

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203510Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	March 20, 2013
From	William M. Boyd, M.D.
Subject	Cross-Discipline Team Leader Review
NDA#	203510
Applicant	Paragon Biotech, Inc.
Date of Submissions	September 20, 2012
PDUFA Goal Date	March 21, 2012
Proprietary Name / Established (USAN) names	Phenylephrine Hydrochloride Ophthalmic Solution, 2.5% and 10%
Dosage forms / Strength	Topical ophthalmic solution, 2.5% and 10%
Proposed Indication(s)	Indicated to dilate the pupil
Recommended:	Recommended for Approval

1. Introduction

NDA 203510 has been submitted as a 505(b)(2) application. Phenylephrine is an alpha-1 adrenergic receptor agonist that has been used for more than 70 years to dilate the pupil in ocular diagnostic, therapeutic and surgical procedures due to its vasoconstrictor and mydriatic action. Phenylephrine was included in the OTC monograph for use as an ophthalmic vasoconstrictor for relief of ocular redness at concentrations of between 0.08% and 0.2%.

NDA 203-826 phenylephrine hydrochloride injection, USP was approved December 12, 2012, and is indicated to increase blood pressure in acute hypotensive states, such as shock and peri-operative hypotension.

Phenylephrine hydrochloride ophthalmic solutions, 2.5% and 10%, are currently being marketed and supplied in the US for use as a mydriatic without approved new drug applications.

2. Background

NDA 203510, phenylephrine hydrochloride ophthalmic solution, 2.5 % and 10% was originally submitted October 19, 2011, and was received on October 21, 2011.

On December 16, 2011, a REFUSAL TO FILE letter was sent that noted:

After a preliminary review, we find your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 314.101(d) for the following reasons:

The NDA does not provide sufficient stability data to establish the stability profile of the drug product over the requested shelf-life. Per ICH Q1A (R2), 12-month long-term and 6-month accelerated stability data for three batches should be provided for us to be able to evaluate the stability of the drug product over the requested shelf-life.

Release data for the two exhibit batches, one each for the two strengths, 2.5% and 10%, have been provided in the NDA but the submission does not provide stability data for these batches. Stability data submitted for the historical batches are inadequate since they were only tested for a few quality attributes. Furthermore, the long-term and accelerated data were generated from different batches which limits evaluating stability of any one batch stored under different conditions.

Additionally, the NDA lacks data on freeze-thaw and weight loss studies.

In addition, we request that you submit patent certifications for the listed drugs to which you refer in your application.

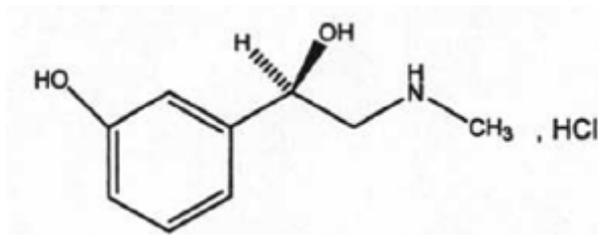
On October 21, 2012, Paragon Biotech, Inc. re-submitted NDA 203510 for the use of phenylephrine hydrochloride ophthalmic solution 2.5% and 10% in adults and phenylephrine hydrochloride ophthalmic solution 2.5% in infants to dilate the pupil.

Consistent with the recently issued FDA Guidance for FDA Staff and Industry entitled "Marketed Unapproved Drugs - Compliance Policy Guide: See 440.100 Marketed New Drugs Without Approved NDAs or ANDAs" dated September 19, 2011, Paragon submitted this NDA to help address this unapproved drug product being supplied and marketed as an unapproved product.

NDA 203510 was granted a Priority review at filing to fill an unmet medical need.

3. Product Quality

Chemical structure of phenylephrine hydrochloride



Chemical Name: C₉H₁₃NO₂-HCl

Contains:

Active: phenylephrine hydrochloride 25 mg (2.5%); phenylephrine hydrochloride 100 mg (10.0%)

Preservative: benzalkonium chloride 0.01%

Inactives: sodium phosphate monobasic, sodium phosphate dibasic; boric acid, water for injection. Hydrochloric acid and/or sodium hydroxide may be added to adjust pH (6.0-6.4)

From the original Product Quality Review:

This NDA is recommended for approval from the CMC perspective.

This is a Type 7 NDA for a drug already marketed without an approved NDA. These solutions have been manufactured by the drug product manufacturer, (b) (4), since 2001 except that the previously manufactured solutions had a (b) (4). The solutions described in this NDA have (b) (4)

The product is a sterile, (b) (4), preserved, multi-use solution in opaque white LDPE bottles fitted with dropper tips and caps. The 2.5% solution contains 15 mL per bottle and the 10% solution contains 5 mL per bottle.

The two solutions are identical except that the 10% solution does not contain boric acid because the high concentration phenylephrine hydrochloride (b) (4)

DRUG SUBSTANCE SPECIFICATIONS:

Table 1: Specifications for Phenylephrine HCl

Test	Acceptance Criteria	Supplier Analytical Method	Sponsor Analytical Method
Description	White or practically white (b)(4) powder or fine powder	310-QT-862	USP
Solubility	Freely soluble in water and alcohol	310-QT-981	USP
Identification A ¹	IR absorbance spectrum matches reference standard	310-QT-863	USP
Identification B ¹	Responds to chloride test	310-QT-864	USP
Melting Range ¹	Between 140° and 145°C	310-QT-865	USP
Specific Rotation ¹	Between -42° and -47.5°	310-QT-866	USP
Loss on Drying ¹	NMT (b)(4)	310-QT-867	USP
Residue on Ignition ¹	NMT (b)(4)	310-QT-868	USP
		(b)(4) 310-QT-869	USP
		310-QT-870	USP
		310-QT-871	USP
		310-QT-872	USP
		310-QT-873	USP
		310-QT-1298	NA
Test	Acceptance Criteria	Supplier Analytical Method	Sponsor Analytical Method
Impurities ²	(b)(4)	310-QT-1323	NA

¹ USP Test NMT=Not More Than; NLT = Not Less Than; NA = Not Applicable

² Not performed by Sponsor

DRUG PRODUCT COMPOSITION:

Table 1: Phenylephrine HCl Ophthalmic Solution, 2.5% and 10% Quantitative Composition

Component	2.5% Formulation Quantity (%w/v)	10% Formulation Quantity (%w/v)	Function	Quality Standard
Phenylephrine HCl	2.5%	10%	Active Ingredient	USP
Sodium Phosphate Monobasic, (b) (4)	(b) (4)			USP
Sodium Phosphate Dibasic, (b) (4)				USP
Boric Acid				USP
Benzalkonium Chloride	0.01%	0.01%	Antimicrobial preservative	USP
Sodium Hydroxide	As needed	As needed	pH adjustment	USP
Hydrochloric Acid	As needed	As needed	pH adjustment	USP
Water for Injection	Q.S.	Q.S.	(b) (4)	USP

