U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 203510
Supplement #:	0000
Drug Name:	Phenylephrine Hydrochloride Ophthalmic Solution, 2.5% and 10%
Indication(s):	Dilate the Pupil (b) (4)
Applicant:	Paragon BioTek, Inc.
Date(s):	Re-submitted: 09/21/2012 PDUFA date: 03/21/2012
Review Priority:	Priority
Biometrics Division:	DBIV
Statistical Reviewer:	Yunfan Deng, Ph.D.
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Keywords: 505(b)2, mydriasis

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1 EXECUTIVE SUMMARY

This NDA seeks approval for 2.5% and 10% phenylephrine hydrochloride ophthalmic solution for the indication of dilating the pupil (b) (4). The proposed dosage and administration in the labeling are:

- In adult patients one drop of the 2.5% or 10% ophthalmic solution should be instilled at 3-5 minute intervals up to a maximum of 3 drops per eye.
- The 10% ophthalmic solution is contraindicated in infants and (b) (4) due to increased risks of systemic toxicity. The 2.5% solution should be used in these patients.

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

A total of eleven studies were included in the submission for the above four groups. And the Applicant focused on the first three groups of five studies to support the efficacy claim, and considered the other six studies as supportive. This review will also focus on these five studies. The following table is a brief summary of the five studies reviewed.

Table 1: Summary of Studies Reviewed

Authors	Title	Design	Efficacy	Safety
Gambill 1967	Mydriatic effect of four drugs determined with pupilograph	15 subjects (Caucasians) Cross over; untreated eye used as control 0.5% tropicamide 2% homatropine 1% hydroxyamphetamine 10% phenylephrine (PE) hydrochloride	10% PE and Homatropine were similar in effect All showed greater efficacy in blue v brown eyes	None reported
Haddad 1970	Mydriatic effect of phenylephrine hydrochloride	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)	Dose response established. 10% commercial less effective than 10% aqueous fresh	No effect on accommodation or IOP. A dose related rebound miosis seen at 24 hrs
Chawdhary 1984	Mydriatic-use of Phenylephrine (a dose response concept)	10%, 5%, 2.5% 1.25% (N=10/group) Double masked. Dose response/controlled	There was no Statistically significant difference between the pupillary dilatations achieved with 10%, 5% and 2.5% concentrations of Phenylephrine	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	N=564 randomized into Group 1 (n=293) 1%	Statistically significant difference in favor 10%	No difference in BP. Statistically significantly

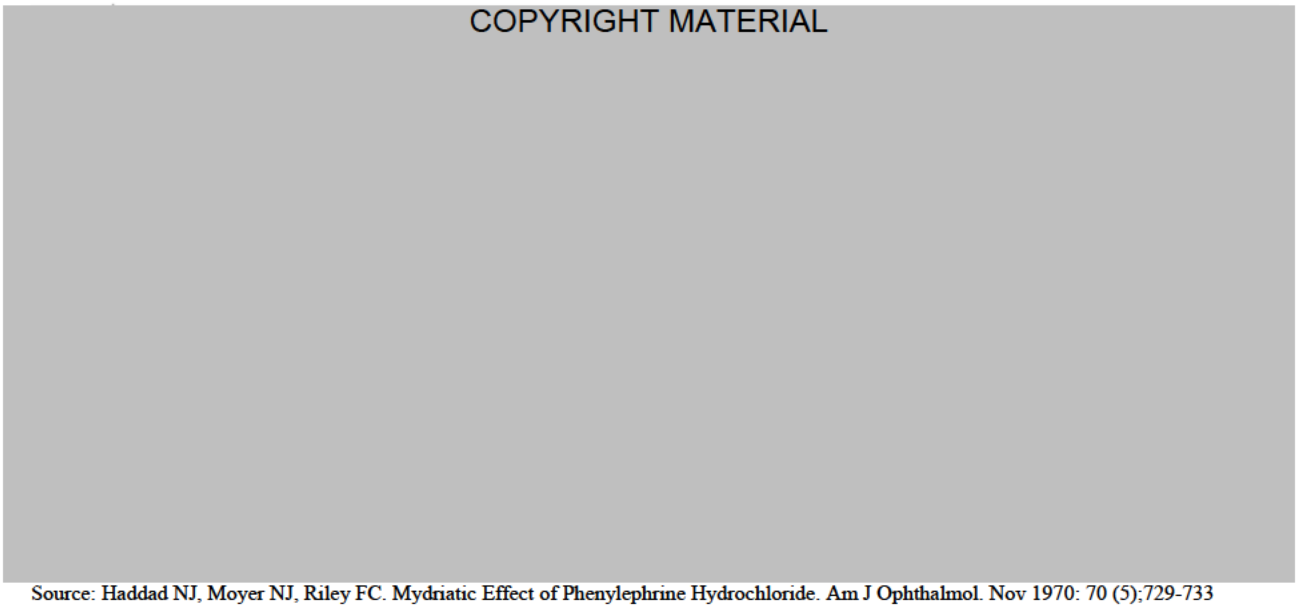
	Pupillary Dilation in subjects with dark irides	tropicamide and 30 minutes later 10% phenylephrine. Grp 2 (n=271) 1% tropicamide and 30 minutes later 2.5% phenylephrine	phenylephrine over 2.5% phenylephrine	higher HR in Group 1
Sindel 1986	A Comparison of the Pupillary and Cardiovascular Effects of Various Mydriatic Agents in Preterm Infants	Four groups, ten subjects each A)phenylephrine 2.5% plus tropicamide 1.0%, B) phenylephrine 2.5% plus tropicamide 0 5%, C) phenylephrine 1.0% plus tropicamide 1.0% and D) saline	Dilatation was sufficient in groups A, B, and C to conduct the examination. Group C had lesser degree of mydriasis than A and B. All were greater than D (7.4 +0.5, 7.3 +0.4, 7.1 + 0.6, 2.9 +0.2 mm respectively)	BP and HR changes significantly less in group C versus group A and B

Source: Based on the Applicant's Table 1 of Summary of Clinical Efficacy section.

