CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-670

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**Clinical Pharmacology & Biopharmaceutics (HFD 860/870/880) Tracking/Action Sheet for Formal/Informal Consults**

From: Edward Dennis Bashaw, Pharm.D.			**To: DOCUMENT ROOM (LOG-IN and LOG-OUT) Please log-in this consult and review action for the specified IND/NDA submission**	
DATE: 3/10/04	IND No Serial No.:	NDA No. 21-670	DATE OF DOCUMENT **12/31/03**	
NAME OF DRUG **VisionBlue (Trypan Blue)**	PRIORITY CONSIDERATION **1-P**		Date of informal/Formal Consult: **3/10/04**	

☐ PRE-IND	☐ DISSOLUTION/IN-VITRO RELEASE	☐ FINAL PRINTED LABELING
☐ ANIMAL to HUMAN SCALING	☐ BIOAVAILABILITY STUDIES	☐ LABELING REVISION
☐ IN-VITRO METABOLISM	XX IN-VIVO WAIVER REQUEST	☐ CORRESPONDENCE
☐ PROTOCOL	☐ SUPAC RELATED	☐ DRUG ADVERTISING
☐ PHASE II PROTOCOL	☐ CMC RELATED	☐ ADVERSE REACTION REPORT
☐ PHASE III PROTOCOL	☐ PROGRESS REPORT	☐ ANNUAL REPORTS
☐ DOSING REGIMEN CONSULT	☐ SCIENTIFIC INVESTIGATIONS	☐ FAX SUBMISSION
☐ PK/PD- POPPK ISSUES	☐ MEETING PACKAGE (EOP2/Pre-NDA/CMC/Pharmacometrics/Others)	☐ OTHER *(SPECIFY BELOW)*: [ ]
☐ PHASE IV RELATED		

REVIEW ACTION

☐ NAI (No action indicated)	☐ Oral communication with	☐ Formal Review/Memo (attached)
☐ E-mail comments to:	Name: [ ]	☐ • See comments below
☐ Medical ☐ Chemist ☐ Pharm-Tox	☐ Comments communicated in meeting/Telecon. see meeting minutes dated: [ ]	☐ • See submission cover letter
☐ Micro ☐ Pharmacometrics ☐ Others		XX OTHER *(SPECIFY BELOW)*:
(Check as appropriate and attach e-mail)		Acceptable from Clinical Pharmacology perspective.

REVIEW COMMENT(S)

XX **NEED TO BE COMMUNICATED TO THE SPONSOR** ☐ **HAVE BEEN COMMUNICATED TO THE SPONSOR**

Background

Trypan blue is a blue dye that has been used historically as both a biological staining agent and as a dye in the clothing industry. Since the 1970s trypan blue 0.2% has been injected into the anterior chamber of the eye during surgery, to evaluate the corneal endothelium after intracapsular cataract extraction. VisionBlue™ was approved in Europe in 1999 as a device and, according to the sponsor, over — units have been used with few side effects being noted.

The clinical benefit of VisionBlue™ is the visualization of the capsulorhexis[1] during surgery. Improper visualization is known to result in an increased risk of capsule related complications, such as a radial tear, vitreous loss, or dropped nucleus. The use of VisionBlue™ therefore aids the efficacy and safety of cataract surgical procedures. It is estimated that for mature cataract surgery, in which the lens capsule is most often invisible to the surgeon, capsule staining may reduce the risk of complications by 50%.

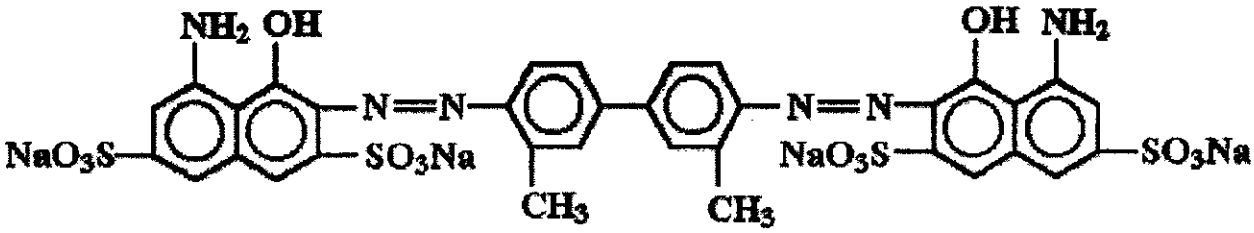
Formulation

The proprietary name of the product is VisionBlue™. Each milliliter of VisionBlue™ is made up of the following

0.6 mg trypan blue
1.9 mg sodium mono-hydrogen orthophosphate
0.3mg sodium di-hydrogen orthophosphate
8.2mg sodium chloride

Water for injection q.s. to volume

Trypan blue has the following chemical structure:



Chemically it is, sodium ditolyldisazobis-8-amino-1-naphthol-3,6-disulfonate ($C_{34}H_{24}N_6Na_4O_{14}S_4$) with a molecular weight of 960.83. VisionBlue™is supplied in —

Clinical Use

VisionBlue™ is administered intraoperatively to provide visible contrast to aid in the visualization of the anterior lens capsule when performing the capsulorhexis in cataract surgery.

Prior to administration, the drug product is drawn up into a syringe at full strength. After filling the anterior chamber completely with air, VisionBlue™,(trypan blue) is introduced into the anterior chamber by placing a few drops (estimated 0.1 to 0.3 mL) directly onto the anterior lens capsule. Sufficient staining is achieved as soon as the dye contacts the lens capsule

The anterior chamber is then irrigated to remove all excess dye. During phacoemulsification[2] the anterior chamber is also continuously irrigated, thereby further removing any excess dye. The larger part of the stained lens capsule is excised and removed from the eye (to enable removal of the cataractous lens mass). Any residual staining of the lens capsule fades within 5 to 15 minutes.

Waiver Request

The current NDA submission contains no in vivo biopharmaceutic information. The sponsor is basically requesting a waiver of in vivo biostudies under the "good cause" provisions of 21CFR320.22 (e). They contend that given the method of use, the exposure of drug to the systemic circulation would be such that it would be undetectable. They also raise the issue that after administration, excess dye is flushed away almost immediately and that ultimately the majority of the stained material (the anterior lens capsule) is removed as part of the procedure.

Labeling

At the present time the sponsor has not submitted any labeling for this product beyond the current European label. Appropriate labeling should be submitted.

Recommendation

Given the fact that this product is indicated for topical administration in cataract surgery, at low doses with physical removal of excess "drug", a waiver of in vivo biostudies under the "good cause" provisions of 21CFR320.22(e) is granted.

SIGNATURE OF REVIEWER: _____	Date _____
SIGNATURE OF TEAM LEADER: _____	Date _____
CC.: HFD # [880]; TL: [Selen]; DD: [Lazor]	Project Manager: _____ Date _____

[1] Capsulorhexis is the most commonly performed technique to create an anterior capsule opening during cataract surgery

Phacoemulsification refers to a method of cataract surgery in which energy is delivered to the lens by a probe inserted through a small self-sealing wound is used to break up the lens and allow its removal as small fragments. The probe is usually an ultrasonic probe, although laser probes also exist.

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/s/

Dennis Bashaw
4/1/04 09:55:11 AM
BIOPHARMACEUTICS

Arzu Selen
4/1/04 07:16:52 PM
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