CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203510Orig1s000

MEDICAL REVIEW(S)

Deputy Division Director Review of NDA 203-510

Date	March 20, 2013
From	Wiley A. Chambers, M.D.
NDA#	203510
Applicant	Paragon Bioteck, Inc.
Date of Re-Submission after Refuse to File	September 20, 2012
Established (USAN) name	Phenylephrine Hydrochloride Ophthalmic Solution
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 203-510 has been submitted as a 505(b)(2) application. Phenylephrine is an alpha-1 adrenergic receptor agonist that has been used for more than 75 years to dilate the pupil due to its mydriatic action. With the exception of one combination product (ANDA 84-300), drug products including phenylephrine for pupil dilation have been marketed, without approved new drug applications during this period of time. Drug products containing phenylephrine were also marketed for a variety of different indications associated with its vasoconstrictor properties. With the exception of the products incorporated into the OTC monograph for use as ophthalmic vasoconstrictors for relief of ocular redness at concentrations of between 0.08% and 0.2%, most of these products are no longer marketed.

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.

NDA 19-849, Dapiprazole hydrochloride ophthalmic solution, is indicated in the treatment of iatrogenically induced mydriasis produced by adrenergic (phenylephrine) or parasympatholytic (tropicamide) agents.

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.

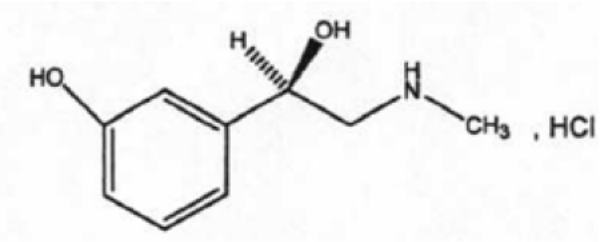
On December 16, 2011, a REFUSAL TO FILE letter was sent that noting that the NDA did not appear to provide sufficient stability data to establish the stability profile of the drug product over the requested shelf-life.

On October 21, 2012, Paragon Bioteck, 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.

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: $C_9H_{13}NO_2$-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)

This NDA has been recommended for approval from the CMC perspective. The product has been manufactured by the drug product manufacturer, [redacted] (b) (4). since 2001, although previously manufactured solutions had a [redacted] (b) (4) e. The solutions described in this NDA have no [redacted] (b) (4)

The product is a sterile, [redacted] (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 [redacted] (b) (4)

DRUG PRODUCT COMPOSITION:

Component	2.5% Formulation	10% Formulation	Function
Phenylephrine HCl	2.5%	10%	Active
Sodium Phosphate Monobasic	[redacted]		(b) (4)
Sodium Phosphate dibasic			
Boric Acid			
Benzalkonium Chloride	0.01%	0.01%	Preservative
NaOH/HCl	As needed to adjust pH	As needed to adjust pH	
Water for Injection	q.s.	q.s.	Diluent

Drug Product Specifications:

Identification A (TLC)	Reddish orange spot from test solution
Identification B (HPLC) Retention time	Retention time for major peak corresponds to standard
pH at 25°C	4.0 – 7.5
Osmolality	2.5% 450-550 mOsm/kg
	10% 950-1050 mOsm/kg
Assay Phenylephrine HCl	90-110% label claim
Assay Benzalkonium Chloride	80-120% label claim
[redacted]	(b) (4)
Minimum Fill	Meets USP requirement
Deliverable Fill	Meets USP requirement
Sterility	Meets USP requirement <71>
Bacterial Endotoxins	[redacted] (b) (4)

INSPECTIONS:
An "Acceptable" site recommendation has been received from the Office of Compliance.

POSTMARKETING COMMITMENT:
The following post-marketing commitment was submitted:

> 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.

4. Nonclinical Pharmacology/Toxicology

The nonclinical safety information is based on literature reports and 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. Target tissues identified included the eyes in both species, the testes and seminal vesicles in male rats, and ovaries in female rats.

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

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.

I agree with Dr. Norman Stockbridge's assessment for the intravenous phenylephrine product [also based on the literature] that "the non-clinical data were not particularly informative, giving little insight into what vascular beds are acted upon, not giving the usual detailed view of off-target toxicology. There are published carcinogenicity studies, but irrelevant for the intended use." I concur with dropping the entire non-clinical section of labeling.

5. Clinical Pharmacology/Biopharmaceutics

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

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

The Gambill 1967 study compared 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.

10% phenylephrine

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

The Haddad 1970 study determined the dose-response curve for phenylephrine HCI 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.

	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.

Chawdhary 1984 studied 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.

	1.25 % phenylephrine (N=10)		2.5 % phenylephrine (N=10)		5 % phenylephrine (N=10)		10% phenylephrine (N=10)	
Mean and SD (mm)	Baseline Pupil 4.1 ± 0.2	Maximal Pupil 5.8 ± 0.3	Baseline Pupil 4.2 ± 0.3	Maximal Pupil 7.2 ± 0.7	Baseline Pupil 4.3 ± 0.3	Maximal Pupil 7.6 ± 0.2	Baseline Pupil 4.2 ± 0.3	Maximal Pupil 8.2 ± 0.3

Yospaiboon 2004 studied the safety and efficacy of phenylephrine 2.5% versus 10% in combination with tropicamide 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 in each eye. Pupil 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.

