

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**207926Orig1s000**

**SUMMARY REVIEW**

NDA 207926  
Phenylephrine Hydrochloride Ophthalmic Solution  
Proposed Indication: Dilate the Pupil

## Summary Review for Regulatory Action

<b>Date</b>	See electronic stamp date
<b>From</b>	Renata Albrecht, MD Division of Transplant and Ophthalmology Products
<b>Subject</b>	Division Director Summary Review
<b>NDA Number</b>	NDA 207926
<b>Related IND</b>	pIND 121700
<b>Applicant Name</b>	Akorn, Inc.
<b>Date of Submission</b>	July 11, 2014
<b>Date of Receipt</b>	July 11, 2014
<b>Review Type</b>	Standard
<b>Division Goal Date</b>	January , 2015 (to minimize drug shortage)
<b>PDUFA Goal Date</b>	May 11, 2015
<b>Proprietary Name / Established (USAN) Name</b>	None approved at this time Phenylephrine hydrochloride ophthalmic solution, USP
<b>Formulation Presentation</b>	Ophthalmic solution in LDPE bottle with red cap <ul style="list-style-type: none"><li>• 2.5% concentration:<ul style="list-style-type: none"><li>○ 2 mL in 6 cc bottle;</li><li>○ 15 mL in 15 cc bottle</li></ul></li><li>• 10% concentration:<ul style="list-style-type: none"><li>○ 5 mL in 10 cc bottle</li></ul></li></ul>
<b>Use</b>	One drop every 3 to 5 minutes for maximum of 3 drops
<b>Proposed Indication</b>	Dilation of pupil
<b>Action for Application</b>	<i>Approval</i>

NDA 207926  
 Phenylephrine Hydrochloride Ophthalmic Solution  
 Proposed Indication: Dilate the Pupil

<b>Material Reviewed/Consulted</b> OAP Action Package, including:	<b>Names of discipline reviewers</b>
Medical Officer Review	Bill Boyd 1/9/2015
CDTL Review	Bill Boyd 1/15/2015
Statistical Review	Solomon Chefo, Yan Wang 10/30/2014
Pharmacology/Toxicology Review	Maria Rivera, Lori Kotch 12/8/2014
Clinical Pharmacology Review	Yongheng, Zhang, Philip Colangelo 11/7/2014, 12/8/2014
Product Quality Manufacturing Review OPQ	Mariappan Chelliah, Balajee Shanmugam, Rapti Madurawe 12/22/2014
Product Quality Microbiology Review	Neal Sweeney, John Metcalfe 12/22/2014
Biopharmaceutics Review, OPQ	Banu Zolnik, Okponanabofa Eradiri 23/9/2014
OC/Facilities Inspection	Acceptable (see CMC review)
OSI/DGCPC	N/A
OSE/DMEPA Labeling Review	Rachna Kapoor, Yelena Maslov 11/12/2014
OPDP/DPDP (formerly DDMAC)	Christine Corser 12/5/2014
Project Manager	Eithu Lwin

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

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## 1. Summary and Recommendations

Akorn submitted NDA 207926 for Phenylephrine Hydrochloride Ophthalmic Solution USP, 2.5% and 10%. The Drug Shortage Staff (DSS) has requested the Division expedite the review of NDA 207926 to avoid a possible drug shortage.

Phenylephrine hydrochloride ophthalmic solution is a topical ophthalmic product intended to dilate the pupil. NDA 207926 was submitted as a 505(b)(2) application and relies on literature data for the clinical and non-clinical information. The applicant mentioned that NDA 203510, for phenylephrine hydrochloride ophthalmic solution by Paragon Biotech, was approved March 21, 2013, for the indication to dilate the pupil. Of note, the applicant does not rely on NDA 203510 and does not need to do so because all necessary clinical and non-clinical information is from the published. Parenthetically, Paragon did not conduct any new clinical studies with their product, and also relied on the published non-clinical and clinical information.

The labeling was submitted in physician labeling rule (PLR) format and except for differences in the description of the products (Sections 3, 11, and 16), the information in the other sections is derived from the published literature.

Phenylephrine has been marketed for over 70 years, and used in various concentrations to dilate the pupil. The applicant identified 6 publications with phenylephrine hydrochloride ophthalmic solution. These trials confirmed the ability of both the 2.5% and 10% to achieve pupil dilation, starting as soon as 15 minutes after instillation and generally achieving maximum dilation by 20-90 minutes. The effect resolves after around 5 hours (range of 3 to 8 hours). In these studies, the 2.5% product increased pupil diameter between 1 to 3 mm compared to the baseline size or to the contralateral pupil, and the 10% product increased pupil diameter 1 to 4 mm. Under lit condition, the difference between the two pupils was greater, due to the reflective constriction of the untreated pupil in response to light.

In addition Akorn also submitted 5 publications that specifically mention the use of AK-Dilate, the Akorn phenylephrine product marketed [as an unapproved product] since 1993. The implicit evidence that the Akorn product was efficacious is derived from the documentation that patients could successfully undergo the clinical examination or surgical procedure that depended on adequate dilation of the pupil.

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

### 1 INDICATIONS AND USAGE

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

## **2 DOSAGE AND ADMINISTRATION**

### **2.1 General Dosing Recommendations**

In patients 1 year of age or greater, apply one drop of either phenylephrine hydrochloride ophthalmic solution 2.5% or 10% every 3 to 5 minutes to the conjunctival fornix as required up to a maximum of 3 drops per eye per day.

