CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-670

MEDICAL REVIEW(S)

LW of NDA 21-670

Application Type	NDA
Submission Number	21-670
Submission Code	N-000
Letter Date	October 24, 2003
Received Date	October 27, 2003
Reviewer Name	Wiley A. Chambers, MD
Review Completion Date	April 5, 2004
Established Name	Trypan Blue Ophthalmic Solution
(Proposed) Trade Name	Vision Blue
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
Dosing Regimen	A few drops (0.1 to 0.3 mL) of Vision Blue are administered intracamerally after filling the anterior chamber with air.
Indication	Capsular staining
Intended Population	Patients undergoing cataract surgery

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Approvability

NDA 21-670 is recommended for approval from a clinical prospective with the labeling identified in this review. The indication as described in the labeling as proposed in this review is supported by literature studies.

1.2 Recommendation on Post-marketing Actions

1.2.1. Risk Management Activity

No risk management activities recommended.

1.2.2 Required Phase 4 Commitments

No additional Phase 4 studies are recommended.

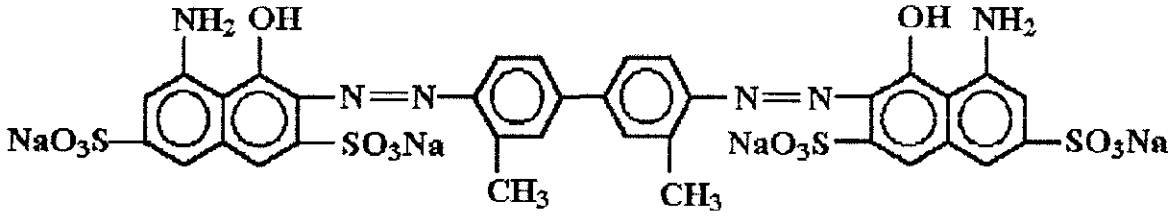
1.2.3 Other Phase 4 Requests

No additional Phase 4 studies are recommended.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Vision Blue (trypan blue ophthalmic solution)



Trypan blue is a blue bis-azo dye. It is a symmetrical molecule with three parts connected by two azo bonds. The molecular weight is 961. The empirical formula is: $C_{34}H_{23}N_6O_{14}S_4Na_4$. It is water soluble. A few drops (0.1-0.3 mL) are administered by intracameral injection, usually under an air bubble, and then rinsed out of the anterior chamber with an ophthalmic irrigating solution.

The proposed indication is for staining of the anterior lens capsule — 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.

Vision Blue has been marketed in Europe since 1999 for the same indication proposed in this application. The applicant reports over — units have been used during cataract surgery.

Approximately 350 patients are reported on in this review from over 10 separate studies.

1.3.2 Efficacy

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. The lens capsule stains. Trypan blue 0.06% is 100% effective in staining the anterior capsule. Dose ranging studies demonstrate that a concentration of 0.025% or higher is effective in staining the anterior capsule.

1.3.3 Safety

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 30,000 corneas have been screened and transplanted after administration of trypan blue, 0.3%. This dose is approximately 5 times the proposed dose. In donor corneal grafts, there are no documented adverse effects.

1.3.4 Dosing Regimen and Administration

A few drops (0.1 to 0.3 mL) of Vision Blue are administered intracamerally after filling the anterior chamber with air. Staining occurs within seconds and the anterior chamber is then irrigated with an ophthalmic irrigating solution to remove any excess dye. The majority of the stained capsule is removed as part of the cataract operation.

1.3.5 Drug-Drug Interactions

There are no known drug-drug interactions. The use of a viscoelastic substance in the anterior chamber may limit staining of the anterior capsule due to the physical barrier caused by the viscoelastic substance.