DRUG PRODUCT REGULATORY SPECIFICATIONS:

Table 1: Quality Control Specifications

Test	Limit	Method
Description	Clear, colorless to yellowish solution	TMQC-205
Identification A (TLC)	Reddish orange spot from test solution compares to standard solution	TMQC-205
Identification B (HPLC Retention Time)	Retention time for major peak in sample from assay corresponds to standard	TMQC-205
pH at 25°C	4.0 – 7.5	TMQC-205
Osmolality	2.5% - 450 – 550 mOsm/kg H ₂ O 10% - 950 – 1050 mOsm/kg H ₂ O	TMQC-205
Assay Phenylephrine HCl	90% – 110% label claim	TMQC-205
Assay Benzalkonium Chloride	80% – 120% label claim	TMQC-205
Related Substances: Specified Identified Impurity (b) (4) Specified Identified Impurity (b) (4) Specified Unidentified Impurity (b) (4) Largest Individual Unknown Impurity (b) (4) Total Impurities (b) (4)	(b) (4)	TMQC-205
Particulate Matter (b) (4)	NMT (b) (4) NMT (b) (4) NMT (b) (4)	TMQC-29
Minimum Fill	Meets USP requirements <755>	TMQC-205
Test	Limit	Method
Deliverable Volume	Meets USP requirements <698>	TMQC-205
Sterility	Meets USP requirements <71>	TMQC-205
Bacterial Endotoxins	(b) (4) USP <85>	TMQC-205

INSPECTIONS:

An "Acceptable" site recommendation from the Office of Compliance has been made.

**FDA CDER EES
 ESTABLISHMENT EVALUATION REQUEST
 DETAIL REPORT**

Application:	NDA 203510/000	Action Goal:	
Stamp Date:	21-OCT-2011	District Goal:	22-MAY-2013
Regulatory:	21-JUL-2013		
Applicant:	PARAGON BIOTECK 11501 SOUTHWEST PACIFIC HWY STE 201 TIGARD, OR 97223	Brand Name:	phenylephrine hydrochloride
Priority:	7	Estab. Name:	
Org. Code:	590	Generic Name:	phenylephrine hydrochloride
Application Comment:		Product Number; Dosage Form; Ingredient; Strengths	001; SOLUTION; PHENYLEPHRINE HYDROCHLORIDE; 2.5% 002; SOLUTION; PHENYLEPHRINE HYDROCHLORIDE; 10%
FDA Contacts:	A. CUFF	Project Manager	(HF-01) 3017964061
	G. LUNN	Review Chemist	3017961701
	B. SHANMUGAM	Team Leader	3017961457
Overall Recommendation:	ACCEPTABLE	on 03-DEC-2012	by R. SAFAAI-JAZI () 3017964463
	PENDING	on 24-SEP-2012	by EES_PROD
	ACCEPTABLE	on 10-AUG-2012	by EES_PROD
	PENDING	on 07-NOV-2011	by EES_PROD
	PENDING	on 07-NOV-2011	by EES_PROD

**FDA CDER EES
 ESTABLISHMENT EVALUATION REQUEST
 DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)
 (b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE OTHER TESTER
 FINISHED DOSAGE MANUFACTURER
 FINISHED DOSAGE RELEASE TESTER
 FINISHED DOSAGE STABILITY TESTER

Establishment Comment: (b) (4) THE DRUG PRODUCT MANUFACTURER, THEY WILL ALSO PERFORM STABILITY TESTING (b) (4)
 2011 by A. CUFF (HF-01) 3017964061

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE
 STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	07-NOV-2011				CUFFA
OC RECOMMENDATION	09-NOV-2011			ACCEPTABLE BASED ON PROFILE	TOULOUSEM
SUBMITTED TO OC	02-OCT-2012				CUFFA
SUBMITTED TO DO	09-OCT-2012	10-Day Letter			SAFAAJAZIR
DO RECOMMENDATION LAST EI COMPLETED ON (b) (4) AND CLASSIFY BY NYK CBR AS VAI ON 10/01/12.	31-OCT-2012			ACCEPTABLE BASED ON FILE REVIEW	KGONZALE
OC RECOMMENDATION	01-NOV-2012			ACCEPTABLE DISTRICT RECOMMENDATION	SAFAAJAZIR
SUBMITTED TO OC	07-NOV-2011				CUFFA
SUBMITTED TO DO	09-NOV-2011	10-Day Letter			TOULOUSEM
DO RECOMMENDATION LAST EI COVERED (b) (4) PROFILE CLASS AND WAS VAI(11/2010).	25-NOV-2011			ACCEPTABLE BASED ON FILE REVIEW	KGONZALE
OC RECOMMENDATION	29-NOV-2011			ACCEPTABLE DISTRICT RECOMMENDATION	STOCKM
SUBMITTED TO OC	02-OCT-2012				CUFFA
SUBMITTED TO DO	03-OCT-2012	10-Day Letter			SAFAAJAZIR
DO RECOMMENDATION LAST EI COMPLETED ON (b) (4) WAS CLASSIFY VAI ON 10/01/12 BY NYK CBR.	31-OCT-2012			ACCEPTABLE BASED ON FILE REVIEW	KGONZALE
OC RECOMMENDATION	01-NOV-2012			ACCEPTABLE DISTRICT RECOMMENDATION	SAFAAJAZIR

**FDA CDER EES
 ESTABLISHMENT EVALUATION REQUEST
 DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)
 (b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
 DRUG SUBSTANCE RELEASE TESTER
 DRUG SUBSTANCE STABILITY TESTER

Establishment Comment: (b) (4) IS THE DRUG SUBSTANCE SUPPLIER, WILL PERFORM STABILITY ON THE DRUG SUBSTANCE AS WELL AS RELEASE TESTING AND MANUFACTURING. (b) (4) by A. CUFF (HF-01) 3017964061
Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	07-NOV-2011				CUFFA
SUBMITTED TO DO	09-NOV-2011	GMP Inspection			TOULOUSEM
ASSIGNED INSPECTION TO IB	23-NOV-2011	GMP Inspection			PHILPYE
INSPECTION PERFORMED	(b) (4)				IRIVERA
INSPECTION SCHEDULED	(b) (4)				IRIVERA
DO RECOMMENDATION	10-AUG-2012			ACCEPTABLE	BRYKMANR
				BASED ON FILE REVIEW	
OC RECOMMENDATION	10-AUG-2012			ACCEPTABLE	STOCKM
				DISTRICT RECOMMENDATION	
SUBMITTED TO OC	02-OCT-2012				CUFFA
SUBMITTED TO DO	03-OCT-2012	10-Day Letter			SAFAAIJAZIR
PROFILE STILL INITIAL					
UNDER REVIEW	13-OCT-2012				PHILPYE
DO RECOMMENDATION	24-NOV-2012			ACCEPTABLE	PHILPYE
				INSPECTION	
OC RECOMMENDATION	03-DEC-2012			ACCEPTABLE	SAFAAIJAZIR
				DISTRICT RECOMMENDATION	

POSTMARKETING COMMITMENT:

The following post-marketing commitment was recommended by ONDQA:

Evaluate leachables present in the drug product: Analyze drug product that has been stored 6 months at accelerated (25C/60% RH) and 24 months long-term (refrigerated) storage conditions for the presence of leachables using a screening analytical method. Use an appropriate control solution for this analysis. Submit a report with numerical data to show the amount of leachables present, if any.