Gambill et al (1967) used an infrared electronic pupillograph to determine the degree of mydriasis produced by various agents by measuring the difference in papillary response to a light stimulus between the two eyes of a subject following instillation of the drug into one eye only. The amount of maximum mydriasis (Mean, SD mm) was Tropicamide, 2.69 (0.55), Homatropine, 2.47 (0.66), Hydroxyamphetamine 1.93(0.70), Phenylephrine 10% 2.42 (1.16). The study also showed the mydiatic effect for phenylephrine was greater in light irides compared to dark irides (2.69 (1.29) vs 2.01(0.76) mm respectively

Haddad et al also (1970) used the infrared electronic pupillography to evaluate the difference between the treated and untreated eyes of a subject when a light stimulus is applied to eyes in dim illumination. In Group 1, 8 subjects received two drops into the right eye of a fresh aqueous solution of phenylephrine at concentrations of 0.1%, 0.25%, 0.5%, 1.0%, 5.0% and 10.0%. Eight subjects also received a commercially made 10.0% phenylephrine solution. The following figure shows the dose response curve with for phenylephrine.

Figure 1: Dose Response Curve for Phenylephrine Mydriasis Based on Haddad (1970) Study



Source: Haddad NJ, Moyer NJ, Riley FC. Mydriatic Effect of Phenylephrine Hydrochloride. Am J Ophthalmol. Nov 1970: 70 (5);729-733

In Group 2 of Haddad (1970) study, 24 subjects received either 1% aqueous phenylephrine (n=12) or 10% commercial phenylephrine (n=12). The maximal mydriasis as measure by pupillography at 75 mins was 3.40+0.35 and 3.57 + 0.02 mm respectively.

Chawdhary et al (1984) studied the effectiveness of phenylephrine in concentrations of 1.25%, 2.5%, 5% and 10% in 40 subjects. Pupil sizes were measured at baseline, 2, 4, 6, 8, 10, 15, 20, 30 and 70 minutes post instillation. The results are shown in the following table.

Table 2: Effects on pupil dilation of four concentrations of phenylephrine based on Chawdhary (1984) Study

Source: Chawdhary S, Angra SK, Zutshi R, Sachev S. Mydriasis – use of Phenylephrine (A dose-response concept). Ind J Ophthalmol. July 1984, 34: 213-216

Yospaiboon et al (2004) ran the largest trial to date of the mydriatic effect of phenylephrine to determine whether 10% phenylephrine was more effective than 2.5% phenylephrine in subjects with dark irides. Five hundred and sixty four patients with dark irides were randomized into two groups. Patients in Group 1 received 1% tropicamide and 10% phenylephrine 30 minutes later, those in Group 2 received 1% tropicamide and 2.5% phenylephrine 30 minutes later. Pupil size measurement was taken at baseline, 30 minutes after tropicamide instillation (before instilling phenylephrine), and 30 minutes after phenylephrine instillation. The change in pupil size 30 minutes after instilling tropicamide and 30 minutes after instilling phenylephrine shows in the following table.

Source: Yospaiboon P, Luanratanakorn P, Noppawinyoowong C. Randomized Double-Blind Study of Phenylephrine 2.5% vs 10% on Pupillary Dilation. J Med Assoc Thai, 2004; Vol 87:11: 1380- 1384

In Sindel et all (1986) study, for babies weighing <1500 grams at birth four groups were compared: A) phenylephrine 2.5% plus tropicamide 1.0%, B) phenylephrine 2.5% plus tropicamide 0.5%, C) phenylephrine 1.0% plus tropicamide 1.0% and D) saline. Dilatation was sufficient in groups A, B and C to conduct the examination. Group C had lesser degree of

mydriasis than A and B. All were greater than D (MEAN ± SD for each group: 7.4 ± 0.5, 7.3 ± 0.4, 7.1 ± 0.6, 2.9 ± 0.2 mm respectively).

There were several limitations in relying on evidence from the published literature, such as the possibility of publication bias, lack of pre-specified protocols, non-standardized reporting of results, lack of study site inspections to ensure data quality, and lack of patient-level data with which to conduct independent analysis. In spite of these limitations, the above studies' results provided substantial statistical evidence that there was a treatment effect for both 2.5% and 10% phenylephrine solution in diluting the pupil.

There is some evidence that 10% phenylephrine has slightly higher treatment effects compared with 2.5% concentration, however, the clinical relevance of the magnitude of the difference is unclear to this reviewer, and deferral to the clinical reviewer Dr. Martin Nevitt. Given that some articles reported possible adverse effects on heart rate (HR) and blood pressure (BP) for 10% phenylephrine, whether to approve both concentrations or just one concentration would be a clinical judgment based on overall benefit-risk profile for each concentration.

2 INTRODUCTION

2.1 Overview

2.1.1 Phenylephrine

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. In the eye, phenylephrine acts locally to constrict ophthalmic blood vessels and the radial muscle of the iris.

Phenylephrine hydrochloride is approved in the US as a mydriatic in combination with cyclopentolate hydrochloride (Cyclomydril) as an ophthalmic solution containing 1% phenylephrine hydrochloride. It is also approved as a nasal and oral decongestant. Consequently, this NDA is being submitted as a 505(b)(2) application cross referring to NDAs 084-300, 007-953 and 22-565 for additional information on the safety and efficacy of phenylephrine hydrochloride.

2.1.2 Pupil Dilation

Dilation of the pupil is necessary to conduct numerous procedures in ophthalmology including routine eye examinations, surgical procedures and laser retinal procedures. Enlarging the pupil during routine examinations allows the ophthalmologist to view the entire retina and optic nerve. Dilation of the pupils during cataract surgery makes it easier for the surgeon to remove the lens. Pupil dilation can be achieved with either sympathetic agonists (sympathomimetic agents) like phenylephrine or with parasympathetic antagonists (parasympatholytics) anticholinergic / antimuscarinic compounds, such as tropicamide, cyclopentolate or homatropine.