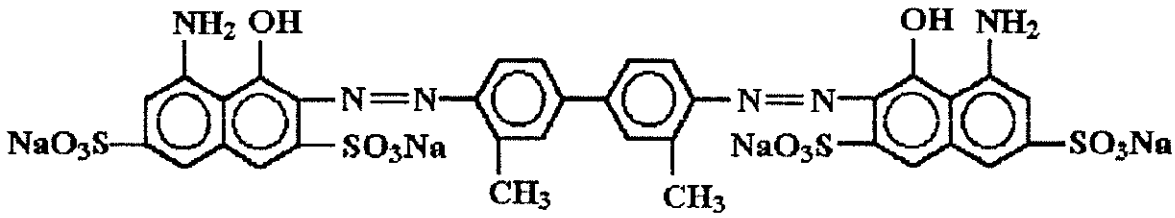
1.3.6 Special Populations

There are no known differences between any segments of the population. Pediatric patients have been studied in adequate and well controlled studies.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Vision Blue (trypan blue ophthalmic solution)



Trypan blue is a blue bis-azo dye. It is a symmetrical molecule with three parts connected by two azo bonds. The molecular weight is 961. The empirical formula is: $C_{34}H_{23}N_6O_{14}S_4Na_4$. It is water soluble. A few drops (0.1-0.3 mL) are administered by intracameral injection, usually under an air bubble and then rinsed out of the anterior chamber with an ophthalmic irrigating solution.

The proposed indication is for staining of the anterior lens capsule — y. The product is expected to be able to be used equally in all segments of the population undergoing cataract surgery.

2.2 State of Armamentarium For Indication(s)

There are currently no products approved for staining the anterior lens capsule — — . Fluorescein sodium (FS) and indocyanine green (ICG) have each been used "off-label" to stain the lens capsule.

2.3 Availability of Proposed Product in the U.S.

Trypan blue as been used as a chemical agent for *in vivo* and *in vitro* testing and for the proposed indication. There are no reported safety issues.

2.4 Important Issues with Pharmacologically Related Products

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

2.5 Pre-submission Regulatory Activity

Trypan blue has been the subject of a "request for designation" to appropriately classify the regulatory status of the product. 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.

2.6 Other Relevant Background Information

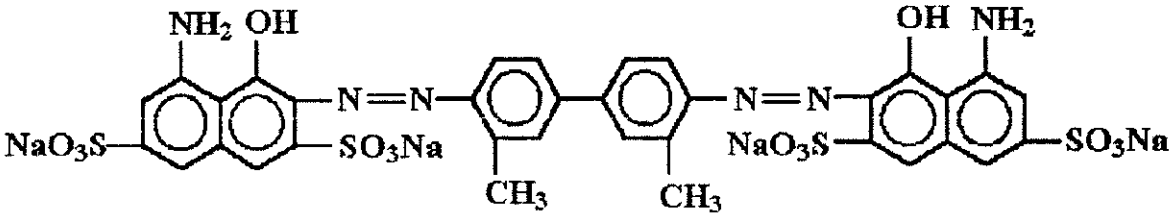
In Europe, Vision Blue obtained CE approval as a medical device Class IIa in 1999. Vision Blue is currently marketed in 30 countries and has never been withdrawn from marketing.

—

3 Significant Findings from Other Review Disciplines

Include here the relevant findings from the chemistry, microbiology (if applicable), and pharmacology/toxicology reviews. Do not include the results of the biometrics review. This should be discussed in the appropriate sections of the integrated efficacy review (and safety review, applicable).

3.1 Chemistry (and Product Microbiology, if applicable)



Formulation: Each milliliter of Vision Blue is made up of:

0.6 mg trypan blue
1.9 mg sodium mono-hydrogen orthophosphate ($Na_2HPO_4 \bullet 2H_2O$)
0.3 mg sodium di-hydrogen orthophosphate ($NaH_2PO_4 \bullet 2H_2O$)
8.2 mg sodium chloride

—

water for injection

The product is —

Intraocular Lens Interaction Studies

In a study of dye uptake in intraocular lenses (IOL), there was minimal dye uptake in silicone lens, slight uptake in PMMA lens and strong staining in acrylic lenses with trypan blue. (Fritz WL. *J Cataract Refract Surg* 2002; 28: 1034-1038.)