In order to obtain a greater degree of mydriasis, phenylephrine hydrochloride ophthalmic solution 10% may be needed.

### **2.2 Dosing in Pediatric Patients Less Than 1 Year of Age**

In pediatric patients less than 1 year of age, one drop of phenylephrine hydrochloride ophthalmic solution 2.5% should be instilled at 3 to 5 minute intervals up to a maximum of 3 drops per eye.

Phenylephrine is an  $\alpha_1$ -adrenergic agonist (sympathomimetic) and its pharmacodynamics effect on the eye and on the cardiovascular system has been described in the literature. As far as adverse reactions, local effects of the ophthalmic solution include stinging, pain, blurring on installation and photophobia associated with the dilation of the pupil. Rebound miosis on re-installation of phenylephrine has been reported.

Systemic effects include increased blood pressure, and cardiac events including tachycardia, ventricular arrhythmias, myocardial infarction, syncope and subarachnoid hemorrhage. Although these events could be associated with both concentrations, they are more likely to be associated with the 10% formulation, and in younger children and elderly patients with underlying hyperthyroidism and cardiovascular disease. The 10% product is contraindicated in infants under the age of 1 year because of the serious risk of hypertension and systemic toxicity, and in patients with hypertension and thyrotoxicosis. Atropine may enhance the pressor effects of phenylephrine. Phenylephrine may potentiate the depressor effects of anesthetic agents. This safety information is incorporated in the package insert. Although information on animal studies from the literature was provided, the labeling provides brief cautionary language about use in pregnant women and nursing mothers; this labeling is consistent with the advice given in the recently approved intravenous product, phenylephrine hydrochloride (NDA 203826, approved December 20, 2012) and topical ophthalmic products (NDA 203510, approved March 21, 2013).

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

### **1.1 Deficiencies**

None, the application will be approved.

### **1.2 Post-Marketing Studies:**

None

### **1.3 Other Issues**

None

## 2. Background

This application is submitted as a 505(b)(2) application and relies on published literature for clinical and preclinical information. The applicant (Akorn, Inc.) states that phenylephrine has been used as an ophthalmic agent since the 1930's to induce mydriasis for fundus examination, ophthalmic surgery and other uses. The first description of its topical ocular use in the literature is in 1936<sup>1</sup> and since then numerous other articles have been published.

The NDA is submitted in response to the unapproved drug initiative started by the Agency in 2006.<sup>2</sup> The products in this application (2.5% and 10% solutions) are the same as the marketed products and differ only in the absence of a (b)(4) from the marketed unapproved product, as noted by the CMC reviewer.

Ophthalmic topical products for over-the-counter (OTC) use are allowed to contain phenylephrine hydrochloride 0.08% to 0.2% and labeled for relief or redness or vasoconstriction.<sup>3</sup>

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

### 2.1 NDA Submission

(b)(4)



Akorn submitted pre-IND 121700 and met with the Division on April 3, 2014 to discuss the filing of their planned 505(b)(2) NDA for phenylephrine hydrochloride ophthalmic solution, USP 2.5% and 10%. During the meeting, guidance was provided on the submission of clinical, non-clinical, pharmacology/toxicology and a range of expected CMC data.

<sup>1</sup> Heath P. Neosynephrine; some uses and effects in ophthalmology. Arch Ophth 1936;16:839.

<sup>2</sup> FDA guidance for FDA Staff and Industry, Marketed Unapproved Drugs – Compliance Policy Guide: Sec 444.100 Marketed New Drugs without Approved NDAs or ANDAs, revised September 2011.

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070290.pdf>

and Unapproved Drugs Initiative:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/SelectedEnforcementActionsonUnapprovedDrugs/ucm118990.htm>

<sup>3</sup> 21 CFR 349 Ophthalmic drug products for over-the-counter use. Paragraphs 349.18 and 349.75.

Akorn submitted NDA 207926 on July 11, 2014 for the indication “to dilate the pupil.”

## 2.2 Standard Review

Akorn was granted a standard review. The Division, including the ONDQA members of the review team, agreed to expedite the review of the application to minimize any drug shortage. There is currently only one FDA-approved supplier of phenylephrine hydrochloride ophthalmic solution, 2.5% and 10%, packaged as a single active ingredient at concentrations necessary to induce adequate pupil dilation for diagnostic, therapeutic or surgical procedures: NDA 203510, Paragon. The Drug Shortage group has received multiple reports of drug shortages of this product.

## 3. CMC/Product Quality Microbiology

See complete CMC review, Microbiology Sterility review and Biopharmaceutics review.

### 3.1 Product Quality

The CMC reviewers (CMC, Micro Sterility, and Biopharmaceutics) recommend approval. They conclude the NDA provides adequate information to assure the identity, strength, purity, and quality of the drug product. The Office of Compliance has given an acceptable recommendation for both the drug substance manufacturing facility (b) (4) and the drug product manufacturing facility (Akorn). Labeling has been finalized.

The CMC review notes that DMF (b) (4) covers the drug substance (b) (4).

