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APPLICATION NUMBER:

203510Orig1s000

STATISTICAL REVIEW(S)

MEMORANDUM

DATE: February 25, 2013

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SUBJECT: Team leader's efficacy evaluation of NDA 203510 for phenylephrine hydrochloride ophthalmic solution, 2.5% and 10%

This memorandum evaluates the efficacy evidence of phenylephrine in NDA 203510 for the indication of dilating the pupil [REDACTED] (b) (4).

Background

NDA 203510 is a 505b(2) submission, relying entirely on published clinical studies. This NDA seeks approval of phenylephrine hydrochloride ophthalmic solution, 2.5% and 10% for the indication of dilating the pupil [REDACTED] (b) (4). The applicant provided the following background information regarding the submitted efficacy data:

“Phenylephrine hydrochloride has been the subject of hundreds of clinical trials since its introduction into the marketplace over 70 years ago. Consequently most of these published clinical studies were not designed in a way that is consistent with modern regulatory trials. From this large volume of clinical trials, we have identified several that were designed as randomized, masked studies and that contain statistical analysis.”

The applicant submitted a total of eleven published clinical studies (see appendix) to support the efficacy claim. Among these eleven studies, the applicant considered four of them as most relevant. These four studies are: Chawdhary et al 1984, Haddad et al 1970, Gambill et al 1967, and Yospaiboon et al 2004. The applicant provided detailed summaries for these four studies.

The primary statistical review also focused on these four studies and concluded that the application provided substantial statistical evidence of efficacy for both the 2.5% and 10% phenylephrine solutions. The team leader concurs with this conclusion.

The team leader found that the primary statistical review provided very detailed summaries of the study designs and the results reported in the submitted publications. However, limited statistical evidence of the efficacy of phenylephrine 2.5% or 10% was provided in either the publications or the primary statistical review. One exception is the Yospaiboon study in which p-values for comparing the 2.5% and 10% concentrations were reported. Thus, it is not clear whether the

remaining three studies demonstrated statistically significant results to support the efficacy of either one or both concentrations. To address this issue, the team leader conducted this review to investigate the specific statistical evidence for this application.

In addition to the four studies mentioned above, this review also includes three studies: Filho et al 2007, Neuhaus et al 1980, and Ozturk et al 2000. These three studies were all randomized and double-blinded studies and as shown in the next section, provided relevant efficacy data for comparing phenylephrine 2.5% and 10% concentrations. The applicant included these three studies as part of the supporting studies and therefore did not provide a detailed summary for these studies. The Filho study was published in Portuguese and no English version was included in the original NDA submission. Per FDA's request, the applicant submitted its English version on December 20, 2012.

The remaining 4 studies, 1 study in preterm infants and 3 studies listed as supporting studies by the applicant, do not allow for a comparative assessment of efficacy of phenylephrine and will not be discussed in this review.

The next section provides details on the statistical findings of these seven studies that support the efficacy of phenylephrine.

Statistical Evaluation of Efficacy of Phenylephrine 2.5% and 10% Concentrations

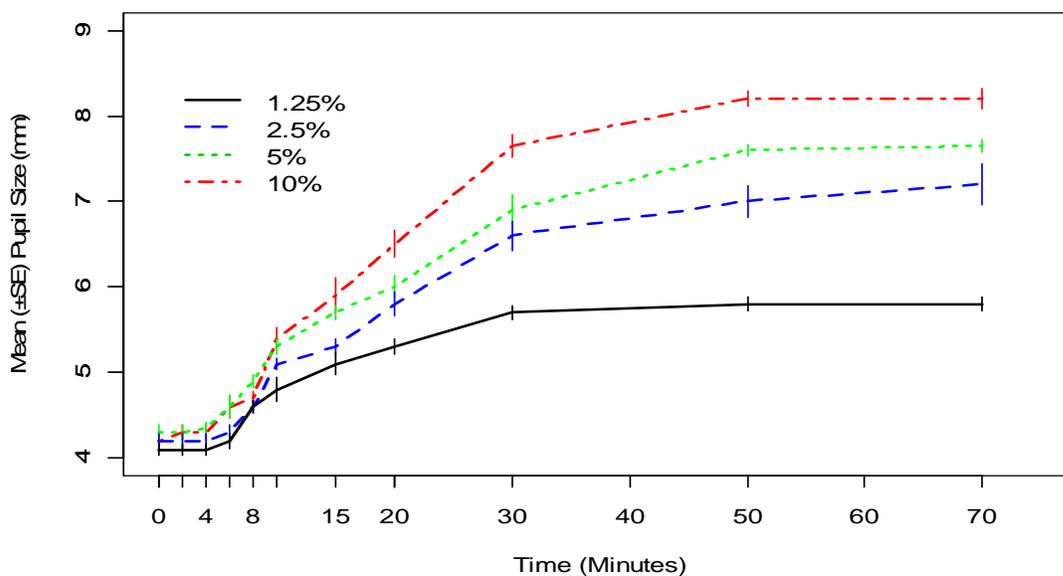
Chawdhary et al. 1984: "Mydriasis Use of Phenylephrine (A Dose Response Concept)"

This study investigated the mydriatic effect of fresh aqueous solution of phenylephrine in four concentrations: 1.25%, 2.5%, 5%, and 10%. The study enrolled 40 Indian patients, all with dark brown irides and in the age of 20-40 years. The four drugs were masked and randomly assigned to the study subjects who were divided into four groups of 10 each. One drop of the drug solution was instilled every minute for three times in the lower conjunctival cul-de-sac. Pupil size was recorded at 11 time points: 0 (baseline), 2, 4, 6, 8, 10, 15, 20, 30, 50, and 70 minutes post instillation.

The means and standard deviations of the pupil size data were provided in the article. The means and standard errors of the pupil size data were plotted by the team leader in Figure 1. This figure shows a clear dose response starting at 15 minutes and maintained through the end of the observation period (70 minutes). Compared with the three higher concentrations, the 1.25% concentration is clearly less effective.

The maximal mydriatic effect was observed at 70 minutes post instillation. This observation is consistent with the data reported in both Haddad and Gambill studies (presented later in this review). The analysis results for the pupil size data at 70 minutes are provided in Table 1. 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.

Figure 1: Mydriatic Effects of Four Concentrations of Phenylephrine



Compared with the 1.25% concentration, the three higher concentrations produced a statistically significantly larger pupil size. The mean differences between the 1.25% and each of the higher concentrations are: 1.4 (95% CI: 0.84, 1.96; p-value < 0.0001) for the 2.5% group, 1.85 (95% CI: 1.61, 2.09; p-value < 0.0001) for the 5% group, and 2.4 (95% CI: 2.10, 2.70; p-value < 0.0001) for the 10% group.

Compared with the 2.5% concentration, the 10% concentration produced a statistically significantly larger pupil size. The difference in pupil size (mm) between these two concentrations at 70 minutes is: 1.0 (95% CI: 0.44, 1.56; p-value < 0.005). The team leader also compared these two concentrations at 30 and 50 minutes. The differences in pupil size (mm) are: 1.0 (95% CI: 0.60, 1.49; p-value < 0.0001) at 30 minutes and 1.2 (95% CI: 0.78, 1.62; p-value < 0.0001) at 50 minutes. These results suggest that the differences between these two concentrations are similar at 30, 50, and 70 minutes.

Compared with the 5% concentration, the 10% concentration also produced a statistically significantly larger pupil size. The difference in pupil size (mm) between these two concentrations at 70 minutes is: 0.55 (95% CI: 0.26, 0.84; p-value < 0.005).

The article provided only means and standard deviations for the pupil size data. The statistical significance, confidence intervals and p-values were calculated by the team leader. Given the small sample sizes, non-parametric tests might be more appropriate; however it was not possible to conduct a non-parametric test given the data provided. The p-values and confidence intervals reported rely on the assumption of normality of the mean and might be anti-conservative. The p-values however are quite significant and the conclusion of significance is likely correct.

Table 1: Mydriatic Effects of Four Phenylephrine Concentrations at 70 minutes (Chawdhary et al. 1984)

	1.25% (N=10)	2.5% (N=10)	5% (N=10)	10% (N=10)
Mean ± SD Pupil Size (mm)				
Baseline	4.1 ± 0.22	4.20 ± 0.27	4.3 ± 0.27	4.2 ± 0.27
70 Minutes	5.8 ± 0.27	7.20 ± 0.75	7.65 ± 0.22	8.2 ± 0.37
Mean (95% CI)* and P-values* for Change from Baseline in Pupil Size (mm)				
	1.7 (1.5, 1.9) < 0.0001	3.0 (2.5, 3.5) < 0.0001	3.4 (3.1, 3.6) < 0.0001	4.0 (3.7, 4.3) < 0.0001
Concentration Comparisons: Mean Difference (95% CI)* and P-values* for Pupil Size				
1.25% vs. other		1.4 (0.84, 1.96) < 0.0001	1.85 (1.61, 2.09) < 0.0001	2.4 (2.10, 2.70) < 0.0001
2.5% vs. other			0.45 (-0.10, 1.00) > 0.09	1.0 (0.44, 1.56) < 0.005
5% vs. other				0.55 (0.26, 0.84) < 0.005

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

Haddad et al. 1970: “Mydriatic Effect of Phenylephrine Hydrochloride”

This study had two groups and in both groups, two drops of the drug solution were instilled into the right eye of each subject. Thus, the study subjects served as their own controls: right eye was treated and left eye was un-treated.

