CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203510Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	See electronic stamp date
From	Renata Albrecht, MD Division of Transplant and Ophthalmology Products
Subject	Division Director Summary Review
NDA Number	NDA 203510
Related IND	None
Applicant Name	Paragon BioTech, Inc.
Date of Submission **Date of Receipt**	September 20, 2012 (cover letter) September 21, 2012
Review Type:	Priority
PDUFA Goal Date	March 21, 2013
Proprietary Name / **Established (USAN) Name**	None approved at this time Phenylephrine hydrochloride ophthalmic solution
Formulation **Presentation** **Use**	Ophthalmic solution in vial with red cap • 2.5% concentration: 15 mL fill volume in 15 mL LDPE vial • 10% concentration: 5 mL fill volume in 10 mL LDPE vial One drop every 3 to 5 minutes for maximum of 3 drops
Proposed Indication	Dilation of pupil
Action for Application	*Approval*

Material Reviewed/Consulted OAP Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Martin Nevitt, Bill Boyd 3/5/2013
CDTL Review	Bill Boyd 3/20/2013
Deputy Division Director Review	Wiley Chambers 3/20/2013
Statistical Review Team Leader Review	Yunfan Deng, Yan Wang 2/21/2013 Yan Wang, Daphne Lin 3/1/2013
Pharmacology/Toxicology Review	Maria Rivera, Lori Kotch 2/20/2013
Clinical Pharmacology Review	Yongheng, Zhang, Philip Colangelo 12/12/2012
Product Quality Manufacturing Review ONDQA	Balajee Shanmugam, Rapti Madurawe 11/27/2012 George Lunn, Rapti Madurawe 2/20/2013, 3/14/2013
Product Quality Microbiology Review	Steven Donald, Bryan Riley 1/3/2013
OC/Facilities Inspection	Acceptable (see CMC review)
OSI/DGCPC	N/A
Proprietary Name Review	Karen Townsend 3/14/2013
OSE/DMEPA Labeling Review	Jung Lee, Jamie Wilkins Parker 2/22/2013
OPDP/DPDP (formerly DDMAC)	Christine Corser 2/26/2013
Pediatric Review Committee	Mitchell Berger, email 3/19/2013
Project Manager	Diana Willard

OND=Office of New Drugs,
CDTL=Cross-Discipline Team Leader
ONDQA = Office of New Drug Quality Assessment
OSI/DGCPC=Office of Scientific Investigations/Division of Good Clinical Practice Compliance (formerly Division of Scientific Investigation (DSI)
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OPDP/DPDP=Office of Prescription Drug Promotion/Division of Professional Drug Promotion; formerly, DDMAC=Division of Drug Marketing, Advertising and Communication

Table of Contents:

1. Summary and Recommendations

Phenylephrine hydrochloride ophthalmic solution is a topical ophthalmic product intended to dilate the pupil. The application was submitted as a 505(b)(2) application and relies on literature data for the clinical and non-clinical information.[1]

As summarized below, phenylephrine has been marketed for over 70 years, and used in various concentrations to dilate the pupil. The applicant submitted over 30 publications on clinical trials and/or safety information to support the efficacy and safety of the application. Briefly, these trials confirmed the ability of both the 2.5% and 10% to achieve pupil dilation, starting as soon as 15 minutes after instillation and generally achieving maximum dilation by 20-90 minutes. The effect resolved after around 5 hours (range of 3 to 8 hours). In these studies, the 2.5% product increased pupil diameter between 1 to 3 mm compared to the baseline size or to the contralateral pupil, and the 10% product increased pupil diameter 1 to 4 mm. Under lit condition, the difference between the two pupils was greater, due to the reflective constriction of the un-treated pupil in response to light.

The Indications and Usage section, and the Dosing and Administration section of labeling will provide the following information:

1 Indications and Usage
Phenylephrine Hydrochloride Ophthalmic Solution, USP 2.5% and 10% is indicated to dilate the pupil.

2 Dosage and administration
General Dosing Recommendations
In patients 1 year of age or greater, apply one drop of either Phenylephrine Hydrochloride Ophthalmic Solution, USP 2.5% or 10% every 3 to 5 minutes to the conjunctival fornix as required up to a maximum of 3 drops. If necessary, this dose may be repeated.

In order to obtain a greater degree of mydriasis, Phenylephrine Hydrochloride Ophthalmic Solution, USP 10% may be needed.

Pediatric Patients Less Than 1 Year of Age
In pediatric patients less than 1 year of age, one drop of Phenylephrine Hydrochloride Ophthalmic Solution, USP 2.5% should be instilled at 3 to 5 minute intervals up to a maximum of 3 drops per eye.