The drug product uses phosphoric acid along with sodium hydroxide to adjust the pH. By comparison, Paragon’s 2.5% solution uses (b) (4) and sodium hydroxide to adjust the pH, and the pH of the 10% solution is adjusted with sodium hydroxide alone. The reviewer comments that the high load of phenylephrine hydrochloride (100 mg/mL) likely lowers the pH below 6.5 such that only sodium hydroxide is required to adjust the pH. (CMC review, page 22). Benzalkonium chloride, 0.1 mg (0.01%), is used as an antimicrobial preservative. The bulk formulated solution is (b) (4) filled-into low-density polyethylene bottles.

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

Ingredient	Quality Standard	Function	Composition	
			2.5%	10%
Phenylephrine Hydrochloride	USP	API	2.5%	10%
Benzalkonium Chloride	NF	Preservative	0.01%	
Dibasic Sodium Phosphate, (b) (4)	(b) (4)	(b) (4)		
Monobasic Sodium Phosphate, (b) (4)	(b) (4)			
Phosphoric Acid	NF	Adjusting pH	to pH 6.5	
Sodium Hydroxide (b) (4)	NF	Adjusting	OS to pH 6.5	
Water for Injection (b) (4)	USP (b) (4)	(b) (4)		

(Source: OPQ review, page 21)

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

**Release specification for phenylephrine hydrochloride, 2.5% and 10% solutions**

Test Parameter	Label Claim or Target	Acceptance Range	USP Specification
Phenylephrine Hydrochloride <sup>a</sup> Assay	100 mg/mL (10% solution) 25 mg/mL (2.5% solution)	(b) (4)	(b) (4)
Individual Degradants <sup>a</sup>	NMT (b) (4) %	NMT (b) (4)	
Unidentified Impurity <sup>c</sup>	NMT (b) (4) %	NM	
Total Degradants <sup>a</sup>	NMT (b) (4) % NMT (b) (4) % <sup>c</sup>	NM NM	
Benzalkonium Chloride <sup>a</sup>	0.1 mg/mL	80-110%	
Identification by HPLC <sup>b</sup>	Retention time conforms to reference standard	Conforms	
Identification by TLC <sup>a</sup>	Conforms	Conforms	Conforms
Identification of BAC <sup>c</sup>	Conforms	Conforms	
pH <sup>c</sup>	6.5	6.0 to 7.0	4.0 to 7.5
Osmolality <sup>a</sup>	985 mOsm/kg (10% solution) 340 mOsm/kg (2.5% solution)	895-1095 mOsm/kg 320-380 mOsm/kg	
Recovery volume <sup>a</sup>	5 mL (Akorn code: 5023) 2 mL (Akorn code: 5031) 15 mL (Akorn code: 5030)	NLT (b) (4) NLT NLT	
Product Appearance <sup>a</sup>	Clear, colorless to yellow solution	Clear, colorless to yellow solution	
Container Appearance <sup>a</sup>	No visual deterioration	No visual deterioration	
Impurity (b) (4)	NMT (b) (4) %	NMT (b) (4) %	
Residual Solvents <sup>a,d</sup>	USP <467>	Conforms	
Viscosity <sup>c</sup>	0.63-1.42 cps (Akorn code: 5023) 0.69-1.04 cps (Akorn code: 5031) 0.46-1.17 cps (Akorn code: 5030)	0.63 to 1.42 cps 0.69-1.04 cps 0.46-1.17 cps	

Test Parameter	Label Claim or Target	Acceptance Range	USP Specification
Color <sup>c</sup>	(b) (4)	(b) (4)	
Container Closure <sup>c</sup>	Integral	Integral	
Sterility <sup>a</sup>	Sterile	Sterile	USP <71>
Particulate Matter <sup>c</sup>	USP <789>	NMT NMT NMT	(b) (4)

Phenylephrine Hydrochloride Ophthalmic Solution, USP is a sterile, clear, colorless solution formulated for topical ophthalmic application. The 2.5% solution is filled in 15 mL fill-sizes in 15 mL containers and 2 mL fill-sizes in 6 mL containers. The 10% solution has a 5 mL fill-size in a 10 mL container.

All the containers are made of white LDPE bottles with red (b) (4) caps that are fitted with dropper tips made of natural LDPE. The container closure system for all the three drug product configurations have satisfactory leachable profile and deliver the drug product in consistent drop sizes. The freeze-thaw study indicates that the quality of the drug product remains uncompromised. The container should be stored at 20-25°C. The current data support a 2-year shelf life.

There are no post-marketing commitments.

### 3.2 Product Quality Microbiology

The drug product is sterile (b) (4). In-process controls include bioburden testing of drug substance, excipients, and bulk solution, bioburden and endotoxin testing of WFI, established maximum hold times, (b) (4) testing. Media fills include simulations, interventions and environmental monitoring. Formulation containing (b) (4)% of the labeled benzalkonium chloride preservative concentration meets USP <51> Antimicrobial Effectiveness Testing acceptance criteria for Category 1 products. Sterilization of filling equipment and container/closure components utilize validated processes, and (b) (4) process was validated by microbial retention validation studies for the two product concentrations. Container/closure integrity was demonstrated for each of the three product configurations. Therefore the applicant has mitigated the risk for drug product non-sterility.

### 3.3 Biopharmaceutics – BA/BE Waiver

The Biopharmaceutics team recommends the BA/BE waiver under 21 CFR 320.22(e) is appropriate for these products.

*Comment:*

*The ONDQA CMC reviewers recommend approval of the application from their perspective.*

## **4. Nonclinical Pharmacology/Toxicology**

See Pharmacology/Toxicology review.