A second postmarketing commitment (PMC) was originally proposed (see Medical Officer's review, Section 4.1), but after internal discussion between OND and ONDQA, this evaluation of chiral purity of the drug product was not pursued as a PMC.

4. Nonclinical Pharmacology/Toxicology

From the original Pharmacology/Toxicology Review:

Approval is recommended.

This NDA is being submitted as a 505(b)2 application.

On the basis of the well established use of phenylephrine hydrochloride, the nonclinical safety information is largely based on the comprehensive toxicology testing conducted on phenylephrine hydrochloride by the National Toxicology Program in 1987.

No new clinical or nonclinical studies were conducted.

In 12-week repeated-dose studies, the approximate lethal daily dose was 300 mg/kg for male rats and 1,400 mg/kg for male mice (139-fold and 334-fold, respectively, the recommended maximal ocular doses based on body surface area). Target tissues identified included the eyes in both species, the testes and seminal vesicles in male rats, and ovaries in female rats. At the no observed adverse effect level (NOAEL), the safety margins for these findings are at least 555-fold and 139-fold the recommended maximal ocular dose at 2.5% and 10%, respectively, based on body surface area.

Phenylephrine hydrochloride showed no evidence of carcinogenicity in rats or mice. Several non-neoplastic lesions considered related to phenylephrine hydrochloride were observed in the liver (both species), prostate (rats), and lungs (rats). Based on body surface area, the non-neoplastic findings in the rat (no NOAEL) were observed at 44-fold and 11-fold, the recommended maximal ocular dose at 2.5% and 10%, respectively. The NOAEL in mice was 122-fold and 31-fold the recommended maximal ocular dose at 2.5% and 10%, respectively.

Phenylephrine given to pregnant rabbits during the last third of gestation produced a decrease in fetal weight and the onset of early labor at a dose 3.69-fold and 0.93-fold the recommended maximal ocular dose at 2.5% and 10%, respectively.

In sheep, phenylephrine administered during the third trimester depressed uterine blood flow and maternal heart rate and increased maternal mean arterial blood pressure at a dose 1-fold and 0.25-fold the recommended maximal ocular dose at 2.5% and 10%, respectively. In the fetus, it produced acidosis and hypoxemia.

Phenylephrine hydrochloride was not mutagenic in bacteria (*Salmonella typhimurium* strains) with or without metabolic activation. At nearly toxic doses, the evidence for mutagenicity was equivocal in the mouse lymphoma L5178Y/TK+/- assay in incubations without metabolic activation. Phenylephrine induced sister chromatid exchanges in CHO cells.

Except for the findings of decreased fetal body weight and the onset of early labor in rabbits, and maternal hypertension and reduced uterine blood flow and subsequent oxygen delivery to the fetus in the sheep, the data support low potential for similar systemic adverse effects to be observed in humans following treatment with up to 3 drops of phenylephrine 2.5% or 10%. It must be considered that the actual safety margins are expected to be higher, as the intended dosing in humans is for only a single day and 100% systemic absorption after ocular administration is not expected. Since this data is not consistent with human data as described in the NDA for systemic use of phenylephrine, it will not be included in the labeling.

5. Clinical Pharmacology/Biopharmaceutics

From the original Clinical Pharmacology Review:

The office of Clinical Pharmacology, Division of Clinical Pharmacology IV has reviewed the submission, and it is acceptable from a clinical pharmacology perspective.

Phenylephrine hydrochloride ophthalmic solutions, 2.5% and 10%, are currently being marketed and supplied in the US for use as a mydriatic. However, these products are outside of the approved OTC monograph (i.e., between 0.08% and 0.2%) and have never been cleared by a FDA approval process. To address this unapproved drug product issue, the applicant submitted this NDA as a 505(b)(2) application on 10/19/2011. The Refusal to File (RTF) letter was issued on 12/16/2011, citing CMC deficiencies. The applicant resubmitted the NDA on 12/21/2012 and the application is now under the priority review.

Due to the wealth of scientific literature and extensive clinical use the applicant considers that the safety and efficacy of phenylephrine hydrochloride ophthalmic solution, 2.5% and 10%, have been well established. Therefore, the applicant believes it is unnecessary to conduct any additional clinical studies to support this literature-based NDA.

The applicant did not conduct any clinical pharmacology related studies and did not request the waiver of evidence of in vivo bioavailability or bioequivalence. In accordance with the 21CFR §320.22(e) – “FDA, for good cause, may waive a requirement for the submission of evidence of in vivo bioavailability or bioequivalence if waiver is compatible with the protection of the public health”, the Clinical Pharmacology review team will grant the waiver of evidence of in vivo bioavailability or bioequivalence to this NDA, considering the extensive clinical experience of the product.

6. Sterility Assurance

Phenylephrine Hydrochloride Ophthalmic solution, 2.5% and 10%, is a topical, ophthalmic preparation of the active ingredient in a (b) (4), preserved, aqueous solution in a multidose dropper bottle. The drug product is preserved with benzalkonium chloride (0.01%).

Product Quality Microbiology recommends approval.

7. Clinical/Statistical - Efficacy

From the original Medical Officer Review:

The support for efficacy for Phenylephrine Hydrochloride Ophthalmic Solution 2.5% and 10% ophthalmic solution comes from multiple literature studies including four representative studies: Gambill 1967, Haddad 1970, Chawdhary 1984 and Yospaiboon 2004 and the Pediatric Study by Sindel 1986.

See Appendix of this CDTL review for a list of these literature articles.