2.1.3 Proposed Labeling

The Applicant proposes that the Indications and Usage section of the product label indicate the drug for "To dilate the pupil (b) (4)". The proposed dosage and administration in the labeling are:

- In adult patients one drop of the 2.5% or 10% ophthalmic solution should be instilled at 3-5 minute intervals up to a maximum of 3 drops per eye.
- The 10% ophthalmic solution is contraindicated in infants and (b) (4) due to increased risks of systemic toxicity. The 2.5% solution should be used in these patients.

The Applicant also proposes that the Clinical Studies section of the label state that (b) (4)

2.1.4 Development History

To this reviewer's knowledge, the Applicant submitted this New Drug Application without meeting with FDA reviewers to discuss evidence needed for the submission.

2.1.5 Studies Reviewed

The evidence submitted by the Applicant consists of articles from the published literature. The Applicant did not conduct any clinical studies.

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

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

The Applicant focused on the first three groups of five studies to support the efficacy claim. This review will also focus on these five studies. The references for these five studies are as follows:

1. Gambill HD, Ogle KN, Kearns TP. Mydriatic Effect of Four Drugs Determined with Pupillogrpah. Arch Ophthal Vol 77, June 1967, 740-746
2. Haddad NJ, Moyer NJ, Riley FC. Mydriatic Effect of Phenylephrine Hydrochloride. Am J Ophthalmol. Nov 1970: 70 (5);729-733
3. Chawdhary S, Angra SK, Zutshi R, Sachev S. Mydriasis – use of Phenylephrine (A dose-response concept). Ind J Ophthalmol. July 1984, 34: 213-216

4. Yospaiboon P, Luanratanakorn P, Noppawinyoowong C. Randomized Double-Blind Study of Phenylephrine 2.5% vs 10% on Pupillary Dilation. J Med Assoc Thai, 2004; Vol 87:11: 1380- 1384
5. 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. 23(6); 273-6 Nov 1986

The reviewed studies are summarized in the table below and the design for each study is discussed in Section 3 of this review.

Table 4: Brief Summary of Reviewed Studies

Authors	Title	Design	Efficacy	Safety
Gambill 1967	Mydriatic effect of four drugs determined with pupilograph	15 subjects (Caucasians) Cross over; untreated eye used as control 0.5% tropicamide 2% homatropine 1% hydroxyamphetamine 10% phenylephrine (PE) hydrochloride	10% PE and Homatropine were similar in effect All showed greater efficacy in blue v brown eyes	None reported
Haddad 1970	Mydriatic effect of phenylephrine hydrochloride	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)	Dose response established. 10% commercial less effective than 10% aqueous fresh	No effect on accommodation or IOP. A dose related rebound miosis seen at 24 hrs
Chawdhary 1984	Mydriatic-use of Phenylephrine (a dose response concept)	10%, 5%, 2.5% 1.25% (N=10/group) Double masked. Dose response/controlled	There was no Statistically significant difference between the pupillary dilatations achieved with 10%, 5% and 2.5% concentrations of Phenylephrine	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 in subjects with dark irides	N=564 randomized into Group 1 (n=293) 1% tropicamide and 30 minutes later 10% phenylephrine. Grp 2 (n=271) 1% tropicamide and 30 minutes later 2.5% phenylephrine	Statistically significant difference in favor 10% phenylephrine over 2.5% phenylephrine	No difference in BP. Statistically significantly higher HR in Group 1
Sindel 1986	A Comparison of the Pupillary and Cardiovascular Effects of Various Mydriatic Agents in Preterm Infants	Four groups, ten subjects each A)phenylephrine 2.5% plus tropicamide 1.0%, B) phenylephrine 2.5% plus tropicamide 0 5%, C) phenylephrine 1.0% plus tropicamide 1.0% and D) saline	Dilatation was sufficient in groups A, B, and C to conduct the examination. Group C had lesser degree of mydriasis than A and B. All were greater than D (7.4 +0.5, 7.3 +0.4, 7.1 + 0.6, 2.9 +0.2 mm respectively)	BP and HR changes significantly less in group C

Source: Based on the Applicant's Table 1 of Summary of Clinical Efficacy section.

2.2 Data Sources

The Applicant's clinical summaries of safety and efficacy and submitted articles from the published literature are available to FDA reviewers at the following link: \\CDSESUB5\EVSPROD\NDA203510\203510.enx.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Without patient-level datasets submitted and with only published literatures, it was not possible to directly assess the data quality or replicate statistical analysis in this review. As such, there are many limitations of relying on the published literature for evidence of safety and efficacy.

First, the extent of publication bias is unknown, meaning it is unknown whether the articles submitted constitute the totality of available information.

Second, there were no pre-specified protocols or statistical analysis plans to review. Therefore, there was no FDA's feedback regarding study designs, primary efficacy endpoints. For example, pupil size evaluations were made at different times and were summarized in different ways, it was unknown if reported results were influenced by "random high" effects.

Third, there were no site inspections by the FDA Division of Scientific Investigations to evaluate the quality of the data.

Fourth, the information on pupil size outcomes within the articles was not comprehensive. For instance, as will be described in this review, some studies reported the change from baseline of the pupillary sizes, some reported the pupil size difference between one treated eye and the other untreated fellow eye within the same subject, and others summarized the mean pupillary sizes. Therefore, it generally was not possible to replicate the sponsor's computation of summary statistics, or p-values based only on the information in the articles. In addition, some articles made statistical significance claim; yet, the exact statistical method employed was not mentioned.

In summary, review of the data and analysis quality was limited due to the fact that the application relied on the published literature.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

This section describes the design of the five studies considered in this review. The five studies were all different in one way or the other. The following table summarizes the major design differences among the studies.

