

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207926Orig1s000

STATISTICAL REVIEW(S)



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 #: 207926

Drug Name: Phenylephrine Hydrochloride Ophthalmic Solution USP, 2.5% and 10%

Indication(s): To dilate the pupil (Mydriasis).

Applicant: Akorn, Inc.

Date(s): Stamp Date: July 11, 2014
PDUFA Date: May 11, 2015
Review Date: October 20, 2014

Review Priority: Standard

Biometrics Division: IV

Statistical Reviewer: Solomon Chefo, Ph.D.

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Keywords: Mydriasis

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1. EXECUTIVE SUMMARY

The applicant, Akorn, has submitted a 505(b)(2) application to support approval of phenylephrine hydrochloride ophthalmic solution USP, 2.5% and 10% for the indication of inducing mydriasis. The applicant has been marketing the product under ‘Grandfather’ status since August 18, 1993 and has filed this application pursuant to compliance policy guide (CPG).

To support the efficacy claim, the application relied entirely on literature-based clinical studies. The applicant submitted seven studies that are considered the most relevant in supporting the effectiveness of the test product for the indication sought. These studies are:

- Three double-blind parallel group comparison studies (Suwan-Apichon et al, 2010; Yospaiboon et al, 2004; Chawdhary et al, 1984)
- Three crossover studies (Eyeson-Annan et al, 1998; Gambill et al, 1967; Haddad et al, 1970), and
- One study in pediatric subjects (Sindel et al, 1986).

The applicant provided detailed summaries for these studies; brief summary of these studies are presented in [Table 1](#).

Phenylephrine Hydrochloride Ophthalmic Solution USP, 2.5% and 10%, was recently approved for dilating the pupils (NDA 203510, approved 22 March 2013; Paragon BioTeck, Inc.); the approval was based on literature-based studies. Seven of the studies submitted to support the efficacy claim in the current NDA (with the exception of the study by Suwan-Apichon et al 2010) were also submitted and reviewed to support the efficacy claim in NDA 203510. The statistical review for NDA 203510 was conducted by Dr. Yan Wang and by Dr. Yunfan Deng.

In Dr. Wang’s statistical review for NDA 203510, the mydriatic effect of phenylephrine hydrochloride ophthalmic solution USP, 2.5% and 10% was evaluated based on seven literature-based studies.

- Four of these studies (Chawdhary et al 1984, Haddad et al 1970, Gambill et al 1967, and Yospaiboon et al 2004) are also submitted by Akorn to support the efficacy claim in the current NDA.
- Two studies (Sindel et al, 1986; Eyeson-Annan et al , 1998) that were included to support the efficacy claim in NDA 203510 (which are also included in the current NDA) were not discussed in Dr. Wang’s review due to lack of sufficient information for a comparative assessment of the efficacy of phenylephrine. The reviewer concurs with Dr. Wang’s assessment.
- Three additional studies which are not included in the current NDA but were considered supporting studies in NDA 203510 (Filho et al 2007, Neuhaus et al 1980, and Ozturk et al 2000.) were also included in Dr. Wang’s statistical review. Even though these studies are not included in the current NDA application, the reviewer believes in the relevance of these additional studies to assess the mydriatic effect phenylephrine.

Therefore, in this review, the efficacy evidence of phenylephrine to induce mydriasis was based on the statistical findings in the NDA 203510 review and based on the efficacy evaluation of the outstanding study that was not included in NDA 203510 application (Suwan-Apichon et al, 2010).

The key statistical findings from Dr. Wang's review were as follows:

- Dose response of phenylephrine was established in two studies (Chawdhary and Haddad (Part 1)).
- Four studies (Chawdhary, Filho, Neuhaus, and Yospaiboon) demonstrated statistically significant efficacy results of both 2.5% and 10% phenylephrine solutions.
- The Haddad (Part 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:
 - Three studies (Chawdhary, Filho, and Yospaiboon) demonstrated that the 10% solution is more effective than the 2.5% solution;
 - 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.

The single study summarized by the reviewer (Suwan-Apichon et al, 2010) also provided efficacy data for comparing the effects of 2.5% and 10% phenylephrine solutions in diabetic patients with darkly pigmented irides. Based on review of this study:

- Both concentrations of phenylephrine administered after instillation of one drop of 1% tropicamide clearly demonstrated significant mydriatic effect (see [Table 2](#)).
- The 10% concentration was more effective compared to the 2.5% concentration in diabetic patients with darkly pigmented irides; the difference in the mean change in pupil size between the two concentrations (10% phenylephrine minus 2.5% phenylephrine) was 0.25 (95% CI: 0.08, 0.42; p-value = 0.005) in the right eye and was 0.19 (95% CI: 0.02, 0.36; 0.040) in the left eye.