Phenylephrine is an α_1-adrenergic agonist (sympathomimetic) and its pharmacodynamics effect on the eye and cardiovascular system has been described in the literature. As far as adverse reactions, local effects of the ophthalmic solution include stinging, pain, blurring on installation and photophobia associated with the dilation of the pupil. Rebound miosis on re-installation of phenylephrine has been reported.

Systemic effects include increased blood pressure, and cardiac events including tachycardia, ventricular arrhythmias, myocardial infarction, syncope and subarachnoid hemorrhage. Although these events could be associated with both concentrations, they are more likely to be associated

[1] The application is cleared from a 505(b)(2) perspective based on email dated 2/27/2013 from the OND Associate Director for Regulatory Affairs, Beth Duvall.

with the 10% formulation, and in younger children and elderly patients with underlying hyperthyroidism and cardiovascular disease. The 10% product is contraindicated in infants under the age of 1 year because of the serious risk of hypertension and systemic toxicity, and in patients with hypertension and thyrotoxicosis. Atropine may enhance the pressor effects of phenylephrine. Phenylephrine may potentiate the depressor effects of anesthetic agents. This safety information is incorporated in the package insert. Although information on animal studies from the literature was provided, the labeling provides brief cautionary language about use in pregnant women and nursing mothers; this labeling is consistent with the advice given in the recently approved intravenous product, phenylephrine hydrochloride (NDA 203826, approved December 20, 2012).

Product labeling, including carton and container labels for both concentrations have been finalized. There is no approved trade name at this time so the product will be approved under the established name. The Office of Compliance recommended the manufacturing facilities are acceptable.

1.1 Deficiencies
None, the application will be approved.

1.2 Post-Marketing Studies:
See Section 13.3.

1.3 Other Issues
None

2. Background

This application is submitted as a 505(b)(2) application and relies on published literature for clinical and preclinical information. The applicant (Paragon BioTech, Inc.) states that phenylephrine 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. The first description of its topical ocular use in the literature is in 1936 [2] and since then numerous other articles have been published. Paragon estimates that since 1970 phenylephrine hydrochloride ophthalmic solutions have been used more than 3 billion times and that annual clinical ophthalmic exposure is in excess of 80 million uses per year.

The NDA is submitted in response to the unapproved drug initiative started by the Agency in 2006.[3] The products in this application (2.5% and 10% solutions) are the same as the marketed

[2] Heath p. Neosynephrine; some uses and effects in ophthalmology. Arch Ophth 1936;16:839.
[3] FDA guidance for FDA Staff and Industry, Marketed Unapproved Drugs – Compliance Policy Guide: Sec 444.100 Marketed New Drugs without Approved NDAs or ANDAs, revised September 2011.
http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070290.pdf
and Unapproved Drugs Initiative:
http://www fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/SelectedEnforcementActionsonUnapprovedDrugs/ucm118990.htm

products and differ only in the absence of a (b) (4) from the marketed unapproved product, as noted by the CMC reviewer.

Some of approved FDA prescription products containing epinephrine are:

- Cyclomydril ophthalmic solution NDA 084300 by Alcon - This is a combination ophthalmic solution of phenylephrine hydrochloride 1% and cyclopentolate hydrochloride 0.2% approved for the production of mydriasis
- Prefrin-A opththalmic solution, NDA 007953 by Allergan – This is a combination of phenylephrine hydrochloride 0.12% and pyrilamine maleate 0.1% intended for relief of ocular redness. The product is not marketed.
- Phenylephrine HCl Injection, USP, 10 mg/mL, NDA 203826 – approved December 20, 2012 for increasing blood pressure in adults with clinically important hypotension resulting primarily from vasodilation, in such settings as septic shock or anesthesia. Note: The labeling of this product was examined for precedent for various sections.

Ophthalmic topical products for over-the- counter (OTC) use are allowed to contain phenylephrine hydrochloride 0.08% to 0.2% and labeled for relief or redness or vasoconstriction.[4]

In the eye, phenylephrine acts locally to constrict ophthalmic blood vessels and the radial (dilator) muscle of the iris. Dilation of the pupil is necessary to conduct numerous procedures in ophthalmology including routine eye examinations to view the retina and optic nerve, surgical procedures such as cataract extraction and IOL placement, and lysis of synechiae.

2.1 NDA Submission and User Fee Overview

The original NDA 203510 was submitted on October 19, 2011 and was issued a refuse-to-file letter on December 16, 2011 because the application lacked sufficient stability data; 12 months data on three registration batches were not included in the submission. A teleconference was held on February 10, 2012, with Point Guard Partners, LLC on behalf of the applicant, Paragon BioTech, Inc., during which needed stability data were discussed, and the alternative option of submitting the marketed products, (b) (4) strengths, for which stability data presumably exist was also discussed.

Paragon resubmitted their application on September 20, 2012, received September 21, 2012. The application contained adequate stability data and was filed.