	2.5 % phenylephrine (N=271)				10% phenylephrine (N=293)			
Mean and SD (mm)*	Baseline Pupil (OD) 4.5 ± 1.0	Maximal Pupil (OD) 7.2 ± 1.0	Baseline Pupil (OS) 4.3 ± 0.9	Maximal Pupil (OS) 7.1 ± 1.1	Baseline Pupil (OD) 4.4 ± 1.1	Maximal Pupil (OD) 7.6 ± 1.0	Baseline Pupil (OS) 4.3 ± 1.0	Maximal Pupil (OS) 7.6 ± 1.0

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

Sindel 1986 compared 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. 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.

	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	
Mean and SD (mm)	Baseline Pupil 2.8 ± 0.8	Maximal Pupil 7.4 ±0.5	Baseline Pupil 3.0 ± 0.6	Maximal Pupil 7.3 ±0.4	Baseline Pupil 2.9 ± 0.6	Maximal Pupil 7.1 ±0.6	Baseline Pupil 2.9 ± 0.2	Maximal Pupil 2.9 ±0.2

Becker *et. al.* 1959 evaluated the time course and aqueous dynamics of phenylephrine (listed below as neosynephrine:

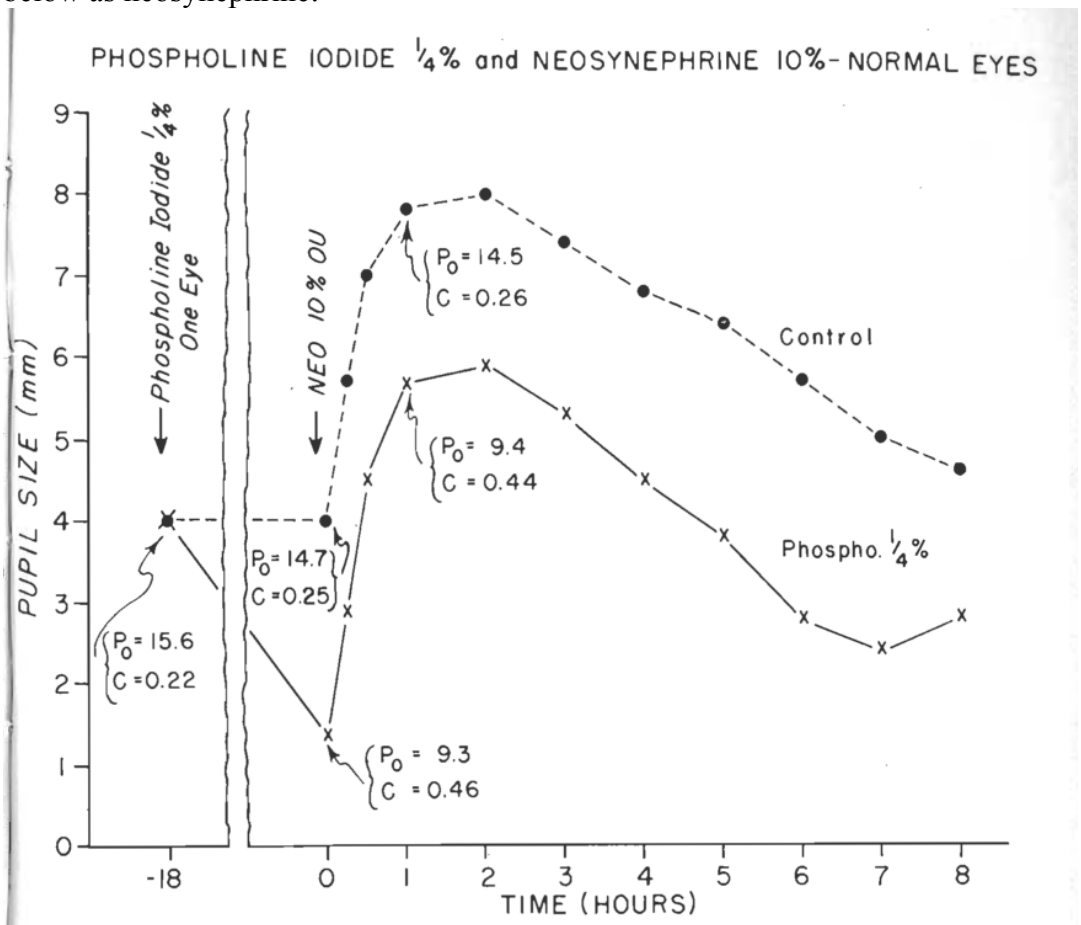


Fig. 1 (Becker, et al.). Time course of the pupillary changes induced by phenylephrine hydrochloride (10 percent) in nonglaucomatous eyes.
(●--●--● control eye; x-x-x echothiophate iodide-treated eye)
P_0 = intraocular pressure
C = outflow facility

Pupil dilation is variable but usually peaks during the first 90 minutes. The effects are wearing off between 3 and 8 hours later.

8. Safety

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%.