3.2 Animal 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 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

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

4.2 Tables of Clinical Studies

The following clinical studies with Vision Blue for staining the anterior capsule during cataract surgery have been conducted and published. The following abbreviations are used in the following tables: Trypan Blue (TB), Fluorescein sodium (FS), Indocynanine green (ICG), Rose Bengal (RB), Gentian violet (GV), Autologous blood (AB).

First Author	Journal	Number of patients treated with Test Product	Controls	Results
Suresh Pandey	J Cataract Refract Surg 2000; 26:1052-1059	4 TB 0.1%	FS 2% ICG 0.5%	Staining graded on a scale of 1-3 FS Avg: 1.5 TB Avg: 2 ICG Avg: 2.5
Liliana Werner	J Cataract Refract Surg 2000; 26:1060-1065	8 TB 0.1%	ICG 0.5% No dye	TB and ICG enhanced visualization of capsule in all cases
Huseyin Yetik	J Cataract Refract Surg 2002; 28:988-991	5 TB 0.1%	10 each of TB 0.05%, 0.025%, 0.0125%, 0.00625%	TB 0.1% staining good TB 0.5% staining good TB 0.025% staining good TB 0.0125% staining intermediate TB 0.00625% staining faint
Suresh Pandey	J Cataract Refract Surg 2000; 26:1066-1071	4 TB 0.1%	ICG 0.5%	TB and ICG enhanced visualization of capsule in all cases
VK Dada	J Cataract Refract Surg 2004; 30:326-333.	10 TB 0.1%	10 each of GV 0.001% ICG 0.5% FS 2% AB	Best visualization was achieved with TB, ICG and GV. Follow-up through 1 month revealed no complications.
Soosan Jacob	J Cataract Refract Surg 2002; 28:1819-1825	52 TB	None	Continuous curvilinear capsulorrhexis was accomplished in 96% of cases. The mean follow-up was 6 months. There were no complications.
Gerrit RJ Melles	J Cataract Refract Surg 1999; 25:7-9	30 TB 0.1%	None	All eyes stained. No stain visible at 24 hours. No evidence of toxicity at 12 months.
Kulin Kothari	Indian J Ophthalmol 2001:177-180	25 TB 0.1%	None	Capsulorrhexis completed in all cases. No adverse events through 3 months follow-up.
Jagjit Saini	J Cataract Refract	21 TB 0.1%	No dye	Continuous curvilinear

First Author	Journal	Number of patients treated with Test Product	Controls	Results
	Surg 2003:29:1733-1737	Pediatric Patients age 3-15, mostly under 5.		capsulorrhexis in 91.3% versus 73.6% of controls.
Tanuj Dada	J Cataract Refract Surg 2002:28: 575-576	10 TB	No dye	Continuous curvilinear capsulorrhexis completed in 100% of TB cases, 30% of no dye cases.
P Bhartiya	Br J Ophthalmolol 2002; 86:857-859.	11 TB 0.1%	None	Improved visualization of the anterior capsule and a complete capsulorrhexis could be performed in all eyes, in spite of corneal haze and/or corneal opacities.
AJ Singh	Eye (2003) 17, 567–570.	10 TB 0.06%	None	Continuous curvilinear capsulorrhexis was successfully and easily completed in all cases. Adequate contrast and visibility was reported in all cases. No complications. Histopathology performed. Trypan blue stains mostly in the basement membrane adjacent to the epithelial layer of the lens capsule with minimal laminar staining in the superficial basement membrane. The lens cortex does not stain.
Bart TH vanDooren	J Cataract Refract Surg 2002: 28:574-575	25 TB	Contralateral eye	No difference in endothelial cell densities at 12 months. No difference in Visual Acuity or in aspect of clinical examination.
Mehmer Baykara	J Cataract Refract Surg 2002; 28:1832-1835.	10 TB 0.1%	None	Cases of ocular trauma. Capsulorrhexis successful. No adverse events.
MS Norn	Acta Ophthalmologica 1971; 49: 725-733	120 TB 0.1%	10 RB 10 FS 88 No dye	No difference in safety between trypan blue treated eyes and eyes undergoing cataract surgery without dye.