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

	Groups	Design	Study Population and Treated Eye	Pupil Size Evaluation Method	Evaluation Time
Gambill 1967	a) 0.5% tropicamide b) 2% homatropine c) 1% hydroxyamphetamine d) 10% phenylephrine	Prospective, crossover study, not blinded	Healthy Caucasians Treated: left eye Control: right eye	pupillary diameters at maximal as a response to a light flash of constant intensity and duration	After instillation, every two minutes for 40 minutes, then every five minutes for 20 minutes
Haddad 1970	Fresh aqueous solutions of phenylephrine HCI in concentrations of 0.1, 0 25, 0 5, 1, 5, and 10%; and a commercially available 10% solution was used for comparison	Prospective, crossover study	Normal subjects Treated: right eye Control: left eye	Pupillary size and response to the standard light stimulus	at 15-minute intervals for 90 minutes and then hourly until recovery from mydriasis had occurred
Chawdhary 1984	Fresh aqueous solution of Phenylephrine hydrochloride was prepared in concentrations of 10%, 5%, 2 5% and 1 25%	Prospective, randomized, and masked	Healthy Indian Subjects Both eyes were treated	pupil size on Goldmann perimeter telescope	at 2, 4, 6, 8, 10, 15, 20, 30, 50 and 70 minute post instillation
Yospaiboon 2004	1% tropicamide plus phenylephrine 2.5% 30 minutes later versus 1% tropicamide plus phenylephrine 10% 30 minutes later	Prospective, randomized, double-blinded study	Subjects with dark irides Both eyes were treated	Not specified	immediately before 1% tropicamide, 30 minutes after 1% topicamide (before 10% or 2.5% phenylephrine) and 30 minutes after 10% or 2.5% phenylephrine
Sindel 1986	a) phenylephrine 2 5% plus 1.0% tropicamide b) phenylephrine 2.5% plus 0.5% tropicamide plus 0.5% cyclopentolate c) phenylephrine 1.0% plus 1.0% tropicamide d) saline	prospective, masked, randomized study	Babies < 1500 grams at birth Both eyes were treated	Pupillary dilation was measured with a metric ruler by direct observation	at one hour

Below a description is provided of the seven studies reviewed, with respect to objectives, design, intervention, inclusion criteria, and outcomes. Much of the wording from these summaries is taken from either the published articles or the Applicant's summary.

3.2.1.1 Gambill (1967) Study

Purpose: The purpose of this study was to compare, with the aid of accurate measurements, the mydriasis produced by four drugs: 0.5% tropicamide, 2% homatropine hydrobromide, 1% hydroxyamphetamine hydrobromide, and 10% phenylephrine hydrochloride.

Design: The study was a prospective study; however, the paper did not specify whether the study was randomized / blinded or not. The information given in this publication indicated that it was a crossover study in which each enrolled subjects was given all four drugs sequentially. It is not clear to the reviewer the exact amount of 10% phenylephrine hydrochloride instilled into the eye.

Participants: Participants were 15 healthy subjects, eight males and seven females; all were Caucasians. The average age was 26.4 years (range 12 to 88). Nine subjects had blue irides, three had hazel irides, and three had brown irides. None of the subjects had any apparent eye disease.

Methods: 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.

3.2.1.2 Haddad (1970) Study

Purpose: The purpose of this 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.

Design: The study was a prospective study; however, the paper did not specify whether the study was randomized / blinded or not. The information given in this publication indicated that for study group 1, it was a crossover study in which each enrolled subjects was given all six different drug concentrations sequentially.

Participants: Two groups of subjects were studies:
Group 1: eight normal subjects ranging in age from 21 to 53 years. Fresh aqueous solutions of phenylephrine HCI were prepared in concentrations of 0.1, 0.25, 0.5, 1, 5, and 10%; and a commercially available 10% solution was used for comparison.
Group 2: 24 subjects over age 50 with no known eye disease were divided into two subgroups of 12 each. One subgroup received 1% aqueous phenylephrine solution while the other received the commercial 10% solution.

Methods: 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 detemined 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.

3.2.1.3 Chawdhary (1984) Study

Purpose: The purpose of this study was to study the effects of various dilutions of Phenylephrine hydrochloride in terms of effective mydriasis and cardiovascular mileu. in Indian population having brown irides.

Design: This was a prospective, randomized, and masked study.

Participants: 40 lndian patients, all with dark brown irides, in the age group 20-40 years, were subjects of this masked study.

Methods: Subjects were divided into 4 groups of 10 patients each. Fresh aqueous solution of Phenylephrine hydrochloride was 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.

3.2.1.4 Yospaiboon (2004) Study

Purpose: The purpose of this study was to compare the efficacy of phenylephrine 2.5% versus 10% on pupillary dilation for dark irides, and also compare their side-effects.

Design: This was a prospective, randomized, double-blinded study.

Participants: Five hundred and sixty four (564) patients were randomized into two groups:
Group 1 (293 patients): one drop of 1% tropocamide + one drop of 10% phrenylephrine 30 minutes later for both eyes
Group 2 (271 patients): one drop of 1% tropocamide + one drop of 2.5% phrenylephrine 30 minutes later for both eyes

Methods: 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. Using a vital sign monitor (Visomat compact), systolic and diastolic blood pressure and heart rate were also measured before and 30 minutes after 10% phenylephrine or 2.5% phenylephrine. Both eyes were included and evaluated in the study.

3.2.1.5 Sindel (1986) Study

Purpose: The purpose of this study was to evaluate the safety and efficacy of the combination of mydriatic drops (phenylephrine 2.5% plus 0.5% tropicamide plus 0.5% cyclopentolate) with two other potentially less toxic combinations of mydriatic drops (phenylephrine 2.5% plus 1.0% tropicamide, and phenylephrine 1.0% plus 1.0% tropicamide) in preterm infants.

Design: This was a prospective, randomized, observer-masked study.

Participants: Thirty-four (34) preterm babies (< 1500 grams at birth) were randomized to receive the following four treatment groups:
Group A (10 subjects): phenylephrine 2.5% plus 1.0% tropicamide
Group B (10 subjects): phenylephrine 2.5% plus 0.5% tropicamide plus 0.5% cyclopentolate
Group C (10 subjects): phenylephrine 1.0% plus 1.0% tropicamide
Group D (4 subjects): saline
One drop of the solution was placed in each eye and repeated five minutes later.

Methods: 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 (BDS, MBD) was available to perform the measurements. Using a table of random numbers, 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, using an oscillometer, 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.