Efficacy studies using the consensual light reflex to demonstrate phenylephrine’s ability in producing mydriasis

Gambill 1967 Study and Haddad 1970 Study – Group 2

The purpose of the Gambill 1967 study was to compare, with the aid of accurate measurements, the mydriasis produced by four drugs: 0.5% tropicamide, 2% homatropine hydrobromide, 1% hydroxyamphetamine hydrobromide, and 10% phenylephrine hydrochloride. In each patient, after instillation of the drug in the left eye (the right eye served as the control), the pupillary diameters at maximal constriction of both eyes as a response to a light flash of constant intensity and duration were measured every two minutes for 40 minutes, then every five minutes for 20 minutes. At any given time after instillation of the drug, the difference in constriction between the two eyes (less than any initial anisocoria) was then taken as a measure of the degree of mydriasis.

The purpose of the Haddad 1970 study was to determine the dose-response curve for phenylephrine HCl in a group of young, normal subjects and to evaluate the mydriatic effect of this drug in a group of older subjects in order to better characterize the effects of this drug on the iris. For both groups, after a baseline tracing was made, two drops of the drug solution being evaluated were instilled into the right eye of each subject (the left eye served as the control). The study endpoints were the difference in pupillary diameter of the two eyes at maximal constriction produced by light stimulation at appropriate time intervals.

Group 1: all subjects were tested with each concentration; at least seven days elapsed between dosing when a solution stronger than 1% was used. Pupillary size and response to the standard light stimulus were recorded at 15-minute intervals for 90 minutes and then hourly until recovery from mydriasis had occurred. The tracing was repeated at 24 hours after instillation of the drug.

Group 2: The drug was instilled after an initial tracing, and a repeat tracing was recorded at 75 minutes, the average time for mydriasis to occur as determined in Group 1. Pupillary size and reactivity were again recorded at 24 hours after initial instillation of the drug; the same drug solution then instilled and a final tracing obtained 75 minutes later.

Gambill Study
 (10% phenylephrine)

	All Subjects (N=15)	Light Irides (N=9)	Dark Irides (N=6)
Amount of maximal pupil mydriasis (mm)*			
Mean	2.42	2.69	2.01

*Measured with infrared pupillography to evaluate the difference in pupil size between treated and untreated eyes of a subject when a light stimulus is applied to the eyes in dim illumination.

Haddad Study – Group 2

	1.0 % phenylephrine (N=12)	10% phenylephrine (N=12)
Amount of maximal pupil mydriasis (mm)*		
Mean and SD	3.4 (± 0.35)	3.57 (± 0.02)

*Measured with infrared pupillography to evaluate the difference in pupil size between treated and untreated eyes of a subject when a light stimulus is applied to the eyes in dim illumination.

The degree of mydriasis was determined by measuring the difference in pupillary responses of the two eyes to a light stimulus when the drug has been instilled in only one eye. Normally both pupils constrict equally when one eye alone is stimulated.

These studies demonstrate that the eyes dosed with phenylephrine remain dilated approximately 2.5 – 3.5 mm more than the contralateral eye when stimulated by a light reflex. These results confirm the ability of phenylephrine to dilate the pupil.

Efficacy studies comparing various concentrations of phenylephrine to produce mydriasis

Chawdhary 1984 Study and Yospaiboon 2004 Study

The purpose of the Chawdhary 1984 study was to study the effects of various dilutions of phenylephrine hydrochloride ophthalmic solution in terms of effective mydriasis and cardiovascular effects in an Indian population having brown irides. Subjects were divided into 4 groups of 10 patients each. Fresh aqueous solutions of phenylephrine hydrochloride were prepared in concentrations of 10%, 5%, 2.5% and 1.25%. The drugs were coded and used randomly. One drop of the drug was put every 1 minute three times in the lower conjunctival cul-de-sac. Pupillary sizes at 2, 4, 6, 8, 10, 15, 20, 30, 50 and 70 minute were measured.

The purpose of the Yospaiboon 2004 study was to compare the safety and efficacy of phenylephrine 2.5% versus 10% on pupillary dilation for dark irides. All patients first received one drop of 1% tropicamide and 30 minutes later one drop of 10% or 2.5% phenylephrine by simple random allocation. Pupillary measurement was performed immediately before 1% tropicamide, 30 minutes after 1% tropicamide (before 10% or 2.5% phenylephrine) and 30 minutes after 10% or 2.5% phenylephrine. Systolic and diastolic blood pressure and heart rate were also measured before and 30 minutes after 10% phenylephrine or 2.5% phenylephrine.

Chawdhary Study
 N=40

Mean and standard deviation of pupil size in mm at maximal dilation

	1.25 % phenylephrine (N=10)		2.5 % phenylephrine (N=10)		5 % phenylephrine (N=10)		10% phenylephrine (N=10)	
	Baseline Pupil	Maximal Pupil	Baseline Pupil	Maximal Pupil	Baseline Pupil	Maximal Pupil	Baseline Pupil	Maximal Pupil
Amount of maximal pupil mydriasis (mm)*								
Mean and SD	4.1 ± 0.22	5.8 ± 0.27	4.2 ± 0.27	7.2 ± 0.75	4.3 ± 0.27	7.65 ± 0.22	4.2 ± 0.27	8.2 ± 0.27

Yospaiboon Study*
 N=564
 Mean and standard deviation of pupil size in mm at maximal dilation

	2.5 % phenylephrine (N=271)				10% phenylephrine (N=293)			
	Baseline Pupil (OD)	Maximal Pupil (OD)	Baseline Pupil (OS)	Maximal Pupil (OS)	Baseline Pupil (OD)	Maximal Pupil (OD)	Baseline Pupil (OS)	Maximal Pupil (OS)
Amount of maximal pupil mydriasis (mm)*								
Mean and SD	4.45 ± 1.0	7.17 ± 1.04	4.32 ± 0.92	7.07 ± 1.06	4.43 ± 1.13	7.58 ± 0.96	4.31 ± 0.95	7.6 ± 1.03

* All eyes had also received one drop of 1% tropicamide

These results confirm the ability of phenylephrine to dilate the eye. Baseline pupillary dilation ranged from 4.1 to 4.4 mm while after instillation of phenylephrine pupillary dilation ranged from 7.0 to 8.2 mm.

Efficacy study in newborns demonstrating phenylephrine’s ability to produce mydriasis

Sindel 1986 Study

The purpose of the Sindel 1986 study was to compare the safety and efficacy of the combination of mydriatic drops (phenylephrine 2.5% plus 0.5% tropicamide plus 0.5% cyclopentolate) with two other combinations of mydriatic drops (phenylephrine 2.5% plus 1.0% tropicamide, and phenylephrine 1.0% plus 1.0% tropicamide) in preterm infants.

Infants scheduled for routine screening ophthalmoscopy (for retinopathy of prematurity) were eligible for study. They were selected if their cardiovascular status was stable, and one of the principle investigators was available to perform the measurements. 30 infants were randomly assigned to receive one of three single drop mydriatic solutions prepared. Four additional infants received only saline solution and served as controls (investigators not blinded in this group). Each infant received one drop of the solution in each eye, and a second drop, five minutes later. Pupillary dilation was measured with a metric ruler by direct observation at one hour. Blood pressure (BP) and heart rate (HR) were monitored immediately prior to the instillation of the drops and at five-minute intervals, for 60 minutes. For each subject, both eyes were included and evaluated in the study.