Use in Retinal Surgery for identifying Epiretinal membranes

EJ Feron	Arch Ophthalmol 2002; 120:141-144.	6 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.
Francisco A Teba	Ophthalmology 2003; 110: 2409-2412	50 TB 0.2%	None	Epiretinal membranes can be identified.

4.3 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 all ocular studies using trypan blue was conducted. A total of 284 articles were identified in the search. The majority of the articles refer to the use of trypan blue as a diagnostic aid to evaluate the cornea. All available abstracts were reviewed. All articles which could be identified as relevant for the proposed indication were reviewed.

4.4 Data 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.

4.5 Compliance with Good Clinical Practices
There is no evidence to suggest that the clinical trials were not conducted in compliance with good clinical practices.

4.6 Financial Disclosures
Not applicable. The applicant has not conducted any independent clinical studies. Gerrit RJ Melles has an acknowledged financial interest as a result of a patent for the use of trypan blue.

5 Clinical Pharmacology

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

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

5.3 Exposure-Response Relationships
Not applicable.

6 Integrated Review of Efficacy

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

6.2 General Discussion of Endpoints
The proposed claim is the . The need to visualize the anterior capsule is based on the need to complete a continuous curvilinear

capsulorrhexis. The ability to complete a continuous curvilinear capsulorrhexis has been shown to decrease the risk of vitreous loss and dropped nuclei. The application references the paper by Gimbel HV and Neuhann T. Development, advantages, and methods of the continuous circular capsulorrhexis technique. *J Cataract Refract Surg* 1990; 16:31-37 to support the need to visualize the anterior capsule to complete the procedure. The agency has previously accepted the need to visualize the anterior lens capsule in its approval of ophthalmic drug products which inhibit intraoperative miosis. It is self evident that it is necessary to see the capsule to be able to manipulate it and remove a portion of it. If a good red reflex is present, staining of the capsule is not necessary. In cases where the lens is opaque, staining the capsule without staining the underlying cortex is necessary to manipulate and remove a portion of the capsule.

6.3 Efficacy Findings

The published clinical studies demonstrate that concentrations of trypan blue between 0.025% and 0.3%, inclusive, are 100% effective in staining the anterior capsule. All published studies support this indication. Published studies which demonstrate superiority of trypan blue over fluorescein sodium have not been submitted.

6.4 Clinical Microbiology

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

6.5 Efficacy Conclusions

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. The lens capsule stains. Trypan blue 0.06% is 100% effective in staining the anterior capsule. Dose ranging studies demonstrate that concentrations between 0.025% and 0.3%, inclusive, are effective in staining the anterior capsule. No additional information is needed to support the efficacy.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

There are no reported deaths in any of the published studies, with the exception of the study which includes an 8 year follow-up period after administration of trypan blue. The mean age at the start of study was 70 years old and some people died of various causes during the 8 year follow-up period.

7.1.2 Other Serious Adverse Events

Only two serious adverse events has been reported. These two events were the permanent discoloration of hydrogel intraocular lenses (IOL) necessitating the replacement of the lenses. (Werner, L et al. Permanent blue discoloration of a hydrogel intraocular lens by intraoperative trypan blue. *J Cataract Refract Surg* 2002; 28:1279-1286.) The applicant reports being unable to reproduce these events *in vitro*.

