9 mg sodium monohydrogen orthophosphate (Na₂HPO₄·2H₂O), 0.3 mg sodium di-hydrogen orthophosphate (NaH₂PO₄·2H₂O), 8.2 mg sodium

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Considering the drug history and clinical experience, nonclinical study results, proposed indication, and dosage, the reviewing pharmacologist believes that, from the nonclinical standpoint, the data are adequate for the approval of the drug. The labeling of MembraneBlue™, which is based on the approved labeling of VisionBlue, is considered acceptable.

5. Clinical Pharmacology/Biopharmaceutics

MembraneBlue is packaged in a volume of 0.5 mL in a 2.25 mL single-use syringe for application to the retinal membrane by blunt cannula. The actual dosage of MembraneBlue is determined by the ophthalmic surgeon, but is in the range of 0.3 to 0.5 mL.

No clinical PK studies evaluating the systemic absorption of trypan blue following administration of MembraneBlue have been conducted. A waiver of the in vivo bioavailability requirement is granted, based on the expected negligible systemic exposure of trypan blue following use of MembraneBlue 0.15% (trypan blue ophthalmic solution) during ophthalmic surgical vitrectomy procedures. The Clinical Pharmacology and Biopharmaceutics information provided by the Applicant was considered acceptable.

6. Sterility Assurance

The primary package consists of a 2.25 mL BD _____ glass syringe, a _____ tip cap and a _____ plunger stopper. The manufacturing process for MembraneBlue™ is nearly identical to the manufacturing process for the approved product, VisionBlue™. The container closure system is identical for both products.

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The container closure system is identical to that approved for VisionBlue. The container closure integrity test for VisionBlue was evaluated in the product quality microbiology review for NDA 21-670 and approved in November of 2004.

MembraneBlue™ has a bacterial endotoxin limit of NMT - EU/mL. This endotoxin limit was found to be satisfactory by the medical division because excess dye will be washed from the eye and stained tissue will be surgically removed. Endotoxin testing will be conducted according to USP <85> methodology. The results of inhibition/enhancement testing for the drug product were provided in the June 2008 amendment. The results show that inhibition was overcome at a dilution of _____. The applicant has chosen a working dilution of _____ for use with an endotoxin sensitivity of _____ EU/mL. This allows for detection of endotoxin levels of _____ EU/mL.

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Sterility testing will be conducted according to USP <71>. The results of bacteriostasis/fungistasis testing were provided in the June 2008 amendment and found to be satisfactory. Because the product label states that the syringe containing membrane blue is sterile, a sterility test should be conducted on the syringe as well. The applicant provided a commitment

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chloride (NaCl), and water for injection. The pH is 7.3 - 7.6. The osmolality is 257-314 mOsm/kg. MembraneBlue is filled in glass syringes to a volume of 0.5 mL.

The drug product is manufactured by a contract firm, _____ located in _____ . The drug product is manufactured from _____ obtain a 0.15% solution. The _____ is supplied by _____ in _____

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During drug product manufacturing process, the pH of the solution is verified and the solution is _____ . The prepared solution is then filled into a single-use Luer Lok 2.25 ml glass syringe (_____ ml/syringe) and the syringe is closed with a tip cap and stopper. The solution is _____ sterilized. The syringes are then placed into _____ pouches and the outside surface of the syringes is _____ sterilized.

b(4)

A two year expiry dating period was proposed for this product when stored at 15-25°C (59-77°F) and protected from direct sunlight. Stability data was available on one batch of MembraneBlue 0.15% up to 3 months at long-term and accelerated conditions. Supporting stability data was available on three batches of VisionBlue 0.06% up to 26 months.

An inspection of the manufacturing site was performed from _____ . This inspection revealed multiple GMP deficiencies, and a 483 was issued. Corrections were made and a re-inspection found the facility to be in compliance with cGMP.

b(4)

From a manufacturing/quality control standpoint, the application is acceptable for approval.

