

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207926Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	January 15, 2015
From	William M. Boyd, M.D.
Subject	Cross-Discipline Team Leader Review
NDA#	207926
Applicant	Akorn, Inc.
Date of Submissions	July 11, 2014
PDUFA Goal Date	May 11, 2015
Proprietary Name / Established (USAN) names	Phenylephrine Hydrochloride Ophthalmic Solution, 2.5% and 10%
Dosage forms / Strength	Topical ophthalmic solution, 2.5% and 10%
Proposed Indication(s)	Indicated to dilate the pupil
Recommended:	Recommended for Approval

1. Introduction

NDA 207926 was submitted as a 505(b)(2) application. All portions of the application for which Akorn, Inc. does not have right to reference come from literature sources for studies not conducted by/for Paragon, Inc.

Phenylephrine is an alpha-1 adrenergic receptor 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. Phenylephrine is included in the OTC monograph for use as an ophthalmic vasoconstrictor for relief of ocular redness at concentrations of between 0.08% and 0.2%.

NDA 203826, phenylephrine hydrochloride injection, USP was approved December 12, 2012, and is indicated to increase blood pressure in acute hypotensive states, such as shock and peri-operative hypotension.

Phenylephrine hydrochloride ophthalmic solutions, 2.5% and 10%, is currently being marketed and supplied in the United States by Paragon Biotech, Inc. for use as a mydriatic under NDA 203510 approved March 21, 2013.

2. Background

NDA 19-849 for dapiprazole hydrochloride ophthalmic solution, 0.5% was approved on December 31, 1990, with the following indication: the treatment of iatrogenically induced mydriasis produced by adrenergic (phenylephrine) or parasympatholytic (tropicamide) agents.

This NDA 19-849 application was not utilized or referenced in this current new drug application for phenylephrine ophthalmic solution.

(b) (4)

The primary difference between formulations is that the Akorn product does not contain (b) (4) which is an ingredient in the 2.5% strength of the reference product. While the remaining inactive ingredients (b) (4), not all of them are present at concentrations that are within the 5% limits when compared to the reference product.

Table 1: Comparison between Reference Listed Drug and Proposed Drug Product for Phenylephrine Hydrochloride Ophthalmic Solution USP, 2.5%

	Reference Listed Drug, By Paragon BioTeck, Inc.	Proposed Drug Product By Akorn
Condition of Use:	Phenylephrine Hydrochloride Ophthalmic Solution, USP, is indicated to dilate the pupil.	Phenylephrine Hydrochloride Ophthalmic Solution, USP, is indicated to dilate the pupil.
Active Ingredient	25mg of Phenylephrine Hydrochloride	25mg of Phenylephrine Hydrochloride, USP
Inactive Ingredients	<ul style="list-style-type: none"> • Monobasic Sodium Phosphate • Dibasic Sodium Phosphate • Boric Acid* • Sodium Hydroxide and/or Hydrochloric Acid for pH adjustment • Water for Injection • Benzalkonium chloride 0.01% is added as preservative 	<ul style="list-style-type: none"> • Monobasic Sodium Phosphate (b) (4), USP • Dibasic Sodium Phosphate (b) (4) USP • --- --- --- • Sodium Hydroxide, NF and/or Phosphoric Acid, NF for pH adjustment • Water for Injection, USP • Benzalkonium chloride NF, 0.01% is added as preservative
Route of Administration	Ophthalmic	Ophthalmic
Dosage Form	Solution/Drops	Solution/Drops
Strengths	2.5%	2.5%

*Boric Acid is not present in Akorn proposed drug product.