Therefore, based on the overall efficacy assessment from seven of the clinical studies reviewed by Dr. Wang (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) and from the single study summarized by the reviewer (Suwan-Apichon et al, 2010), there is a substantial evidence regarding the efficacy of phenylephrine hydrochloride solution, 2.5% and 10% in inducing mydriasis.

2. INTRODUCTION

2.1. OVERVIEW

In this 505(b)(2) NDA application, the applicant seeks approval of phenylephrine hydrochloride ophthalmic solution USP, 2.5% and 10% for the indication of inducing mydriasis; the application relied entirely on literature-based clinical studies. The applicant has been marketing the product under ‘Grandfather’ status since August 18, 1993, and has filed this NDA pursuant to compliance policy guide (CPG).

2.1.1. Class and Indication

Mydriasis is dilation of the pupil due to either disease or a drug. Pupil dilation is measured in mm; normal pupil size tends to range between 2.0 and 5.0 mm depending on the lighting and it is typically larger in younger people. In clinical studies, either pupil size or percentage of subjects with pupils larger than 5 or 6 mm is an acceptable endpoint.

Phenylephrine Hydrochloride Ophthalmic Solution, 2.5% and 10% is indicated to dilate the pupil. It was in the market since 1938 as an ophthalmic solution; however, there was no FDA approved drug application for phenylephrine hydrochloride ophthalmic solution until recently. Phenylephrine Hydrochloride Ophthalmic Solution USP, 2.5% and 10%, was recently approved for dilating the pupils (NDA 203510, approved 22 March 2013; Paragon BioTeck, Inc.). It has also been approved as an ophthalmic mydriatic agent at a concentration of 1% in combination with 0.2% cyclopentolate hydrochloride; Cyclomydril (ANDA 084300).

2.1.2. Studies Reviewed

The applicant indicated that they have not conducted or sponsored clinical studies due to the wealth of scientific literature and extensive clinical use of phenylephrine hydrochloride ophthalmic solution, 2.5% and 10%. As a result, to support the safety and mydriatic effect of the test product, the applicant relied entirely on literature-based studies.

Using PubMed database, the applicant identified several hundred published articles on the efficacy of phenylephrine in inducing mydriasis. Based on relevance of study objectives and results, completeness of information presented, and overall quality of the publication, the applicant selected seven studies to support the efficacy of phenylephrine. Four of the studies included in this 505(b)(2) application (Chawdhary et al 1984, Haddad et al 1970, Gambill et al 1967, and Yospaiboon et al 2004) were reviewed during NDA 203510 application. Thus, these studies are not included in this review; the efficacy evaluation and key statistical findings of these studies are discussed in the statistical review reports by Dr. Yan Wang (see DARRTs entry; 03/01/2013) and by Dr. Yunfan Deng (see DARRTs entry; 02/21/2013). Two of the studies (Sindel et al, 1986; Eyeson-Annan et al, 1998) are not included in this review due to lack of sufficient information for a comparative assessment of the efficacy of phenylephrine.

Therefore, in this review, the efficacy evidence of phenylephrine to induce mydriasis is based on the statistical findings in the NDA 203510 review and based on the efficacy evaluation of the single study that was not included in the NDA 203510 application (Suwan-Apichon et al, 2010).

In [Table 1](#) below, a brief summary of the four studies reviewed during the NDA 203510 application and the one study summarized in this review are presented.

Table 1: Brief summary of studies reviewed in supporting the efficacy of phenylephrine hydrochloride ophthalmic solution, 2.5% and 10%