Akorn did not conduct or sponsor any non-clinical studies. Akorn provided a list of published non-clinical studies in which their AK-Dilate® formulation was used, in which the drug was used as a mydriatic. Neither toxicity nor lack of efficacy was reported in these studies. The sponsor summarized nonclinical studies to support systemic safety including repeat dose toxicity, genotoxicity, and carcinogenicity studies conducted by the National Toxicology Program (NTP). The same NTP source was used to support the non-clinical section of NDA 203510. The studies showed phenylephrine was not mutagenic or carcinogenic. (P/T review page 9). Given the long history of phenylephrine use and the over 20 years of experience with Akorn's AK-Dilate, the P/T reviewer has not objection to the approval of the application.

*Comment: The Pharmacology/Toxicology (P/T) reviewers recommend approval. The labeling recommendations have been incorporated.*

## **5. Clinical Pharmacology/Biopharmaceutics**

See Clinical Pharmacology review.

The reviewers note there were no clinical pharmacology studies submitted for review, and there is extensive clinical use of the product. Information for the labeling is derived from the literature. In accordance with 21 CFR 320.22(b)(1) waiver of in vivo bioavailability or bioequivalence testing was granted. Labeling revisions have been incorporated

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

## **6. Clinical Microbiology/Immunology**

Not Applicable

## **7. Clinical/Statistical-Efficacy**

See clinical and biostatistics reviews.

The applicant did not conduct any clinical trials for this application. Another NDA for phenylephrine hydrochloride ophthalmic solution, NDA 203510 by Paragon BioTeck was approved for marketing in 2013 and relied on published clinical studies for evidence of safety and effectiveness. Many of the same studies were submitted in the current NDA application, along with additional studies, including ones that used the Akorn product AK-Dilate® to achieve mydriasis so patients could undergo other procedures in studies evaluating these additional procedures.

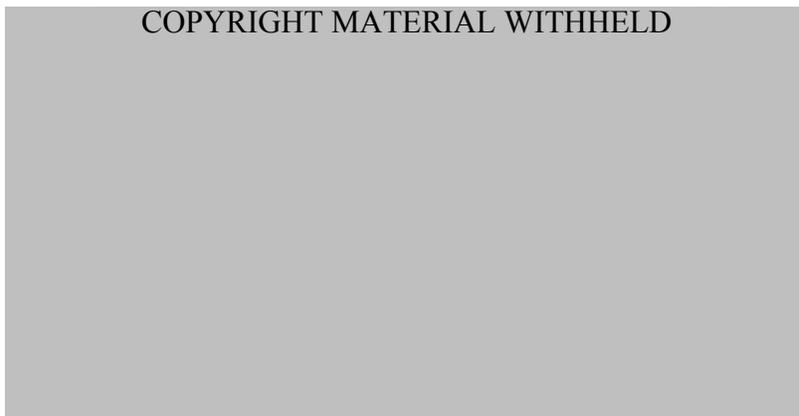
The ophthalmologic usefulness of phenylephrine is due to its pharmacodynamic activity; pupil movement is generally seen within 15 minutes, maximal mydriasis between 20 to 90 minutes and recovery after 3 to 8 hours. Darker irides tend to dilate slower than lighter irides.

Efficacy studies evaluated phenylephrine alone, or in combination with other topical drops. The articles included controlled studies that reported on 2.5% and 10% formulations and other concentrations. As noted in the Medical Officer Review, six studies support the efficacy of phenylephrine. Three studies [Suwan-Apichon, et al. 2010; Yospaiboon, et al. 2004; Chawdhary, et al. 1984] were randomized, double-masked, parallel-group comparisons. One study in pediatric subjects [Sindel, 1986], was a randomized, partially masked, parallel group comparison. The comparisons were between different strengths of phenylephrine plus tropicamide or comparisons between phenylephrine alone and phenylephrine plus tropicamide. Two studies [Gambill, et al. 1967; Haddad, et al. 1970] were crossover studies comparing different strengths of phenylephrine or comparing phenylephrine with other mydriatic agents. Highlights of selected publications are provided below:

Published clinical studies submitted to this NDA and also previously reviewed

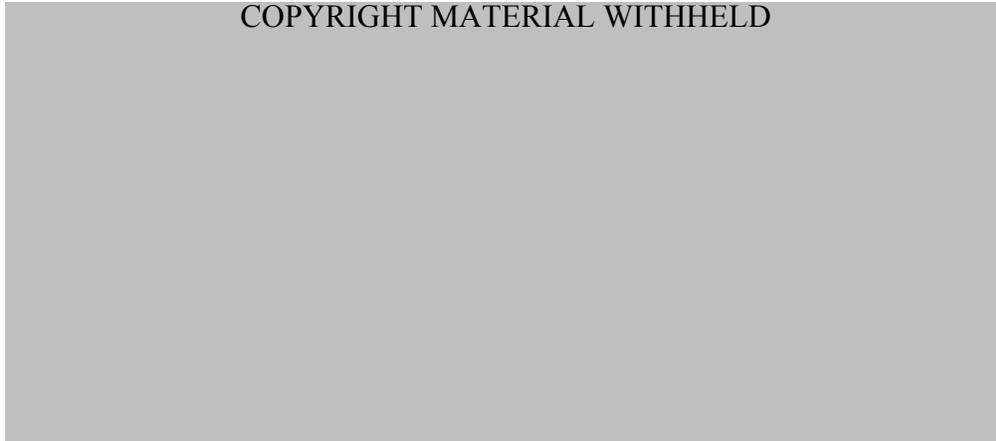
1. **Chawdhary et al**<sup>4</sup> (India) evaluated 1.25%, 2.5%, 5%, and 10% phenylephrine concentrations and measured pupil size over 70 minutes. The mean changes from baseline in pupil size (mm) are statistically significant for all four concentrations: 1.7 (95% CI: 1.5, 1.9; p-value < 0.0001) in the 1.25% group, 3.0 (95% CI: 2.5, 3.5; p-value < 0.0001) in the 2.5% group, 3.4 (95% CI: 3.1, 3.6; p-value < 0.0001) in the 5% group, and 4.0 (95% CI: 3.7, 4.3; p-value < 0.0001) in the 10% group. These results demonstrate that the three higher concentrations were highly effective in dilating pupils. The difference in pupil size among the four concentrations was also significant.