Phenylephrine is a sympathomimetic and systemic absorption can occur via the nasal mucosa, cornea, and conjunctiva. As with the other dilating agents, the drug product stings upon instillation and as dilation occurs, the product may cause temporary blurred vision and photophobia. There is a very small population in which conjunctival sensitization may occur, although the vasoconstrictor property of the drug product may mask this reaction.

Ophthalmic use of phenylephrine can occasionally cause systemic sympathomimetic effects resulting in elevations of pulse rate and blood pressure. The elevations in pulse rate and blood pressure may lead to systemic symptoms such as palpitations, premature ventricular contractions, occipital headaches, trembling or tremors, and increased perspiration. There is a report of the hypertension in one patient being severe enough to cause subarachnoid hemorrhage. This case and some of the other more severe manifestations of hypertension such as pulmonary edema have followed exaggerated dosing such as the 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. They are more likely to occur if the drug is instilled after the corneal epithelium has been damaged (e.g., by trauma or instrumentation), in cases where the permeability is increased by tonometry, inflammation, surgery of the eye, or topical application of a local anesthetic or systemic anesthesia. The risk of severe hypertension is greatest in infants receiving instillations of 10% phenylephrine hydrochloride solutions.

A summary and/or list of individual events is included in the primary Medical Officer Review and in the Team Leader's secondary review. The lowest concentrations (0.08% to 0.2%) are associated with "weak" dilation of the pupil and in patients with anatomically narrow angles, angle closure attacks have occurred.

While the labeling is recommended to include Warnings/Precautions of the potential for systemic hypertension, it is not recommended that the labeling include all (or even most) of the consequences of systemic hypertension since this list could include hundreds of related events and detract from the rest of the labeling.

In summary as described in the submission and reviews, 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. Caution should also be exercised when administering the 10% solution to patients with cardiovascular conditions of any age.

9. Advisory Committee Meeting

The review of this application was not believed to benefit from an advisory committee meeting.

10. Pediatrics

Phenylephrine ophthalmic solution 10% is recommended to be 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.

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
The Biostatistical reviewers based their review on eleven studies to submitted to support efficacy of both 2.5% and 10% phenylephrine solution, *Gambill et al 1967, Haddad 1970, Chawdhary et al 1984, Yospaiboon 2004,Chawdhary et al 1984,Yospaiboon 2004, Sindell 1986, Filho 2007, Ozturk 2000, Tanner 1996, Eyeson-Annan 1998, Paggiarino 1993, Neuhaus 1980.*

The review concludes that the application provides substantial statistical evidence of a treatment effect for both 2.5% and 10% phenylephrine on dilating pupil, with the 10% concentration having a slightly higher treatment effect and defers the clinical significance of the pupil size results to the clinical reviewer.

DMEPA
The Division of Medication Error Prevention and Analysis (DMEPA) found the following proprietary names unacceptable: (b) (4) in March 2013. The applicant, after discussion with DMEPA, plans to supply the product to the market, following NDA approval, using the nonproprietary without a trademark. The applicant will further consider alternate 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

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

During the review of the application, a number of labeling recommendations were conveyed to the applicant and have been incorporated into the latest submitted draft. These recommendations have included deleting statements or phrases which have not been supported by literature references including statements to use the 10% based solely on iris pigmentation, contraindications for patients with any form of cardiac disease or diabetes, development of transient pigment floaters.

Other statements have been changed or deleted because they are misleading, including (b) (4) [redacted]" While it may be true that there will be no stinging in an anesthetized eye, the anesthetic will sting when administered.

Sections 8.1 Pregnancy and 13 Nonclinical Toxicology have been modified to be consistent with the systemic phenylephrine labeling since both products reference the same literature data.

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

(b) (4)

[redacted]

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.

Wiley A. Chambers, MD
Deputy Division Director
Division of Transplant and Ophthalmology

Reference ID: 3279638

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/s/

WILEY A CHAMBERS
03/20/2013

CLINICAL REVIEW

Application Type	NDA 203510
Submission Number	SDN 006
Letter Date	September 20, 2012
Stamp Date	September 21, 2012
PDUFA Goal Date	March 21, 2013
Reviewer Name	Martin P. Nevitt, M.D., M.P.H.
Review Completion Date	February 20, 2013
Established Name	Phenylephrine Hydrochloride Ophthalmic Solution, 2.5 % and 10%
(Proposed) Trade Name	(b) (4)
Therapeutic Class	α-adrenergic agonist
Applicant	Paragon Bioteck, Inc.
Priority Designation	P
Formulation	Ophthalmic solution
Dosing Regimen	One drop of the 2.5% or 10% solution instilled at 3 – 5 minute intervals up to a maximum of 3 drops
Indication	Dilate the pupil
Intended Population	2.5% or 10% used in Adults, 2.5% used in infants less than 1 year old

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

NDA 203510 is recommended for approval with the revised labeling identified in this review. The submitted literature references contained in this submission support the 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 recommended for approval for use in pediatric patients less than 1 year old.

1.2 Risk Benefit Assessment

NDA 203510 is being submitted as a 505(b)(2) application. 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 and include palpitation, tachycardia, premature ventricular contractions, hypertension, syncope, myocardial infarction, arrhythmia and fatal 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.