Studies	Population/Sample size/Age	Arms (Sample size)	Comment	Measurement/Endpoint	Details with respect to statistical tests.
Suwanapicho, et al. ^[1] (2010)	Diabetic subjects with Darkly Pigmented Irises / N=100 (58 F and 42 M)/ 21-78 yrs.	2.5% PE (N=50) 10% PE (N=50)	All subjects received 1 drop of 1% tropicamide; 30 minutes later subjects received PE 2.5 or 10%	Pupil size was measured in both eyes 30 minutes after instillation of PE.	Paired t-test for change from baseline assessment and 2-sample t-test to compare 2.5% vs 10% PE
Yospaiboon, et al. ^[2] (2004)	Subjects with dark irides/ N=564 (315 F and 249 M)/ Mean Age = 51.2 yrs	2.5% PE (N=271) 10% PE (N=293)	All subjects received 1 drop of 1% tropicamide; 30 minutes later subjects received PE 2.5 or 10%	Pupil size measured immediately before 1% tropicamide, 30 minutes after 1% tropicamide (before 10% or 2.5% PE) and 30 minutes after 10% or 2.5% PE.	Paired t-test for change from baseline assessment and 2-sample t-test to compare 2.5% vs 10% PE
Chawdhary, et al. ^[2] (1984)	Indian patients with dark brown irides / N = 40/(NS F and NS M) 20-40 yrs.	1.25% PE (N=10) 2.5% PE (N=10) 5.0% PE (N=10) 10% PE (N=10)	One drop of the drug solution was instilled every minute for three times	Pupil size was measured at 11 time points: 0 (baseline), 2, 4, 6, 8, 10, 15, 20, 30, 50, and 70 minutes post instillation.	For each concentration of PE, means and standard deviations of the pupil size data were provided in the article. No formal statistical test performed.
Gambill, et al. (1967) ^[2]	Healthy Caucasian subjects/ N=15 (7 F and 8 M)/ 12-38 yrs; mean age=26.4 yrs 9 subjects had blue irides 3 subjects had hazel irides 3 subjects had brown irides	10% PE 0.5% Tropicamide 2% Homatropine 1% Hydroxyamphetamine	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 measured 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.	For each group, means and standard deviations for the amount of maximal mydriasis (mm) were provided. No formal statistical comparison was performed in the article.
Haddad, et al. (1970) ^[2]	Part 1: Health subjects/ N = 8 (NS F and NS M)/ 21-53 yrs. Part 2: N = 24 subjects/ 50+ yrs	Part 1: 0.1, 0.25, 0.5, 1.0, 5.0, and 10% PE Part 2: 1% PE (N=12) 10% PE (N=12)	Study subjects served as their own controls: right eye was treated and left eye was un-treated. Part 1: all subjects were tested with each concentration. Part 2: subjects received either PE 1 or 10%.	Pupil size was recorded at 15-minute intervals for 90 minutes and then hourly until recovery from mydriasis had occurred.	Part 1: The article provided plot of the mean (\pm SE) maximal mydriasis data. Part 2: means and standard deviations for the change in pupil size were provided. No statistical test performed.

^[1] The statistical review for this study was performed by the reviewer (See Section 3); PE: Phenylephrine

^[2] The statistical review for these studies was performed by Dr Yan Wang (see DARRTs entry; 03/01/2013) and by Dr. Yunfan Deng (see DARRTs entry; 02/21/2013) during NDA 203510 application.

2.2. DATA SOURCES AND QUALITY

This 505(b)(2) NDA application was based entirely on literature based studies and hence no data was submitted as part of the application.

The applicant submitted seven studies to support the efficacy of phenylephrine hydrochloride ophthalmic solution, 2.5% and 10% in inducing mydriasis. The submitted studies and the clinical summaries of safety and efficacy from these studies are located at:

[\\CDSESUB1\evsprod\NDA207926\](\\CDSESUB1\evsprod\NDA207926).

Note that since the application was based on literature based studies, review of the data and the analysis quality was very limited.

3. STATISTICAL EVALUATION

The applicant submitted seven literature-based studies to support the mydriatic effect of phenylephrine hydrochloride ophthalmic solution, 2.5% and 10%.

Four of the studies (Chawdhary et al 1984, Haddad et al 1970, Gambill et al 1967, and Yospaiboon et al 2004) were reviewed during the recent application and subsequent approval of Phenylephrine Hydrochloride Ophthalmic Solution USP, 2.5% and 10% for dilating the pupils (NDA 203510, approved 22 March 2013; Paragon BioTeck, Inc.). Thus, for the efficacy evaluation and key statistical findings of these studies, the reviewer directs readers to the statistical review by Dr. Yan Wang (see DARRTs entry; 03/01/2013) and by Dr. Yunfan Deng (see DARRTs entry; 02/21/2013). Two of the studies (Sindel et al, 1986; Eyeson-Annan et al, 1998) were also not included in this review due to lack of sufficient information for a comparative assessment of the efficacy of phenylephrine even though these studies were included in the current NDA application as well as in NDA 203510 application and may provide safety data for the phenylephrine treatment.