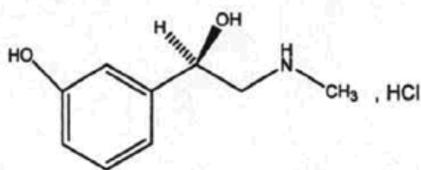
Table 2: Comparison between Reference Listed Drug and Proposed Drug Product for Phenylephrine Hydrochloride Ophthalmic Solution USP, 10%

	Reference Listed Drug, By Paragon BioTeck, Inc.	Proposed Drug Product By Akorn
Condition of Use:	Phenylephrine Hydrochloride Ophthalmic Solution, USP, is indicated to dilate the pupil.	Phenylephrine Hydrochloride Ophthalmic Solution, USP, is indicated to dilate the pupil.
Active Ingredient	100 mg of Phenylephrine Hydrochloride	100 mg of Phenylephrine Hydrochloride, USP
Inactive Ingredients	<ul style="list-style-type: none"> • Monobasic Sodium Phosphate • Dibasic Sodium Phosphate • Sodium Hydroxide and/or Hydrochloric Acid for pH adjustment • Water for Injection • Benzalkonium chloride 0.01% is added as preservative 	<ul style="list-style-type: none"> • Monobasic Sodium Phosphate (b) (4), USP • Dibasic Sodium Phosphate (b) (4) USP • Sodium Hydroxide, NF and/or Phosphoric Acid, NF for pH adjustment • Water for Injection, USP • Benzalkonium chloride NF, 0.01% is added as preservative
Route of Administration	Ophthalmic	Ophthalmic
Dosage Form	Solution/Drops	Solution/Drops
Strengths	10 %	10 %

A Pre-IND teleconference for this product was held with the Division on 4/3/2014 under IND 121700.

3. Product Quality

Chemical structure of phenylephrine hydrochloride



Chemical Name: (R)-3-hydroxy-α-[(methylamino)methyl]benzenemethanol hydrochloride.
Molecular Formula: C₉H₁₃NO₂-HCl **Molecular Weight:** 203.67 g/mol

Each mL of Phenylephrine Hydrochloride Ophthalmic Solution, USP 2.5% contains: **Active:** Phenylephrine Hydrochloride 25 mg (2.5%); **Inactives:** Sodium Phosphate Monobasic, Sodium Phosphate Dibasic; Water for Injection. Phosphoric Acid and/or Sodium Hydroxide may be added to adjust pH (4.0 to 7.5). The solution has a tonicity of 340 mOsm/kg; **Preservative:** Benzalkonium Chloride 0.1 mg (0.01%).

Each mL of Phenylephrine Hydrochloride Ophthalmic Solution, USP 10% contains: **Active:** Phenylephrine Hydrochloride 100 mg (10%); **Inactives:** Sodium Phosphate Monobasic, Sodium Phosphate Dibasic; Water for Injection. Phosphoric Acid and/or Sodium Hydroxide may be added to adjust pH (4.0 to 7.5). The solution has a tonicity of 985 mOsm/kg; **Preservative:** Benzalkonium Chloride 0.1 mg (0.01%).

**Unit Composition for Phenylephrine Hydrochloride Ophthalmic Solution USP, 2.5%
(15 mL Fill, Akorn Code 5030 and 2 mL Fill, Akorn Codes 5031)**

Ingredient	Reference to Quality Standard	Function	Unit Composition (mg/mL)
Phenylephrine Hydrochloride	USP	API	25.0 mg
Benzalkonium Chloride	NF	Preservative	0.1 mg
Dibasic Sodium Phosphate, (b) (4)	USP		
Monobasic Sodium Phosphate, (b) (4)	USP	pH Adjusting Agent	
Phosphoric Acid	NF		
Sodium Hydroxide (b) (4)	NF	Q.S to adjust target pH to 6.5	(b) (4)
Water for Injection	USP		
(b) (4)			

**Unit Composition for Phenylephrine Hydrochloride Ophthalmic Solution USP, 10%
(5 mL Fill, Akorn Code 5023)**

Ingredient	Reference to Quality Standard	Function	Unit Composition (mg/mL)
Phenylephrine Hydrochloride	USP	API	100.0 mg
Benzalkonium Chloride	NF	Preservative	0.1 mg
Dibasic Sodium Phosphate, (b) (4)	USP		
Monobasic Sodium Phosphate, (b) (4)	USP	pH Adjusting Agent	
Phosphoric Acid	NF		
Sodium Hydroxide (b) (4)	NF	Q.S to adjust target pH to 6.5	(b) (4)
Water for Injection	USP		
(b) (4)			