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.

1.3 Recommendations for Postmarketing Risk Management Activities

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

1.4 Recommendations for other Post Marketing Study Commitments

There are no recommended Phase 4 clinical study commitments.

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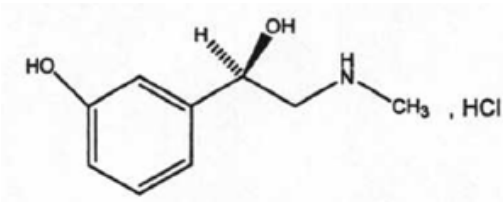
2 Introduction and Regulatory Background

2.1 Product Information

Chemical structure of phenylephrine hydrochloride



Chemical Name: $C_9H_{13}NO_2$-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)

2.2 Tables of Currently Available Treatments for Proposed Indications

Cyclomydril (NDA 011663) is a combination ophthalmic solution of phenylephrine hydrochloride 1% and cyclopentolate hydrochloride 0.2% approved for the production of mydriasis that was withdrawn April 30, 1984. Cyclomydril was not withdrawn for safety or efficacy reasons.

PREDNEFRIN® Forte eye drops (prednisolone acetate, 1.0% and phenylephrine hydrochloride, 0.12%), for another indication (severe inflammation (non-infectious) of the eye) was withdrawn in 1975.

2.3 Availability of Proposed Active Ingredient in the United States

Phenylephrine is an a-adrenergic receptor sympathetic 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.

Reference ID: 3271568

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.

2.4 Important Safety Issues With Consideration to Related Drugs

There have been rare reports of serious cardiovascular reactions, including ventricular arrhythmias and myocardial infarctions in patients using phenylephrine 10%. These episodes, some fatal, have usually occurred in patients with pre-existing cardiovascular diseases. For this reason, 10% phenylephrine should not be used in patients known to have these risk factors. Phenylephrine 2.5% should be used in these patients.

A significant elevation in blood pressure is rare but has been reported following conjunctival instillation of recommended doses of phenylephrine 10%. The risk is less with phenylephrine 2.5%. Caution should be exercised in infants of low body weight, and patients with hypertension, hyperthyroidism. The post-treatment blood pressure of these patients, and any patients who develop symptoms, should be carefully monitored.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

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.

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On October 21, 2012, Paragon Bioteck, Inc. re-filed 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 (b) (4)

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.

2.6 Other Relevant Background Information

Phenylephrine hydrochloride has been the subject of hundreds of clinical trials since its introduction into the marketplace over 70 years ago. From this large volume of clinical trials, several studies that were designed as randomized, masked studies and that contain statistical analysis are reviewed in Sections 5.0 and 6.0 of this Medical Officer's review.

NDA 19-849 for dapiprazole hydrochloride ophthalmic solution, 0.5% was approved on December 31, 1990, with the following indication: th (b) (4) . This NDA 19-849 application was not utilized or referenced in this current new drug application for phenylephrine ophthalmic solution.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This New Drug Application is being submitted as a 505(b)2 application. Paragon Bioteck, Inc. certified that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Reference literature reports, surveys, and articles cited in this review are representative of the published literature. There is no evidence that these references refer to trials not conducted in accordance with acceptable clinical ethical standards.

Reference ID: 3271568

3.2 Compliance with Good Clinical Practices

Reference literature reports, surveys, and articles cited in this review are representative of the published literature. There is no evidence that these references refer to trials not conducted in accordance with acceptable clinical ethical standards.

3.3 Financial Disclosures

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.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

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) except that the previously manufactured solutions had a (b) (4). The solutions described in this NDA have (b) (4). The container-closure system described in this NDA is the same as that previously employed.

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 composition is as follows:

Component	Function	2.5% Solution	10% Solution
Phenylephrine HCl	Active	2.5%	10%
NaH_2PO_4, USP	(b) (4)	(b) (4)	
Na_2HPO_4, USP			
Boric acid, NF			
Benzalkonium chloride, NF	Preservative	0.01%	0.01%
Sodium hydroxide, NF	pH adjustment	qs	qs
Hydrochloric acid, NF	pH adjustment	qs	qs
Water for injection, USP	(b) (4)		

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The (b) (4) 10% solution does not contain boric acid (b) (4)

The following post-marketing commitments were recommended by ONDQA. Note that the exact wording has not yet been finalized at the time of this review and that these issues are not thought to pose a safety risk.

1) Evaluate chiral purity of the drug product: Develop a chiral HPLC method to measure (b) (4) (b) (4) phenylephrine in the drug product and analyze newly manufactured batches, stability batches until 24-months, and retained samples of drug substance (if available). When sufficient information has been collected, submit a report with numerical data.

2) 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.

Reviewer's comments:

Clinically in the eye, there is no difference between the (b) (4) forms of phenylephrine.

4.2 Sterility Assurance

Phenylephrine HCl 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%).

Refer to Clinical Microbiology review.

4.3 Preclinical Pharmacology/Toxicology

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.

Refer to Pharmacology/Toxicology review.

4.4 Clinical Pharmacology

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 21 CFR §320.22(e) – *"FDA, for good cause, may waive a requirement for the submission of evidence of*

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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.