4. Nonclinical Pharmacology/Toxicology

Trypan blue has been approved for ocular staining in cataract surgery (VisionBlue™ 0.06%) under NDA 21-670 and is cross-referenced for this NDA. The toxicological profile for carcinogenicity, teratogenicity, and mutagenicity has already been established. It is reported that trypan blue was teratogenic in rats, mice, rabbits, hamsters, dogs, guinea pigs, pigs, and chickens. It caused external, skeletal, and internal malformations. Trypan blue was mutagenic in Ames test. Trypan blue is carcinogenic in rats. Chronic intermittent exposure by subcutaneous injection of trypan blue in Wistar/Lewis rats induced a reticuloendothelial neoplasm, predominantly in the liver. The aforementioned information has been listed in the proposed labeling for MembraneBlue™.

Trypan blue is a vital stain widely used to selectively stain dead cells. The drug is not absorbed in a viable cell. Therefore, only the epiretinal membranes are stained in contrast to the retina. Clinically, only 0.75 mg of trypan blue will be administered to the eye, and almost all dye will be immediately irrigated out from the eye, leaving less than _____ to mark the membrane that too will be removed from the eye. Therefore the amount of the drug left in the patient after the surgery will be very low. The applicant indicated that the final dose used in vitreoretinal surgery is less than _____ mg. It appears that possible systemic and ocular toxic effect of MembraneBlue™ is small.

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to conduct sterility testing on both the contents of the syringe and the contents of the pouch in the June 2008 amendment.

7. Clinical/Statistical - Efficacy

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.
F Uno	Retina 2006;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 osmolarity; and photodynamic effect of TB, which may absorb wavelengths of light from the endoilluminator.

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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.

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 epiretinal surgery was conducted. Articles which could be identified as relevant for the proposed indication were reviewed.

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. 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, and that concentrations at or above 0.15% provide more contrast than concentrations of 0.06%.

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.

Of the clinical studies referenced, 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.

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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 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.

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.

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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 ($p = 0.002$).

EFFICACY CONCLUSIONS

These four clinical trials with control groups and the other studies listed in the Medical Officer's review support the efficacy of MembraneBlue as an aid in ophthalmic surgery by staining the epiretinal membranes during ophthalmic surgical vitrectomy procedures, facilitating removal of the tissue.

8. Safety

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

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)

Adverse reactions reported following use of MembraneBlue 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. There are no known safety concerns that have arisen with other members of this pharmacologic class.

Of the clinical studies referenced in the application, 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.

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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.

SAFETY CONCLUSIONS

These four clinical trials with control groups and the other studies listed in the Medical Officer's review support the safety of MembraneBlue as an aid in ophthalmic surgery by staining the epiretinal membranes during ophthalmic surgical vitrectomy procedures, facilitating removal of the tissue.

9. Advisory Committee Meeting

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

10. Pediatrics

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

The use of Trypan Blue in lower concentrations in pediatric patients was supported by the literature reports of adequate and well controlled studies in NDA 21-670 for VisionBlue (trypan blue ophthalmic solution) which was approved April 12, 2004.

11. Other Relevant Regulatory Issues

A Division of Scientific Investigations (DSI) audit was not requested since this was a literature review.

A consult was requested from the Office of Surveillance and Epidemiology regarding a trade name review for the proposed name "MembraneBlue." The results of the Proprietary Name Risk Assessment found that the proposed name, MembraneBlue, appears to be vulnerable to product confusion with VisionBlue. The Division of Medication Error Prevention believes that the risk

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may be mitigated by differentiating the proposed labels and labeling of MembraneBlue from the labels and labeling of the existing product VisionBlue.

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed _____ proposed product labeling (PI) for this application submitted to the Agency on 30 January 2008. Their recommendations regarding the proposed indication, Warnings and Precautions, and Clinical Pharmacology sections of the labeling have been incorporated into the draft label.

b(4)

12. 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 with the labeling submitted by Dutch Ophthalmic Research Center on January 30, 2009, and February 12, 2009, and found in Cross-Discipline Team Leader Review.

13. 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.

RISK BENEFIT ASSESSMENT:

Based on the following four adequate and well controlled clinical trials from the literature, 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. The application supports the safety of MembraneBlue 0.15% (trypan blue ophthalmic solution) 0.15% for use as an aid in ophthalmic surgery by staining the epiretinal membranes during ophthalmic surgical vitrectomy procedures, facilitating removal of the tissue.