Figure 1: Mydriatic Effects of Four Concentrations of Phenylephrine



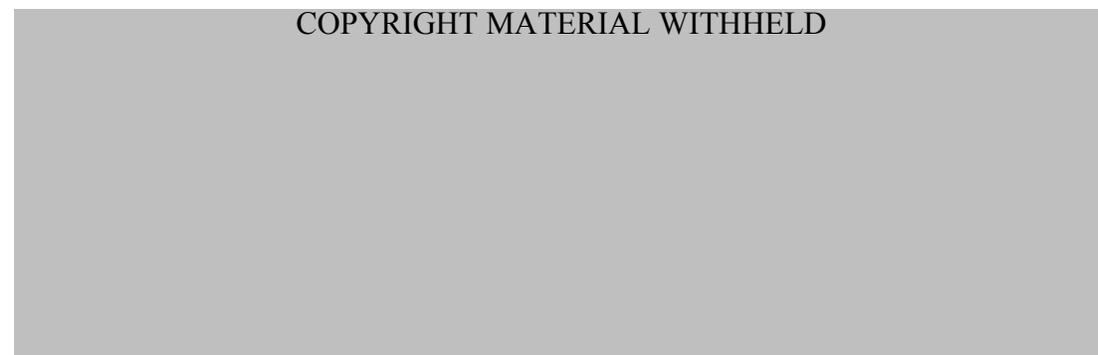
<sup>4</sup> Chawdhary S, Angra SK, Zutshi R, Satchev S. Mydriasis use of phenylephrine (A dose response Concept). Ind J Ophthalmol. 1984; 34:213-216.

2. **Haddad et al**<sup>5</sup> (Rochester, Minnesota) conducted a two part study, comparing pupil dilation at various concentrations of aqueous phenylephrine formulations and the 10% marketed product measured for up to 90 minutes. A dose response was seen as shown in the figure below:



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

3. **Gambill et al**<sup>6</sup> (Rochester, Minnesota) investigated the effect of four drugs, including 10% phenylephrine in a cross-over design. Maximal mydriasis occurred at 70 minutes, recovery occurred greater than 5 hours after instillation. The maximal mydriatic effect of 10% phenylephrine compared to the un-treated eyes was statistically significant: 2.42 mm (95% CI: 1.83, 3.01; p-value<0.0001). As noted in the MOR, light irides dilated a mean of 2.69 mm, dark irides a mean of 2.01 mm.



<sup>5</sup> Haddad NJ, Moyer NJ, Riley FC. Mydriatic effect of phenylephrine hydrochloride. Am J Ophthalmol. 1970;70(5):729-733.

<sup>6</sup> Gambill HD, Ogle KN, Kearns TP. Mydriatic effect of four drugs determined with pupillograph. Arch Ophthalmol 1967;77:740-746.

4. **Yospaiboon et al**<sup>7</sup> (Thailand) conducted a large randomized trial in Thailand, randomized patients to 1% tropicamide then 2.5% phenylephrine (n=271) or 1% tropicamide then 10% phenylephrine (n=293). The 2.5% formulation increased pupil size by 0.7 mm and the 10% increased pupil size by 1.1 mm. The difference between the two concentrations is significant.

	2.5% Phenylephrine (N=271)	10% Phenylephrine (N=293)	Treatment Difference
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5. **Sindel et al**<sup>8</sup> (Hershey, Pennsylvania) evaluated the safety and efficacy of 2.5% phenylephrine with tropicamide (1.0% or 0.5%), 1% phenylephrine with tropicamide (1.0%) compared to saline in neonates <1500 grams at birth. All phenylephrine groups achieve pupillary dilation of > 4mm from baseline and final diameter greater than 6 mm stated to be needed for adequate examination. The increase in systolic and diastolic blood pressure was greater after 2.5% compared to the 1% concentration, was transient and returned to baseline in approximately 20 minutes.

	Phenylephrine 2.5% and 1% tropicamide (N=10)	Phenylephrine 2.5% and 0.5% tropicamide (N=10)	Phenylephrine 1.0% and 1.0% tropicamide (N=10)	Saline only (N=4)
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<sup>7</sup> Yospaiboon P, Luanratanakorn P, Noppawinyoowong C. Randomized double-blind study of phenylephrine 2.5% vs 10% on pupillary dilation. J Med Assoc Thai, 2004; 87(11):1380- 1384.

<sup>8</sup> Sindel BD, Baker MD, Maisels MJ, Weinstein J. A comparison of the pupillary and cardiovascular effects of various mydriatic agents in preterm infants. J Ped Optha and Strabismus. 1986;23(6): 273-6.