Therefore, the efficacy evaluation in this review covers only one study that was not included in the NDA 203510 application (Suwan-Apichon et al, 2010). The statistical evaluation of this study is presented in the following section.

Suwan-apichon et al.(2010): “2.5% and 10% Phenylephrine for Mydriasis in Diabetic Patient with Darkly Pigmented Irides”

This study was a prospective randomized double-blind study; 100 diabetic patients with darkly pigmented irides were randomly allocated into 2.5% and 10% phenylephrine groups. The study was adequately powered – at a 2-sided alpha level of 5% and assuming a standard deviation of 1.06¹, the study had > 90% power to detect a pupil size difference of 1 mm between the groups.

All patients in the study received one drop of 1% tropicamide in both eyes after initial visual assessment. After 30 minutes, the test product (either phenylephrine 2.5% or 10%) was given to patients. The authors indicated that pupil sizes (in both eyes) were measured 30 minutes after instillation of the test product; however, they did not specify when pupil sizes were measured at baseline and after tropicamide instillation even though summary data for these time points were provided (See [Table 2](#))

¹ Yospainboon Y, Luanratanakorn P, Noppawin-yoowong C. Randomized double-blind study of phenylephrine 2.5% vs 10% on pupillary dilation. J Med Assoc Thai 2004; 87: 1380-4

The study included all randomized subjects in the analysis. The majority of subjects (58%) were female. The mean age of patients in the study was 55 years (range: 21-28) with 48% of patients being at least 60 years or older. The mean duration of diabetes was about 90 months with mean fasting plasma glucose of 168 mg/dL; the mean duration of diabetes for patients at least 60 years or older was 109 months compared to 79 months for patients less than 60 years old.

In [Table 2](#), the mean pupil sizes at baseline and after instillation of tropicamide and phenylephrine in both eyes are presented. The mean pupil sizes at baseline and after instillation of tropicamide (before phenylephrine was given) were comparable between the two concentrations of phenylephrine; however, after instillation of phenylephrine, the mean pupil sizes in both eyes were slightly higher in the 10% compared to the 2% phenylephrine group.

The mean change from baseline and the difference in the mean change from baseline between the two concentrations of phenylephrine are also given in [Table 2](#). For the change from baseline evaluation, pupil size measured after tropicamide but before phenylephrine instillation was used as the baseline data. We should note that the average pupil size after tropicamide but before phenylephrine instillation increased by about 1.7 mm from baseline (before tropicamide).

The authors carried out independent t-test to determine the efficacy of phenylephrine in different concentrations by comparing the mean pupil size and the mean of difference in pupil size between the two groups. In addition, based on normal distribution approximation, the reviewer provided 95% CI estimates for the mean change in pupil size using paired t-test and for the difference in the mean changes (10% phenylephrine minus 2.5% phenylephrine) using two sample independent t-test in both eyes.

Table 2: Analysis Results of Pupil Sizes (mm) after Administration of Tropicamide and Phenylephrine (Suwan-apichon et al. 2010)

	2.5% phenylephrine (n = 50)	10% phenylephrine (n = 50)
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The mean changes (95% CIs) in pupil size from baseline in the 2.5% and 10% phenylephrine groups, respectively, were 0.59 (0.47, 0.72) and 0.84 (0.73, 0.95) in the right eye and were 0.6 (0.48, 0.72) and 0.79 (0.67, 0.92) in the left eye. Both concentrations of phenylephrine administered after instillation of tropicamide clearly demonstrated a significant mydriatic effect. However, the 10% concentration was more effective in diabetic patients with darkly pigmented irides compared to the 2.5% concentration; the difference in the mean change in pupil size between the two concentrations (10% phenylephrine minus 2.5% phenylephrine) was 0.25 (95% CI: 0.08, 0.42; p-value = 0.005) in the right eye and was 0.19 (95% CI: 0.02, 0.36; 0.040) in the left eye.

4. CONCLUSION

Based on the overall efficacy evaluation and the statistical findings from the relevant studies reviewed in the current NDA and in NDA 203510 submissions (Chawdhary et al 1984, Haddad et al 1970, Gambill et al 1967, and Yospaiboon et al 2004, Filho et al 2007, Neuhaus et al 1980, and Ozturk et al 2000, Suwan-Apichon et al, 2010), there is sufficient evidence regarding the efficacy of phenylephrine hydrochloride ophthalmic solution USP, 2.5% and 10% in inducing mydriasis.