Paragon were granted a Small Business Waiver of the PDUFA fee for this NDA [5]

2.2 Priority Review

[4] 21 CFR 349 Ophthalmic drug products for over-the-counter use. Paragraphs 349.18 and 349.75.
[5] A copy of the user fee cover sheet and the FDA letter granting the waiver are provided in Module 1 Section 1.1.3 User Fee Cover Sheet.

Paragon was granted a priority review, based on the following justification: Currently there are no FDA approved prescription drug products for ophthalmic use containing phenylephrine hydrochloride as a single active ingredient at concentrations necessary to induce adequate pupil dilation (b) (4). Hence, there is an unmet medical need for such a product.

3. CMC/Product Quality Microbiology

See complete CMC review by George Lunn and Rapti Madurawe and Microbiology Sterility review by Steven Donald and Bryan Riley.

3.1 Product Quality

Phenylephrine Hydrochloride Ophthalmic Solution, USP 2.5% and 10%, contain the preservative benzalkonium chloride 0.1%.

Phenylephrine Hydrochloride Ophthalmic Solution, USP 2.5% is supplied as a sterile, aqueous, topical ophthalmic solution with a fill volume of 15 mL in a 15 mL opaque, white low density polyethylene (LDPE) bottle with a linear low density polyethylene (LLDPE) dropper tip and red cap.

Phenylephrine Hydrochloride Ophthalmic Solution, USP 10% is supplied as a sterile, aqueous, topical ophthalmic solution with a fill volume of 5 mL in a 10 mL opaque, white LDPE bottle with a LLDPE dropper tip and red cap.

The composition of the product is shown in the following table:

Table 1. Phenyelephrine HCl ophthalmic solution composition

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

(Table is copied from *description-and-composition.pdf*, pg. 2 of 3)

(Source: product quality microbiology review.)

Drug Product specifications are listed in the table below. The CMC reviewer notes that the acceptable criteria and specifications for impurities were tightened at the request of FDA (amendment 1/30/2013); the specifications are adequate and acceptable justifications have been provided.

Test	Method	Acceptance criterion
Appearance	Visual	Clear, colorless to yellowish solution
Identity	TLC	Reddish orange spot conforms to standard
Identity	HPLC	Retention time conforms
pH at 25°C	pH	4.0-7.5
Osmolality	USP <785> (freezing point depression)	
2.5% solution		450-550 mOsm/kg
10% solution		950-1050 mOsm/kg
Assay for phenylephrine	HPLC	90-110%
Benzalkonium chloride	HPLC	80-120%
Impurities	HPLC	
[redacted] (b) (4)		
Particulate	USP <789>	
[redacted] (b) (4)		
Minimum fill	USP <755>	Conforms
Deliverable volume	USP <698>	Conforms
Sterility	USP <71>	Pass
Endotoxins	USP <85>	[redacted] (b) (4)

This is a Type 7 NDA, a marketed product without an approved NDA. The product has been manufactured by [redacted] (b) (4) since 2001, but the unapproved product has a [redacted] (b) (4). The CMC reviewer notes the manufacturing process is described in detail [redacted] (b) (4) The substance and product follows USP specifications and these are adequate to control quality. Three commercial batches were provided for each concentration and are satisfactory. Expiry of 18 months was granted.

3.2 Product Quality Microbiology

The Product Quality Microbiology reviewers note that testing of the container-closure and package integrity (including (b) (4) sterilization), manufacturing process and process controls, (including (b) (4)) are acceptable, there are no deficiencies, and these data can support (b) (4) expiry. Antimicrobial effectiveness has been established by testing at (b) (4)

3.3 Biopharmaceutics – BA/BE Waiver

Dr. Lunn notes that a BA/BE waiver under 21 CFR 320.22(e) is appropriate for these products.

Comment:
The ONDQA CMC reviewers recommend approval of the application from their perspective. One PMC is requested: See Section 13.3.

4. Nonclinical Pharmacology/Toxicology

See Pharmacology/Toxicology review by Drs. Rivera and Kotch.

The application contained published non-clinical studies. As noted by the reviewers, the applicant cited the toxicology package conducted by the National Toxicology Program (NTP) which includes general toxicology (14-day and 12-week repeated-dose studies), genetic toxicology, carcinogenicity evaluations, and references for reproductive toxicology evaluation. The nonclinical studies are noted to be longer (12 weeks or 2 years) than the intended one-day administration in humans and the calculated safety margins were high based on assumed 100% absorption. In addition, the 70 year history of human use is acknowledged.

Comment: The Pharmacology/Toxicology (P/T) reviewers recommend approval. Initially labeling recommendations summarizing the nonclinical studies were proposed in Sections 8 and 13 of labeling. However, after considering the more abridged labeling in the recently approved phenylephrine HCl solution NDA 203826 (December 20, 2012) in the Division of Cardiovascular and Renal Products, the labeling was modified to reflect that no ocular toxicity studies were conducted, and phenylephrine risk benefit should be considered in pregnant women and nursing mothers.