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The ability of phenylephrine to dilate the eye is also demonstrated in neonates. Baseline pupillary dilation ranges from 2.8 to 3.0 mm while after instillation of phenylephrine pupillary dilation ranges from 7.1 to 7.4 mm.

Additional published studies included in NDA 207926:

**6. Suwan-Apichon et al<sup>9</sup>** enrolled 100 diabetic patients and randomly treated with either 2.5% or 10% phenylephrine, 30 minutes after treatment with 1% tropicamide in both treatment arms. The mean duration of diabetes was ~ 90 months, 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.. The mean age was 55 years (range: 21-78) 48% were at least 60 years or older, 58% were female. As shown below, phenylephrine was effective in dilating the pupil.

**Analysis Results of Pupil Sizes (mm) after Administration of Tropicamide and Phenylephrine**

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Published studies using the Akorn AK-Dilate product:<sup>10</sup>

<sup>9</sup> Suwan-Apichon O, et al. 2.5% and 10% phenylephrine for mydriasis in diabetic patients with dark irides. J Med Assoc Thai 2010;93:467-473.

<sup>10</sup> Hardarson S and Stefánsson E. Oxygen saturation in central retinal vein occlusion. Am J Ophthalmol 2010;150: 871-875.

Lang Y, et al. Evaluation of intravitreal Kenalog toxicity in humans. Ophthalmology 2007;114: 724-731.

Liu S, et al. Recurrent annular peripheral choroidal detachment after trabeculectomy. Case Rep Ophthalmol 2013; 4: 192-198.

Olafsdottir OB, et al. Retinal oximetry in primary open-angle glaucoma. Invest Ophthalmol Vis Sci 2011;52: 6409-6413.

Tekwani N and Huang D. Risk factors for intraoperative epithelial defect in laser in-situ keratomileusis. J Ophthalmol 2002;134: 311-316.

These studies did not evaluate mydriasis, per se, however, as noted in the Medical Officer Review, the authors apparently achieved the degree of mydriasis expected and the publications do not report any lack of efficacy in terms of mydriasis.

**Table 14: Literature reports for clinical studies for safety and efficacy of phenylephrine hydrochloride ophthalmic solution using Akorn's AK-Dilate® formulation.**

Author	Study Objectives	Patient Population	Dosage Regimen for Mydriasis	Efficacy of Mydriasis	Information on safety of phenylephrine
Lang et al., 2007	To evaluate the potential functional toxicity of commercial triamcinolone acetate in patient's retinas	16 patients (32 eyes) with non-proliferative diabetic retinopathy and bilateral macular edema refractory to laser therapy	Phenylephrine, 2.5% + cyclopentolate, 1%	No indication that mydriatics were not effective	No data on adverse events of mydriatics reported.
Tekwani et al., 2002	To report intraoperative epithelial defects in eyes undergoing laser in-situ keratomileusis (LASIK)	Records of 133 patients (247 eyes) undergoing LASIK surgery	Phenylephrine, 2.5%, +tropicamide, 1% +propraracaine, 0.5% or phenylephrine, 2.5% +tropicamide, 1%	No indication that mydriatics were not effective.	No data on adverse events of mydriatics reported.

**Table 14: Literature reports for clinical studies for safety and efficacy of phenylephrine hydrochloride ophthalmic solution using Akorn's AK-Dilate® formulation. (cont.)**

Author	Study Objectives	Patient Population	Dosage Regimen for Mydriasis	Efficacy of Mydriasis	Information on safety of phenylephrine
Hardarson, et al., 2010	To determine whether oxygen saturation is affected in retinal blood vessels in patients with retinal vein occlusion	10 patients (8 evaluable) with central retinal vein occlusion	Tropicamide, 1% supplemented in some cases (number not specified) with phenylephrine, 10%.	No indication that mydriatics were not effective	No data on adverse events of mydriatics reported.
Liu et al., 2013	Case of recurrent flat anterior chamber without hypotony	Single case report	Phenylephrine, 2.5% + atropine, 1%	No indication that mydriatics were not effective.	No data on adverse events were reported.
Olafsdottir et al., 2011	To determine whether retinal vessel oxygen saturation is affected in primary open-angle glaucoma patients	31 patients with primary open-angle glaucoma	Tropicamide, 1% supplemented with phenylephrine, 10% when necessary. The number of supplemental treatments was not specified.	No indication that mydriatics were not effective.	No data on adverse events of mydriatics were reported.

Source MOR for NDA 207926, Module 2.7.3.