In Group 1, the mydriatic effect of fresh aqueous solution of phenylephrine in six concentrations (0.1%, 0.25%, 0.5%, 1%, 5%, and 10%) and a commercial 10% solution was investigated. Eight normal subjects were enrolled in Group 1. All subjects were tested with each concentration; at least seven days elapsed between recordings when a solution stronger than 1% was used. Pupil size was recorded at 15-minute intervals for 90 minutes and then hourly until recovery from mydriasis had occurred. The maximal mydriatic effect for each subject was defined as the greatest difference in pupil size between the treated eye and the un-treated eye over the observation time period.

In Group 2, twenty four subjects were divided into two subgroups of 12 each; one subgroup received 1% aqueous phenylephrine solution while the other received the commercial 10% solution. Pupil size was recorded at 75 minutes post instillation. The mydriatic effect was investigated under two conditions: with or without light stimulation. The mydriatic effect was measured by the difference in pupil size between the treated eye and un-treated eye.

For Group 1, the article reported that maximal mydriasis occurred with all solutions between 60 to 90 minutes (with a mean of 75) and the half-time for recovery from mydriasis occurred around 3.44 hours for the 10% aqueous solution and 2.66 hour for the 1% aqueous solution. The article provided the plot of the mean (\pm SE) maximal mydriasis data as shown in Figure 2. This figure shows a clear dose response curve with the concentrations of 1% and below being clearly less active. Based on the mean (\pm SE) data plotted in the dose-response curve, the mydriatic effect of the 1% aqueous solution is estimated to be in the range of 0.5 mm to 3 mm and the mydriatic effect of the 10% aqueous solution in the range of 2 mm to 4 mm. The commercial 10% solution was less effective compared with the 10% aqueous solution. Only these general conclusions can be made from Group 1 as the actual data was not reported in the article.

Figure 2: Maximal Mydriasis Produced in Group 1 (Haddad et al. 1970)

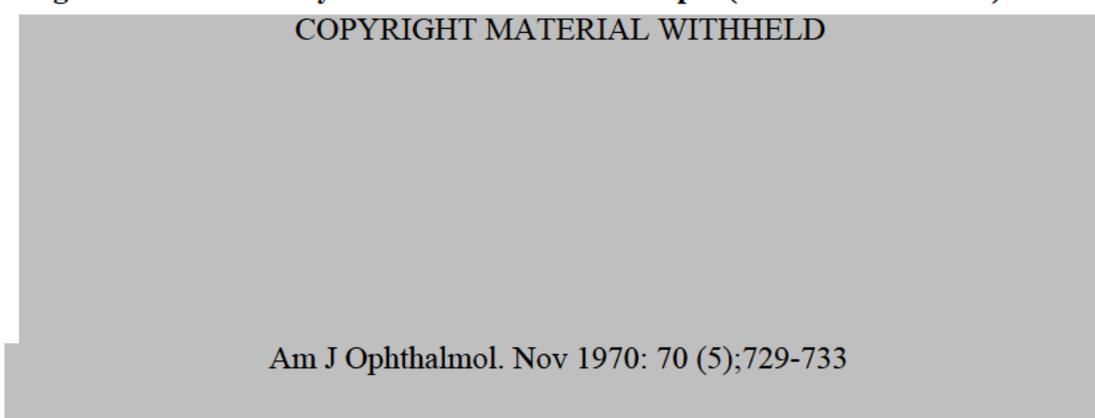


Fig. 1 (Haddad, Moyer, and Riley). Dose-response curve for phenylephrine HCl mydriasis in Group 1 (mean \pm SE). Percent of concentration of phenylephrine HCl is shown across bottom. Lower point at 10% concentration represents commercially available solution.

The results from Group 2 are presented in Table 2. A comparison of the treated eye and the untreated eye demonstrated statistically significant mydriatic effect for both solutions and under both light conditions. Compared with no light stimulation, the mydriatic effect is larger with light stimulation. The commercial 10% solution produced similar mydriatic effect as the 1% aqueous solution.

Without light stimulation, the differences in pupil size (mm) between the treated eye and the untreated eye are: 1.97 (95% CI: 1.58, 2.36; p-value < 0.0001) for the 1% aqueous solution and 2.08 (95% CI: 1.81, 2.35; p-value < 0.0001) for the commercial 10% solution.

With light stimulation, the differences in pupil size (mm) between the treated eye and the untreated eye are: 3.40 (95% CI: 2.71, 4.09; p-value < 0.0001) for the 1% aqueous solution and 3.57 (95% CI: 3.53, 3.61; p-value < 0.0001) for the commercial 10% solution.

It should be noted that regarding the reported statistical significance, confidence intervals and p-values, the limitations discussed in the Chawdhary study also apply in this study and the Gambill study presented below.

Table 2: Difference in Pupil Size (mm) between Treated and Un-treated Eyes at 75 Minutes Post Instillation (Haddad et al. 1970; Group 2)

	1% Phenylephrine Aqueous Solution (N=12)	10% Phenylephrine Commercial Solution (N=12)	Treatment Difference Mean (95% CI)*
Without Light Stimulation			
Mean (95% CI)*	1.97 (1.58, 2.36)	2.08 (1.81, 2.35)	0.11 (-0.37, 0.59)
P-value*	<0.0001	<0.0001	
With Light Stimulation			
Mean (95% CI)*	3.40 (2.71, 4.09)	3.57 (3.53, 3.61)	0.17 (-0.52, 0.86)
P-value*	<0.0001	<0.0001	

* Calculated by the team leader. 95% CI based on the normal distribution approximation, p-value based on paired t-test comparing the treated eye to the untreated eye.

Gambill et al. 1967: “Mydriasis Effect of Four Drugs Determined With Pupilograph”

This study investigated the mydriatic effect of four drugs: 0.5% tropicamide, 2% homatropine, 1% hydroxyamphetamine hydrobromide, and 10% phenylephrine. Fifteen subjects received each drug in a crossover design and served as their own controls: one eye was treated and one eye was un-treated. Pupil size was first recorded every two minutes for 40 minutes, then every five minutes for 20 minutes, and finally every half hour until the difference in the two eyes returned back to baseline. The maximal mydriatic effect for each subject was defined as the greatest difference in pupil size between the treated eye and the un-treated eye over the observation time period.

The article reported that for the phenylephrine group, the average time to maximal mydriasis occurred at 70 minutes and the average recovery time from mydriasis occurred at around 5.33 hours after instillation. As shown in Table 3, the maximal mydriatic effect of 10% phenylephrine is statistically significant. Compared to the un-treated eyes, the treated eyes had a statistically significantly larger pupil size (mm): 2.42 (95% CI: 1.83, 3.01; p-value<0.0001).

Table 3: Difference in Maximal Pupil Size (mm) between Treated and Un-treated Eyes (Gambill et al. 1991)

	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.

Filho et al. 2007: “Cardiovascular and Mydriatic Effects of Topical Ophthalmic 2.5% and 10% Phenylephrine in Healthy Volunteers”

This study was a randomized, double-blinded, and crossover study conducted in a hospital in Brazil. Twenty eight healthy subjects (aged 18-40 years) were randomly distributed in two treatment sequences: “2.5% concentration administered on Day 1 and 10% concentration on Day 2” and “10% concentration administered on Day 1 and 2.5% concentration on Day 2”. On each study day, two drops of phenylephrine concentration were instilled in each eye (both eyes were treated) at a 5-minute interval. Pupil size was measured at baseline (5 minutes before instillation) and 30 minutes post instillation. Non-parametric Kruskal-Wallis test was used to compare the two concentrations in the article.

As shown in Table 4, both concentrations had a statistically significant mydriatic effect, and the 10% concentration was shown to be more effective compared with the 2.5% concentration. As expected, the mydriatic effects of each concentration were almost the same for both eyes.

For the right eyes, the mean changes from baseline in the pupil size (mm) are: 1.30 (95% CI: 0.93, 1.67; p-value < 0.0001) for the 2.5% concentration and 2.0 (95% CI: 1.59, 2.41; p-value < 0.0001) for the 10% concentration. The difference between the two concentrations is: 0.7 (95% CI: 0.13, 1.27; p-value < 0.02).

For the left eyes, the mean changes from baseline in the pupil size (mm) are: 1.4 (95% CI: 1.03, 1.80; p-value < 0.0001) for the 2.5% concentration and 2.0 (95% CI: 1.67, 2.33; p-value < 0.0001) for the 10% concentration. The difference between the two concentrations is: 0.6 (95% CI: 0.10, 1.10; p-value < 0.03).

The mydriatic effect of 10% concentration over the 2.5% concentration appears to be smaller than the one observed in the Chawdhary study: 0.6-0.7 mm in the Filho study and about 1.0 mm in the Chawdhary study. One contributing factor might be the difference in the baseline pupil size: 5.8 mm in the Filho study and 4.2 mm in the Chawdhary study. It is impossible to know whether iris color might be another contributing factor, as the Filho study did not report any data on iris color and only indicated that the study was conducted in a hospital in Brazil. The Chawdhary study included only Indian patients with dark brown irides.