5. Clinical Pharmacology/Biopharmaceutics

See Clinical Pharmacology review by Drs. Zhang and Colangelo.

The reviewers note there were no clinical pharmacology studies submitted for review, and there is extensive clinical use of the product. Information for the labeling is derived from the literature.

Comment: The reviewers recommend approval from the Clinical Pharmacology perspective, and provide labeling revisions to Clinical Pharmacology section of labeling.

6. Clinical Microbiology/Immunology

Not Applicable

7. Clinical/Statistical-Efficacy

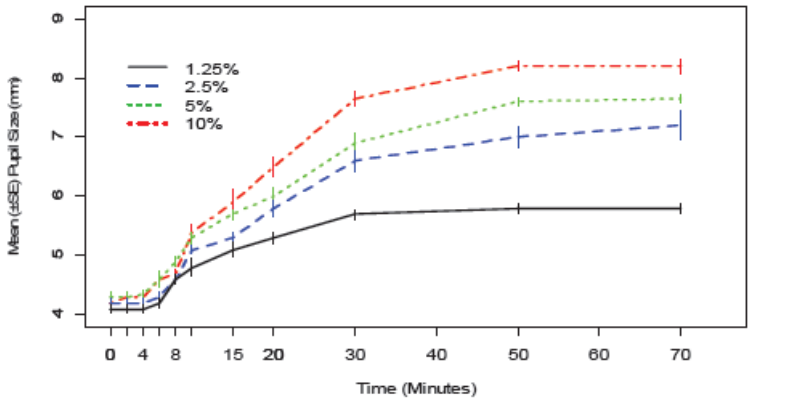
See clinical reviews by Drs. Nevitt, Chambers and Boyd, and biostatistics reviews by Drs. Deng and Wang.

The applicant noted that phenylephrine has been marketed for over 70 years for ophthalmic use, has been the subject of numerous publications of which over 30 publications are cited reporting on efficacy (controlled clinical trials) and safety in this 505(b)(2) application. The applicant did not conduct any further clinical trials.

Efficacy studies evaluated phenylephrine alone, or in combination with other topical drops. The articles included controlled studies that reported on 2.5% and 10% formulations and other concentrations. Highlights of selected publications are provided below:[6]

1. Chawdhary et al[7] (India) evaluated 1.25%, 2.5%, 5%, and 10% phenylephrine concentrations and measured pupil size over 70 minutes. The mean changes from baseline in pupil size (mm) are statistically significant for all four concentrations: 1.7 (95% CI: 1.5, 1.9; p-value < 0.0001) in the 1.25% group, 3.0 (95% CI: 2.5, 3.5; p-value < 0.0001) in the 2.5% group, 3.4 (95% CI: 3.1, 3.6; p-value < 0.0001) in the 5% group, and 4.0 (95% CI: 3.7, 4.3; p-value < 0.0001) in the 10% group. These results demonstrate that the three higher concentrations were highly effective in dilating pupils. The difference in pupil size among the four concentrations was also significant.

Figure 1: Mydriatic Effects of Four Concentrations of Phenylephrine



[6] Summaries of the first 7 articles are excerpted from the references and Dr. Wang's review.
[7] Chawdhary S, Angra SK, Zutshi R, Sachev S. Mydriasis use of phenylephrine (A dose response Concept). Ind J Ophthalmol. 1984; 34:213-216.

2. **Haddad et al** [8] (Rochester, Minnesota) conducted a two part study, comparing pupil dilation at various concentrations of aqueous phenylephrine formulations and the 10% marketed product measured for up to 90 minutes. A dose response was seen as shown in the figure below:

Am J Ophthalmol. Nov 1970: 70 (5);729-733

Fig. 1 (Haddad, Moyer, and Riley). Dose-response curve for phenylephrine HCl mydriasis in Group 1 (mean ± SE). Percent of concentration of phenylephrine HCl is shown across bottom. Lower point at 10% concentration represents commercially available solution.

The second part of the study compared pupil size with our without light stimulation in patients who received a 1% phenylephrine aqueous solution and a 10% solution. The differences in pupil size (mm) between the treated eye and the untreated eye without light stimulation was 2.08 mm (95% CI: 1.81, 2.35; p-value < 0.0001) and with light stimulation was 3.57 mm (95% CI: 3.53, 3.61; p-value < 0.0001). Recovery was reported after approximately 3 hours. The authors also describe rebound miosis, the finding that the pupil is smaller on the day after instillation and may dilate to less than the original diameter after a second installation one day later in subjects over 50 years with pigmented irides.