APPENDICES

1. Chawdhary S, Angra S K, Zutshi R, and Sachdev M S. Mydriasis-use of phenylephrine (a dose-response concept). *Indian J Ophthalmol* 1984; 32:213-216,.
2. Eyeson-Annan M L, Hirst, L W, Battistutta D, and Green A. Comparative pupil dilation using phenylephrine alone or in combination with tropicamide. *Ophthalmology* 105: 726-732, 1998.
3. Filho A D, Frasson M, Merula R V, Morais P R, 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 H D, Ogle K N, and Kearns T P. Mydriatic effect of four drugs determined with pupillograph. *Arch Ophthal* 77: 740-746, 1967.
5. Haddad N J, Moyer N J, and Riley F C. Mydriatic effect of phenylephrine hydrochloride. *Am J Ophth* 70: 729-733, 1970.
6. Neuhaus R W, Helper R S. Mydriatic Effect of Phenylephrine 10% (aq) vs Phenylephrine 2.5% (aq). *Annals of Ophthalmol* Oct 1980: 1159-1160
7. Ozturk F, Kurt E, Inan U U, Ilker S S. The efficacy of 2.5% pheynylephrine and flurbiprofen combined in inducing and maintaining papillary dilatation during cataract surgery. *European J of Ophthal* 10; 2:144-148 2000
8. Sindel B D, Baker M D, Maisels M J, and Weinstein J. Comparison of the pupillary and cardiovascular effect of various mydriaticagents in preterm infants. *J Pediatr Ophthalmol Strabismus* 23: 273-276, 1986.
9. Suwan-Apichon O, Ratanapakorn T, Panjaphongse R, Sinawat S, Sunguansak T, and Yospaiboon Y. 2.5% and 10% phenylephrine for mydriasis in diabetic patients withdark irides. *J Med Assoc Thai* 93: 467-473, 2010.
10. Yospaiboon Y, Luanratanakorn P, and Noppawinyoowong C. Randomized double-blind study of phenylephrine 2.5% vs 10% on pupil diameter. *J Med Assoc Thai* 87:1380-1384, 2004.

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/s/

SOLOMON CHEFO
10/30/2014

YAN WANG
10/30/2014
I concur.

Statistics Filing Checklist for NDA - 207926

NDA Number:	207926
NDA Type:	Standard Review
Drug Name:	Phenylephrine Hydrochloride Ophthalmic Solution USP, 2.5% and 10%
Indication:	To dilate the pupil (Mydriasis)
Applicant:	Akorn, Inc.
Stamp Date:	July 11, 2014
Reviewer:	Solomon Chefo
EDR Location:	\\CDSESUB1\evsprod\NDA207926\0000

1. Brief Summary of Controlled Clinical Trial(s)

This is a 505(b)(2) NDA application based entirely on literature-based clinical studies. In this NDA application, the applicant seeks approval of phenylephrine hydrochloride ophthalmic solution USP, 2.5% and 10% for the indication of inducing mydriasis. The applicant indicated that they have been marketing the product under ‘Grandfather’ status since August 18, 1993, and are filing this NDA pursuant to compliance policy guide (CPG).

On March 21, 2013, Paragon BioTeck Inc. received FDA approval (NDA 203510) of phenylephrine hydrochloride ophthalmic solution, USP 2.5% and 10% to dilate the pupil based on literature-based studies. In this NDA application, Akorn is seeking approval of the product for the same indication with minor modification to the 2.5% concentration. The applicant indicated that their formulation with the exception of excluding boric acid in the 2.5% concentration is the same as the reference product (Paragon BioTeck) formulation.

To support the efficacy claim, the applicant indicated that they identified several articles on the efficacy of phenylephrine in inducing mydriasis from a search of the PubMed database; and **seven** articles were considered the most relevant in supporting the effectiveness of the product for the indication sought. These studies are: three double-blind parallel group comparisons (Suwan-Apichon et al, 2010; Yospaiboon et al, 2004; Chawdhary et al, 1984), three crossover studies (Eyeson-Annan et al, 1998; Gambill et al, 1967; Haddad et al, 1970), and one study in pediatric subjects (Sindel et al, 1986). Note that six of the articles with the exception of Suwan-Apichon et al were used and reviewed to support the efficacy claim in NDA 203510. A brief summary of the seven articles are presented in Appendix Table 4.

Therefore, in this NDA application, support for the efficacy claim of the test product in inducing mydriasis was based on the seven articles. The applicant provided summaries for these seven studies in the NDA.