3.2.2 Statistical Methodologies

The statistical methods for summarizing and analyzing treatment effects on pupillary diameter (or change in pupillary diameter) are summarized for each study in the table below. As described earlier in this review there were major limitations in terms of it not being possible to evaluate pre-specified statistical analysis plans or to replicate results using patient-level data. All studies reported summary statistics for pupillary diameter. Chawdhary (1984) study reported inferential statistical conclusion, however, the exact statistical testing methods employed were not mentioned. In general, the summary statistics are relatively straightforward for estimating effects of phenylephrine on pupillary diameter outcomes. And the testing methods used by Yospaiboon (2004) study and Sindel (1986) study deemed appropriate by this reviewer.

Table 6: Statistical Reviewer's Summary of Statistical methodologies

Study	Statistical Methods for Pupillary Diameter Described in Publication
Gambill 1967	Summary statistics for change in pupillary diameters to a light stimulus over time were reported; summary statistics of the latency time, and the time at which maximal mydriasis occurred were also reported.
Haddad 1970	Summary statistics for the difference in pupillary diameter of the two eyes at maximal constriction produced by light stimulation were reported.
Chawdhary 1984	Mean and standard deviation of pupil size at different intervals were reported. No information about the exact statistical method used.
Yospaiboon 2004	**"**The mean pupil size was compared between the two groups using the independent t-test"
Sindel 1986	"The data were analyzed using a two-tailed t-test."

Formal meta-analysis techniques were not used to analyze or combine the reviewed studies for because the published results were not reported in a standardized manner to allow combination.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

The table below summarizes available baseline information for the five studies reviewed. Most of the published articles provided information on gender, age, and irides color, and these baseline variables were reasonably well-balanced between groups.

Table 7: Statistical Reviewer's Summary of Baseline Characteristics

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

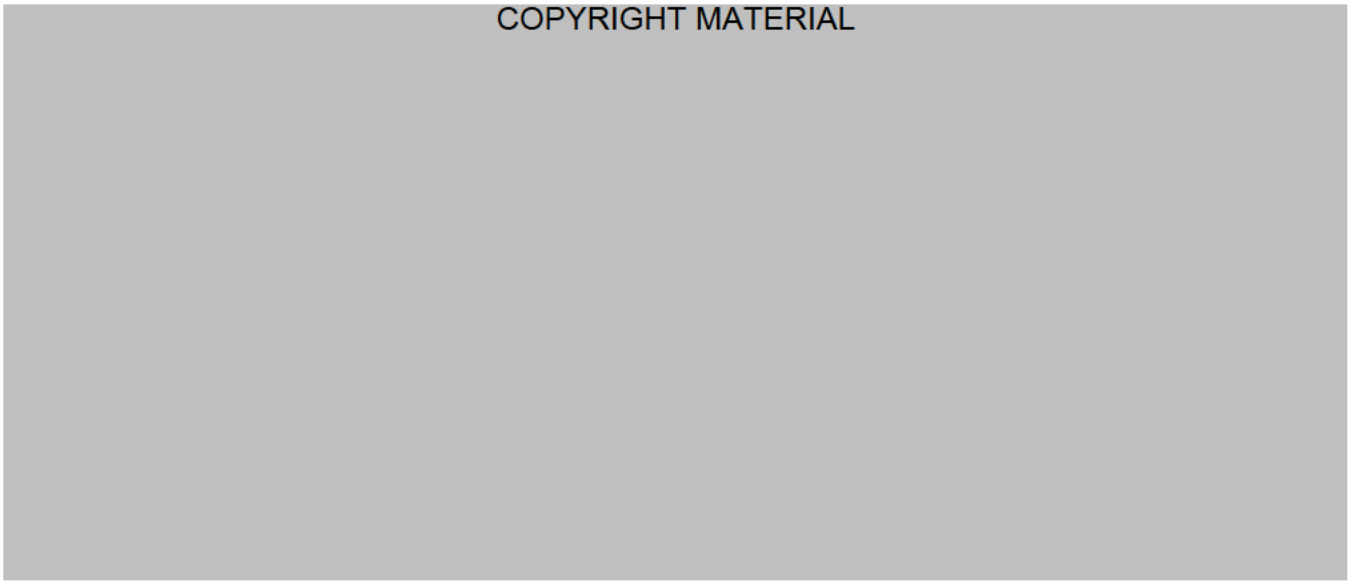
Because the information was taken from publications, summarized variables could not be completely standard across studies.

3.2.4 Results and Conclusions

Gambill et al (1967) used an infrared electronic pupillograph to determine the degree of mydriasis produced by various agents by measuring the difference in papillary response to a light stimulus between the two eyes of a subject following instillation of the drug into one eye only. The amount of maximum mydriasis (Mean, SD mm) was Tropicamide, 2.69 (0.55), Homatropine, 2.47 (0.66), Hydroxyamphetamine 1.93 (0.70), Phenylephrine 10% 2.42 (1.16).

Haddad et al also (1970) used the infrared electronic pupillography to evaluate the difference between the treated and untreated eyes of a subject when a light stimulus is applied to eyes in dim illumination. In Group 1, 8 subjects received two drops into the right eye of a fresh aqueous solution of phenylephrine at concentrations of 0.1%, 0.25%, 0.5%, 1.0%, 5.0% and 10.0%. Eight subjects also received a commercially made 10.0% phenylephrine solution. The following figure shows the dose response curve with for phenylephrine.

Figure 2: Dose Response Curve for Phenylephrine Mydriasis



Source: Haddad NJ, Moyer NJ, Riley FC. Mydriatic Effect of Phenylephrine Hydrochloride. Am J Ophthalmol. Nov 1970: 70 (5);729-733

In Group 2 of Haddad (1970) study, 24 subjects received either 1% aqueous phenylephrine (n=12) or 10% commercial phenylephrine (n=12). The maximal mydriasis as measure by pupillography at 75 mins was 3.40+0.35 and 3.57 + 0.02 mm respectively.