3. **Gambill et al**[9] (Rochester, Minnesota) investigated the effect of four drugs, including 10% phenylephrine in a cross-over design. Maximal mydriasis occurred at 70 minutes, recovery occurred greater than 5 hours after instillation. The maximal mydriatic effect of 10% phenylephrine compared to the un-treated eyes was statistically significant: 2.42 mm (95% CI: 1.83, 3.01; p-value<0.0001).

	10% Phenylephrine (N=15)	**0.5% Tropicamide (N=15)**	**1% Hydroxyampheta mine (N=15)**	**2% Homatropine (N=15)**
Mean ± SD (95% CI)*	2.42 ± 1.16 (1.83, 3.01)	2.69 ± 0.55 (2.41, 2.97)	1.93 ± 0.70 (1.58, 2.28)	2.47 ± 0.60 (2.14, 2.80)
P-value*	<0.0001	<0.0001	<0.0001	<0.0001

* Calculated by the team leader. 95% CI based on the normal distribution approximation and p-value based on paired t-test for each treatment group.

[8] Haddad NJ, Moyer NJ, Riley FC. Mydriatic effect of phenylephrine hydrochloride. Am J Ophthalmol. 1970;70 (5):729-733.
[9] Gambill HD, Ogle KN, Kearns TP. Mydriatic effect of four drugs determined with pupillograph. Arch Ophthal 1967:77:740-746.

4. Filho et al[10] (Brazil) evaluated the safety and efficacy of 2.5% and 10% phenylephrine solutions and found that the 10% solution achieved greater mydriasis than the 2.5% solution. The baseline pupil size was 5.8 mm (smaller than the 4.2 mm in Chawdhary study), the pupil size increased by 1.3 – 1.4 mm after 2.5% phenylephrine and 2 mm after 10% phenylephrine. The difference between the two concentrations is: 0.6 (95% CI: 0.10, 1.10; p-value < 0.03).

		2.5% Phenylephrine (N=28)	10% Phenylephrine (N=28)	Treatment Difference Mean (95% CI)* P-value
Right Eye	Baseline Mean ± SD	5.8 ± 1.2	5.8 ± 1.0	
	Change from Baseline			
	Mean ± SD	1.3 ± 1.0	2.0 ± 1.1	0.7 (0.13, 1.27)
	(95% CI)*	(0.93, 1.67)	(1.59, 2.41)	0.015*
	P-value*	<0.0001	<0.0001	0.016**
Left Eye	Baseline Mean ± SD	5.8 ± 1.2	5.8 ± 1.0	
	Change from Baseline			
	Mean ± SD	1.4 ± 1.0	2.0 ± 0.9	0.6 (0.09, 1.11)
	(95% CI)*	(1.03, 1.8)	(1.67, 2.33)	0.028*
	P-value	<0.0001	<0.0001	0.022**

* P-value based on Kruskal-Wallis test for testing treatment difference.
** Calculated by the team leader. 95% CI based on the normal distribution approximation, p-value based on paired t-test for each treatment group, and p-value based on 2-sample t-test for comparing the two concentrations.

5. Yospaiboon et al[11] (Thailand) conducted a large randomized trial in Thailand, randomized patients to 1% tropicamide then 2.5% phenylephrine (n=271) or 1% tropicamide then 10% phenylephrine (n=293). The 2.5% formulation increased pupil size by 0.7 mm and the 10% increased pupil size by 1.1 mm. The difference between the two concentrations is significant.

	2.5% Phenylephrine (N=271)	10% Phenylephrine (N=293)	Treatment Difference
Mean (±SD) Pupil Size			
Right Eye			
Baseline	4.45 ± 1.00	4.43 ± 1.13	
Tropicamide	6.38 ± 0.96	6.46 ± 0.99	
Phenylephrine	7.17 ± 1.04	7.58 ± 0.96	
Left Eye			
Baseline	4.32 ± 0.92	4.31 ± 0.95	
Tropicamide	6.34 ± 1.01	6.45 ± 0.99	
Phenylephrine	7.07 ± 1.06	7.60 ± 1.03	
Mean (95% CI, P-value)* Change in Pupil Size			
Right Eye	0.79 (0.72, 0.86)	1.12 (1.04, 1.20)	0.33 (0.22, 0.44)
Δ Phenylephrine	<0.0001	<0.0001	<0.0001
Left Eye	0.73 (0.66, 0.80)	1.16 (1.07, 1.25)	0.43 (0.31, 0.55)
Δ Phenylephrine	<0.0001	<0.0001	<0.0001

Δ is the difference in pupil size before and after phenylephrine treatment. This measure the added effect over tropicamide administration.
* Calculated by the team leader. 95% CI based on normal distribution approximation, p-value for each treatment group based paired t-test, and p-value for treatment difference based on 2-sample t-test.