Sindel Study
 (N=34)

	Phenylephrine 2.5% and 1% tropicamide (N=10)		Phenylephrine 2.5% and 0.5% tropicamide (N=10)		Phenylephrine 1.0% and 1.0% tropicamide (N=10)		Saline only (N=4)	
Age at study (days)	53.9		52.9		52.3		54.0	
Birth weight (grams)	1022 ± 226		1115 ± 281		1110 ± 317		980 ± 155	
Amount of maximal pupil mydriasis (mm)*	Baseline Pupil	Maximal Pupil	Baseline Pupil	Maximal Pupil	Baseline Pupil	Maximal Pupil	Baseline Pupil	Maximal Pupil
Mean and SD	2.8 ± 0.8	7.4 ± 0.5	3.0 ± 0.6	7.3 ± 0.4	2.9 ± 0.6	7.1 ± 0.6	2.9 ± 0.2	2.9 ± 0.2

The ability of phenylephrine to dilate the eye is also demonstrated in neonates. Baseline pupillary dilation ranges from 2.8 to 3.0 mm while after instillation of phenylephrine pupillary dilation ranges from 7.1 to 7.4 mm.

Summary Efficacy Statement

The submitted literature references contained in this submission support the efficacy of phenylephrine hydrochloride ophthalmic solution 2.5% and 10% in adults and pediatric patients.

8. Safety

From the original Medical Officer Review:

A review of the published literature shows there are a substantial number of publications describing the safety of the use of phenylephrine hydrochloride for topical ophthalmic use at concentrations ranging from 1 % to 10%. Key safety articles with their summaries are listed in the following table.

See Appendix of this CDTL review for a list of these literature articles.

Cross-Discipline Team Leader Review
 William M. Boyd, M.D.
 NDA 203510
 Phenylephrine Hydrochloride Ophthalmic Solution, 2.5% and 10%

Authors	Study title	a) Design b) Efficacy data c) Safety data
Allinson 1990	Reversal of Mydriasis/ Dipiprazole	a) 50 subjects, within subject, randomized Dipiprazole treatment eye. All eyes received 1% Trop and 2.5% PE. b) 5mm mydriasis on T+PE (p=0.01<0.05) Reduced post D by over 3 mm in two hours and completely in 24 hrs. c) BP and Pulse, IOP. No sig diff. No data given
Brown 1980	Lack of Side Effects From Topically Administered 10% Phenylephrine Eyedrops A Controlled Study	a) Controlled, Double masked. PE 10% n=100, Trop 1% n=50 b) 3 drops 2 mins apart in both eyes. No data on efficacy. c) No difference between the PE and T on DBP, SBP or Pulse
Samantary 1975	Systemic effects of topical phenylephrine (10%)	a) 10% PE c) They found elevations of 10-40 mmHg SBP and 10--30mmHg of SBP
Chowdhary 1984	Mydriasis-use of Phenylephrine (a dose response concept)	a) 10%, 5%, 2.5% 1.25% (N=10/group) Double masked. Dose response/controlled b) Mydiatic dose response. .Sig diff? between 2.5% and 1.25% c) safety is dose related. 2.5% and 1.25% had no effect on pulse and BP whereas 10% and 5% did. .More so with 10% and at 6-8 mins.
Chin 1994	PE eye drops in ophthalmic surgery – a clinical study of cardiovascular effects.	a) Double masked. Saline (n=30), 2.5% (n=29) and 10% (n=30)PE and mydriacyl. undergoing cataract surgery 50% were hypertensive b) No efficacy data c) Higher BP in the PE groups more sig in 10% than 2.5% more significant in non hypertensives . 10.3% of 10% and 3% on 2.5% required hypotensive treatment.
Filho 2007	Cardiovascular and papillary effects of topical Ophthalmic 2.5% and 10% in healthy volunteers. In Portuguese with an English abstract	a) Case controlled randomized crossover study of 2.5% and 10% PE in 28 HV's b) Stat sig difference in mydiatic effect p=OD 0.015/ OS 0.028 c) no difference in safety
Malhotra 1998	Comparison of cardiovascular effects of 2.5% and 10% PE during ophthalmic surgery	a) N=54. DM, Randomized. 0.25% or 10% PE and 1% Trop. In subjects without CV disease history. c) both cause an increase in SBP 14.1 – 18.9 mmHg but no SSD between them
Symons 1997	Letter to the Editor With response from Tanner.	Review publication a) Comparison of BP and pulse 10% phenylephrine plus 1% tropicamide (n=126) vs a 1% tropicamide (n=14) b) No data on mydriasis presented c) No difference in mean BP but significant difference on the percent of subjects with 30mm Hg fluctuation in BP.

Authors	Study title	a) Design b) Efficacy data c) Safety data
Yospaiboon 2004	Randomized Double-blind Study of Phenylephrine 2.5% vs 10% on papillary dilatation	a) Phenylephrine 2.5% (n=293) vs phenylephrine 10% (n=271). Both groups received 1% tropicamide. b) Phenylephrine 10% more effective than 2.5% with significant difference between groups for the amount of additional dilatation after tropicamide p<0.001 c) Significant difference on pulse rate p=0.005 but not SBP or DBP.
Lansche RK 1966	Systemic reactions to topical epinephrine and phenylephrine	Case reports of 2 subjects 40F had a headache and passed out after 2% epinephrine, 57M experienced increased BP and HR and fainting after a single drop of 10% phenylephrine . Contributing factors discussed.
Fraunfelder 1978.	Possible adverse effects from topical ocular 10% phenylephrine	
Solosky 1972	Hypertension following 10% phenylephrine ophthalmic.	3 case reports of subjects of subjects experiencing increased BP (69F, 3mth F, 62 M)
Wilensky 1973	Acute Systemic Hypertension after conjunctival instillation of Phenylephrine Hydrochloride	Case report: BP went from 150/100 to 270/170 after proparacaine one drop and three drops 10% phenylephrine
McReynolds 1956	Hazards of use of sympathomimetic drugs in ophthalmology	Acute subarachnoid hemorrhage in a 35 yo. A cotton wick soaked in 10% phenylephrine inserted in lower cul de sac to induce dilatation and separate posterior synechia. BP went from 118/68 to 230/130 and had subarachnoid bleed.
Heath 1939	Use of phenylephrine hydrochloride (neo-synephrine Hydrochloride) in ophthalmology	Reported BP unaltered in 40%, lowered in slightly in about 58% and slightly increased in 2% (Criterion was \pm 4mm Hg was no change) N=60.
Biggs 1959	The effect of sympathomimetic drugs upon the amplitude of accommodation	Phenylephrine 10% administered intensively caused only a slight recession of the near point. No effect was noted at dosage levels which the clinician might employ for refraction purposes.
Becker 1959	The effect of phenylephrine hydrochloride on the miotic treated eye.	In normal subjects phenylephrine 10% produced mydriasis and had little or no effect on the IOP of eyes treated with miotics. In subjects with glaucoma on demercurium bromide 0.25% phenylephrine 10% caused a very slight increase in IOP.
Borromeo-McGraill 1973	Systemic hypertension following ocular administration of 10% phenylephrine in the neonate.	a) Double –masked comparison of phenylephrine 10% (n=3) and phenylephrine 2.5% (n=4) in low birth weight infants. b) No efficacy data c) With phenylephrine 10% SBP up 12-16mmHg DBP up 10-14mmHg . Phenylephrine 2.5% had no effect
Barbee 1957	A comparative study of mydiatic and cycloplegic agents in human subjects without eye disease.	10% phenylephrine produced similar mydriasis in blue brown and black eyes. Although numerically the mydriasis was less in black eyes.
Martha Meyer 1980	Phenylephrine hydrochloride in Pharmacology of Ocular Drugs	Review of the safety issues.