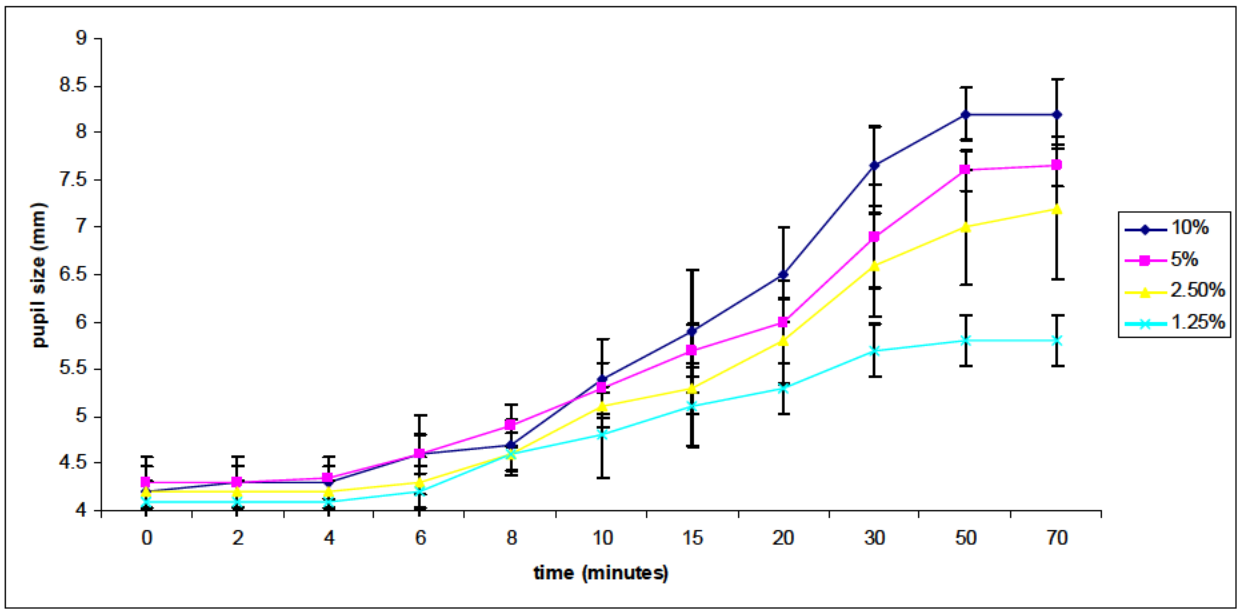
Chawdhary et al (1984) studied the effectiveness of phenylephrine in concentrations of 1.25%, 2.5%, 5% and 10% in 40 subjects. Pupil sizes were measured at baseline, 2, 4, 6, 8, 10, 15, 20, 30 and 70 minutes post instillation. The results are shown in the following table.

Table 8: Effects on pupil dilation of four concentrations of phenylephrine based on Chawdhary (1984) Study

Source: Chawdhary S, Angra SK, Zutshi R, Sachev S. Mydriasis – use of Phenylephrine (A dose-response concept). Ind J Ophthalmol. July 1984, 34: 213-216

The following figure by the statistical reviewer depicts the results of Chawdhary (1984) study listed above. From the figure, it appears that the higher the concentration, the larger the mydriatic effect.

Figure 3: Effects on pupil dilation of four concentrations of phenylephrine based on Chawdhary (1984) Study



Yospaiboon et al (2004) ran the largest trial to date of the mydriatic effect of phenylephrine to determine whether 10% phenylephrine was more effective than 2.5% phenylephrine in subjects with dark irides. Five hundred and sixty four patients with dark irides were randomized into two groups. Patients in Group 1 received 1% tropicamide and 10% phenylephrine 30 minutes later, those in Group 2 received 1% tropicamide and 2.5% phenylephrine 30 minutes later. Pupil size measurement was taken at baseline, 30 minutes after tropicamide instillation (before instilling phenylephrine), and 30 minutes after phenylephrine instillation. The change in pupil size 30 minutes after instilling tropicamide and 30 minutes after instilling phenylephrine shows in the following table.

Table 9: Change in pupil size after tropicamide and phenylephrine

Source: Yospaiboon P, Luanratanakorn P, Noppawinyoowong C. Randomized Double-Blind Study of Phenylephrine 2.5% vs 10% on Pupillary Dilation. J Med Assoc Thai, 2004; Vol 87:11: 1380- 1384

In Sindel et all (1986) study, for babies weighing <1500 grams at birth four groups were compared: A) phenylephrine 2.5% plus tropicamide 1.0%, B) phenylephrine 2.5% plus tropicamide 0.5%, C) phenylephrine 1.0% plus tropicamide 1.0% and D) saline. Dilatation was sufficient in groups A, B and C to conduct the examination. Group C had lesser degree of mydriasis than A and B. All were greater than D (MEAN ± SD for each group: 7.4 ± 0.5, 7.3 ± 0.4, 7.1 ± 0.6, 2.9 ± 0.2 mm respectively).

The above summary statistics of the pupillary diameter results for each study and the dose-response curve reported in one of the publications have convincing evidence to support the mydriatic effect of both 2.5% and 10% phenylephrine. And there is some evidence that 10% phenylephrine has slightly higher treatment effect compared with 2.5% concentration.

However, there were several limitations. First, as noted earlier, reliance on the published literature created limitations related to the possibility of publication bias, the lack of pre-specification of statistical analysis, the inconsistent evaluation methods of pupillary diameters, the various times of evaluation, the difference in presenting summary statistics, the lack of study site inspections, and the inability to perform independent analyses using patient-level data. Second, even granting the dilation effect, the clinical significance of the pupil size results was unclear to this reviewer, and deferral to the clinical reviewer Dr. Martin Nevitt.

3.3 Evaluation of Safety

Primary review of safety is deferred to the clinical reviewer Dr. Martin Nevitt, but some comments are provided in this section regarding safety results in the seven studies considered in this document. This reviewer acknowledges that the Applicant's literature search for studies relating to the safety resulted in a modified set of articles from the published literature than the literature search for efficacy. However, for simplicity this section restricts comments to the seven studies already discussed.