Table 4: Pupil Size (mm) at Baseline and Change from Baseline at 30 Minutes Post Instillation (Filho et al. 2007)

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

The article reported the p-values based on the non-parametric Kruskal-Wallis test for comparing the 2.5% and 10% concentrations. Given the data presented in the article, it is impossible to conduct this non-parametric test. Therefore, the team leader calculated the confidence intervals based on the normal distribution approximation and the parametric p-values based on a 2-sample t-test. These confidence intervals and the p-values rely on the assumption of normality of the mean data. As shown in Table 4, the differences between the non-parametric and parametric p-values are small. This observation is not unexpected as the study sample is 28 and probably large enough to ensure the adequate use of the assumption of normality for the mean data.

This study had a cross-over design with two treatment sequences and approximately one day apart separating the two treatment periods. The article however didn't describe how its non-parametric testing method for comparing the two concentrations took into account the nature of this design and addressed potential confounding issues related to treatment sequence and carry-over effects. Without access to the pupil size data at the subject level, it is impossible to address these issues directly.

The confidence intervals and the parametric p-values for comparing the two concentrations reported by the team leader rely on three assumptions: 1) no carry-over effect, 2) no treatment sequence effect (or no treatment period effect), and 3) no dependence (or independence) of the two pupil size measurements recorded on the two treatment days for each subject.

The carry-over effect could be considered as minimal based on the data reported in Gambill and Haddad. The Gambill study reported that the average recovery time from phenylephrine

mydriasis occurred at around 5.33 hours after instillation (much shorter than the washout period of approximately 24 hours in the current study). The Haddad study reported that the young group of subjects (aged 20-43 years) showed no evidence of rebound miosis following instillation of seven phenylephrine concentrations (including the 10% concentration). Based on these reported data, it is reasonable to consider that the carry-over effect was minimal.

The treatment period effect seems also minimal because the relevant study procedures (including instilling phenylephrine concentrations and measuring pupil sizes) were routine and the study subjects' health conditions didn't vary significantly from Day 1 to Day 2. Furthermore, if a treatment period effect was present in this randomized and double-blinded study, it would likely bias the results of treatment difference towards null.

The assumptions of independence of the two pupil size measurements recorded on the two treatment days for each subject is difficult to validate. In fact, the two pupil size measurements would probably have a positive correlation because they were from the same subject. A positive correlation however is not a cause for concern, as a positive correlation would render the team leader's testing results (confidence intervals and p-values) more conservative, because the variation of the difference in the mean pupil size measurements between the two treatments is larger under the assumption of independence than under the assumption of dependence of a positive correlation.

Considering these potential limitations of the parametric analysis methods discussed above, the conclusion of significances is likely correct.

Yospaiboon et al. 2004: "Randomized Double-blind Study of Phenylephrine 2.5% vs. 10% on Pupillary Dilation"

This study was a randomized, double blind study in a large population with dark irides (this study was conducted in Thailand). Five hundred and sixty four patients were randomized into two groups:

- Group 1 (271 patients): one drop of 1% tropicamide + one drop of 2.5% phenylephrine 30 minutes later for both eyes
- Group 2 (293 patients): one drop of 1% tropicamide + one drop of 10% phenylephrine 30 minutes later for both eyes

Pupil size was recorded immediately before 1% tropicamide, 30 minutes after 1% tropicamide (before 10% or 2.5% phenylephrine) and 30 minutes after 10% or 2.5% phenylephrine.

As shown in Table 5, both concentrations had a statistically significant mydriatic effect when given with tropicamide, and the 10% concentration is more effective compared with the 2.5% concentration.

For the right eyes, the mean changes from baseline (30 minutes after tropicamide administration) for phenylephrine (30 minutes after tropicamide administration) in the pupil size (mm) are: 0.79 (95% CI: 0.72, 0.86; p-value < 0.0001) for the 2.5% concentration and 1.12 (95% CI: 1.04, 1.20; p-value < 0.0001) for the 10% concentration. The difference between the two concentrations is:

0.33 (95% CI: 0.22, 0.44; p-value < 0.001).

For the left eyes, the mean changes from baseline (30 minutes after tropicamide administration) for phenylephrine (30 minutes after tropicamide administration) in the pupil size (mm) are: 0.73 (95% CI: 0.66, 0.80; p-value < 0.0001) for the 2.5% concentration and 1.16 (95% CI: 1.07, 1.25; p-value < 0.0001) for the 10% concentration. The difference between the two concentrations is: 0.43 (95% CI: 0.31, 0.55; p-value < 0.001).

The mydriatic effects of 10% over 2.5% concentrations shown in this study appear to be much smaller than those observed in both Chawdhary and Filho studies. This is likely due to the fact that this study measured the added effect of phenylephrine over tropicamide. As shown in Table 5, after tropicamide administration, the average pupil sizes were already dilated to around 6.3 mm to 6.5 mm, and thus it would be difficult to achieve additional larger mydriatic effect on top of what have been achieved by tropicamide administration.

Table 5: Analysis Results of Pupil Sizes (mm) after Administration of Tropicamide and Phenylephrine (Yospaiboon et al. 2004)

	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			
Δ Phenylephrine	0.79 (0.72, 0.86) <0.0001	1.12 (1.04, 1.20) <0.0001	0.33 (0.22, 0.44) <0.0001
Left Eye			
Δ Phenylephrine	0.73 (0.66, 0.80) <0.0001	1.16 (1.07, 1.25) <0.0001	0.43 (0.31, 0.55) <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.			

Neuhaus et al. 1980: “Mydriatic Effect of Phenylephrine 10% vs Phenylephrine 2.5%”

This study was a randomized and double-blinded study. Eleven subjects (aged 21 to 60 year) were selected at random from patients being dilated by the ophthalmic nursing staff. Patients with diabetes, hypertension, anterior segment disease, or previous ocular surgery were excluded from the study. Also excluded were patients who had received tonometry, corneal sensation testing, or topical medications within the previous month.

Each patient received 1 drop of commercial phenylephrine 10% solution in one eye and commercial phenylephrine 2.5% solution in the fellow eye in a double-blind, random fashion. Pupil size was recorded at baseline (before the instillation) and at 60 minutes. For each eye, the amount of mydriasis was calculated as change in pupil size from baseline. The article provided the pupil size data for all individual subjects as follows:

2.5%	0.7	2.6	2.8	0.0	1.8	2.4	0.5	2.8	1.3	0.9	1.8
10%	1.7	2.7	2.4	0.2	2.3	2.2	1.1	2.6	1.7	1.0	2.8
Difference	1.0	0.1	-0.4	0.2	0.5	-0.2	0.6	-0.2	0.4	0.1	1.0

To evaluate the mydriatic effects of the two concentrations, both parametric (Student’s t) and non-parametric (Sign and Signed Rank) tests were performed by the team leader and the results were presented in Table 6. Despite the differences in the p-values between the parametric test and the non-parametric tests, the statistical conclusions are the same: both concentrations had a statistically significant mydriatic effect and the effect of the 10% concentration is not statistically significantly larger than the 2.5% concentration.

Table 6: Pupil Size (mm) Change from Baseline at 60 Minutes Post Instillation (Neuhaus et al. 1980)

	2.5% Phenylephrine (N=11)	10% Phenylephrine (N=11)	Difference
Mean ± SD (95% CI)	1.60 ± 0.99 (0.94, 2.26)	1.88 ± 0.83 (1.32, 2.44)	0.28 ± 0.47 (-0.03, 0.59)
P-value			
Student’s t	0.0003	<0.0001	0.0741
Sign	0.0020	0.0010	0.2266
Signed Rank	0.0020	0.0010	0.1045

The mean changes from baseline in the pupil size (mm) are: 1.60 (95% CI: 0.94, 2.26; p-value ≤ 0.002) for the 2.5% concentration and 1.88 (95% CI: 1.32, 2.44; p-value ≤ 0.001) for the 10% concentration. The mydriatic effect of the 10% phenylephrine in this study is similar to the one observed in the Haddad study (Group 2) for the 10% commercial phenylephrine. Note: both the Neuhaus and Haddad studies tested a 10% commercial phenylephrine solution.

Compared with the 2.5% concentration, the 10% concentration produced a larger mydriatic effect, but the difference is not statistically significant. The difference between the two concentrations is: 0.28 (95% CI: -0.03, 0.59; p-value = 0.23).

The article did not provide detailed information on iris color. It only noted that the study population was a general population, and some subjects had blue irides and some subjects had brown irides.