4.4.1 Mechanism of Action

Phenylephrine is an alpha receptor sympathetic agonist used (b) (4) due to its vasoconstrictor and mydriatic action. Phenylephrine possesses predominantly α-adrenergic effects. In the eye, phenylephrine acts locally as a potent vasoconstrictor and mydriatic, by constricting ophthalmic blood vessels and the radial muscle of the iris.

4.4.2 Pharmacodynamics

The ophthalmologic usefulness of phenylephrine is due to its rapid effect and moderately prolonged action; maximal mydriasis occurs in 60-90 minutes with recovery after 5-7 hours.

4.4.3 Pharmacokinetics

The systemic exposure following topical administration of phenylephrine has not been studied. A higher systemic absorption is expected for the 10% solution than the 2.5% solution, and when the corneal barrier function is compromised.

5 Sources of Clinical Data

5.1 Tables of Clinical Studies

See Appendix 9.1 of this review for a list of these literature articles.

Reference ID: 3271568

Summary of Key Efficacy Studies

Author - date	Title	Description a) Design b) Efficacy c) Safety
Gambill 1967	Mydriatic effect of four drugs determined with pupillography	a) 15 subjects (Caucasians) Cross over Infra red pupillography Comparison of effect of bright light on pupil diameter change in dark adapted eyes Untreated eye used as control b) Tropicamide showed fastest onset most effect and shortest duration 10% PE and Homatropine were similar in effect Hydroxyamphetamine showed least effect All showed greater efficacy in blue v brown eyes c) None reported
Haddad 1970	Mydriatic effect of phenylephrine hydrochloride	a) Grp 1 (n=8) crossover (7 day washout) 0 1%, 0 25%, 0 5%, 1%, 5%, 10% using IR Pupillograph Grp 2 1% fresh aqueous solution PE (n=25) 10% commercial formulation PE (n=25) b) Dose response established 10% commercial less effective than 10% aqueous fresh c) No effect on accommodation or IOP A dose related rebound miosis seen at 24 hrs
Chawdhary 1984	Mydriatic-use of Phenylephrine (Dose response study)	a) 10%, 5%, 2 5% 1 25% (N=10/group) Double masked Dose response/controlled b) Mydriatic dose response 1 25% was significantly worse than 2 5% and higher c) Safety was dose related 2 5% and 1 25% had no effect on pulse and BP whereas 10% and 5% did Effect was greater with 10% and at 6-8 mins
Yospaiboon 2004	Randomized Double –blind Study of Phenylephrine 2 5% vs 10% on Pupillary Dilation	a) N=564 randomized into Group 1 (n=293) 1% tropicamide and 10% phenylephrine Grp 2 (n=271) 1% tropicamide and 2 5% phenylephrine b) Statistically significant difference in favor of group 1 (10% phenylephrine) c) No difference in BP Statistically significantly higher HR in Group 1

Pediatric Efficacy Study

Author - date	Title	Description a) Design b) Efficacy c) Safety
Sindel 1986	Comparison of the Pupillary 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 > 6 mm c) Blood pressure and heart rate change significantly less in group C

Reference ID: 3271568

5.2 Review Strategy

The September 20, 2012, submission was submitted electronically. Subsequent amendments were also submitted in electronically. All literature reports were reviewed.

A literature search conducted by this reviewer failed to identify any additional literature references which were contrary to the information provided or referenced by Paragon Bioteck, Inc. in this application for this indication.

5.3 Discussion of Individual Studies

The key efficacy studies listed in Section 5.1 are based on studies with a control group demonstrating efficacy of phenylephrine in producing mydriasis, in studies where a dose response was used comparing the efficacy of 2.5% and 10% phenylephrine and in studies in children.

This application relies on articles from the published literature, and no new efficacy studies were conducted by the applicant. 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)

6 Review of Efficacy

Efficacy Summary

6.1 Indication

The indication is for the use of Phenylephrine Hydrochloride Ophthalmic solution 2.5% and 10% to dilate the pupil (b) (4).

6.1.1 Methods

The support for efficacy for Phenylephrine Hydrochloride Ophthalmic solution 2.5% and 10% ophthalmic solution comes from the four studies listed in Section 5.1: Gambill 1967, Haddad 1970, Chawdhary 1984 and Yospaiboon 2004 and the Pediatric Study by Sindel 1986.

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See Appendix 9.1 of this review for a list of these literature articles.

6.1.2 Demographics

Key Efficacy Studies

	Gambill study	Haddad study		Chawdhary study	Yospaiboon study
Number of Subjects	15	8 (Group 1) First Phase of Study**	24 (Group 2)	40	564
Gender					
Male	8	NR	NR	NR	248
Female	7	NR	NR	NR	316
Age					
Range in years	12 - 38	21- 53	All > 50	20 - 40	5 - 87
mean	26.4	NR	NR	NR	51.1
Iris color					
Blue	9	3	NR	-	-
Hazel	3	2	NR	-	-
Brown	3	3	NR	40	564

*NR – not reported
** Group 1 subjects confirmed a dose response curve from 0.1% up to 10% phenylephrine. The dose response began to plateau off at 5% phenylephrine with a complete plateau established at 10% phenylephrine.