Authors	Study title	a) Design b) Efficacy data c) Safety data
Pless 2003	Topical phenylephrine may result in worsening of visual loss when used to dilate pupils in patients with vaso-occlusive disease of the optic nerve.	Report on 4 patients with non-arteritic ischemic optic neuropathy who experienced acute worsening of visual function after phenylephrine used for fundus exam. 45 mins to 12 hrs later. All on 2.5% phenylephrine plus 0.5-1.0% tropicamide.
Alpay 2010	The local vasoconstriction of infant's skin following instillation of mydriatic eye drops.	Two case reports in neonates of extensive blanching of the skin after 2.5% phenylephrine. Suggests reducing drop size and wiping away excess.
Lee 1958	The influence of epinephrine and phenylephrine on Intraocular Pressure.	Patients with OAG and normals IOP effect variable Studied phenylephrine 1% and 10%.
Sindel 1986	A comparison of the papillary and cardiovascular effects of various mydriatic agents in preterm infants.	a) Randomized, A. Phenylephrine 2.5% tropicamide 1.0% (n= 10) B. Phenylephrine 2.5% tropicamide 0.5% (n=10) C. phenylephrine 1.0% tropicamide 1.0% (n=10) D. Saline (n=4) b) Mydriasis in groups A and B was not different. Group C was less in bright light but still >6mm c) BP and HR changes significantly less in group C
Vaughan 1973	Ventricular arrhythmias after topical vasoconstrictors.	Case report of an 8 yo under GA for squint surgery. 4-5 drops 10% phenylephrine sent BP up 100/60 to 190/120 HR slowed. Multiple premature ventricular contractions.

Exposure

From the Table of publications listed in Section 7.1.1 addressing the safety of phenylephrine topically applied to the eye, at least 1229 subjects were exposed to phenylephrine of which 630 received phenylephrine 10%.

Since the use of phenylephrine ophthalmic drops 2.5% and 10%, is for examinations and surgical procedures there are no data on long term exposure and safety.

Deaths

No deaths were reported due to the use of topical ophthalmic phenylephrine solution in the randomized, controlled clinical trials utilized to establish the safety and efficacy of the drug product. There are case reports of death with the use of phenylephrine applied topically for other indications.

Common Adverse Events

Since the use of phenylephrine ophthalmic drops 2.5% and 10%, is for single dose examinations and procedures there are no data on long term exposure and safety.

Phenylephrine is a sympathomimetic and systemic absorption of eye drops is known to occur via the nasal mucosa, cornea, and conjunctiva. Within minutes of application ocular reactions including eye pain and stinging on instillation, temporary blurred vision, photophobia, and conjunctival sensitization may occur.

The most common adverse reactions that occur following topical ophthalmic administration of phenylephrine are ocular reactions including eye pain and stinging on instillation, temporary blurred vision, photophobia, and conjunctival sensitization.

Ophthalmic use of phenylephrine can occasionally cause systemic sympathomimetic effects such as palpitation, tachycardia, premature ventricular contractions, occipital headache, pallor or blanching, trembling or tremors, increased perspiration, and hypertension. In one patient, hypertension was reported to be severe enough to cause subarachnoid hemorrhage followed insertion of a cotton wick saturated with 10% phenylephrine hydrochloride in the lower conjunctival cul-de-sac.

Systemic effects occur only rarely after topical application of solutions containing 2.5% or less of phenylephrine hydrochloride to the conjunctiva but are more likely to occur if the drug is instilled after the corneal epithelium has been damaged (e.g., by trauma or instrumentation) or permeability is increased by tonometry, inflammation, surgery of the eye or adnexa, or topical application of a local anesthetic; when the eye or adnexa are diseased; or when lacrimation is suppressed such as during anesthesia. The risk of severe hypertension is greatest in infants receiving instillations of 10% phenylephrine hydrochloride solutions.

Drug- Specific Safety Explorations

Special safety studies were performed in neonates in the Sindel 1986 Study and the Borromeo-McGrail 1973 Study.

Sindel Study
(N=34)

	Group A Phenylephrine 2.5% and 1% tropicamide (N=10)	Group B Phenylephrine 2.5% and 0.5% tropicamide (N=10)	Group C Phenylephrine 1.0% and 1.0% tropicamide (N=10)	Group D Saline only (N=4)
Age at study (days)	53.9	52.9	52.3	54.0
Birthweight (grams)	1022 ± 226	1115 ± 281	1110 ± 317	980 ± 155
Maximum change in blood pressure and heart rate after eye drops instilled				
Blood pressure (%)				
Systolic	+14.9 ± 9.6*	+17.2 ± 12.5**	+7.1 ± 10.1	-0.8 ± 6.9
Mean	+17.1 ± 10.4*	+22.8 ± 17.4**	+7.7 ± 9.3 ^{tt}	+3.0 ± 6.0
Diastolic	+15.9 ± 7.8*	+19.5 ± 14.2*	+5.4 ± 7.6 ^{ttt}	+0.8 ± 10.6
Heart rate (%)	+6.0 ± 6.1*	+10.0 ± 10.6*	+4.4 ± 5.2	+2.1 ± 2.0

*p < 0.02 vs. baseline

**p < 0.01 vs. baseline

^{tt} A vs. C p=0.04, B vs C p=0.02

^{ttt} A vs. C p=0.007, B vs. C p=0.01

Phenylephrine ophthalmic solution 2.5% results in an acceptable increase of heart rate and blood pressure in neonates.