We should note that:

- i) None of the seven articles summarized in Akorn’s clinical study report provided data on the new formulation for the 2.5% concentration.
- ii) The applicant provided five additional articles using their formulation; however, none of the articles provided data on the extent of mydriasis produced by the Akorn phenylephrine solution.

2. Assessment of Protocols and Study Reports

Table 1: Summary of Information from Review of the Protocol and the Study Report

Content Parameter	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	<input checked="" type="checkbox"/>			- Three studies were randomized double-blind, and parallel group. - One study was a randomized, partially blinded, parallel group in pediatric subjects. - Three studies were crossover studies
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.			<input checked="" type="checkbox"/>	No protocols and statistical analysis plan since submission is 505(b)(2) NDA application based on literature-based clinical studies
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			<input checked="" type="checkbox"/>	
Appropriate references for novel statistical methodology (if present) are included.			<input checked="" type="checkbox"/>	
Safety data organized to permit analyses across clinical trials in the NDA.			<input checked="" type="checkbox"/>	In addition to the literature data, the applicant intends to rely on the findings of safety for Paragon BioTeck's Phenylephrine Hydrochloride Ophthalmic Solution USP, 2.5% and 10% (NDA203510).
Investigation of effect of missing data and discontinued follow-up on statistical analyses as described by applicant appears adequate.			<input checked="" type="checkbox"/>	

3. Electronic Data Assessment

Table 2: Information Regarding the Data

Content Parameter	Response/Comments
Dataset location	505(b)(2) literature-based so no data
Dataset structure (e.g., SDTM or ADaM)	505(b)(2) literature-based so no data
Based on the analysis datasets, can results of the primary endpoint(s) be reproduced? (Yes or No)	505(b)(2) literature-based so no data
List the dataset(s) that contains the primary endpoint(s)	505(b)(2) literature-based so no data
Are there any concerns about site(s) that could lead to inspection? If so, list of site(s) that needs inspection and rationale	NA

4. Filing Issues

Table 3: Initial overview of the NDA/BLA application for refuse-to-file (RTF):

Content Parameter	Yes	No	NA	Comments
Index is sufficient to locate necessary reports, tables, data, etc.	<input checked="" type="checkbox"/>			
ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	<input checked="" type="checkbox"/>			No study reports or protocols; Studies are summarized in Module 2.7.3 Summary of Clinical Efficacy
Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.	<input checked="" type="checkbox"/>			Suwan-Apichon et al presented pupil size summary by age group (Age < 60 versus >=60)
Data sets in EDR are accessible and conform to applicable guidance (e.g., existence of define.pdf file for data sets).	<input checked="" type="checkbox"/>			505(b)(2) literature-based so no data

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? YES

Based on our preliminary review, the NDA is fileable.

Appendix:

Table 4: Seven studies considered pivotal in supporting the efficacy of phenylephrine hydrochloride ophthalmic solution, 2.5% and 10%.

Author (Reference)	Design	Population	Drugs/Dose/Duration/Route of Administration	Measurement/Endpoint	Results																														
Suwanapichon, et al., 2010	Randomized, double-blind, dose-controlled, parallel group comparison	100 diabetic subjects (50 per group); 58 females; 42 males; 21-78 yrs.	All subjects received 1 drop of 1% tropicamide; 30 minutes later 50 subjects received 2.5% phenylephrine and 50 subjects received 10% phenylephrine	Digital images of the pupil were obtained with Humphrey 598 automatic refractor; pupillary diameter was measured with Image-Pro Plus 4.5 analysis program	<p>Mean Pupil Diameter</p> <table border="1"> <thead> <tr> <th></th> <th colspan="2">2.5%</th> <th colspan="2">10%</th> </tr> <tr> <th></th> <th>R</th> <th>L</th> <th>R</th> <th>L</th> </tr> </thead> <tbody> <tr> <td>Baseline</td> <td>4.73</td> <td>4.66</td> <td>4.97</td> <td>4.87</td> </tr> <tr> <td>Tropic 1%</td> <td>6.46</td> <td>6.45</td> <td>6.56</td> <td>6.50</td> </tr> <tr> <td>Phenyl</td> <td>7.05</td> <td>7.05</td> <td>7.40</td> <td>7.39</td> </tr> <tr> <td>Difference (Phen-Trop)</td> <td>0.59</td> <td>0.59</td> <td>0.83</td> <td>0.79</td> </tr> </tbody> </table> <p>10% phenylephrine was significantly more effective than 2.5%. There were no clinically significant differences in heart rate or blood pressure. No adverse event was reported.</p>		2.5%		10%			R	L	R	L	Baseline	4.73	4.66	4.97	4.87	Tropic 1%	6.46	6.45	6.56	6.50	Phenyl	7.05	7.05	7.40	7.39	Difference (Phen-Trop)	0.59	0.59	0.83	0.79
	2.5%		10%																																
	R	L	R	L																															
Baseline	4.73	4.66	4.97	4.87																															
Tropic 1%	6.46	6.45	6.56	6.50																															
Phenyl	7.05	7.05	7.40	7.39																															
Difference (Phen-Trop)	0.59	0.59	0.83	0.79																															
Eyeson-Annan, et al., 1998	Two-period fixed sequence with a one week wash-out.	47 subjects; 27 females, 20 males; 20-79 yrs.	All subjects received 1 drop of 0.4% oxybuprocaine in each eye. Phenylephrine 10%, 3 drops Phenylephrine 10%, 3 drops + tropicamide 1%, 3 drops. Sequence of treatment was not specified.	Pupillary diameter was determined by photography with a Neitz Cataract camera and measurements were made with a calibrated grid to 0.5 mm.	<p>Mean maximal pupil size with phenylephrine 10% and tropicamide 1% was significantly larger than with phenylephrine 10% alone. From a mean baseline diameter of 3 mm, mean pupillary diameter at 40 minutes with phenylephrine + tropicamide was 8.0 mm compared to 6.9 mm for phenylephrine alone. P<0.0003</p> <p>No adverse event was reported for either treatment group.</p>																														