Reviewer's comments:

Various reports and observations by clinicians have demonstrated that light colored irides dilate more easily with phenylephrine. Therefore, to study the mydriatic effect of phenylephrine in clinical trials many investigators enrolled a majority of subjects with dark colored irides (the more difficult cases) to demonstrate the dilation effect of the drug. While not preferred, this is acceptable.

6.1.3 Patient Disposition

The efficacy results are based on the all randomized patients enrolled in the four studies. The effect of topical phenylephrine hydrochloride ophthalmic solution 2.5% and 10% occurs nearly immediately; therefore all subjects that were randomized and enrolled into the studies were evaluated.

6.1.4 Analysis of Primary Endpoint(s)

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

Reference ID: 3271568

Gambill 1967 Study and Haddad 1970 Study – Group 2

The purpose of the Gambill 1967study 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 HCI 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

Reference ID: 3271568

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

Reviewer's comments:

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.

6.1.4.2 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. Puillary 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. Pupil measurement was performed immediately before 1% tropicamide, 30 minutes after 1% topicamide (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.

Reference ID: 3271568

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)	
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	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)			
Amount of maximal pupil mydriasis (mm)*	Baseline Pupil (OD)	Maximal Pupil (OD)	Baseline Pupil (OS)	Maximal Pupil (OS)	Baseline Pupil (OD)	Maximal Pupil (OD)	Baseline Pupil (OS)	Maximal Pupil (OS)
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

Reviewer's comments:

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.

6.1.4.3 Efficacy study in newborns demonstrating phenylephrine's ability to produce mydriasis

Reference ID: 3271568

Sindel 1986 Study

The purpose of the Sindel 1886 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)* Mean and SD	Baseline Pupil 2.8 ± 0.8	Maximal Pupil 7.4 ± 0.5	Baseline Pupil 3.0 ± 0.6	Maximal Pupil 7.3 ± 0.4	Baseline Pupil 2.9 ± 0.6	Maximal Pupil 7.1 ± 0.6	Baseline Pupil 2.9 ± 0.2	Maximal Pupil 2.9 ± 0.2

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Reviewer's comments:

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.
See also Section 7.4.5 of this review for safety information in neonates.

6.1.4.4 Dark versus Light Irides

(b) (4)

Per Gambill 1967, computed mydriasis-time curves and the average experimental data for homatropine in subjects with light and dark irides in the study were constructed. It was reported, "…essentially the same results were found for the other three mydriatic drugs" (which included 10% phenylephrine). Per Haddad 1970, "…significant differences in degree of mydriasis occur with variations in iris pigmentation. Of our subjects, those with hazel irides consistently developed the least mydriasis while those with blue irides developed the greatest."

Reviewer's comments:

There is evidence that 10% phenylephrine has slightly higher treatment effects compared with 2.5% concentration in patients with dark irides,

6.1.5 Analysis of Secondary Endpoints(s)

Not applicable.

6.1.6 Other Endpoints

Not applicable.

6.1.7 Subpopulations

The overall age range of patients from the key efficacy studies was 5-87 years. Neonates were evaluated separately for safety and efficacy. Based on a comparison across studies, the effectiveness results do not appear to vary with age.

In general, more females than males participated in these studies. None of the studies examined the effects of gender on the effectiveness outcome.

None of the demographic factors described appeared to correlate with any specific efficacy outcome.

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6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

See Section 6.1.4 of this review. The studies support a dosing regime of 2.5% and 10% phenylephrine solution instilled at 3 – 5 minute intervals up to a maximum of 3 drops per eye in patients aged 1 or older and 2.5% phenylephrine in pediatric patients < 1 year old.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The drug's maximal effect occurs in 60-90 minutes with recovery after 5-7 hours.

6.1.10 Additional Efficacy Issues/Analyses

None.

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Clinical Studies Used to Evaluate Safety

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 below:

See Appendix 9.1 of this review for a list of these literature articles.

Reference ID: 3271568

Authors	Study title	a) Design b) Efficacy data c) Safety data
Allinson 1990	Reversal of Mydiasis/ 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 synechiae. 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 ± 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 demercarium bromide 0.25% phenylephrine 10% caused a very slight increase in IOP.
Borromeo-McGrail 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 mydriatic 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.

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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.

7.1.2 Adequacy of Data

Reference literature reports, surveys, and articles cited in this review are representative of the published literature. They are adequate to make a determination of the safety of the 2.5% and 10% phenylephrine hydrochloride concentrations. There is no evidence that these references refer to trials not conducted in accordance with acceptable clinical ethical standards.

7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

Pooling of data across various studies was not informative given the variety of studies performed, i.e. case report studies, non- randomized studies, randomized studies, etc.

7.2 Adequacy of Safety Assessments

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

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.

Phenylephrine ophthalmic solution 2.5% results in an acceptable increase of heart rate and blood pressure; due to these increases the higher dose of phenylephrine ophthalmic solution 10% is not recommended in infants less than 1 year old. See Section 7.4.5 of this review.