Akorn Proposed Specifications for Phenylephrine Hydrochloride Ophthalmic Solution USP, 2.5% [Akorn Code # 5031]							
PARAMETER DESCRIPTION	LABEL CLAIM or TARGET	IN-PROCESS CONTROL		FINISHED PRODUCT		STABILITY	
		RANGE	METHOD	RANGE	METHOD	RANGE	METHOD
Phenylephrine Hydrochloride Assay	25 mg/mL	(b) (4)	RD046	(b) (4)	RD046	(b) (4) LC	RD046
Individual Degradants	N/A	N/A	N/A	NMT (b) (4) %		NMT (b) (4) %	
Total Degradants	N/A	N/A	N/A	NMT (b) (4) %		NMT (b) (4) %	
Benzalkonium Chloride	0.1 mg/mL	N/A	N/A	80 to 110%	RD045	35-110%	RD045
Identification (HPLC)	Retention Time Conforms to Reference Standard	N/A	N/A	Conforms	RD046	N/A	N/A
Identification (TLC)	Conforms	N/A	N/A	Conforms	RD046	N/A	N/A
Identification (BAC)	Conforms	N/A	N/A	Conforms	RD046	N/A	N/A
pH	6.5	6.4 to 6.6	QC204	6.0 to 7.0	QC204	4.0 to 7.5	QC 204
Osmolality	340 mOsm/Kg	330 to 350 mOsm/Kg	QC276	320 to 380 mOsm/Kg	QC276	N/A	N/A
Recovery Volume	(b) (4)	N/A	N/A	NLT (b) (4)	QC169	NLT (b) (4)	QC169
Product Appearance	Clear, Colorless to yellow solution	Clear, Colorless to yellow solution	Visual	Clear, Colorless to yellow solution	Visual	Clear, Colorless to yellow solution	Visual
Container Appearance	No visual deterioration	N/A	N/A	No visual deterioration	Visual	No visual deterioration	Visual

Akorn Proposed Specifications for Phenylephrine Hydrochloride Ophthalmic Solution USP, 2.5% [Akorn Code # 5031]							
PARAMETER DESCRIPTION	LABEL CLAIM or TARGET	IN-PROCESS CONTROL		FINISHED PRODUCT		STABILITY	
		RANGE	METHOD	RANGE	METHOD	RANGE	METHOD
Impurity (b) (4)	NMT (b) (4)%	N/A	N/A	NMT (b) (4)%	ATM429	NMT (b) (4)%	ATM429
Residual Solvents	cUSP<467> Option (b) (4)	N/A	N/A	Conforms	cUSP<467> (b) (4)	N/A	N/A
Viscosity	0.46 to 1.17 cps	N/A	N/A	0.46 to 1.17 cps	QC278	0.46 to 1.17 cps	QC278
Weight Loss	NMT (b) (4)%	N/A	N/A	N/A	N/A	NMT (b) (4)%	RD075
Color	NMT (b) (4)	N/A	N/A	NMT (b) (4)	ATM010	NMT (b) (4)	ATM010
Container Closure	Integral	N/A	N/A	Integral	RD125	Integral	RD125
Preservative Effectiveness Test	Passes	N/A	N/A	N/A	N/A	Passes	USP
Sterility	Sterile	N/A	N/A	Sterile	MTM 004	Sterile	MTM 004
Particulate Matter	USP<789>	N/A	N/A	NMT (b) (4) NM (b) (4) NM (b) (4)	ML115 ML184	NMT (b) (4) NMT (b) (4) NMT (b) (4)	ML115 ML184
Unidentified Impurity	NMT (b) (4)%	N/A	N/A	NMT (b) (4)%	RD046	NMT (b) (4)%	RD046