Clinical, CMC, Pharmacology/Toxicology, Product Quality Microbiology, and Clinical Pharmacology have recommended approval for this application.

RECOMMENDATION FOR POSTMARKETING RISK MANAGEMENT ACTIVITIES:

There are no additional proposed risk management actions except the usual postmarketing collection and reporting of adverse experiences associated with the use of the drug product.

Wiley A. Chambers, MD
Acting Director, Division of Anti-Infective and Ophthalmology Products

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/s/

Wiley Chambers
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MEDICAL OFFICER

Wiley Chambers
2/20/2009 04:07:45 PM
MEDICAL OFFICER

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Wiley A. Chambers, MD
NDA 22-278
MembraneBlue (trypan blue ophthalmic solution) 0.15%

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Date	August 4, 2008
From	Wiley A. Chambers, M.D.
Subject	MembraneBlue (trypan blue ophthalmic solution) 0.15%
NDA#	22-278
Applicant	Dutch Ophthalmic Research Center
Submission date	January 30, 2008
PDUFA Goal Date	August 4, 2008
Name	MembraneBlue (trypan blue ophthalmic solution)
Dosage forms	ophthalmic solution
Proposed Indication(s)	for use as an aid in ophthalmic surgery by staining the epiretinal membranes during ophthalmic surgical vitrectomy procedures, facilitating removal of the tissue _____
Action:	Approvable

b(4)

1. Introduction

MembraneBlue (trypan blue ophthalmic solution) 0.15% is a sterile solution of trypan blue. MembraneBlue selectively stains membranes of the inner surface of the retina that can lead to visual disturbances. 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 hypocoelular, 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.

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: $C_{34}H_{24}N_6 Na_4O_{14}S_4$. 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.

2. Background

Trypan blue has been marketed as MembraneBlue™ 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. Trypan blue has also been marketed as VisionBlue™ 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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This is a 505(b)(2) application. The safety and efficacy of MembraneBlue for the proposed indication can be supported from published studies which use the applicant's product. The applicant has marketed the product in Europe without doing any studies on their own. Studies were subsequently done with their product and reported in the literature.

The proposed indication, use as an aid in ophthalmic surgery by staining the epiretinal membranes during ophthalmic surgical vitrectomy procedures, facilitating removal of the tissue _____ was not supported by the submitted data. A revised indication, for use as an aid in ophthalmic surgery by staining the epiretinal membranes during ophthalmic surgical vitrectomy procedures, facilitating removal of the tissue, is acceptable. Based on the following four adequate and well controlled clinical trials from the literature (reviewed in Section 6.1.4 of the Medical Officer's review): 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 of the Medical Officer's review, 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.

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3. CMC

DRUG SUBSTANCE:

Trypan blue, the drug substance in MembraneBlue 0.15%, is _____ by _____, DMF _____ is authorized to be referenced for information regarding the _____ trypan blue. Reviews of DMF # _____ were completed and the DMF was noted to be adequate to support the current NDA.

b(4)

DRUG PRODUCT:

The formulation of MembraneBlue 0.15% is similar to VisionBlue 0.06%, which was submitted by the same applicant and approved in June 2004. The only difference is an increased trypan blue concentration from 0.06% to 0.15% for MembraneBlue. Each mL of MembraneBlue 0.15% contains 1.5 ± _____ mg trypan blue, 1.9 mg sodium monohydrogen orthophosphate (Na₂HPO₄·2H₂O), 0.3 mg sodium di-hydrogen orthophosphate (NaH₂PO₄·2H₂O), 8.2 mg sodium

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chloride (NaCl), and water for injection. The pH is 7.3 - 7.6. The osmolality is 257-314 mOsm/kg. MembraneBlue is filled in glass syringes to a volume of 0.5 mL.

The drug product is manufactured by a contract firm, _____ located in _____
_____ The drug product is manufactured from _____
_____ to obtain a 0.15% solution. The _____
_____ is supplied by _____ in _____

b(4)

During drug product manufacturing process, the pH of the solution is verified and the solution is _____) to _____ any _____. The prepared solution is then filled into a single-use Luer Lok 2.25 ml glass syringe (_____ ml/syringe) and the syringe is closed with a tip cap and stopper. The solution is _____ sterilized. The syringes are then placed into _____ pouches and the outside surface of the syringes is _____ sterilized.

b(4)

A two year expiry dating period was proposed for this product when stored at 15-25°C (59-77°F) and protected from direct sunlight. Stability data was available on one batch of MembraneBlue 0.15% up to 3 months at long-term and accelerated conditions. Supporting stability data was available on three batches of VisionBlue 0.06% up to 26 months.