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7.2.2 Explorations for Dose Response

The dose response curve for mydriasis flattens above the 2.5% concentration with little difference between 5% and 10% concentrations (Haddad, 1979). The efficacy difference between the 5% and 10% concentrations is not statistically significant. The optimal dose range appears to be 2.5% to 10%. In general, a subject should receive a dose by instillation, every 3-5 minutes until the desired mydriasis is obtained to a maximum of 3 drops.

7.2.3 Special Animal and/or In Vitro Testing

Phenylephrine hydrochloride is an α-adrenergic receptor sympathetic 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.

Given the extensive use of phenylephrine in humans additional animal / in vitro testing is not required.

7.2.4 Routine Clinical Testing

Additional clinical testing is not required.

7.2.5 Metabolic, Clearance, and Interaction Workup

Metabolic and clearance studies were not performed.

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

Refer to Section 7.2.5.

7.3 Major Safety Results

7.3.1 Deaths

No deaths were reported due to the use of topical ophthalmic phenylephrine solution.

7.3.2 Nonfatal Serious Adverse Events

Several authors describe the potential for 10% phenylephrine to exacerbate vasoconstrictive conditions and cardiovascular conditions following topical ophthalmic use. Marked elevation of blood pressure, tachycardia, ventricular arrhythmias, myocardial infarction, and subarachnoid hemorrhage are reported as rare reactions following topical ocular instillation. Four cases of worsening of visual loss in subjects with non-arteritic ischemic optic neuropathy after 2.5%

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phenylephrine plus 0.5% or 1% tropicamide was used in a dilated fundus exam have been reported.

7.3.3 Dropouts and/or Discontinuations

Not applicable.

7.3.4 Significant Adverse Events

Ophthalmic use of phenylephrine occasionally causes 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 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.

7.3.5 Submission Specific Primary Safety Concerns

Refer to Section 7.3.4.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

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.

7.4.2 Laboratory Findings

There is a potential for 10% phenylephrine to cause an increase in blood pressure particularly systolic blood pressure and to increase or decrease HR. There is evidence that 2.5% is less likely to cause an increase in BP or HR and for this reason is generally preferred in the elderly and the very young.

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7.4.3 Vital Signs

Refer to Section 7.4.2.

7.4.4 Electrocardiograms (ECGs)

ECGs findings were not reported.

7.4.5 Special Safety Studies

Special safety studies were performed in neonates in the Sindel 1986 Study and the Borromeo-McGrail 1973 Study. See Section 6.1.4.3 of this review for a more detailed discussion of Sindel 1986.

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 ± 9.3tt	+3.0 ± 6.0
Diastolic	+15.9 ± 7.8*	+19.5 ± 14.2*	+5.4 ± 7.6ttt	+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

Reviewer's comments:

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

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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

Reference ID: 3271568

Reviewer's comments:

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.

7.4.6 Immunogenicity

Not applicable.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

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.

7.5.2 Time Dependency for Adverse Events

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.

7.5.3 Drug-Demographic Interactions

The risk of severe hypertension is greatest in infants less than 1 year old receiving instillations of 10% phenylephrine hydrochloride solutions.

Many studies have reviewed the safety of phenylephrine and some authors have excluded subjects with a history of cardiovascular conditions from their studies based on the known and expected risks of using sympathomimetic drugs in such subjects.

7.5.4 Drug-Disease Interactions

In subjects with vasoconstrictive disease of the retina the use of phenylephrine eye drops may make the condition worse leading to additional vision loss.

Four patients (age range 54-82, 1F 3M) diagnosed with non-arteritic ischemic optic neuropathy experienced acute worsening of visual function after instillation of phenylephrine for dilated fundoscopy examination.

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Phenylephrine is contraindicated in patients with a history of closed angle glaucoma (unless previously treated with iridectomy) and in patients at risk for narrow angle glaucoma precipitated by mydriatics.

7.5.5 Drug-Drug Interactions

The potential for interaction exists with other drugs administered topically and systemically.

Interaction with topical anticholinergic cycloplegic drugs eg : tropicamide, cyclopentolate hydrochloride, homatropine hydrobromide, or scopolamine hydrobromide and has been shown to be synergistic, resulting in a greater mydriasis. The two drugs are frequently used together for that reason.

The cardiac and pressor effects of phenylephrine are potentiated by prior administration of monoamine oxidase (MAO) inhibitors because the metabolism of phenylephrine is reduced. The potentiation is greater following oral administration of phenylephrine than after parenteral administration of the drug because reduction of the metabolism of phenylephrine in the intestine results in increased absorption of the drug. Topical ocular administration may be regarded as similar to parenteral because of the rapid direct absorption into the blood of the superior vena cava and the heart (McEvoy 2007). Tricyclic antidepressants (e.g., imipramine) or guanethidine may also potentiate the vasopressor effects of phenylephrine. The mydriatic response to phenylephrine may be decreased in patients receiving levodopa (McEvoy 2007).

Rarely, administration of phenylephrine to patients who have received cyclopropane or halogenated hydrocarbon general anesthetics that increase cardiac irritability and seem to sensitize the myocardium to phenylephrine may result in arrhythmias. The manufacturer states that vasopressors should be used only with extreme caution or not at all with these general anesthetics. However, in usual therapeutic doses, phenylephrine is much less likely to produce arrhythmias than is norepinephrine or metaraminol (McEvoy 2007).