Ozturks et al. 2000: “The Efficacy of 2.5% Phenylephrine and Flurbiprofen Combined in Inducing and Maintaining papillary Dilatation During Cataract Surgery”

This was a randomized and double-blinded study, investigating the efficacy of phenylephrine and flurbiprofen in inducing and maintaining papillary dilation during cataract surgery. One hundred (100) patients undergoing extracapsular cataract extraction + intraocular lens implantation were randomized into four treatment groups:

- Group A (N=33): phenylephrine 10% + cyclopentoate 1%
- Group B (N=21): phenylephrine 10% + cyclopentoate 1% + flurbiprofen 0.03%
- Group C (N=21): phenylephrine 2.5% + cyclopentoate 1%
- Group D (N=25): phenylephrine 2.5% + cyclopentoate 1% + flurbiprofen 0.03%

All subjects received Cyclopentoate 1%. Phenylephrine and cyclopentoate were instilled four times in 1 hour before surgery. Flurbiprofen was given four times the day before surgery and two times at hourly intervals before surgery. Preoperative and post-cortex aspiration horizontal pupil diameters were measured. The mydriatic effects of 10% over 2.5% concentrations were evaluated by comparing Group A with Group C and Group B with Group D.

As presented in Table 7.1, the article provided the means and standard deviations of pupil diameters and the p-values based on the non-parametric Mann-Whitney U test for comparing the differences between two groups. Table 7.1 also presents the parametric p-values based on a 2-sample test that were calculated by the team leader.

The statistical significances based on the non- parametric and the parametric p-values are not consistent. For example, for comparing Group A and Group C for the post-surgery data, the non-parametric p-value is > 0.05 whereas the parametric p-value is < 0.001. These inconsistent p-values might be caused by a mistake in the presentation of the standard deviations in the article. The reported standard deviations of 0.1 mm or 0.2 mm are much smaller than those reported in other studies (typically from 0.40 mm to 1.2 mm). Thus, these SD values might be SE values. The 95% CI and the parametric p-values presented in Table 7.2 were calculated by treating these small SD values as SE values. These results indicate that there are no statistically significant differences between the phenylephrine 2.5% and 10% concentrations, although there is a numerical trend favoring the 10% concentration over the 2.5% concentration.

Table 7.1: Comparison of Phenylephrine 2.5% and 10% (Ozturks et al. 2000)

	2.5% Phenylephrine	10% Phenylephrine	P-value for Mean Difference
	N=21	N=33	A vs. C
Pre-surgery Mean ± SD	8.3± 0.1	8.4± 0.1	< 0.05* < 0.001**
Post-surgery Mean ± SD	6.2± 0.2	6.4± 0.1	> 0.05* < 0.001**
	N=25	N=21	B vs. D
Pre-surgery Mean ± SD	8.8± 0.8	8.8± 0.1	> 0.05* > 0.9999**
Post-surgery Mean ± SD	7.1 ± 0.2	7.4± 0.2	> 0.05* < 0.001**

* P-value based on Mann-Whiney U test.

** Calculated by the team leader. P-value based on 2-sample t-test.

Table 7.2: Comparison of Phenylephrine 2.5% and 10% after Correcting the Errors in the Standard Deviation Data (Ozturks et al. 2000)

	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.

Conclusions

This review has evaluated the efficacy of phenylephrine hydrochloride solution, 2.5% and 10% in 7 clinical studies (Chawdhary et al 1984, Haddad et al 1970, Gambill et al 1967, Filho et al 2007, Yospaiboon et al 2004, Neuhaus 1980, and Ozurks 2000). The key statistical findings are the following.

Dose response of phenylephrine was established in two studies (Chawdhary and Haddad (Group 1)).

Four studies (Chawdhary, Filho, Neuhaus, and Yospaiboon) demonstrated statistically significant efficacy results of both 2.5% and 10% phenylephrine solutions.

The Haddad (Group 2) study demonstrated statistically significant efficacy results of both 1% and 10% phenylephrine solutions. The Gambill study demonstrated statistically significant efficacy results of 10% phenylephrine solution.

Five studies (Chawdhary, Filho, Neuhaus, Ozurks, and Yospaiboon) provided efficacy data for comparing the effects of 2.5% and 10% phenylephrine solutions. Among these five studies, three studies (Chawdhary, Filho, and Yospaiboon) demonstrated that the 10% solution is more effective than the 2.5% solution; the other two studies (Neuhaus and Ozurks) did not demonstrate a statistically significant difference, although both studies suggested a numerical trend favoring the 10% solution over the 2.5% solution.

It is noted that both Yospaiboon (564 subjects) and Chawdhary (40 subjects) studies enrolled only subjects with dark irides. The Filho study (28 subjects) did not provide information on iris color. The Neuhaus study (11 subjects) did not provide detailed information on iris color although it stated that the study population was a general population, some subjects had blue irides, and some subjects had brown irides. The Ozurk study (100 subjects) did not provide information on iris color and it was the only submitted study enrolling patients undergoing cataract surgery.

Based on the above findings, this review concludes that there is substantial efficacy evidence of phenylephrine 2.5% and 10% solutions to support approval of this application.

Appendix: The Eleven Clinical Studies Included in the NDA Submission

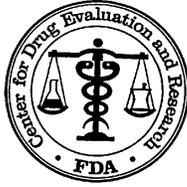
1. Chawdhary S, Angra SK, Zutshi R, Sachev S. Mydriasis use of Phenylephrine (A dose-response concept). *Ind J Ophthalmol*. July 1984, 34: 213-216
2. Eyeson-Annan, Hirst Battistuttat, *Green Ophthalmology* 1998; 105 (4): 726-32
3. Filho AD, Frasson M, Merula RV, Morais PR, Cronenberger S. Cardiovascular and mydriatic effects of topical phenylephrine 2.5% and 10.0% in healthy volunteers. *Arq Bras Oftalmol* 2007; 70 (6):961-6
4. Gambill HD, Ogle KN, Kearns TP. Mydriatic Effect of Four Drugs Determined with Pupillograph. *Arch Ophthalmol* Vol 77, June 1967, 740-746.
5. Haddad NJ, Moyer NJ, Riley FC. Mydriatic Effect of Phenylephrine Hydrochloride. *Am J Ophthalmol*. Nov 1970: 70 (5);729-733
6. Neuhaus RW, Helper RS. Mydriatic Effect of Phenylephrine 10% (aq) vs Phenylephrine 2.5% (aq). *Annals of Ophthalmol* Oct 1980: 1159-1160
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8. Paggiarino DA, Brancata LJ, Newton RE. The Effects of Pupil Size and Accommodation of Sympathetic and Parasympatholytic Agents. *Ann Ophthalmol*, 1993;25:244-253
9. 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.
10. 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.
11. Yospaiboon P, Luanratanakorn P, Noppawinyoowong C. Randomized Double-Blind Study of Phenylephrine 2.5% vs 10% on Pupillary Dilatation. *J Med Assoc Thai*, 2004; Vol 87:11: 1380- 1384

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YAN WANG
03/01/2013

TSAE YUN D LIN
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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.
Concurring Reviewers: Yan Wang, Ph.D.
Medical Division: Division of Transplant and Ophthalmology Products
Clinical Team: Martin Nevitt, MD, Clinical Reviewer
William Boyd, MD, Clinical Team Leader
Project Manager: Diana Willard
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 pupillograph	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

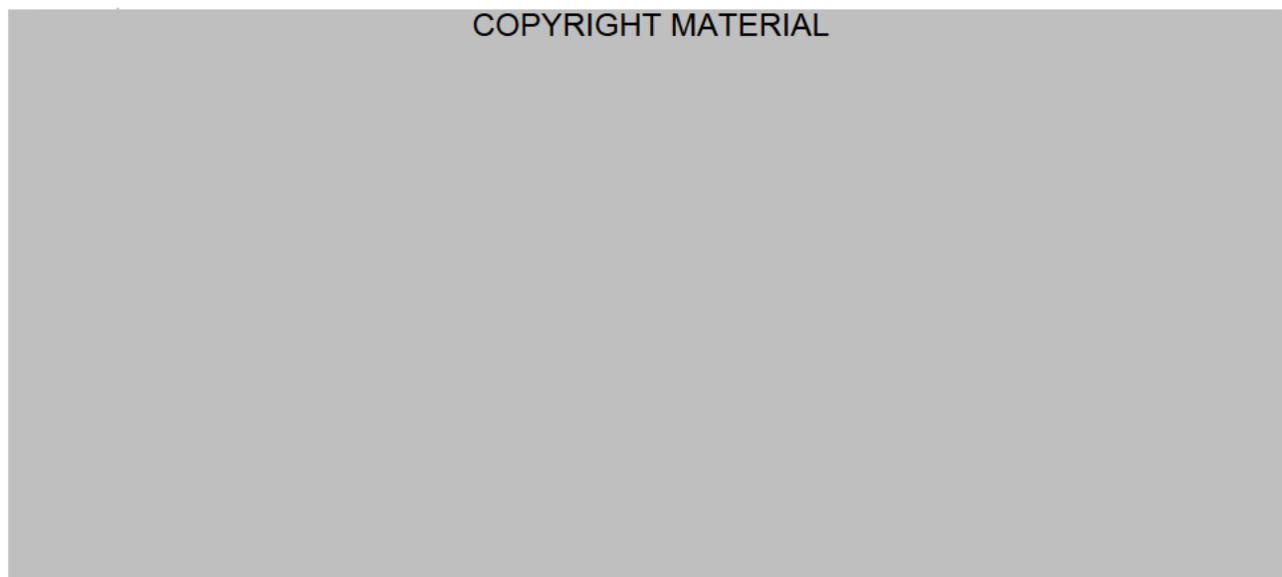
	Pupillary Dilation in subjects with dark irides	tropicamide and 30 minutes later 10% phenylephrine. Grp 2 (n=271) 1% tropicamide and 30 minutes later 2.5% phenylephrine	phenylephrine over 2.5% phenylephrine	higher HR in Group 1
Sindel 1986	A Comparison of the Pupillary and Cardiovascular Effects of Various 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
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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 \pm SD for each group: 7.4 \pm 0.5, 7.3 \pm 0.4, 7.1 \pm 0.6, 2.9 \pm 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 [REDACTED] (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 [REDACTED] (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 [REDACTED] (b) (4)