Source: Table 13 of Applicant’s Summary of Clinical Efficacy Section

Drug Name: Phenylephrine Hydrochloride Ophthalmic Solution USP, 2.5% and 10%
 Indication: Mydriasis

Author (Reference)	Design	Population	Drugs/Dose/Duration/Route of Administration	Measurement/Endpoint	Results																					
Yospaiboon, et al., 2004	Randomize, double-blind, parallel-group comparison	564 patients; 315 females, 249 males Mean age, 51.2 yrs.	All patients received 1% tropicamide and then, at random, one drop PE 2.5% - 271 patients or PE 10% - 293 patients	Pupillary dilation was measured with a Cannon auto-keratorefractor with a resolution of 0.1mm	<p>Pupil Size, mm</p> <table border="1"> <thead> <tr> <th></th> <th>PE 2.5%</th> <th>PE 10%</th> </tr> </thead> <tbody> <tr> <td>Rt Eye Baseline</td> <td>4.45</td> <td>4.43</td> </tr> <tr> <td>After T</td> <td>6.38</td> <td>6.46</td> </tr> <tr> <td>After PE</td> <td>7.17</td> <td>7.58 p<0.001</td> </tr> <tr> <td>Lft Eye Baseline</td> <td>4.32</td> <td>4.31</td> </tr> <tr> <td>After T</td> <td>6.34</td> <td>6.45</td> </tr> <tr> <td>After PE</td> <td>7.07</td> <td>7.65 p<0.001</td> </tr> </tbody> </table> <p>There were no changes in blood pressure from either concentration of phenylephrine. There was a slight but statistically significant increase in heart rate after 10% phenylephrine (2.85 bpm).</p> <p>No adverse event was reported.</p>		PE 2.5%	PE 10%	Rt Eye Baseline	4.45	4.43	After T	6.38	6.46	After PE	7.17	7.58 p<0.001	Lft Eye Baseline	4.32	4.31	After T	6.34	6.45	After PE	7.07	7.65 p<0.001
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Source: Table 13 of Applicant’s Summary of Clinical Efficacy Section