Borromeo-McGrail 1973 Study

Borromeo-McGrail 1973 was a randomized, masked study comparing pupillary dilating capabilities and associated cardiovascular effects of phenylephrine hydrochloride ophthalmic solution 2.5%, 10% and saline in 12 neonates under 1 month of age and weighing from 907 gm to 2,438 gm. Formal pupillary measurements were not made or recorded, the article states, "...all patients who received either 2.5% or 10% phenylephrine had full pupillary dilatation within 25 to 30 minutes. The time of onset and degree of dilatation was not related to the concentration of phenylephrine used."

A separate group of eight low birth weight infants was studied in an open phase with 10% phenylephrine ophthalmic instillation. In this phase, the observer was aware that 10% phenylephrine drops had been instilled.

Borromeo-McGrail Study
Double-blind Phase
 N=12

All neonates < 1 month old, weighed 907 – 2,438 grams

	Phenylephrine 2.5% (N=4)	Phenylephrine 10% (N=3)	Normal Saline (N=5)
Blood pressure (%)			
Systolic	unchanged	Increased 12 – 16 mm Hg (18% to 25%)	unchanged
Diastolic	unchanged	Increased 10 – 14 mm Hg (22% to 50%)	unchanged
Heart rate	unchanged	unchanged	unchanged
Respiratory rate	unchanged	unchanged	unchanged

Borromeo-McGrail Study
Open label Phase
 N=8

All neonates < 1 month old, weighed 907 – 2,438 grams

	Phenylephrine 10% (N=8)
Blood pressure (%)	
Systolic	Increased 6 – 22 mm Hg (7% to 50%)
Diastolic	Increased 4 – 18 mm Hg (13% to 70%)
Heart rate	unchanged
Respiratory rate	unchanged

Phenylephrine ophthalmic solution 2.5% results in an acceptable increase of heart rate and blood pressure in neonates; phenylephrine ophthalmic solution 10% results in an unacceptable increase of heart rate and blood pressure in neonates. Caution should be exercised in pediatric patients less than 5 years of age.

Glaucoma

The applicant has proposed to list the following contraindication in Section 4:

 (b) (4)

There is no literature provided to support this statement. Phenylephrine given in other dosage forms, i.e. cold preparation, and at different lower concentrations which do not completely dilate the pupil may put predisposed patients at risk for narrow angle glaucoma. This statement is not recommended for inclusion in the package insert

Drug-Drug Interactions

The applicant has proposed to list the following drug-drug interactions in Sections 5.4 and 7.1:

 (b) (4)

The applicant supports the inclusion of these statements by referencing the American Hospital Formulary Service (i.e. (McEvoy, G.K. American Hospital Formulary Service. AHFS Drug Information. American Society of Health-System Pharmacists, Bethesda, MD. 2007). There is no specific literature support for these statements provided, and there is no evidence in the adequate and well-controlled trials utilized in the establishment of safety and efficacy that these drug-drug interactions are clinically relevant. These statements are not recommended for inclusion in the package insert

Patient Counseling

The applicant has proposed to list the following advice in Section 17:

 (b) (4)

There is no literature provided to support this statement. This statement is not recommended for inclusion in the package insert. The package insert should contain the following information for the patient in Section 17:

Advise patients not to touch the dropper tip to any surface as this may contaminate the solution.

Inform patients they may experience sensitivity to light and should protect their eyes in bright illumination while their pupils are dilated.

Safety Summary Statement

A review of the published literature shows there are a substantial number of publications describing the safety of the use of phenylephrine hydrochloride for topical ophthalmic use at concentrations ranging from 0.08 % to 10%.

The submitted literature references contained in this submission support the safe use of phenylephrine hydrochloride ophthalmic solution, 2.5% and 10% in adults and pediatric patients over one year in age to dilate the pupil. Phenylephrine hydrochloride ophthalmic solution 10% is not safe for use in pediatric patients less than 1 year old.

Systemic adverse reactions to phenylephrine hydrochloride ophthalmic solution are primarily cardiovascular due to its vasoconstriction activity and have been reported include palpitation, tachycardia, premature ventricular contractions, hypertension, syncope, myocardial infarction, arrhythmia and subarachnoid hemorrhage. These systemic adverse reactions are more frequent with the 10% solution and more frequent in patients with pre-existing cardiovascular diseases.

Ocular adverse reactions include stinging on instillation, temporary blurred vision and photophobia and conjunctival sensitization.

A 120 Day Safety Update was submitted on February 28, 2013. There is no new safety information that would alter the safety conclusions of the original NDA submission.

9. Advisory Committee Meeting

An advisory committee meeting was not required for this application.

10. Pediatrics

PeRC meeting was held on Wednesday, March 6th. PeRC agreed with the Division's plan to consider studies completed for all pediatric subpopulations (i.e. 0 yr. 0 mo. - 16 yr. 11 mo).

Phenylephrine ophthalmic solution 10% is contraindicated in pediatric patients less than 1 year of age; phenylephrine ophthalmic solution 10% results in an unacceptable increase of heart rate and blood pressure in neonates.

Caution should be exercised with the use of phenylephrine 10% in pediatric patients less than 5 years of age.

In pediatric patients less than 1 year of age, one drop of phenylephrine hydrochloride ophthalmic solution, 2.5% should be instilled at 3-5 minute intervals up to a maximum of 3 drops per eye.

11. Other Relevant Regulatory Issues

BIostatISTICS

Per the original Biostatistics review:

The applicant submitted eleven studies to support efficacy of both 2.5% and 10% phenylephrine solution, and the applicant grouped the studies as follows:

1. Studies with a control group demonstrating efficacy of phenylephrine in producing Mydriasis (*Gambill et al 1967, Haddad 1970, Chawdhary et al 1984, Yospaiboon 2004*)
2. Studies comparing the efficacy of 2.5% and 10% phenylephrine (*Chawdhary et al 1984, Yospaiboon 2004*)
3. Studies in children (*Sindell 1986*)
4. Supporting studies (*Filho 2007, Ozturk 2000, Tanner 1996, Eyeson-Annan 1998, Paggiarino 1993, Neuhaus 1980*).