[REDACTED]

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 Pupillograph. *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 dilations 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](https://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 HCl in concentrations of 0.1, 0.25, 0.5, 1, 5, and 10%; and a commercially available 10% solution was used for comparison	Prospective, crossover study	Normal subjects Treated: right eye Control: left eye	Pupillary size and response to the standard light stimulus	at 15-minute intervals for 90 minutes and then hourly until recovery from mydriasis had occurred
Chawdhary 1984	Fresh aqueous solution of Phenylephrine hydrochloride was prepared in concentrations of 10%, 5%, 2.5% and 1.25%	Prospective, randomized, and masked	Healthy Indian Subjects Both eyes were treated	pupil size on Goldmann perimeter telescope	at 2, 4, 6, 8, 10, 15, 20, 30, 50 and 70 minute post instillation
Yospaiboon 2004	1% tropicamide plus phenylephrine 2.5% 30 minutes later versus 1% tropicamide plus phenylephrine 10% 30 minutes later	Prospective, randomized, double-blinded study	Subjects with dark irides Both eyes were treated	Not specified	immediately before 1% tropicamide, 30 minutes after 1% tropicamide (before 10% or 2.5% phenylephrine) and 30 minutes after 10% or 2.5% phenylephrine
Sindel 1986	a) phenylephrine 2.5% plus 1.0% tropicamide b) phenylephrine 2.5% plus 0.5% tropicamide plus 0.5% cyclopentolate c) phenylephrine 1.0% plus 1.0% tropicamide d) saline	prospective, masked, randomized study	Babies < 1500 grams at birth Both eyes were treated	Pupillary dilation was measured with a metric ruler by direct observation	at one hour

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 HCl in a group of young, normal subjects and to evaluate the mydriatic effect of this drug in a group of older subjects in order to better characterize the effects of this drug on the iris.

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 studied:

Group 1: eight normal subjects ranging in age from 21 to 53 years. Fresh aqueous solutions of phenylephrine HCl 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 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.

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 Indian 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	n/a		9/15	
	Hazel	n/a		3/15	
	Brown	n/a		3/15	
Haddad 1970 Group 1		2.5% Phenylephrine		10% Phenylephrine	
	Age (years)	Range: 21 to 53		Range: 21 to 53	
	Irides Color				
	Blue	3/8		3/8	
	Hazel	2/8		2/8	
	Brown	3/8		3/8	
Haddad 1970 Group 2		2.5% Phenylephrine		10% Phenylephrine	
	Age (years)	n/a		Greater than 50 years	
Chawdhary 1984		2.5% Phenylephrine 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.

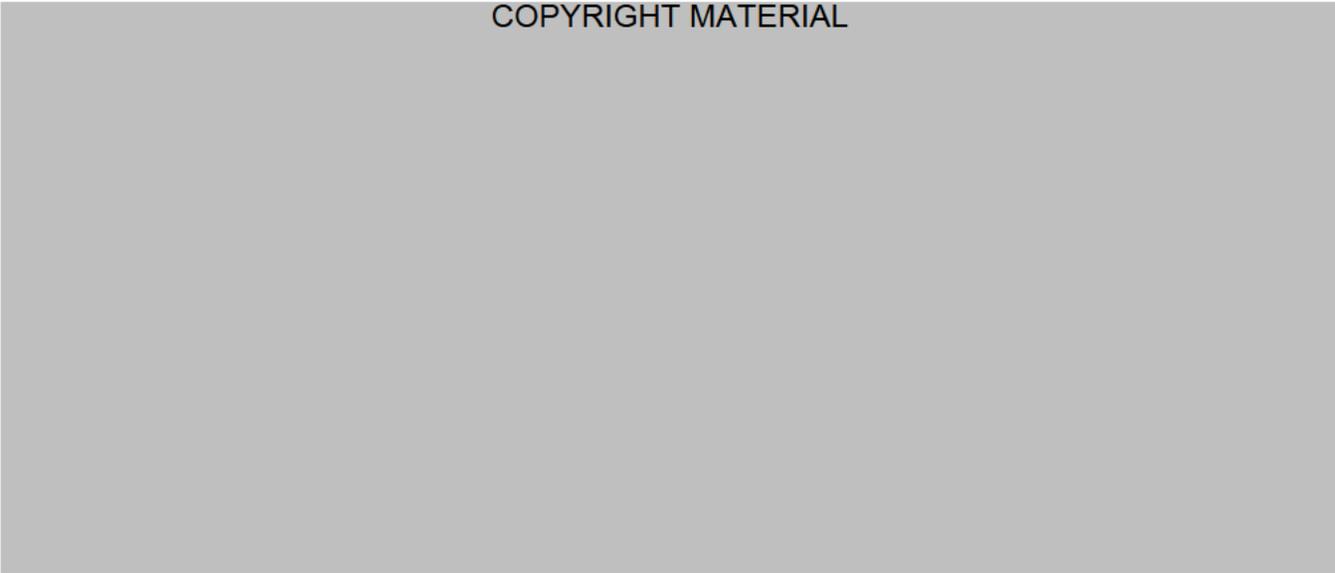
3.2.4 Results and Conclusions

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

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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.

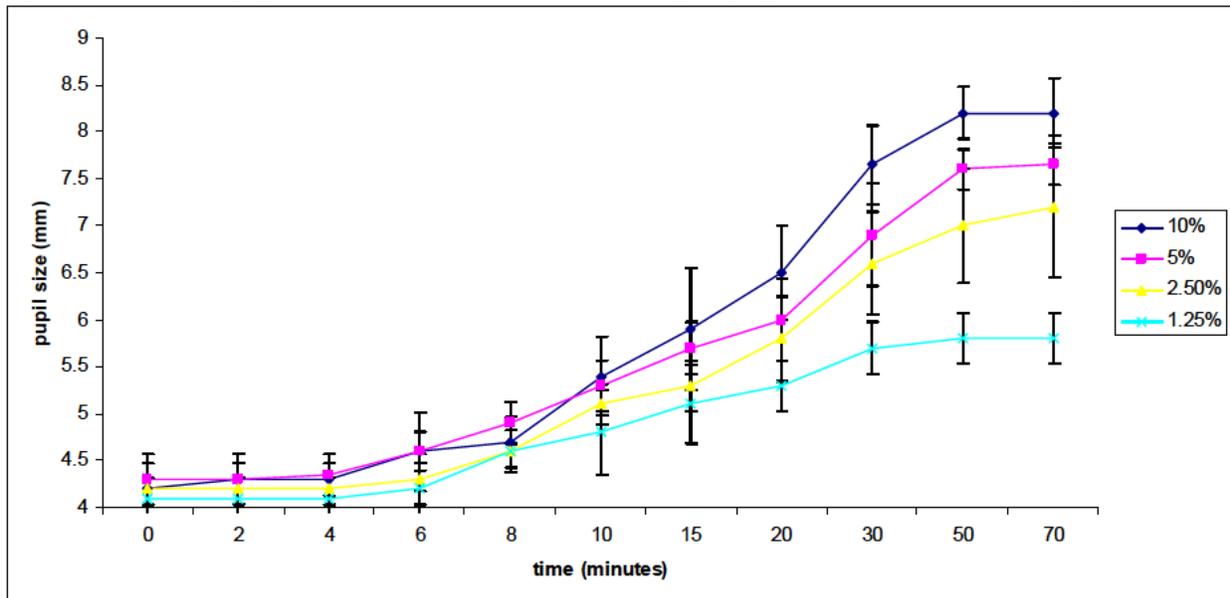
Chawdhary et al (1984) studied the effectiveness of phenylephrine in concentrations of 1.25%, 2.5%, 5% and 10% in 40 subjects. Pupil sizes were measured at baseline, 2, 4, 6, 8, 10, 15, 20, 30 and 70 minutes post instillation. The results are shown in the following table.

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

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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 al (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 \pm 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 1984¹, Samantary 1975², Brown 1980³, Sindel 1986⁴, Borromeo-McGrail 1973⁵, Heath 1949⁶, Yospaiboon 2004⁷, Symons 1997⁸, Malhotra 1998⁹, Filho 2007¹⁰, Chin 1994¹¹). 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 1973¹², McReynolds 1956¹³, Wilensky 1973¹⁴, Solosko 1972¹⁵, Lansche 1966¹⁶).