An inspection of the manufacturing site was performed from _____
_____ This inspection revealed multiple GMP deficiencies, and a 483 was issued.

b(4)

The observations cited in the 483 included:

1. Failure to qualify the maximum amount of sterilizing cycles for which the _____ can be reused without being replaced
2. 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.
3. 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
4. Failure to have an _____ conducted during filing and prior to sterilization of Vision Blue 0.06% trypan blue ophthalmic solution syringes
5. 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.

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From a manufacturing/quality control standpoint, the application cannot be approved until the manufacturing facilities are compliant with cGMPs.

6. Nonclinical Pharmacology/Toxicology

Trypan blue has been approved for ocular staining in cataract surgery (VisionBlue™ 0.06%) under NDA 21-670 and is cross-referenced for this NDA. The toxicological profile for carcinogenicity, teratogenicity, and mutagenicity has already been established. It is reported that trypan blue was teratogenic in rats, mice, rabbits, hamsters, dogs, guinea pigs, pigs, and chickens. It caused external, skeletal, and internal malformations. Trypan blue was mutagenic in Ames test. Trypan blue is carcinogenic in rats. Chronic intermittent exposure by subcutaneous injection of trypan blue in Wistar/Lewis rats induced a reticuloendothelial neoplasm, predominantly in the liver. The aforementioned information has been listed in the proposed labeling for MembraneBlue™.

Trypan blue is a vital stain widely used to selectively stain dead cells. The drug is not absorbed in a viable cell. Therefore, only the epiretinal membranes are stained in contrast to the retina. Clinically, only 0.75 mg of trypan blue will be administered to the eye, and almost all dye will be immediately irrigated out from the eye, leaving less than _____ to mark the membrane that too will be removed from the eye. Therefore the amount of the drug left in the patient after the surgery will be very low. The sponsor indicated that the final dose used in vitreoretinal surgery is less than _____ mg. It appears that possible systemic and ocular toxic effect of MembraneBlue™ is small.

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Considering the drug history and clinical experience, nonclinical study results, proposed indication, and dosage, the reviewing pharmacologist believes that, from the nonclinical standpoint, the data are adequate for the approval of the drug. The labeling of MembraneBlue™, which is based on the approved labeling of VisionBlue, is considered acceptable.

7. Clinical Pharmacology/Biopharmaceutics

MembraneBlue is packaged in a volume of 0.5 mL in a 2.25 mL single-use syringe for application to the retinal membrane by blunt cannula. The actual dosage of MembraneBlue is determined by the ophthalmic surgeon, but is in the range of 0.3 to 0.5 mL.

No clinical PK studies evaluating the systemic absorption of trypan blue following administration of MembraneBlue have been conducted. A waiver of the in vivo bioavailability requirement is granted, based on the expected negligible systemic exposure of trypan blue following use of MembraneBlue (trypan blue ophthalmic solution) during ophthalmic surgical vitrectomy procedures. The Clinical Pharmacology and Biopharmaceutics information provided by the Applicant was considered acceptable.

8. Sterility Assurance

The primary package consists of a 2.25 mL BD _____ glass syringe, a _____ tip cap and a _____ plunger stopper. The manufacturing process for

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MembraneBlue™ is nearly identical to the manufacturing process for the approved product, VisionBlue™. The container closure system is identical for both products.

The container closure system is identical to that approved for VisionBlue. The container closure integrity test for VisionBlue was evaluated in the product quality microbiology review for NDA 21-670 and approved in November of 2004.

MembraneBlue™ has a bacterial endotoxin limit of NMT – EU/mL. This endotoxin limit was found to be satisfactory by the medical division because excess dye will be washed from the eye and stained tissue will be surgically removed. Endotoxin testing will be conducted according to USP <85> methodology. The results of inhibition/enhancement testing for the drug product were provided in the June 2008 amendment. The results show that inhibition was overcome at a dilution of — The applicant has chosen a working dilution of — for use with an endotoxin sensitivity of — EU/mL. This allows for detection of endotoxin levels of — EU/mL.