7.1.3 Dropouts and Other Significant Adverse Events
Treatment is a single exposure during cataract surgery so there is no opportunity to discontinue due to an adverse event. The only adverse events reported have been inadvertent staining. These occurrences of staining have included hydrogel intraocular lenses, the posterior capsule and the vitreous face. The discoloration of an IOL appears to be permanent. Staining of the posterior lens capsule or staining of the vitreous face is self limited lasting up to one week. (Birchall W et al. Inadvertent Staining of the Posterior Lens Capsule With Trypan Blue Dye During Phacoemulsification. *Arch Ophthalmol* 2001; 119:1082-3.

7.1.4 Other Search Strategies
A search of the literature has not identified any adverse events except inadvertent staining.

7.1.5 Common Adverse Events
There are no common adverse events. Only inadvertent staining has been reported.

7.1.6 Less Common Adverse Events
None known.

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

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

7.1.9 Electrocardiograms (ECGs)
No evaluation of ECG data has been performed. It is not considered necessary for the evaluation of this drug product.

7.1.10 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.

7.1.11 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.

7.1.12 Special Safety Studies
A long term study was conducted to evaluate the safety of the eye after the anterior chamber is filled with trypan blue during cataract surgery. The average age of the patients at the start was 70 years old. Pre-operative evaluations were performed on 47 patients who underwent cataract extraction with trypan blue administration to the anterior chamber. All but one (n=24), patients living eight years later were examined. The missing patient had moved and left no forwarding

address. There was no significant change in cornea thickness, specular microscopy, or intraocular pressure. Visual acuity was 20/40 or better in 13 of the eyes. Vision was impaired due to macular degeneration or pre-surgery conditions in the remaining patients.

7.1.13 Withdrawal Phenomena / Abuse Potential
There is no potential to develop a withdrawal phenomena or abuse potential.

7.1.14 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.

7.1.15 Overdose Experience
There is no potential for overdose of this drug product.

7.1.16 Post-marketing Experience
There are no additional reports of adverse experiences except as noted earlier in this review.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Extent and Adequacy of Overall Clinical Experience
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, one year after drug exposure. Follow-up has been continued after drug exposure in some cases longer than the average expected lifetime of the patients.

7.2.2 Adequacy of Special Animal and/or In vitro Testing
Preclinical testing was adequate to establish a testing pattern for the human studies.

7.2.3 Adequacy of Routine Clinical Testing
Clinical testing was adequate to estimate the safety of the drug product.

7.2.4 Adequacy of 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.

7.2.5 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by New Drug; Recommendations for Further Study

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

7.2.6 Assessment of Quality and Completeness of Data
The data necessary to make a determination of safety is sufficiently complete.

7.3 Summary of Selected Drug-Related Adverse Events
Unanticipated staining is the only reported adverse event.

7.4 General Methodology
7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence
Not applicable due to the limited number of events.

7.4.2 Explorations for Predictive Factors
Not applicable due to the limited number of events.

7.4.3 Causality Determination
Unanticipated staining is definitely related to the drug product.

7.5 Safety Conclusions
The drug product is safe when administered as proposed in the package insert (

. Potential inadvertent staining may occur if the drug product is not washed out and either an intraocular lenses capable of absorbing the dye is introduced or a break in the posterior capsule occurs.

8 Additional Clinical Issues
8.1 Dosing Regimen and Administration
A few drops of the drug product should be administered intracamerally onto the anterior capsule under an air bubble and then rinsed out with an irrigating solution. This dosing regimen is well established in clinical studies.

8.2 Drug-Drug Interactions
There are no known drug-drug interactions. The use of a viscoelastic substance in the anterior chamber may limit staining of the anterior capsule due to the physical barrier caused by the viscoelastic substance.

8.3 Special Populations
There are no known differences between any segment of the population. The drug product is not recommended to be used in pregnant women because the drug product is teratogenic. As a general rule, cataract extraction is not expected to be conducted in pregnant women. Pediatric patients have been studied in adequate and well controlled studies.

8.4 Pediatrics
Pediatric patients have been studied in adequate and well controlled studies. The drug product was shown to be effective.