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

⁹ Malhotra,R, Banerjee G, Brampton W, Price NC. Comparison of the cardiovascular effects of 2.5% phenylephrine and 10% phenylephrine during ophthalmic surgery. *Eye* 1998,12,973-975

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 Vasoconstrictors. *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 Hydrochloride. *Am J Ophthalmol* 1973; 76:156-7

¹⁵ Solosko D, Smith RB. Hypertension Following 10 Per Cent Phenylephrine Ophthalmic. *Anesthesiology* 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

[REDACTED] (b) (4)

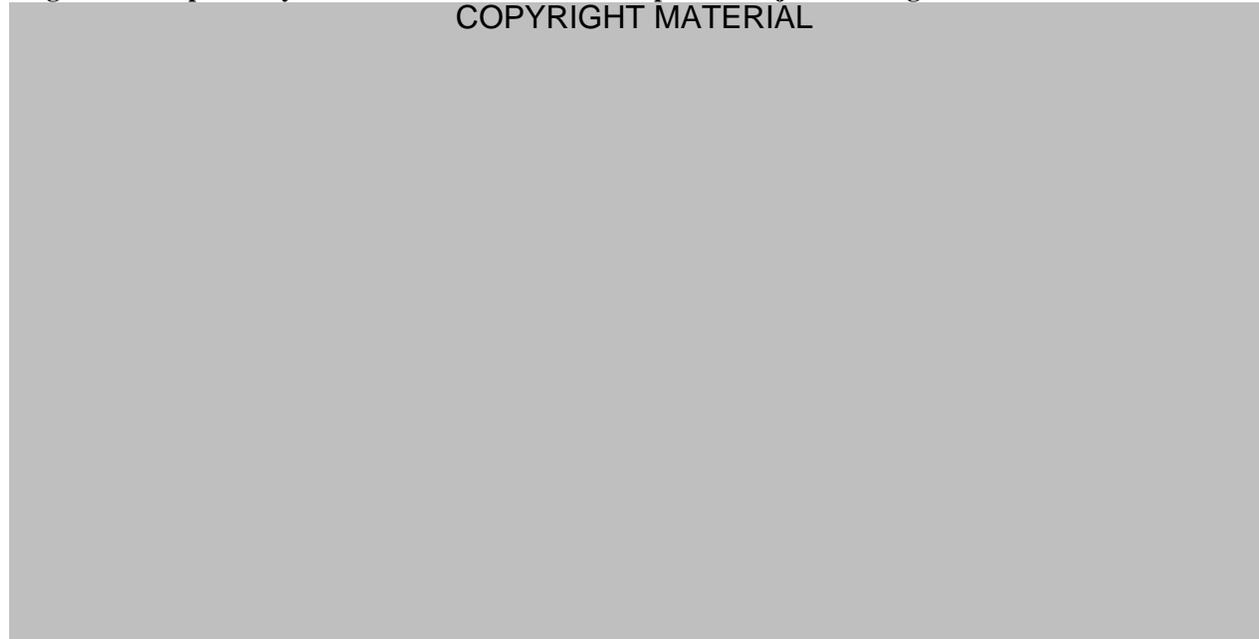
[REDACTED] (b) (4) the reviewer summarizes the pupil size results for the reviewed studies that had reported findings by irides color.

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

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Source: Gambill HD, Ogle KN, Kearns TP. Mydriatic Effect of Four Drugs Determined with Pupillograph. 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.

APPEARS THIS WAY ON ORIGINAL

Reference

1. Gambill HD, Ogle KN, Kearns TP. Mydriatic Effect of Four Drugs Determined with Pupillograph. Arch Ophthalmol 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
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STATISTICS FILING CHECKLIST FOR NDA 203510

NDA Number: 203510

Applicant: Paragon Biotech Inc

Stamp Date: October 21, 2011

PDUFA date: April 20, 2012

Drug Name: Phenylephrine hydrochloride ophthalmic solution, 2.5% and 10%

NDA/BLA Type: NDA, Priority Review

Indication: To dilate the pupil (b) (4)

Overview of the NDA 203510:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	✓			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)			✓	
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.	Gender and geriatric subgroups	✓ Race		
4	Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets).			✓	This is a 505b (2) submission including only published papers.

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

The NDA is fileable from the statistical perspective.

STATISTICS FILING CHECKLIST FOR NDA 203510

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	✓			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	✓			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			✓	
Appropriate references for novel statistical methodology (if present) are included.			✓	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.			✓	This is a 505b (2) submission including only published papers.
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.			✓	This is a 505b (2) submission including only published papers. No investigation effect of dropouts on statistical analyses is available.

STATISTICS FILING CHECKLIST FOR NDA 203510

Background and Overview of Clinical Efficacy

Phenylephrine has been used for the proposed indication (to dilate the pupil ^(b)₍₄₎) for more than 70 years. The first description of its use in the literature is in 1936 (Heath, 1936). Since this time there have been numerous published papers describing the safety and efficacy of various different concentrations of phenylephrine hydrochloride ophthalmic solutions.

Due to the wealth of scientific literature and extensive clinical use the applicant considers that the safety and efficacy of phenylephrine hydrochloride ophthalmic solution, 2.5% and 10% for the proposed indication has been well established and therefore unnecessary to conduct any additional clinical studies to support this NDA. Instead, the applicant has summarized the available published clinical data that describe the well established clinical efficacy of phenylephrine hydrochloride ophthalmic solution as a mydriatic for the proposed indication.

In addition, 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.

Brief summary of controlled clinical trials:

In this NDA submission, the applicant reports that Phenylephrine hydrochloride has been the subject of hundreds of clinical trials since its introduction into the marketplace over 70 years ago. Most of these published clinical studies were not designed in a way that is consistent with modern regulatory trials. From this large volume of clinical trials, the applicant identified several that were designed as randomized; masked studies and that contain statistical analyses:

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

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1) Studies with a control group demonstrating efficacy of phenylephrine in producing mydriasis:

Table 1a includes Studies with a control group demonstrating efficacy of phenylephrine in producing mydriasis.

Table 1a: Summary of Studies with a Control Group

Authors	Title	Description a) Design b) Efficacy c) Safety
Gambill et al 1967	Mydriatic effect of four drugs determined with pupillograph.	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 et al 1970	Mydriatic effect of phenylephrine hydrochloride.	a) Group 1: (n=8) crossover (7 day washout) 0.1%, 0.25%, 0.5%, 1%, 5%, 10% using IR Pupillograph. Group 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.

Data source: Table 1 from NDA 203510: 2.7.3 Summary of Clinical Efficacy on page 6

In the following, we describe the efficacy results of the two studies described in the above table:

Gambill et al 1967 :

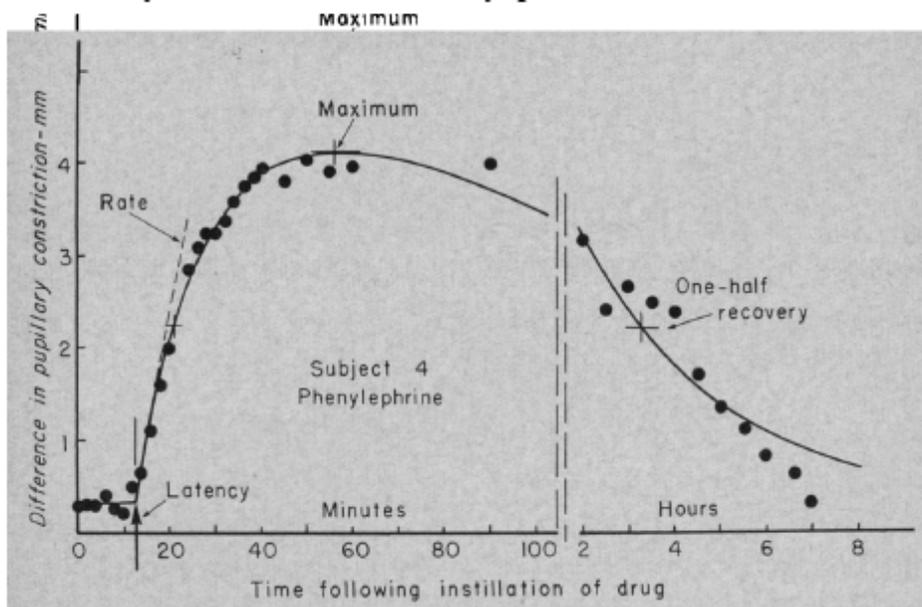
Gambill et al used an Infrared electronic pupillograph to determine the degree of mydriasis produced by various agents by measuring the difference in papillary response to a light stimulus between the two eyes of a subject following instillation of the drug into one eye only. The drugs tested were 0.5% tropicamide, 2% homatropine, 1%

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hydroxyamphetamine hydrobromide and 10% phenylephrine. The subjects (n=15), all Caucasian with an average age of 26.4 yrs, received each drug in a crossover design. 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 (Gambill, 1967).

The graphs below show the effect curve for phenylephrine 10% in a single subject, and the comparison of effect curves for the four drugs studied (Figure 1, Figure 2).