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Sterility testing will be conducted according to USP <71>. The results of bacteriostasis/fungistasis testing were provided in the June 2008 amendment and found to be satisfactory. Because the product label states that the syringe containing membrane blue is sterile, a sterility test should be conducted on the syringe as well. The applicant provided a commitment to conduct sterility testing on both the contents of the syringe and the contents of the pouch in the June 2008 amendment.

9. Clinical/Statistical - Efficacy

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.

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First Author	Journal	Number of patients treated with Test Product	Controls	Results
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.
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 osmolarity; 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.

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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 epiretinal surgery was conducted. Articles which could be identified as relevant for the proposed indication were reviewed.

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. 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.

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, 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 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.

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.

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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 ($p = 0.002$).

EFFICACY CONCLUSIONS

These four clinical trials with control groups and the other studies listed in the Medical Officer's review support the efficacy of MembraneBlue as an aid in ophthalmic surgery by staining the epiretinal membranes during ophthalmic surgical vitrectomy procedures, facilitating removal of the tissue.

10. Safety

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

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

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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.

Adverse reactions reported following use of MembraneBlue 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. There are no known safety concerns that have arisen with other members of this pharmacologic class.

Of the clinical studies referenced in the application, 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.

SAFETY CONCLUSIONS

These four clinical trials with control groups and the other studies listed in the Medical Officer's review support the safety of MembraneBlue as an aid in ophthalmic surgery by staining the epiretinal membranes during ophthalmic surgical vitrectomy procedures, facilitating removal of the tissue.

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11. Advisory Committee Meeting

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

12. Pediatrics

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

The use of Trypan Blue in lower concentrations in pediatric patients was supported by the literature reports of adequate and well controlled studies in NDA 21-670 for VisionBlue (trypan blue ophthalmic solution) which was approved April 12, 2004.

13. Other Relevant Regulatory Issues

A Division of Scientific Investigations (DSI) audit was not requested since this was a literature review.

A consult was requested from the Office of Surveillance and Epidemiology regarding a trade name review for the proposed name "MembraneBlue." The results of the Proprietary Name Risk Assessment found that the proposed name, MembraneBlue, appears to be vulnerable to product confusion with VisionBlue. The Division of Medication Error Prevention believes that the risk may be mitigated by differentiating the proposed labels and labeling of MembraneBlue from the labels and labeling of the existing product VisionBlue.

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed _____ proposed product labeling (PI) for this application submitted to the Agency on 30 January 2008. Their recommendations regarding the proposed indication, Warnings and Precautions, and Clinical Pharmacology sections of the labeling have been incorporated into the draft label.

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14. Labeling

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 Establishment Evaluation Request made via EES.

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The labeling submitted by Dutch Ophthalmic Research Center on 30 January 2008 and found in Cross-Discipline Team Leader Review. The Agency will continue to work with DORC regarding the labeling for MembraneBlue.

15. Recommendations/Risk Benefit Assessment

RECOMMENDED 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 until the manufacturing facility is found to be in compliance with cGMPs. The Division will continue to work with DORC regarding the labeling for MembraneBlue.

RISK BENEFIT ASSESSMENT:

Based on the following four adequate and well controlled clinical trials from the literature, 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. The application supports the safety of MembraneBlue (trypan blue ophthalmic solution) 0.15% for use as an aid in ophthalmic surgery by staining the epiretinal membranes during ophthalmic surgical vitrectomy procedures, facilitating removal of the tissue.

Clinical, CMC, Pharmacology/Toxicology, Product Quality Microbiology, and Clinical Pharmacology have recommended approval for this application.

RECOMMENDATION FOR POSTMARKETING RISK MANAGEMENT ACTIVITIES:

There are no additional proposed risk management actions except the usual postmarketing collection and reporting of adverse experiences associated with the use of the drug product.

Wiley A. Chambers, MD
Acting Director, Division of Anti-Infective and Ophthalmology Products

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/s/

Wiley Chambers
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