Effects on heart rate (HR) and blood pressure (BP)

Eleven studies contained information on the effect on heart rate and blood pressure of 10% phenylephrine compared with either 1% tropicamide or with lower concentrations of phenylephrine

(Chowdhary 1984[1], Samantary 1975[2], Brown 1980[3], Sindel 1986[4], Borromeo-McGrail 1973[5], Heath 1949[6], Yospaiboon 2004[7], Symons 1997[8], Malhotra 1998[9], Filho 2007[10], Chin 1994[11]). Of these 11 studies 6 reported that there was an increase in BP which was in most cases dose related, 4 found no effect on BP and 1 (Heath 1949) found BP either unchanged or lowered.

Some authors found a dose related effect on HR but none on BP. The variability of the results may be in part to the timing of the observations, which varied substantially. The sample size was seldom determined by the power to detect a significant difference. In contrast there are several papers reporting often dramatic increases in BP in subjects undergoing surgical procedures usually following the administration of 10% phenylephrine (Vaughan 1973[12], McReynolds 1956[13], Wilensky 1973[14], Solosko 1972[15], Lansche 1966[16]).

Information on adverse events from the eight reviewed articles in the published literature is summarized below. A limitation of relying on publications for safety assessment is that it is not possible to review case report forms or the quality of data capture.

Table 10: Summary of Safety Information for Reviewed Studies

Authors	Title	Safety
Gambill 1967	Mydriatic effect of four drugs determined with pupilograph	None reported
Haddad 1970	Mydriatic effect of phenylephrine hydrochloride	No effect on accommodation or IOP. A dose related rebound miosis seen at 24 hrs
Chawdhary 1984	Mydriatic-use of Phenylephrine (a dose response concept)	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	No difference in BP. Statistically significantly higher HR in Group 1

[1] Chawdhary S, Angra SK, Zutshi R, Sachev S. Mydriasis – use of Phenylephrine (A dose-response concept). Ind J Ophthalmol. July 1984, 34: 213-216
[2] Samantary S, Thomas A: Indian J Ophthalmol 23:16-17, 1975.
[3] Brown MM, Brown GC, Spaeth GL. Lack of Side Effects From Topically Administered 10% Phenylephrine Eyedrops. Arch Ophthalmol .1980 ,98; 487
[4] 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. 23(6); 273-6 Nov 1986.
[5] Borromeo-McGrail V, Bordiuk JM, Keitel H. Systemic Hypertension Following Ocular Administration of 10% Phenylephrine in the Neonate. Pediatrics 1973; 53: 1032-6
[6] Heath P. Neosynephrine: Some Uses and Effects in Ophthalmology. Arch Ophth. 16:839 Nov 1936.
[7] Yospaiboon P, Luanratanakorn P, Noppawinyoowong C. Randomized Double-Blind Study of Phenylephrine 2.5% vs 10% on Pupillary Dilation. J Med Assoc Thai, 2004; Vol 87:11: 1380- 1384
[8] Symons RCA, Walland MJ, Kaufman DV. Letter to the Editor. EYE 1997 11; 947-950
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[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
[11] Chin KW, Law NM, Chin MK. Phenylephrine Eye Drops in Ophthalmic Surgery – A Clinical Study on Cardiovascular Effects. Med J Malaysia Vol 49.Jun 1994
[12] Vaughan RW. Ventricular Arrhythmias After Topical Vasocontrictors. Anesth Analg 1973; 52:161-5
[13] McReynolds WU, Havener WH, Henderson JW. Hazards of the Use of Sympathomimetic Drugs in Ophthalmology. Arch Ophthalmol 1956;56:176-9
[14] Wilensky JT, Woodward HJ. Acute Systemic Hypertension After Conjunctival Instillation of Phenylephrine Hydrocloride. Am J Ophthalmol 1973; 76:156-7
[15] Solosko D, Smith RB. Hypertension Following 10 Per Cent Phenylephrine Ophthalmic. Anaesthesiology 1972; 36: 187-9
[16] Lansche RK. Systemic Reactions To Topical Epinephrine and Phenylephrine. Am J Ophth 1966 61: 95

	Dilation	(10% phenylephrine group)
Sindel 1986	A Comparison of the Pupillary and Cardiovascular Effects of Various Mydriatic Agents in Preterm Infants	BP and HR changes significantly less in group C (Phenylephrine 1.0% + Tropicamide 1.0%) versus group A (Phenylephrine 2.5% + Tropicamide 1.0%) and group B (Phenylephrine 2.5% + Tropicamide 0.1%)

Source: Based on the Applicant's Table 1 of Summary of Clinical Efficacy section.

3.4 Benefit-Risk Assessment

Primary review of benefit-risk assessment is deferred to the clinical reviewer Dr. Martin Nevitt. This reviewer notes that while there did appear to be substantial replicated evidence of mydriatic effect for both 2.5% and 10% phenylephrine, the clinical significance of the pupil size results was unclear to this reviewer. Regarding safety, in the studies considered by this reviewer there was no evidence of severe adverse effects; however, the 10% concentration has some effect on heart rate and blood pressure.

There is some evidence that 10% phenylephrine has slightly higher treatment effects compared with 2.5% concentration, however, the clinical relevance of the magnitude of the difference would be unclear to this reviewer, and deferral to the clinical reviewer Dr. Martin Nevitt. Given that some articles reported possible adverse effects on heart rate (HR) and blood pressure (BP) for 10% phenylephrine, whether to approve both concentrations or just one concentration would be a clinical judgment based on overall benefit-risk profile for each concentration.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Other Special/Subgroup Populations

None of the other studies reviewed reported pupil results within subgroups defined gender, race, or age.