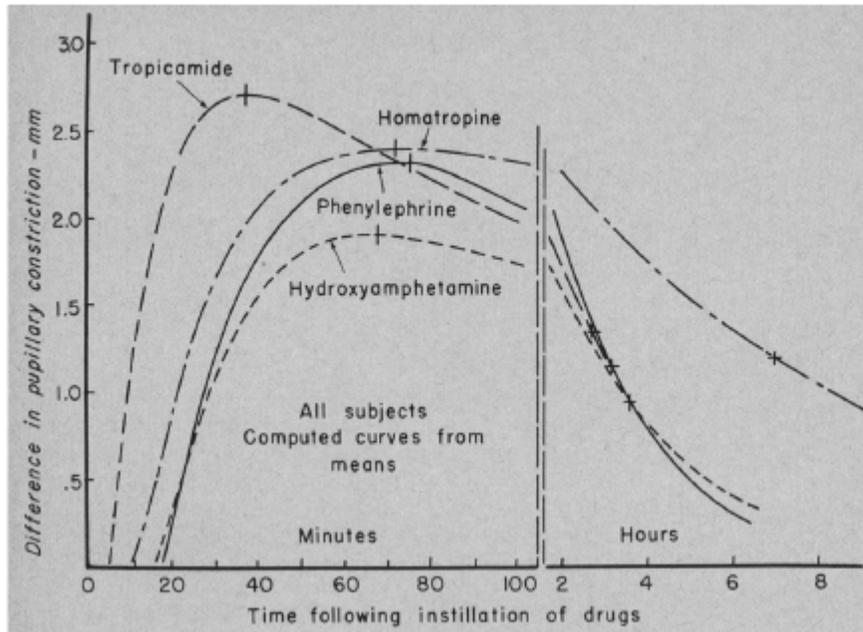
Figure 1: Mydriatic effect curve for Phenylephrine 10% solution



Data source: figure 1 from NDA 203510: 2.7.3 Summary of Clinical Efficacy on page 8

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Figure 2: Effect curves for four mydriatic agents



Data source: Figure 2 from NDA 203510: 2.7.3 Summary of Clinical Efficacy on page 6

The table below (Table 2) shows the means and SD for various characteristics of the onset and decay of mydriatic effect of the four drugs:

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Table 2: Summary of Effects for Four Mydriatic

Summary of Important Characteristics of Four Mydriatic Drugs*

	Drug	All Subjects	Light Irides	Dark Irides
Latency period (min)	Tropicamide	6.8	7.1	6.4
	Homatropine	14.3	14.3	14.2
	Hydroxy-amphetamine	21.1	20.7	21.7
	Phenylephrine	20.6	21.2	19.7
Rate of mydriasis (mm/min)	Tropicamide	0.33	0.37	0.25
	Homatropine	0.19	0.23	0.12
	Hydroxy-amphetamine	0.15	0.15	0.15
	Phenylephrine	0.14	0.16	0.11
Time to maximal mydriasis (min)	Tropicamide	38.8	36.8	42.4
	Homatropine	72.2	68.0	78.4
	Hydroxy-amphetamine	64.8	64.5	65.3
	Phenylephrine	70.2	69.6	71.1
Amount of maximal mydriasis (mm)	Tropicamide	2.69 (0.55)	2.90 (0.57)	2.32 (0.23)
	Homatropine	2.47 (0.66)	2.77 (0.54)	2.03 (0.57)
	Hydroxy-amphetamine	1.93 (0.70)	2.09 (0.61)	1.72 (0.75)
	Phenylephrine	2.42 (1.16)	2.69 (1.29)	2.01 (0.76)
Time to one-half recovery (hr)	Tropicamide	2.73	2.53	3.11
	Homatropine	7.03	7.00	7.09
	Hydroxy-amphetamine	3.22	2.95	3.58
	Phenylephrine	2.81	2.84	2.75
Time to ninetenths recovery (hr)	Tropicamide	7.11	6.53	8.15
	Homatropine	19.85	19.88	19.84
	Hydroxy-amphetamine	7.31	6.35	8.59
	Phenylephrine	5.33	5.53	5.04

*Computed from mydriasis-time curves fitted to experimental data.

Data source: Table 2 from NDA 203510: 2.7.3 Summary of Clinical Efficacy on page 9

Haddad et al 1970:

Haddad et al also 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. A crossover design was employed with at least 7 days between tests for concentrations of greater than 1.0% .

The applicant mentions that the results showed a well defined dose response curve with 5.0% and 10.0% concentrations being clearly on the plateau of the dose response and concentrations of 1.0% and below being clearly less active (Figure 3).

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The authors concluded that the freshly obtained 10% commercial formulation was less active than a freshly made 10% aqueous formulation. The commercial formulation was similar to the 2.25% concentration by extrapolation from the dose response curve.

Figure 3: Phenylephrine Dose Response Curve

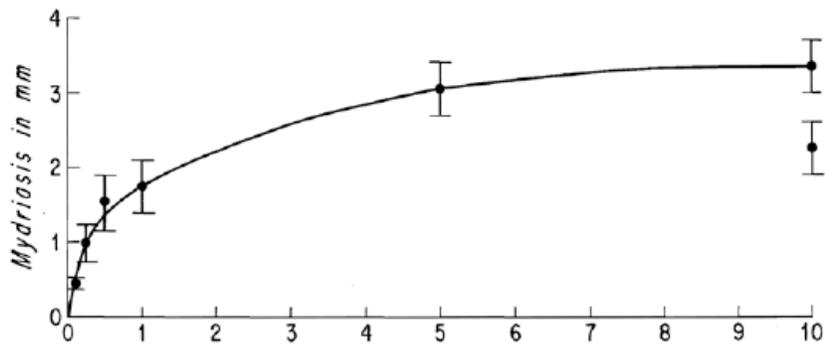


Fig. 1 (Haddad, Moyer, and Riley). Dose-response curve for phenylephrine HCl mydriasis in Group 1 (mean \pm SE). Percent of concentration of phenylephrine HCl is shown across bottom. Lower point at 10% concentration represents commercially available solution.

Data source: Figure 3 from NDA 203510: 2.7.3 Summary of Clinical Efficacy on page 10

In Group 2, 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 (Haddad, 1970). The authors also showed a diminution in response to subsequent instillations, some rebound miosis, and that on either 1% aqueous or 10% commercial phenylephrine the majority of subjects had some detectable pigment floaters after instillation.

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2. Studies comparing the efficacy of 2.5% and 10% phenylephrine

The following table describes two studies which compared different doses (e.g., 2.5% and 10%) of phenylephrine:

Table 1b: Studies comparing the efficacy of 2.5% and 10% phenylephrine

Authors	Title	Description a) Design b) Efficacy c) Safety
Chawdhary et al 1984	Mydriatic-use of Phenylephrine (a dose response concept)	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 et al 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. Group 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.

Data source: Table 1 from NDA 203510: 2.7.3 Summary of Clinical Efficacy on page 6

In the following, we describe the efficacy results of the two studies described in the above table:

Chawdhary et al (1984):

Chawdhary et al (1984) studied the effectiveness of phenylephrine in concentrations of 1.25%, 2.5%, 5% and 10% in 40 subjects. The drugs were coded and used randomly. Pulse rate, systolic and diastolic blood pressure in sitting posture and pupil size on Goldmann perimeter telescope were recorded at different time intervals. One drop of the drug was instilled every minute for three total drops. Observations were made at 2, 4, 6, 8, 10, 15, 20, 30 and 70 minutes. The results are shown in Figure 4 and the mean pupil size and SD at the 70th minute is shown graphically (Figure 5). The 70th minute was the end of the observation period and the maximum mydriasis for all groups, although the maximum was first observed at 50 minutes in Group I, II, and IV.

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Figure 4: Effects on pupil dilation of four concentrations of phenylephrine

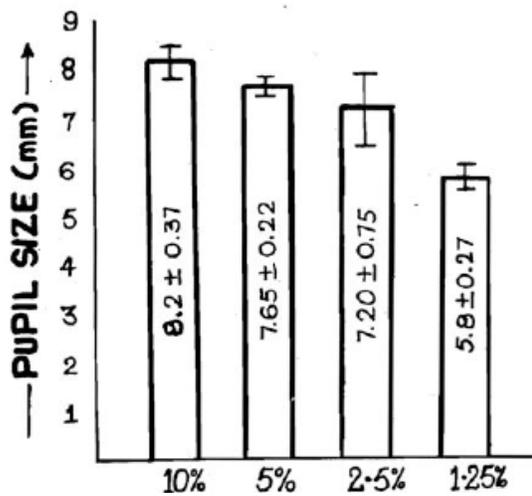
Mean and standard deviation of pupil size in mm at different intervals

N^o=80

Group	Concentration of drug	Basal	2 minutes	4 minutes	6 minutes	8 minutes	10 minutes	15 minutes	20 minutes	30 minutes	50 minutes	70 minutes
I	10%	4.2±0.27	4.3±0.27	4.3±0.27	4.6±0.42	4.7±0.27	5.4±0.42	5.9±0.65	6.5±0.50	7.65±0.42	8.2±0.27	8.2±0.37
II	5%	4.3±0.27	4.3±0.27	4.35±0.22	4.6±0.42	4.9±0.22	5.3±0.27	5.7±0.27	6 ±0.43	6.9±0.55	7.6±0.22	7.65±0.22
III	2.5%	4.2±0.27	4.2±0.27	4.2±0.27	4.3±0.27	4.6±0.22	5.1±0.22	5.3±0.27	5.8±0.45	6.6±0.55	7.0±0.61	7.2±0.75
IV	1.25%	4.1±0.22	4.1±0.22	4.1±0.22	4.2±0.27	4.6±0.22	4.8±0.45	5.1±0.42	5.3±0.27	5.7±0.27	5.8±0.27	5.8±0.27

Data source: Figure 4 from NDA 203510: 2.7.3 Summary of Clinical Efficacy on page 11

Figure 5: Mean pupillary size at the 70th minute following instillation of phenylephr



Concentration of Phenylephrine

Data source: Table 3 and Table 4 from NDA 203510: 2.7.3 Summary of Clinical Efficacy on page 11

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It can be seen from the Figure 4 and 5 that:

Mean pupil diameter at 70 minutes was 8.2mm in the 10% arm, 7.65mm in the 5% arm, 7.2mm in the 2.5% arm and 5.8mm in the 1.25% arm. The 2.5%, 5% and 10% groups all exceeded 7 mm dilation, the threshold necessary to conduct a complete ophthalmic exam, but the differences between the three groups were not statistically significant. The 1.25% concentration did not achieve the minimum requirement of 7 mm and the difference with the other groups was statistically significant. The findings from this study suggest that concentrations of phenylephrine less than 2.5% are not effective for the purpose of mydriasis during routine eye examinations and ophthalmic surgery.