[10] Filho AD, Frasson M, Merula RV, Morais PR, Cronenberger S. Cardiovascular and mydriatic effects of topical phenylephrine 2.5% and 10.0% in healthy volunteers. Arq Bras Oftalmol 2007; 70 (6):961-6 (translation sent December 20, 2012).
[11] Yospaiboon P, Luanratanakorn P, Noppawinyoowong C. Randomized double-blind study of phenylephrine 2.5% vs 10% on pupillary dilation. J Med Assoc Thai, 2004; 87(11):1380- 1384.

6. Neuhaus et al[12] (Los Angeles, CA) tested the two concentrations (2.5% and 10%) in eleven patients in a cross-over trial. The mean change in pupil size was 1.6 mm after the 2.5% concentration and 1.88 mm after the 10% concentration. The difference was not statistically significant. It's noted that this is a smaller study, and patients had pupils measured at one two time points: baseline and 60 minutes.

7. Ozturks et al [13] (Turkey) evaluated the efficacy of 2.5% or 10% phenylephrine in combination with cyclopentolate 1% (and flurbiprofen 0.03%). The study did not show significant difference pupil dilation between 2.5% and 10% phenylephrine concentrations. There was added dilation reported with the addition of flurbiprofen, in both phenylephrine concentrations, but no difference between the 2.5% and 10% concentration groups, as shown below: [In the figure below, the first two rows of data represent the arms not receiving flurbiprofen, the last two rows of data are arms receiving flurbiprofen.]

	2.5% Phenylephrine	10% Phenylephrine	Mean Difference (95% CI) P-value
	N=21	N=33	A vs. C
Pre-surgery Mean ± SD	8.3± 0.46	8.4± 0.57	0.1 (-0.20, 0.40) 0.5024
Post-surgery Mean ± SD	6.2± 0.92	6.4± 0.57	0.2 (-0.26, 0.66) 0.3790
	N=25	N=21	B vs. D
Pre-surgery Mean ± SD	8.8± 0.80	8.8± 0.57	0.0 (-0.42, 0.42) 1.0000
Post-surgery Mean ± SD	7.1 ± 0.92	7.4± 1.1	0.3 (-0.31, 0.92) 0.3273

* Calculated by the team leader. 95% CI based on the normal distribution approximation and p-value based on 2-sample t-test.

Comment:
In summary, these studies show phenylephrine is effective in achieving mydriasis compared to the patient's baseline or contralateral eye, and several studies show a dose response at concentrations spanning 1% to 10%. While some studies show that 10% is more effective than 2.5% (Chawdhary, Filho, and Yospaiboon) others do not confirm this finding (Neuhaus and Ozurks).

Additional publications examined are briefly summarized below:

[12] Neuhaus RW, Helper RS. Mydriatic Effect of Phenylephrine 10% (aq) vs Phenylephrine 2.5% (aq). Annals of Ophthalmol Oct 1980: 1159-1160.
[13]Ozturk F, Kurt E, Inan UU, Ilker SS. The efficacy of 2.5% pheynylephrine and flurbiprofen combined in inducing and maintaining papillary dilatation during cataract surgery. European J of Ophthal 10; 2:144-148 2000

8. Sindel et al[14] (Hershey, Pennsylvania) evaluated the safety and efficacy of 2.5% phenylephrine with tropicamide (1.0% or 0.5%), 1% phenylephrine with tropicamide (1.0%) compared to saline in neonates <1500 grams at birth. All phenylephrine groups achieve pupillary dilation of > 4mm from baseline and final diameter greater than 6 mm stated to be needed for adequate examination. The increase in systolic and diastolic blood pressure was greater after 2.5% compared to the 1% concentration, was transient and returned to baseline in approximately 20 minutes.

9. Allison et al[15] (Tucson, Arizona) report on 50 subjects who received tropicamide 1% and phenylephrine 2.5% and had dilation of pupils. Baseline pupil size in these subjects was 3.7 mm, and dilated to 8.6 mm after tropicamide 1% and phenylephrine 2.5%. After subsequent instillation of dapiprazole 0.5%, an alpha-adrenergic receptor blocker, the treated eyes had a diameter reduced to 4.5 mm at 2 hours and the untreated eyes were still dilated to 8.4 mm. Pupil size was recorded as having returned to baseline in both groups by 24 hours.

10. Paggiarino et al[16] (Newark, NJ) evaluated both concentrations of phenylephrine, and reported maximal pupil diameters of > 8 mm at 60 minutes, and the effect lasting for over 7 hours (11% of patients were reported as having dilated pupils at 15 hours after 2.5% phenylephrine, defined as > 0.5 mm compared to baseline). The reported change in pupil diameter was 2.7 mm with 2.5% and 3.2% with the 10% concentration.

11. Eyeson-Annan et al[17] (Queenland, Australia) report that 10% phenylephrine alone achieves pupil size > 6 mm after 40 minutes.