8.5 Advisory Committee Meeting
Not applicable. No Advisory Committee Meeting is planned.

8.6 Literature Review
The entire review is based on literature studies.

8.7 Other Relevant Materials
There is no other none relevant material.

9 Overall Assessment

9.1 Conclusions on Available Data
The clinical data is considered sufficient to support approvability of the application for the use as an aid in ophthalmic surgery on the front eye segment during cataract extraction.

9.2 Recommendation on Regulatory Action
NDA 21-670 is recommended for approval from a clinical prospective with the labeling identified in this review. The indication as described in the labeling as proposed in this review is supported by literature studies.

9.3 Recommendation on Post-Marketing Actions
9.3.1 Risk Management Activity
No risk management activities recommended.

9.3.2 Required Phase 4 Commitments
No phase 4 studies are recommended.

9.3.3 Other Phase 4 Requests
No other phase 4 requests are recommended.

9.4 Labeling Review
Include here a summary of the major changes needed in the applicant's proposed label. Refer to appendix for a line by line review.

9.5 Comments to Applicant
It is recommended that the labeling be revised to conform with 21 CFR 201.56 and 21 CFR 201.57.

10 APPENDIX

10.1 Review of Individual Study Reports

Not necessary. Specific details of the individual studies are listed in the table in section 4.2. All studies consisted of administration of a few drops of trypan blue intracamerally and evaluation of the capsule after washing out the trypan blue. Except as noted above, no paper identified any adverse events, and no paper identified failure of trypan blue in concentrations greater than 0.025% to adequately stain the anterior capsule.

10.2 Line-by-line Labeling Review

The submitted package insert is listed below. The proposed labeling is not consistent with 21 CFR 201.57. The labeling should be re-submitted in a manner consistent with 21 CFR 201.57.

VisionBlue (trypan blue ophthalmic solution)

\ Draft Labeling Page(s) Withheld

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Wiley Chambers
4/9/04 03:07:46 PM
MEDICAL OFFICER

William Boyd
4/12/04 07:16:26 AM
MEDICAL OFFICER

of NDA 21-670

Application Type	NDA
Application Number	NDA 21-670
Submission Code	N-000
Letter Dates	December 3 & 10, 2004
Reviewer Name	Wiley A. Chambers, MD
Review Completion Date	December 13, 2004
Established Name	Trypan Blue Ophthalmic Solution
(Proposed) Trade Name	Vision Blue
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
Dosing Regimen	A few drops (0.1 to 0.3 mL) of Vision Blue are administered intracamerally after filling the anterior chamber with air.
Indication	Capsular staining
Intended Population	Patients undergoing cataract surgery
Submitted	Revised Labeling and Safety Update

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Approvability

NDA 21-670 is recommended for approval from a clinical prospective.

1.2 Recommendation on Post-marketing Actions

1.2.1. Risk Management Activity

No risk management activities recommended.

1.2.2 Required Phase 4 Commitments

No additional Phase 4 studies are recommended.

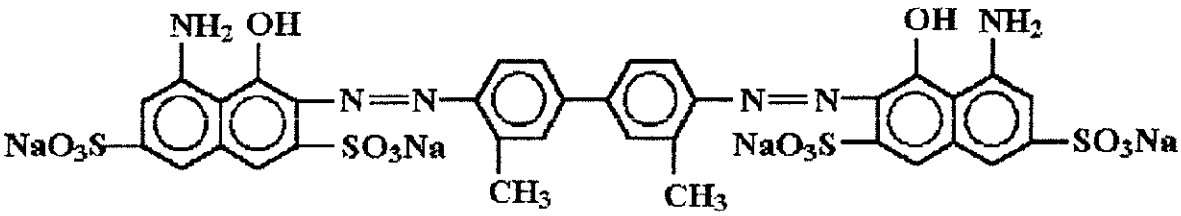
1.2.3 Other Phase 4 Requests

No additional Phase 4 studies are recommended.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Vision Blue (trypan blue ophthalmic solution)



Trypan blue is a blue di-azo dye. It is a symmetrical molecule with three parts connected by two azo bonds. The molecular weight is 961. The empirical formula is: $C_{34}H_{23}N_6O_{14}S_4Na_4$. It is water soluble. A few drops (0.1-0.3 mL) are administered by intracameral injection, usually under an air bubble, and then rinsed out of the anterior chamber with an ophthalmic irrigating solution.