*Comments:*

*Pupil dilation was achieved with the 2.5% and 10% phenylephrine based on the studies provided in the application. The degree of mydriasis was judged to be clinically significant. Several*

*publications note that a pupil > 6 mm is adequate for fundus and retina examination.<sup>11</sup> The labeling of Adrenalin NDA notes that > 5 mm diameter is important to be able to perform cataract surgery and insert an IOL. Of note, the agency approved a product called dapiprazole<sup>12</sup> in 1990 for the indication of reversing the dilation caused by phenylephrine.*

*The effect of phenylephrine is generally seen within 15 minutes of instilling the drops, and reaches maximal effect between 20-90 minutes, and mydriasis resolves after 5 hours (range 3 to 8 hours).*

## 8. Safety

See clinical reviews. The applicant noted there are numerous publications on phenylephrine and submitted 25 publications. Given the long history of phenylephrine use, much has been published. Phenylephrine is a sympathomimetic with known vasoconstrictor effects that can lead to systemic cardiovascular toxicities such as tachycardia, palpitations, hypertension etc. Sympathomimetics such as phenylephrine stimulate the alpha adrenergic receptors found on smooth muscle in the heart and blood vessels causing vasoconstriction in blood vessels and an increase in blood pressure. The increase in blood pressure causes a baroreceptor reflex bradycardia through the vagus nerve. The potent vagal cardiac stimulation initiates serious ventricular arrhythmias. Adverse reactions reported with systemic phenylephrine have included insomnia, nausea, headache, dizziness, CNS stimulation, anxiety, palpitations, reflex bradycardia, tremor, and urinary retention. This information is consistent with the literature and information in the labeling of NDA 203826 and NDA 203510.

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

Phenylephrine ophthalmic solution 2.5% results in an acceptable increase of heart rate and blood pressure in neonates; phenylephrine ophthalmic solution 10% results in an unacceptable increase

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<sup>11</sup> Sindel BD, Baker MD, Maisels MJ, Weinstein J. A comparison of the pupillary and cardiovascular effects of various mydriatic agents in preterm infants. *J Ped Optha and Strabismus*. 1986;23(6): 273-6.  
ML Eyeson-Annan, LW Hirst, D Battistuttat, A Green. Comparative pupil dilation using phenylephrine alone or in combination with tropicamide. *Ophthalmology* 1998;105(4):726-32.

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.

<sup>12</sup> Dapiprazole hydrochloride ophthalmic solution, NDA 019849 was approved December 31, 1990 and is marketed under the trade name Rev-Eyes. It is no longer marketed in the US - <http://www.sharecare.com/question/what-is-dapiprazole>

of heart rate and blood pressure in neonates. Caution should be exercised in pediatric patients less than 5 years of age.

Ocular adverse reactions with topical phenylephrine: The most common adverse reactions that occur following topical ophthalmic administration of phenylephrine are ocular reactions including eye pain and stinging on instillation, temporary blurred vision, photophobia, and conjunctival sensitization. Topical anesthetics potentiate the effect of phenylephrine. Post marketing adverse event reporting is noted to include events that may represent medical conditions and setting where phenylephrine was used for mydriasis to aid in diagnosis, not phenylephrine-related adverse reactions.

*Comment:*

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

## **9. Advisory Committee Meeting**

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

## **10. Pediatrics**

Pediatric studies are complete and the pediatric information is provided in this NDA for Phenylephrine Hydrochloride Ophthalmic Solution USP, 2.5% and 10%.

Phenylephrine ophthalmic solution 10% is contraindicated in pediatric patients less than 1 year of age. Caution should be exercised with the use of phenylephrine 10% in pediatric patients less than 5 years of age. In pediatric patients less than 1 year of age, one drop of phenylephrine hydrochloride ophthalmic solution, 2.5% should be instilled at 3-5 minute intervals up to a maximum of 3 drops per eye.

The Pediatric Research Equity Act (PREA) was not triggered for this application (i.e. there were no new indications, no new dosing regimens, no new active ingredients, no new dosage forms, and no new routes of administration).

## **11. Other Relevant Regulatory Issues**

### **11.1 Compliance Inspection –**

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

### **11.2 Office of Scientific Investigation (OSI) Audits**

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

### 11.3 Debarment Certification

Akorn Inc, certified that it has not and will not use in any capacity the services of any person who has been debarred under section 306(a) and 306(b) of the Generic Drug Enforcement Act of 1992, in connection with this application.

### 11.4 Financial Disclosure

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

### 11.5 Other Regulatory Issues

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

## 12. Labeling

The package insert and carton and container labels for the 2.5% and 10% formulations were reviewed as applicable by DTOP, DMEPA, SEALD and OPDP/DPDP.

- **Package insert (PI):** The PI is written in PLR format.
- **Carton and Container Labels:** The labels have been reviewed by DTOP, ONDQA and DMEPA. The carton/container labels have been finalized.
- **Proprietary Name:** Although Akorn refers to their currently marketed [unapproved] product as AK-Dilate®, they have not submitted a proprietary name for this product. The Akorn regulatory contact informed the Division that they intend to market the product under the name “Phenylephrine Hydrochloride Ophthalmic Solution, USP.” [DARRTS entry 1/12/2015.]

## 13. Decision/Action/Risk Benefit Assessment

### 13.1 Regulatory Action

NDA 207926 will be approved. All disciplines recommend approval of the application.

### 13.2 Risk Benefit Assessment

The safety and efficacy of phenylephrine hydrochloride ophthalmic solution was based on the review of published preclinical and clinical trials submitted in this 505(b)(2) application. Phenylephrine is an alpha-1 adrenergic agonist that has been marketed for over 70 years and used for ophthalmic uses, including dilation of the pupil for diagnostic purposes, use during surgical procedures, and at times for treatment and lysis of synechia in patients. Published studies submitted in the application show that both 2.5% and 10% formulations achieve adequate mydriasis for clinical use, with pupillary diameter exceeding 6 mm. The effect is generally seen within 15 minutes of instilling the drops, and reaches maximal effect between 20-90 minutes,

and mydriasis resolves after 5 hours (range 3 to 8 hours). The pupil dilation reported in the studies was 1 to 3 mm compared to baseline or untreated pupil for the 2.5% concentration and 1 to 4 mm for the 10% concentration. The degree of mydriasis was more prominent under light stimulation compared to no light stimulation.