12. Tanner et al[18] (United Kingdom) reported that post-operative pupil diameter after 2.5% and 10% concentrations were 8.0 mm and 8.2 mm, respectively. There were 5/62 (8%) patients in the 2.5% group and 1/53 patients (2%) patients in the 10% group that did not achieve a diameter > 6 mm.

Comments:
Pupil dilation was achieved with the 2.5% and 10% phenylephrine based on the studies provided in the application. The degree of mydriasis was judged to be clinically significant. Several publications note that a pupil > 6 mm is adequate for fundus and retina examination.[19] *The*

[14] Sindel BD, Baker MD, Maisels MJ, Weinstein J. A comparison of the pupillary and cardiovascular effects of various mydriatic agents in preterm infants. J Ped Optha and Strabismus. 1986;23(6): 273-6.
[15] RW Allinson, DS Gerber, S Bieber and BL Hodes. Reversal of mydriasis by dapiprazole. Ann Ophthalmol 1990; 22:131-138.
[16] Paggiarino DA, Brancata LJ, Newton RE. The effects of pupil size and accomodation of sympathetic and parasympatholytic agents. Ann Ophthalmol, 1993;25:244-253.
[17] ML Eyeson-Annan, LW Hirst, D Battistuttat, A Green. Comparative pupil dilation using phenylephrine alone of in combination with tropicamide. Ophthalmology 1998;105(4):726-32.
[18] Tanner V, Caswell G. A Comparative Study of the efficacy of 2.5% phenylephrine and 10% phenylephrine in pre-operative mydriasis for routine cataract surgery. Eye 1996; 10:95-98.
[19] Sindel BD, Baker MD, Maisels MJ, Weinstein J. A comparison of the pupillary and cardiovascular effects of various mydriatic agents in preterm infants. J Ped Optha and Strabismus. 1986;23(6): 273-6.
Ibid Eyeson-Annan
Ibid Tanner.

labeling of Adrenalin NDA notes that > 5 mm diameter is important to be able to perform cataract surgery and insert an IOL. Of note, the agency approved a product called dapiprazole[20] in 1990 for the indication of reversing the dilation caused by phenylephrine.

8. Safety

See complete reviews by Drs. Nevitt, Boyd, Chambers, Deng and Wang.

The applicant noted that phenylephrine is a sympathomimetic with know vasoconstrictor effects that can lead to systemic cardiovascular toxicities such as tachycardia, palpitations, hypertension etc. Sympathomimetics such as phenylephrine stimulate the alpha adrenergic receptors found on smooth muscle in the heart and blood vessels causing vasoconstriction in blood vessels and an increase in blood pressure. The increase in blood pressure causes a baroreceptor reflex bradycardia through the vagus nerve. The potent vagal cardiac stimulation initiates serious ventricular arrhythmias. Adverse reactions reported with systemic phenylephrine have included insomnia, nausea, headache, dizziness, CNS stimulation, anxiety, palpitations, reflex bradycardia, tremor, and urinary retention. This information is consistent with the literature and information in the labeling of NDA 203826.

As already noted, ophthalmic phenylephrine products have been available for over 70 years. The applicant estimates that in the US the average number of patient exposures is in excess of 80 million per year over the last 40 years. This experience and multiple publications have contributed to the understanding of the products' safety profile.

Systemic adverse reactions associated with topical ophthalmic use: In the submitted articles, topical phenylephrine was associated with increases in blood pressure, both systolic and diastolic, and the increase generally retuned to baseline with half-hour. Some authors describe the potential for 10% phenylephrine to exacerbate vasoconstrictive conditions and cardiovascular conditions following topical ophthalmic use. Serious systemic effects such as myocardial infarction, syncope, ventricular arrhythmia, subarachnoid hemorrhage have been reported infrequently. Other events include palpitation, tachycardia, premature ventricular contractions, occipital headache, pallor or blanching, trembling or tremors, increased perspiration, and hypertension. The risk of severe hypertension is greatest in infants receiving instillations of 10% phenylephrine hydrochloride solutions.

Ocular adverse reactions with topical phenylephrine: 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. Topical anesthetics potentiate the effect of phenylephrine.

Comment:
The adverse reaction information from the literature is incorporated in the product labeling.

[20] Dapiprazole hydrochloride ophthalmic solution, NDA 019849 was approved December 31, 1990 and is marketed under the trade name Rev-Eyes. It is no longer marketed in the US - http://www.sharecare.com/question/what-is-dapiprazole

9. Advisory Committee Meeting

There were no efficacy and safety issues raised by this application to bring before the Advisory Committee. Epinephrine is not a new molecular entity.

10. Pediatrics

The application was presented before PeRC on March 6, 2013 and it was concluded that safety and efficacy has been established across all age groups, and that infants under the age of 1 year should not receive the 10% concentrations because of risk of severe hypertension and associated toxicities.