Akorn Proposed Specifications for Phenylephrine Hydrochloride Ophthalmic Solution USP, 2.5% [Akorn Code # 5030]							
PARAMETER DESCRIPTION	LABEL CLAIM or TARGET	IN-PROCESS CONTROL		FINISHED PRODUCT		STABILITY	
		RANGE	METHOD	RANGE	METHOD	RANGE	METHOD
Phenylephrine Hydrochloride Assay	25 mg/mL	(b) (4)	RD046	(b) (4)	RD046	(b) (4) LC	RD046
Individual Degradants	N/A	N/A	N/A	NMT (b) (4) %		NMT (b) (4) %	
Total Degradants	N/A	N/A	N/A	NMT (b) (4) %		NMT (b) (4) %	
Benzalkonium Chloride	0.1 mg/mL	N/A	N/A	80 to 110%	RD045	35-110%	RD045
Identification (HPLC)	Retention Time Conforms to Reference Standard	N/A	N/A	Conforms	RD046	N/A	N/A
Identification (TLC)	Conforms	N/A	N/A	Conforms	RD046	N/A	N/A
Identification (BAC)	Conforms	N/A	N/A	Conforms	RD046	N/A	N/A
pH	6.5	6.4 to 6.6	QC204	6.0 to 7.0	QC204	4.0 to 7.5	QC 204
Osmolality	340 mOsm/Kg	330 to 350 mOsm/Kg	QC276	320 to 380 mOsm/Kg	QC276	N/A	N/A
Recovery Volume	(b) (4)	N/A	N/A	NLT (b) (4)	QC169	NLT (b) (4)	QC169
Product Appearance	Clear, Colorless to yellow solution	Clear, Colorless to yellow solution	Visual	Clear, Colorless to yellow solution	Visual	Clear, Colorless to yellow solution	Visual
Container Appearance	No visual deterioration	N/A	N/A	No visual deterioration	Visual	No visual deterioration	Visual

Akorn Proposed Specifications for Phenylephrine Hydrochloride Ophthalmic Solution USP, 2.5% [Akorn Code # 5030]							
PARAMETER DESCRIPTION	LABEL CLAIM or TARGET	IN-PROCESS CONTROL		FINISHED PRODUCT		STABILITY	
		RANGE	METHOD	RANGE	METHOD	RANGE	METHOD
Impurity (b) (4)	NMT (b) (4)%	N/A	N/A	NMT (b) (4)%	ATM429	NMT (b) (4)%	ATM429
Residual Solvents	cUSP<467> Option (b) (4)	N/A	N/A	Conforms	cUSP<467> (b) (4)	N/A	N/A
Viscosity	0.46 to 1.17 cps	N/A	N/A	0.69 to 1.04 cps	QC278	0.69 to 1.04 cps	QC278
Weight Loss	NMT (b) (4)%	N/A	N/A	N/A	N/A	NMT (b) (4)%	RD075
Color	NMT (b) (4)	N/A	N/A	NMT (b) (4)	ATM010	NMT (b) (4)	ATM010
Container Closure	Integral	N/A	N/A	Integral	RD125	Integral	RD125
Preservative Effectiveness Test	Passes	N/A	N/A	N/A	N/A	Passes	USP
Sterility	Sterile	N/A	N/A	Sterile	MTM 004	Sterile	MTM 004
Particulate Matter	USP<789>	N/A	N/A	NMT (b) (4) NMT (b) (4) NMT (b) (4)	ML115 ML184	NMT (b) (4) NMT (b) (4) NMT (b) (4)	ML115 ML184
Unidentified Impurity	NMT (b) (4)%	N/A	N/A	NMT (b) (4)%	RD046	NMT (b) (4)%	RD046