Table 5: Statistical Reviewer's Summary of Study Design for Reviewed Studies

	Groups	Design	Study Population and Treated Eye	Pupil Size Evaluation Method	Evaluation Time
Gambill 1967	a) 0.5% tropicamide b) 2% homatropine c) 1% hydroxyamphetamine d) 10% phenylephrine	Prospective, crossover study, not blinded	Healthy Caucasians Treated: left eye Control: right eye	pupillary diameters at maximal as a response to a light flash of constant intensity and duration	After instillation, every two minutes for 40 minutes, then every five minutes for 20 minutes
Haddad 1970	Fresh aqueous solutions of phenylephrine HCl in concentrations of 0.1, 0.25, 0.5, 1, 5, and 10%; and a commercially available 10% solution was used for comparison	Prospective, crossover study	Normal subjects Treated: right eye Control: left eye	Pupillary size and response to the standard light stimulus	at 15-minute intervals for 90 minutes and then hourly until recovery from mydriasis had occurred
Chawdhary 1984	Fresh aqueous solution of Phenylephrine hydrochloride was prepared in concentrations of 10%, 5%, 2.5% and 1.25%	Prospective, randomized, and masked	Healthy Indian Subjects Both eyes were treated	pupil size on Goldmann perimeter telescope	at 2, 4, 6, 8, 10, 15, 20, 30, 50 and 70 minute post instillation
Yospaiboon 2004	1% tropicamide plus phenylephrine 2.5% 30 minutes later versus 1% tropicamide plus phenylephrine 10% 30 minutes later	Prospective, randomized, double-blinded study	Subjects with dark irides Both eyes were treated	Not specified	immediately before 1% tropicamide, 30 minutes after 1% tropicamide (before 10% or 2.5% phenylephrine) and 30 minutes after 10% or 2.5% phenylephrine
Sindel 1986	a) phenylephrine 2.5% plus 1.0% tropicamide b) phenylephrine 2.5% plus 0.5% tropicamide plus 0.5% cyclopentolate c) phenylephrine 1.0% plus 1.0% tropicamide d) saline	prospective, masked, randomized study	Babies < 1500 grams at birth Both eyes were treated	Pupillary dilation was measured with a metric ruler by direct observation	at one hour

Table 7: Statistical Reviewer’s Summary of Baseline Characteristics

	2.5% Phenylephrine		10% Phenylephrine		
	Gambill 1967	Male	n/a	8/15	
	Age (years)	n/a	26.4 (range: 12 to 38)		
	Irides Color				
	Blue	n/a	9/15		
	Hazel	n/a	3/15		
	Brown	n/a	3/15		
Haddad 1970 Group 1		2.5% Phenylephrine		10% Phenylephrine	
	Age (years)	Range: 21 to 53		Range: 21 to 53	
	Irides Color				
	Blue	3/8	3/8		
	Hazel	2/8	2/8		
	Brown	3/8	3/8		
Haddad 1970 Group 2		2.5% Phenylephrine		10% Phenylephrine	
	Age (years)	n/a		Greater than 50 years	
Chawdhary 1984		2.5% Phenylephrine		10% Phenylephrine	
		N=40		N=40	
	Age (years)	20 to 40		20 to 40	
	Iridies Color				
	Brown	40/40		40/40	
Yospaiboon 2004		2.5% Phenylephrine		10% Phenylephrine	
	Male	124/293 (42.3%)		125/271 (46.1%)	
	Age (years) (MEAN ± SD)	49.93 ± 17.03		52.37 ± 16.46	
	Irides Color	All subjects had dark irides			
Sindel (1986)	MEAN ± SD	2.5% phenylephrine + tropicamide 1.0% (n=10)	2.5% phenylephrine + tropicamide 0.5% (n=10)	1.0% phenylephrine + tropicamide 1.0% (n=10)	Saline (n=4)
	Gestational Age (weeks)	28.0 ± 1.9	28.3 ± 1.6	29.0 ± 2.4	28.0 ± 1.4
	Birthweight (grams)	1022 ± 226	1115 ± 281	1110 ± 317	980 ± 155
	Age at Study (days)	53.9 ± 15.7	52.9 ± 16.8	52.3 ± 12.9	54.0 ± 9.0

While this reviewer’s conclusion is that the application provides substantial statistical evidence of a treatment effect for both 2.5% and 10% phenylephrine on dilating pupil, the clinical significance of the pupil size results was unclear to this reviewer, and deferral to the clinical reviewer Dr. Martin Nevitt.

There is some evidence that 10% phenylephrine has slightly higher treatment effects compared with 2.5% concentration; however, the clinical relevance of the magnitude of the difference would be unclear to this reviewer, and deferral to the clinical reviewer.

Given that some articles reported possible adverse effects on heart rate (HR) and blood pressure (BP) for 10% phenylephrine, whether to approve both concentrations or just one concentration would be a clinical judgment based on overall benefit-risk profile for each concentration.

DPDP

The Division of Professional Drug Promotion (DPDP) provided a labeling review of the proposed, clean, substantially complete version of the PI sent to OPDP via email by Diana Willard.

DMEPA

The Division of Medication Error Prevention and Analysis (DMEPA) found the following proprietary names unacceptable: (b) (4) and (b) (4) in March 2013.

DMEPA provided a labeling review of the original package insert and original carton and container labeling.

The applicant, after discussion with DMEPA, plans to supply the product to the market, following NDA approval, using the nonproprietary name only and no Trade Name. The applicant will further consider alternate Trade Names following approval and submit these to the Agency for review as per the requirements and guidance.

FINANCIAL DISCLOSURE

This is a 505(b)(2) supplemental application primarily based on literature. In accordance with 21 CFR Part 54, no financial disclosure is appropriate for this application. There are no “covered clinical studies” in this submission.

OSI

An Office of Scientific Investigations (OSI) audit was not requested. This is a 505(b)(2) supplemental application primarily based on literature.

12. Labeling

The labeling found in this Appendix (package insert and carton and container labeling submitted on 3/19/13) is acceptable.

13. Recommendations/Risk Benefit Assessment

RECOMMENDED REGULATORY ACTION:

NDA 203510 for Phenylephrine Ophthalmic Solution, 2.5% and 10% is recommended for approval for dilation of the pupil.

Based on the published clinical literature, the information provided by the applicant supports the approval of this product for the approved indication, i.e. there is a positive benefit to risk ratio.

Systemic adverse reactions to phenylephrine hydrochloride ophthalmic solution are primarily cardiovascular due to its vasoconstriction activity. These systemic adverse reactions are more frequent with the 10% solution and more frequent in patients with pre-existing cardiovascular diseases.

Ocular adverse reactions include stinging on instillation, temporary blurred vision and photophobia and conjunctival sensitization.

The 10% solution is not recommended for use in infants less than 1 year old and patients with hypertension where the 2.5% solution should be used due the risk of increased systemic toxicity.

The benefits of using this drug product outweigh the risks for the above indication.

Appendix 1

Literature References

EFFICACY

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Appendix 2

Labeling

Carton and Container labeling and Package Insert submitted on 3/19/13.

Phenylephrine Hydrochloride Ophthalmic Solution, USP 2.5% Carton



7 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

WILLIAM M BOYD
03/20/2013

WILEY A CHAMBERS
03/20/2013