11. Other Relevant Regulatory Issues

This is a 505(b)(2) application, the preclinical and clinical information was submitted from the literature.

11.1 Compliance Inspection –

Overall the Office of Compliance found that facilities are acceptable as noted in the CMC review.

11.2 Office of Scientific Investigation (OSI) Audits

This is a 505(b)(2) application based on published literature, therefore an OSI inspection was not applicable.

11.3 Debarment Certification

Paragon Biotech, 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.

11.4 Financial Disclosure

This is a 505(b)(2) application based on published literature, and does not include any covered clinical trials as noted in 21 CFR 54, thus the application does not include investigator financial disclosure information.

11.5 Other Regulatory Issues

None

12. Labeling

The package insert and carton and container labels for the 2.5% and 10% formulations were reviewed as applicable by DTOP, DMEPA, and OPDP/DPDP. The labeling recommendations were discussed with the applicant on March 18, 2013 during which time the applicant asked for clarification on the information removed from their draft labeling; the response was that information which was supported by clinical and published data were included while unsupported labeling proposals were omitted.

- **Package insert (PI):** The PI is written in PLR format.

- **Carton and Container Labels**: The labels have been reviewed by DTOP, ONDQA and DMEPA. The carton/container labels have been finalized.

- **Proprietary Name**: DTOP and OPDP concluded that the proposed proprietary name (b) (4) was vulnerable to name confusion with (b) (4) and potentially promotional due to the letters "(b) (4)" implying (b) (4). The applicant was notified of this recommendation and withdrew this name. A preliminary review of the alternative name (b) (4) found it to be similar to (b) (4); the name was also withdrawn. (See Karen Townsend review, 3/14/2013.) There is no approved trade name at this time, the application will be approved and marketed with the established name.

13. Decision/Action/Risk Benefit Assessment

13.1 Regulatory Action

NDA 203510 will be approved. All disciplines recommend approval of the application. CMC initially recommended two PMCs be added, but based on further discussion, only the PMC asking for evaluation of leachables is retained; the PMC requesting stereoisomer testing was not pursued.

13.2 Risk Benefit Assessment

The safety and efficacy of phenylephrine hydrochloride ophthalmic solution was based on the review of published preclinical and clinical trials submitted in this 505(b)(2) application. Phenylephrine is an alpha-1adrenergic agonist that has been marketed for over 70 years and used for multiple uses, including dilation of the pupil for diagnostic purposes, use during surgical procedures, and at times for treatment and lysis of synechia in patients with uveitis. Published studies submitted in the application show that both 2.5% and 10% formulations achieve adequate mydriasis for clinical use, with pupillary diameter exceeding 6 mm. The effect is generally seen within 15 minutes of instilling the drops, and reaches maximal effect between 20-90 minutes, and mydriasis resolved after 5 hours (range 3 to 8 hours). The pupil dilation reported in the studies was 1 to 3 mm compared to baseline or untreated pupil for the 2.5% concentration and 1 to 4 mm for the 10% concentration. The degree of mydriasis was more prominent under light stimulation compared to no light stimulation.

The usual dose is one drop, which can be repeated every 3 to 5 minutes for a total of 3 drops. Local toxicity includes irritation and pain, in infants there can be peri-orbital pallor due to vasoconstriction. After dilation, patients experience photophobia and may be sensitive to glare. Systemic reactions can also be seen and may be more frequent with the higher concentration. These include temporary increase of blood pressure, and in some patients events such as myocardial reactions, ventricular arrhythmias, syncope and subarachnoid hemorrhage have been reported.

Overall, the ability to achieve pupil dilation to be able to complete an examination of the eye, to perform cataract surgery including placement of the intraocular lens in the eye, and to be able to

have movement of the pupil to break any adhesions due to underlying eye disease are benefits. Adverse reactions may occur and these are included in the product labeling. The 10% formulation is contraindicated in infants less than 1 year of age, and in patients with hypertension and thyrotoxicosis. The risk of adverse reactions may be higher with the 10% formulation, thus the 2.5% should be used initially. Atropine use may potentiate the pressor effect of phenylephrine, whereas phenylephrine may potentiate the effect of anesthetic agents.

The product manufacturing and stability were reviewed and found acceptable, and manufacturing facilities were acceptable. There are no outstanding issues that preclude approval.

13.3 Recommendation for other Postmarketing Requirements (PRMs) and Commitments (PMCs)

The applicant agreed to the following PMC from ONDQA:

2019-1 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.

The timetable you submitted on March 12, 2013, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	March 2013
Study Start:	April 2013
Interim Report:	June 2014
Study Completion:	April 2015
Final Report Submission:	June 2015

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

/s/

RENATA ALBRECHT
03/21/2013