Drug Name: Phenylephrine Hydrochloride Ophthalmic Solution USP, 2.5% and 10%

Indication: Mydriasis

Author (Reference)	Design	Population	Drugs/Dose/Duration/Route of Administration	Measurement/Endpoint	Results
Gambill, et al., 1967	Crossover; sequence of treatment and duration of wash-out not specified.	15 healthy subjects; 7 females, 8 males, 12 to 38 yrs.	Phenylephrine 10% Tropicamide 0.5% Homatropine 2% Hydroxyamphetamine 1%	Pupillary diameter measured by infra-red electronic pupillograph; difference in pupillary constriction of treated and untreated eye was determined in response to a light stimulus.	Difference between Treated and Untreated Eye at Maximal Mydriasis, mm Phenylephrine 10% 2.42 Tropicamide 0.5% 2.69 Homatropine 2% 2.47 Hydroxyamphet 1% 1.93 No adverse event was reported.
Haddad, et al., 1970	Two part study: Part 1; dose escalation with wash out between doses Part 2; parallel group comparison of two concentrations of phenylephrine	Part 1: 8 healthy subjects 21-53 yrs. Part 2: 24 subjects 50+ yrs.	Part 1: phenylephrine 0.1, 0.25, 0.5, 1.0, 5.0, and 10% solution. Part 2: 1% - 12 subjects 10% - 12 subjects	Pupillary diameter measured by infra-red electronic pupillograph; difference in pupillary constriction of treated and untreated eye was determined in response to a light stimulus.	Part 1: There was a dose-related increase in pupillary diameter with maximal effect occurring with the 10% concentration. Difference between treated and untreated eyes at maximal effect was more than 3 mm. Part 2 reports on the occurrence of rebound miosis in older subjects. There was no mention of adverse events.

Source: Table 13 of Applicant’s Summary of Clinical Efficacy Section

Author (Reference)	Design	Population	Drugs/Dose/Duration/Route of Administration	Measurement/Endpoint	Results
Chawdhary, et al., 1984	Randomized, double-blind	40 healthy subjects, 20-40 yrs.	Phenylephrine. 3 drops 1.25% 10 subjects 2.50% 10 subjects 5.0 % 10 subjects 10 % 10 subjects	Pupil size was measured with a Goldman perimeter telescope	<p>Pupil size, mm</p> <p>1.25% 5.8 2.50% 7.2 5.0% 7.65 10% 8.2</p> <p>There was no significant difference in response to the three higher concentrations but all were significantly different from 1.25%</p> <p>The 5% and 10% solutions produced statistically significant increase in heart rate and blood pressure between 4 and 6 minutes after application of the drug. The 10% solution produced a mean increase in heart rate from 80.8 to 95.2 and 5% produced an increase from 80.8 to 88.0. Increases in systolic pressure were from 130 to 145 and 124 to 130 mmHg for 10 and 5% respectively. Increases in diastolic pressure were from 85.2 to 96.8 and 82.8 to 87.2 mmHg respectively.</p> <p>No adverse event was reported.</p>

Source: Table 13 of Applicant’s Summary of Clinical Efficacy Section

Drug Name: Phenylephrine Hydrochloride Ophthalmic Solution USP, 2.5% and 10%
 Indication: Mydriasis

Author (Reference)	Design	Population	Drugs/Dose/Duration/Route of Administration	Measurement/Endpoint	Results																				
Sindel et al., 1986	Randomized, partially blinded (control group not blinded)	34 preterm infants, gender not specified, average age = 53 days	A -Phenylephrine 2.5 % + tropicamide 1% - 10 subjects; B -Phenylephrine 2.5% + tropicamide 0.5% + cyclopentolate 0.5% - 10 subjects; C -Phenylephrine 1% + tropicamide 1%- 10 subjects D -Saline - 4 subjects	Pupillary size was measured with a transparent metric ruler by direct observation before administration of the first drop in ambient light and 60 minutes after the second drop both in ambient light and after exposure to bright light of an indirect ophthalmoscope.	Mean Pupillary Diameter, mm Post <table border="1"> <thead> <tr> <th></th> <th>Baseline</th> <th>Dilation</th> <th>Difference</th> </tr> </thead> <tbody> <tr> <td>A-</td> <td>2.8</td> <td>7.4</td> <td>4.6</td> </tr> <tr> <td>B-</td> <td>3.0</td> <td>7.3</td> <td>4.3</td> </tr> <tr> <td>C-</td> <td>2.9</td> <td>7.1</td> <td>4.2</td> </tr> <tr> <td>D-</td> <td>2.9</td> <td>2.9</td> <td>0</td> </tr> </tbody> </table> <p>BP and HR increased transiently in all groups receiving mydriatics but returned to baseline values in 25 minutes. The increase was significant in Groups A and B (2.5%PE; p<0.02). Group D (saline) showed no change in BP or HR.</p> <p>No adverse event was reported.</p>		Baseline	Dilation	Difference	A-	2.8	7.4	4.6	B-	3.0	7.3	4.3	C-	2.9	7.1	4.2	D-	2.9	2.9	0
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C-	2.9	7.1	4.2																						
D-	2.9	2.9	0																						

Source: Table 13 of Applicant’s Summary of Clinical Efficacy Section

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/s/

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08/20/2014

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