Yospaiboon et al 2004:

The question regarding the mydriatic effect of phenylephrine in dark irides was addressed by Yospaiboon et al in the largest published study to date. Phenylephrine 2.5% and 10.0% were administered to a total of 564 patients with dark irides. The study demonstrated that in patients with dark irides, 10% phenylephrine was more effective than 2.5% phenylephrine in pupil dilation.

In prospective randomized trials in Caucasians, 2.5% phenylephrine has been found to be as effective as 10% phenylephrine, with fewer systemic side effects. However, there have been various reports indicating that in dark irides, 10% phenylephrine was more effective than 2.5% phenylephrine in maintaining mydriasis during cataract surgery. Yospaiboon et al 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, those in Group 2 received 1% tropicamide and 2.5% phenylephrine (Yospaiboon 2004).

Mean pupil diameter before instillation in Group 1 were 4.43 ± 1.13 mm in the right eye and 4.31 ± 0.95 mm in the left eye, whereas those in Group 2 were 4.45 ± 1.0 mm in the right eye and 4.32 ± 0.92 mm in the left eye. After instillation, mean pupil diameters in Group 1 were 7.58 ± 0.96 mm in the right eye and 7.60 ± 1.03 mm in the left eye. In group 2 the means were 7.17 ± 1.04 mm in the right eye and 7.07 ± 1.06 mm in the left eye. The difference was statistically significant ($p < 0.05$) (see Table 3 and Table 4 below).

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Table 3: Pupil size following administration of phenylephrine and tropicamide

Pupil size (mm)	10% Phenylephrine (n=293)	2.5% Phenylephrine (n=271)
Right eyes		
Baseline	4.43 ± 1.13	4.45 ± 1.0
Tropicamide	6.46 ± 0.99	6.38 ± 0.96
Phenylephrine	7.58 ± 0.96	7.17 ± 1.04
Left eyes		
Baseline	4.31 ± 0.95	4.32 ± 0.92
Tropicamide	6.45 ± 0.99	6.34 ± 1.01
Phenylephrine	7.60 ± 1.03	7.07 ± 1.06

Values are the mean ± SD

Table 4: Change in pupil size after tropicamide and phenylephrine
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J Med Assoc Thai, 2004; Vol 87:11: 1380- 1384

Data source: Figure 4 from NDA 203510: 2.7.3 Summary of Clinical Efficacy on page 11

3. Studies in children

In a study (Sindel, 1986) in babies weighing <1500grams 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. See Table 5 below for mydriatic effect of phenylephrine in newborns:

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Table 5: Mydriatic effect of phenylephrine in newborns

TABLE 2				
PATIENT DATA, MYDRIATIC EFFECTS AND CARDIOVASCULAR EFFECTS OF MYDRIATIC AND SALINE SOLUTIONS (MEAN ± 1 SD) (SEE TABLE 1 FOR SOLUTIONS USED IN GROUPS A-D)				
Group	A (n=10)	B (n=10)	C (n=10)	D (n=4)
Gestational Age (wks)	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
Pupillary Diameter (mm)				
Baseline	2.8 ± 0.8	3.0 ± 0.6	2.9 ± 0.6	2.9 ± 0.2
Post dilation	7.4 ± 0.5	7.3 ± 0.4	7.1 ± 0.6	2.9 ± 0.2
Difference from baseline	4.6 ± 0.8	4.3 ± 0.7	4.2 ± 1.0	0
"Bright light"	7.4 ± 0.6	7.2 ± 0.4	6.8 ± 0.6†	1.6 ± 0.4
Difference from baseline	4.6 ± 0.8	4.3 ± 0.6	3.9 ± 1.1	1.3 ± 0.2
Maximum change in blood pressure and heart rate after eyedrops instilled				
Blood pressure (%)				
Systolic	+14.9 ± 9.6*	+17.2 ± 12.5**	+7.1 ± 10.1	-0.6 ± 6.9
Mean	+17.1 ± 10.4*	+22.8 ± 17.4**	+7.7 ± 9.3††	+3.0 ± 6.0
Diastolic	+15.9 ± 7.8*	+19.5 ± 14.2*	+5.4 ± 7.6†††	+0.8 ± 10.6
Heart Rate (%)	+6.0 ± 6.1	+10.0 ± 10.6*	+4.4 ± 5.2	+2.1 ± 2.9
*p<0.02 vs baseline				
**p<.01 vs baseline				
†A vs C p=0.002, B vs C p=0.004				
††A vs C p=0.04, B vs C p=0.02				
†††A vs C p=0.007, B vs C p=0.01				

Data source: Table 1 from NDA 203510: 2.7.3 Summary of Clinical Efficacy on page 14

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4. Supporting studies.

Several studies provide confirmatory data for the studied cited above. These studies (*Filho 2007, Ozturk 2000, Tanner 1996, Eyeson-Annan 1998, Paggiarino 1993, Neuhaus 1980*) are presented in Table 6.

Table 6: Summary of Supporting Studies

Authors	Title (Abbreviated)	a) Design b) Efficacy c) Safety
Filho 2007 Ozturk 2000 Tanner 1996 Eyeson-Annan, 1998 Paggiarino 1993 Neuhaus 1980	Cardiovascular and papillary effects of topical ophthalmic 2.5% and 10% phenylephrine in healthy volunteers	In Portuguese with an English abstract a) Case controlled randomized crossover study of 2.5% and 10% phenylephrine in 28 healthy volunteers b) Significant difference in mydriatic effect p=OD 0.015/ OS 0.028 c) No difference in safety
Ozturk 2000	Efficacy of 2.5% phenylephrine and flurbiprofen combined in inducing and maintaining pupillary dilatation during cataract surgery.	a) Total 100 pts. 1. PE 10%, 2. PE 10% +Flb 3. 2.5% 4. 2.5% + Flb. (all received Tropicamide 1%) b) 2.5% and 10% showed no difference either alone or with Flb 0.03%
Tanner 1996	Comparative study of the efficacy of 2.5% and 10% phenylephrine on preoperative mydriasis for routine cataract surgery	a) 2.5% phenylephrine (n=62) v 10% phenylephrine (n=53) plus 1% cyclopentolate in both groups. b) No difference between 10% and 2.5% in pre operative pupil dilation 8.2mm and 8.0mm respectively. No difference in number of patients achieving 6 mm dilation.
Eyeson-Annan, 1998	Comparison of pupil dilatation using phenylephrine alone or in combination with tropicamide.	a) 10% phenylephrine alone compared to 10% phenylephrine with tropicamide on pupil size and ability to recognize cataracts b) 10% alone was less effective on pupil size compared to 10% + Tropicamide but no effect on cataract detection. c) No safety data reported
Paggiarino 1993	The effects on pupil size and accommodation of sympathetic and parasympatholitic agents.	a) 524 eyes evaluated with 4 different agents 150 subjects crossed over)) 2.5% phenylephrine, 10% phenylephrine, 0.5% tropicamide, 2.5% phenylephrine + 0.5% tropicamide. b) Recovery occurs between 5.5-7hrs for 2.5% phenylephrine, over 7 hrs for 10% phenylephrine. Tropicamide produced rapid dilation lasting over 7 hours. 2.5% phenylephrine + 0.5% tropicamide produced greatest dilation for over 7 hours. Maximum mydriasis was 8.13 vs 8.48 vs 8.22, vs 8.88 mm for each group respectively. No difference in loss of accomodation. c) No safety data.
Neuhaus 1980	Mydriatic effect of phenylephrine 10% (aq) vs phenylephrine 2.5% (aq)	a) N=11. Pupillography. Double blind randomized study. 10% phenylephrine in one eye 2.5% phenylephrine in the other. b) No significant difference

Data source: Table 1 from NDA 203510: 2.7.3 Summary of Clinical Efficacy on page 15

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Mushfiqur Rashid

Reviewing Statistician

Date: 12/05/2011

Yan Wang

Supervisor/Team Leader

Date: 12/05/2011

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