7.6 Additional Safety Explorations

7.6.1 Human Carcinogenicity

Human carnicogenicity studies were not performed. There was no evidence of carcinogenicity of phenylephrine hydrochloride in male or female rats given 620 or 1,250 ppm in feed or in male or female mice given 1,250 or 2,500 ppm in feed.

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7.6.2 Human Reproduction and Pregnancy Data

It is not known whether phenylephrine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Phenylephrine ophthalmic solution, 2.5% and 10% should be given to a pregnant woman only if clearly needed.

7.6.3 Pediatrics and Effect on Growth

Phenylephrine ophthalmic solution 10% is contraindicated in pediatric patients less than 1 year of age.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Rebound miosis has been reported in elderly patients one day after receiving phenylephrine ophthalmic solution, and re instillation of the drug produced a lesser mydriatic effect. This may be of clinical importance in dilating the pupils of older subjects prior to retinal detachment or cataract surgery.

Topical overdosing is unlikely since the excess spills onto the face. However, repeated instillation may be dangerous particularly in the elderly, the very young, those with cardiovascular disease and long standing diabetics.

7.7 Additional Submissions

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.

8 Postmarketing Experience

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) .

A market review of phenylephrine sales in the US in 2010 showed that approximately (b) (4) mL of eye drops were purchased. Per the applicant, this volume equates to approximately (b) (4) patient exposures annually.

In a FDA Adverse Event Reporting System (FAERS) Standard Case Series Summary Report run December 14, 2012, for "Phenylephrine ophthalmic," the following events were identified:

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Preferred Term	Count Of Events	Percent Of Total Cases
TOXIC ANTERIOR SEGMENT SYNDROME	20	15.38%
INFLAMMATION	16	12.31%
EYE DISORDER	15	11.54%
IRIDOCYCLITIS	14	10.77%
BRADYCARDIA	8	6.15%
DRUG EFFECT PROLONGED	7	5.38%
APNOEA	6	4.62%
CYANOSIS	6	4.62%
BLINDNESS	5	3.85%
CORNEAL ABRASION	5	3.85%
EYE PAIN	5	3.85%
MYDRIASIS	5	3.85%
VISUAL IMPAIRMENT	5	3.85%
DIZZINESS	4	3.08%
ENDOPHTHALMITIS	4	3.08%
HYPERTENSION	4	3.08%
HYPOTENSION	4	3.08%
MALAISE	4	3.08%
NECROTISING COLITIS	4	3.08%
VISION BLURRED	4	3.08%
CARDIAC ARREST	3	2.31%
CONJUNCTIVITIS	3	2.31%
DRUG INEFFECTIVE	3	2.31%

Reviewer's comments:

Only a portion of the search is presented here. Many of the counted events are unrelated to the sole use of phenylephrine hydrochloride ophthalmic solution; they appear to be associated with ocular conditions for which topical phenylephrine was used diagnostically or therapeutically to dilate the pupil, e.g. toxic anterior segment syndrome, inflammation, iridocyclitis, etc.

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9 Appendices

9.1 Literature Review/References

This review is based on the literature submitted.

EFFICACY

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SAFETY

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9.2 Advisory Committee Meeting

No Advisory Committee Meeting was held. There were no new issues raised in the review of the application which were thought to benefit from an Advisory Committee Meeting.

9.3 Labeling Recommendations

Following is the draft labeling submitted by the applicant on 10/21/11 (in the "original" NDA submission which received a REFUSAL TO FILE letter).

Revised carton and container labeling and revised package insert, consistent with the revised, track changes versions noted here, should be submitted to the NDA.

Reference ID: 3271568

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Reviewer's Comments:

1) To avoid selection error, revise the color scheme of the labeling (i.e. carton and container labeling) for one of the product strengths from (b) (4) *to another color scheme so that they are well differentiated from each another.*

2) Change the font color of the proprietary name on the carton and container to a color that provides better contrast against a (b) (4) *background.*

3) Ensure that the established name is at least half the size of the proprietary name. Ensure the established name has prominence commensurate with the proprietary name taking into account all pertinent factors including typography, layout, contrast and other printing features per 21 CFR 201.10(g)(2). Remove the (b) (4) *outline around the letters of the proprietary name unless you also utilize the* (b) (4) *outline on the established name.*

4) The strength statement should directly follow after the established name on the principal display panel of the carton and container labels. For example: (b) (4) *(phenylephrine ophthalmic solution) 2.5%.*

5) Revise the net quantity statement to include a space between the number and the unit of measure. For example: 5mL should read 5 (space) mL.

6) Delete or relocate the word (b) (4) *that appears directly below the strength statement to a location away from the strength statement.*

7) The statement on the container labeling, "Do not use if imprinted seal on cap is torn, broken or missing," is printed in a (b) (4) *font color against a* (b) (4) *background. Change the font color to a color that provides better contrast against a* (b) (4) *background, such as black.*

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/s/

MARTIN P NEVITT
03/05/2013

WILLIAM M BOYD
03/05/2013