Studies that used the AK-Dilate® Akorn product were included in the application; these studies provided evidence that the product achieved the level of mydriasis desired by the investigators for performing clinical examination or surgical procedure.

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

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

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

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

None

## Appendix A:

Published studies reviewed for another 505(b)(2) application, and applicable to NDA 207926

1. **Filho et al**<sup>13</sup> (Brazil) evaluated the safety and efficacy of 2.5% and 10% phenylephrine solutions and found that the 10% solution achieved greater mydriasis than the 2.5% solution. The baseline pupil size was 5.8 mm (smaller than the 4.2 mm in Chawdhary study), the pupil size increased by 1.3 – 1.4 mm after 2.5% phenylephrine and 2 mm after 10% phenylephrine. The difference between the two concentrations is: 0.6 (95% CI: 0.10, 1.10; p-value < 0.03).

	2.5% Phenylephrine (N=28)	10% Phenylephrine (N=28)	Treatment Difference Mean (95% CI)* P-value
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2. **Neuhaus et al**<sup>14</sup> (Los Angeles, CA) tested the two concentrations (2.5% and 10%) in eleven patients in a cross-over trial. The mean change in pupil size was 1.6 mm after the 2.5% concentration and 1.88 mm after the 10% concentration. The difference was not statistically significant. It's noted that this is a smaller study, and patients had pupils measured at one two time points: baseline and 60 minutes.

3. **Ozturks et al**<sup>15</sup> (Turkey) evaluated the efficacy of 2.5% or 10% phenylephrine in combination with cyclopentolate 1% (and flurbiprofen 0.03%). The study did not show significant difference pupil dilation between 2.5% and 10% phenylephrine concentrations. There was added dilation reported with the addition of flurbiprofen, in both phenylephrine concentrations, but no difference between the 2.5% and 10% concentration groups, as shown below: [In the figure below, the first two rows of data represent the arms not receiving flurbiprofen, the last two rows of data are arms receiving flurbiprofen.]

<sup>13</sup> Filho AD, Frasson M, Merula RV, Morais PR, Cronenberger S. Cardiovascular and mydriatic effects of topical phenylephrine 2.5% and 10.0% in healthy volunteers. Arq Bras Oftalmol 2007; 70 (6):961-6 (translation sent December 20, 2012).

<sup>14</sup> Neuhaus RW, Helper RS. Mydriatic Effect of Phenylephrine 10% (aq) vs Phenylephrine 2.5% (aq). Annals of Ophthalmol Oct 1980: 1159-1160.

<sup>15</sup> Ozturk F, Kurt E, Inan UU, Ilker SS. The efficacy of 2.5% phenylephrine and flurbiprofen combined in inducing and maintaining papillary dilatation during cataract surgery. European J of Ophthal 10; 2:144-148 2000

	2.5% Phenylephrine	10% Phenylephrine	Mean Difference (95% CI) P-value
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**10. Allison et al<sup>16</sup>** (Tucson, Arizona) report on 50 subjects who received tropicamide 1% and phenylephrine 2.5% and had dilation of pupils. Baseline pupil size in these subjects was 3.7 mm, and dilated to 8.6 mm after tropicamide 1% and phenylephrine 2.5%. After subsequent instillation of dapiprazole 0.5%, an alpha-adrenergic receptor blocker, the treated eyes had a diameter reduced to 4.5 mm at 2 hours and the untreated eyes were still dilated to 8.4 mm. Pupil size was recorded as having returned to baseline in both groups by 24 hours.

**11. Paggiarino et al<sup>17</sup>** (Newark, NJ) evaluated both concentrations of phenylephrine, and reported maximal pupil diameters of > 8 mm at 60 minutes, and the effect lasting for over 7 hours (11% of patients were reported as having dilated pupils at 15 hours after 2.5% phenylephrine, defined as > 0.5 mm compared to baseline). The reported change in pupil diameter was 2.7 mm with 2.5% and 3.2% with the 10% concentration.

**12. Eyeson-Annan et al<sup>18</sup>** (Queenland, Australia) report that 10% phenylephrine alone achieves pupil size > 6 mm after 40 minutes.

**13. Tanner et al<sup>19</sup>** (United Kingdom) reported that post-operative pupil diameter after 2.5% and 10% concentrations were 8.0 mm and 8.2 mm, respectively. There were 5/62 (8%) patients in the 2.5% group and 1/53 patients (2%) patients in the 10% group that did not achieve a diameter > 6 mm.

<sup>16</sup> RW Allinson, DS Gerber, S Bieber and BL Hodes. Reversal of mydriasis by dapiprazole. *Ann Ophthalmol* 1990; 22:131-138.

<sup>17</sup> Paggiarino DA, Brancata LJ, Newton RE. The effects of pupil size and accommodation of sympathetic and parasympatholytic agents. *Ann Ophthalmol*, 1993;25:244-253.

<sup>18</sup> ML Eyeson-Annan, LW Hirst, D Battistuttat, A Green. Comparative pupil dilation using phenylephrine alone or in combination with tropicamide. *Ophthalmology* 1998;105(4):726-32.

<sup>19</sup> 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.

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/s/  
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RENATA ALBRECHT  
01/15/2015