Akorn Proposed Specifications for Phenylephrine Hydrochloride Ophthalmic Solution USP, 10% [Akorn Code # 5023]							
PARAMETER DESCRIPTION	LABEL CLAIM or TARGET	IN-PROCESS CONTROL		FINISHED PRODUCT		STABILITY	
		RANGE	METHOD	RANGE	METHOD	RANGE	METHOD
Phenylephrine Hydrochloride Assay	100 mg/mL	(b) (4)	RD046	(b) (4)	RD046	(b) (4)	RD046
Individual Degradants	N/A	N/A	N/A	NMT (b) (4) %		NMT (b) (4) %	
Total Degradants	N/A	N/A	N/A	NMT (b) (4) %		NMT (b) (4) %	
Benzalkonium Chloride	0.1 mg/mL	N/A	N/A	80 to 110%	RD045	35-110%	RD045
Identification (HPLC)	Retention Time Conforms to Reference Standard	N/A	N/A	Conforms	RD046	N/A	N/A
Identification (TLC)	Conforms	N/A	N/A	Conforms	RD046	N/A	N/A
Identification (BAC)	Conforms	N/A	N/A	Conforms	RD046	N/A	N/A
pH	6.5	6.4 to 6.6	QC204	6.0 to 7.0	QC204	4.0 to 7.5	QC 204
Osmolality	985 mOsm/Kg	985 to 1015 mOsm/Kg	QC276	895 to 1095 mOsm/Kg	QC276	N/A	N/A
Recovery Volume	(b) (4)	N/A	N/A	NLT (b) (4) mL	QC169	NLT (b) (4) mL	QC169
Product Appearance	Clear, Colorless to yellow solution	Clear, Colorless to yellow solution	Visual	Clear, Colorless to yellow solution	Visual	Clear, Colorless to yellow solution	Visual

Akorn Proposed Specifications for Phenylephrine Hydrochloride Ophthalmic Solution USP, 10% [Akorn Code # 5023]							
PARAMETER DESCRIPTION	LABEL CLAIM or TARGET	IN-PROCESS CONTROL		FINISHED PRODUCT		STABILITY	
		RANGE	METHOD	RANGE	METHOD	RANGE	METHOD
Container Appearance	No visual deterioration	N/A	N/A	No visual deterioration	Visual	No visual deterioration	Visual
Impurity (b)(4)	NMT (b)(4)%	N/A	N/A	NMT (b)(4)%	ATM429	NMT (b)(4)%	ATM429
Residual Solvents	cUSP<467> Option (b)(4)	N/A	N/A	Conforms	cUSP<467> (b)(4)	N/A	N/A
Viscosity	0.63 to 1.42 cps	N/A	N/A	0.63 to 1.42 cps	QC278	0.63 to 1.42 cps	QC278
Weight Loss	NMT (b)(4)%	N/A	N/A	N/A	N/A	NMT (b)(4)%	RD075
Color	NMT (b)(4)	N/A	N/A	NMT (b)(4)	ATM010	NMT (b)(4)	ATM010
Container Closure	Integral	N/A	N/A	Integral	RD125	Integral	RD125
Preservative Effectiveness Test	Passes	N/A	N/A	N/A	N/A	Passes	USP
Sterility	Sterile	N/A	N/A	Sterile	MTM 004	Sterile	MTM 004
Particulate Matter	USP<789>	N/A	N/A	NMT (b)(4) NMT NMT	ML115 ML184	NMT (b)(4) NMT NMT	ML115 ML184
Unidentified Impurity	NMT (b)(4)%	N/A	N/A	NMT (b)(4)%	RD046	NMT (b)(4)%	RD046

Phenylephrine Hydrochloride Ophthalmic Solution USP, 2.5%, 2 mL Fill, Code 5031

Phenylephrine Hydrochloride Ophthalmic Solution USP, 2.5%, 15 mL Fill, Code 5030

Phenylephrine Hydrochloride Ophthalmic Solution USP, 10%, 5 mL Fill, Code 5023

POSTMARKETING STABILITY STUDIES:

The applicant has voluntarily committed (in a submission dated 12/16/14) to conduct post-marketing stability studies on the commercial batches of the drug products. Akorn had revised the drug product specification after the exhibit batches were manufactured for the purposes of this NDA. As a result, only a partial list of the specification tests were captured by the completed stability studies. Therefore, as a post approval commitment, Akorn has promised to carry out future stability studies according to the revised stability protocol on three commercial batches for each fill-volume of the drug product. However, the available data is sufficient to grant the 2 year shelf-life requested by the applicant.