The proposed indication is for staining of the anterior lens capsule – 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.

Vision Blue has been marketed in Europe since 1999 for the same indication proposed in this application. The applicant reports over – units have been used during cataract surgery.

Approximately 350 patients are reported on in this review from over 10 separate studies.

1.3.2 Efficacy

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. The lens capsule stains. Trypan blue 0.06% is 100% effective

in staining the anterior capsule. Dose ranging studies demonstrate that a concentration of 0.025% or higher is effective in staining the anterior capsule.

1.3.3 Safety

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 30,000 corneas have been screened and transplanted after administration of trypan blue, 0.3%. This dose is approximately 5 times the proposed dose. In donor corneal grafts, there are no documented adverse effects.

1.3.3.1 Safety Update- December 2004

Submitted Safety update NDA 21-670 VisionBlue® December 2004

1. **Significant changes or findings in the safety profile**

There are no significant changes or findings in the safety profile.

2. **Substantial change in the incidence of common adverse events**

There are no substantial changes or common adverse events reported.

3. **Summary of worldwide experience on the safety**

Vision Blue has been marketed since 1999 as a device for the same indication proposed in this drug application. The product VisionBlue® has not been sold as a drug product yet.

The marketing of VisionBlue® in syringes (as opposed to vials) began in Europe in May 2004. - boxes of 10 syringes were sold during the month of May 2004. In the period June to November 2004, only - boxes of 10 vials were sold. The supply and sale of product sold in vials has ceased.

Although the total amount of VisionBlue® marketed is sufficient for over - eye surgeries, no complaint or other information about adverse events has been received by DORC International since May. Twelve reports of possible deviations have been filed; these reports have not resulted in an acknowledged complaint by DORC International bv.

DORC Conclusion: No new information on the use of VisionBlue® has been received that may lead to any change in the statement of contraindications, warnings and adverse reactions in the labeling.

Reviewer's Comments: *Concur. No new safety information.*

1.3.4 Dosing Regimen and Administration

A few drops (0.1 to 0.3 mL) of Vision Blue are administered intracamerally after filling the anterior chamber with air. Staining occurs within seconds and the anterior chamber is then irrigated with an ophthalmic irrigating solution to remove any excess dye. The majority of the stained capsule is removed as part of the cataract operation.

1.3.5 Drug-Drug Interactions

There are no known drug-drug interactions. The use of a viscoelastic substance in the anterior chamber may limit staining of the anterior capsule due to the physical barrier caused by the viscoelastic substance.

1.3.6 Special Populations

There are no known differences between any segments of the population. Pediatric patients have been studied in an adequate and well controlled study.

9 OVERALL ASSESSMENT

9.1 Conclusions on Available Data

The clinical data is considered sufficient to support approvability of the application for the use as an aid in ophthalmic surgery on the front eye segment during cataract extraction.

9.2 Recommendation on Regulatory Action

NDA 21-670 is recommended for approval from a clinical prospective.

9.3 Recommendation on Post-Marketing Actions

9.3.1 Risk Management Activity

No risk management activities recommended.

9.3.2 Required Phase 4 Commitments

No phase 4 studies are recommended.

9.3.3 Other Phase 4 Requests

No other phase 4 requests are recommended.

9.4 Labeling Review

3 Draft Labeling Page(s) Withheld

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Wiley Chambers
12/13/04 02:06:21 PM
MEDICAL OFFICER

William Boyd
12/13/04 02:13:56 PM
MEDICAL OFFICER