4.2 Irides Color

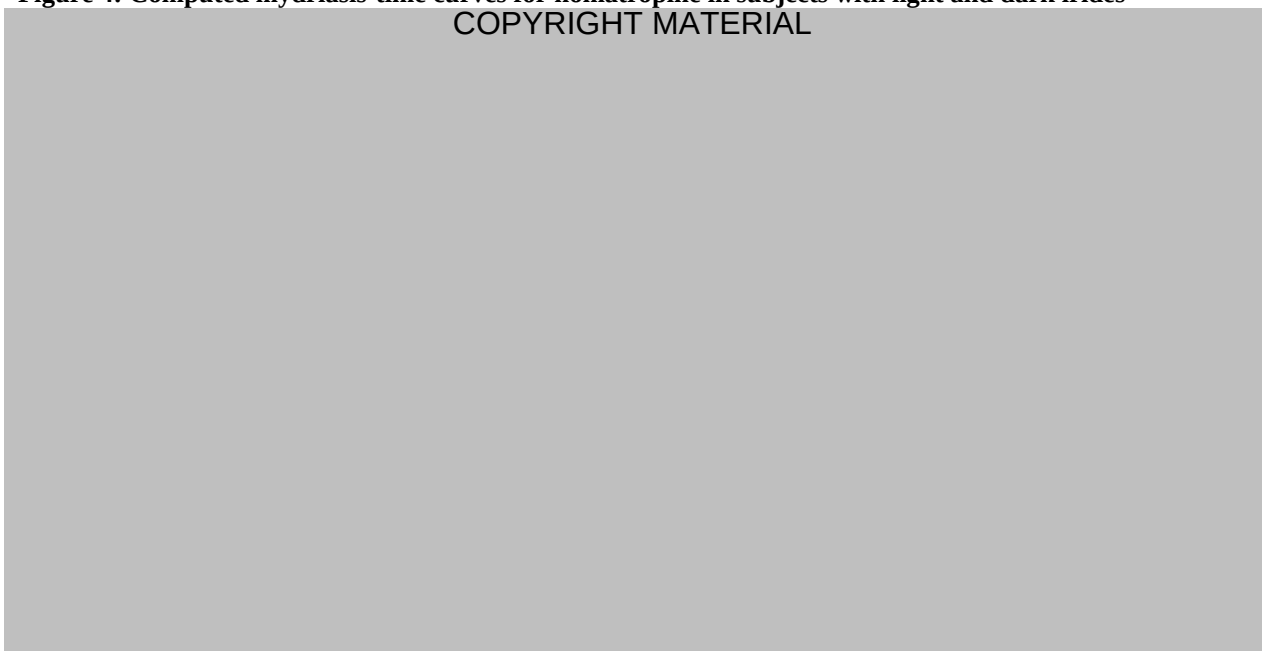
(b) (4)

(b) (4) the reviewer summarizes the pupil size results for the reviewed studies that had reported findings by irides color.

Table 11: Statistical Reviewer's Summary of Pupillary Results by Irides Color

Gambill 1967	illustrated (see the figure below) the computed mydriasis-time curves and the average experimental data for homatropine in subjects with light and dark irides in the study. It was reported "Essentially the same results were found for the other three mydriatic drugs." (which included 10% Phenylephrine).		
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."		
Chawdhary 1984		2.5% Phenylephrine N=40, 80 eyes	10% Phenylephrine N=40, 80 eyes
	Brown	7.20 ± 0.75	8.2 ± 0.37
	"There was no statistically significant difference between the pupillary dilatations achieved with 10%, 5% and 2.5% concentrations of Phenylephrine."		
Yospaiboon 2004		2.5% Phenylephrine N=271, 542 eyes	10% Phenylephrine N=293, 586 eyes
	Dark (Change in pupil size)	OD: 0.79 ± 0.59 OS: 0.73 ± 0.57	OD: 1.12 ± 0.68 OS: 1.16 ± 0.79
	p-values	< 0.0001 for both OD and OS	

Figure 4: Computed mydriasis-time curves for homatropine in subjects with light and dark irides



Source: Gambill HD, Ogle KN, Kearns TP. Mydriatic Effect of Four Drugs Determined with Pupillogrpah. Arch Ophthal Vol 77, June 1967, 740-746

Based on the above summary, there was some evidence that 10% phenylephrine has slightly higher treatment effects compared with 2.5% concentration in patients with dark irides, however, the clinical relevance of the magnitude of the difference would be unclear to this reviewer, and deferral to the clinical reviewer Dr. Martin Nevitt.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

As discussed in Sections 2 and 3 of this review, an important statistical issue in this application was the fact that the Applicant relied on articles from the published literature to provide evidence of efficacy. Limitations were related to the possibility of publication bias, the lack of prespecification of statistical analysis, inconsistent reporting over pupil sizes, timepoints, and summary statistics, lack of site inspections, and lack of patient-level data. It was not possible to adjust for these limitations in this statistical review.

A second statistical issue was that several studies reported inferential statistics (p-value), however, the exact statistical testing methods employed were not mentioned and therefore the validity of the methods used can't be examined. All the reviewed studies reported summary statistics for pupillary size outcomes (although in different format). This reviewer found the summary statistics are relatively straightforward for estimating effects of phenylephrine on pupillary diameter outcomes.

5.2 Collective Evidence

In spite of the limitations mentioned above regarding reliance on the published literature, the collective evidence supported a treatment effect for both 2.5% and 10% phenylephrine solution in diluting the pupil. Although precise outcome definitions varied, pupil dilating effects were reported for all seven reviewed articles, so there was substantial independent replication of positive efficacy results. However, as discussed next, clinical judgment will be required to interpret the totality of the evidence.

5.3 Conclusions and Recommendations

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

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

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

5.4 Labeling Recommendations

As discussed, clinical judgment will be required to interpret the totality of the data on benefit-risk assessment and consequent granting of the proposed indication in labeling.

Reference

1. Gambill HD, Ogle KN, Kearns TP. Mydriatic Effect of Four Drugs Determined with Pupillogrpah. Arch Ophthal Vol 77, June 1967, 740-746
2. Haddad NJ, Moyer NJ, Riley FC. Mydriatic Effect of Phenylephrine Hydrochloride. Am J Ophthalmol. Nov 1970: 70 (5);729-733
3. Chawdhary S, Angra SK, Zutshi R, Sachev S. Mydriasis – use of Phenylephrine (A dose-response concept). Ind J Ophthalmol. July 1984, 34: 213-216
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