INSPECTIONS:

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).

**FDA CDER EES
 ESTABLISHMENT EVALUATION REQUEST
 DETAIL REPORT**

Application:	NDA 207926/000	Action Goal:	
Stamp Date:	11-JUL-2014	District Goal:	12-NOV-2014
Regulatory:	11-MAY-2015		
Applicant:	AKORN INC 1925 WEST FIELD CT STE 300 LAKE FOREST, IL 60045	Brand Name:	PHENYLEPHRINE HYDROCHLORIDE OPHTHALMIC
		Estab. Name:	
		Generic Name:	PHENYLEPHRINE HYDROCHLORIDE OPHTHALMIC
Priority:	7	Product Number; Dosage Form; Ingredient; Strengths	
Org. Code:	590		001; SOLUTION; PHENYLEPHRINE HYDROCHLORIDE; 25MG 002; SOLUTION; PHENYLEPHRINE HYDROCHLORIDE; 100MG
Application Comment:			
FDA Contacts:	M. CHELLIAH	Prod Qual Reviewer	3017951724
	N. SWEENEY	Micro Reviewer	(HFD-305) 2404023793
	N. BHANDARI	Product Quality PM	2404023815
	E. LWIN	Regulatory Project Mgr	3017950725
Overall Recommendation:	ACCEPTABLE	on 14-AUG-2014	by J. WILLIAMS 0 3017954198
	PENDING	on 12-AUG-2014	by EES_PROD

FDA CDER EES
 ESTABLISHMENT EVALUATION REQUEST
 DETAIL REPORT

Establishment: CFN: 1450114 FE: 1450114
 AKORN, INC.
 1222 W GRAND AVE/130 S WYCKLES
 DECATUR, IL 625221412

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE RELEASE TESTER
 FINISHED DOSAGE MANUFACTURER
 FINISHED DOSAGE RELEASE TESTER
 FINISHED DOSAGE STABILITY TESTER

Establishment Comment: API RELEASE TESTING, EXCIPIENT RELEASE TESTING, PACKAGING COMPONENT RELEASE TESTING, RESEARCH AND DEVELOPMENT LABORATORY, MANUFACTURING OF FINISHED DRUG PRODUCT, FINISHED PRODUCT RELEASE AND STABILITY TESTING, MICROBIOLOGY TESTING, PHYSICOCHEMICAL TESTING. (on 26-JUL-2014 by N. BHANDARI () 2424023615)

Profile: (b) (4) **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					
SUBMITTED TO OC	12-AUG-2014				BHANDARIN
SUBMITTED TO DO FDF; AC INITIAL 06-JUN-2014	12-AUG-2014	10-Day Letter			MOORER
DO RECOMMENDATION	13-AUG-2014			ACCEPTABLE	LHAYKA
THE COMPLIANCE FOLLOW-UP INSPECTION TO THE 5/13 INSPECTION AND THE OAI REGULATORY MEETING HELD 12/19/13 WAS CLOSED OUT ON 6/5/14. A ONE-POINT FDA-403 WAS ISSUED. THE INSPECTION TEAM A NE AND CH-DO PI OSD RECOMMENDED VAI AND RECOMMENDED ACCEPTABLE INITIAL PROFILES. SINCE THIS IS A COMPLIANCE FOLLOW-UP INSPECTION, THE EIR WAS FORWARDED TO CH-DO COMPLIANCE BRANCH FOR THE DISTRICT FINAL DECISION AND FOR FINALIZATION OF PROFILE CODES.					
OC RECOMMENDATION	14-AUG-2014			ACCEPTABLE	WILLIAMSJJ

FDA CDER EES
 ESTABLISHMENT EVALUATION REQUEST
 DETAIL REPORT

Establishment: CFN: (b) (4) FE: (b) (4)
 (b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER
 DRUG SUBSTANCE OTHER TESTER
 DRUG SUBSTANCE RELEASE TESTER

Establishment Comment: API MANUFACTURING FACILITY, API TESTING AND RELEASE FACILITY, (b) (4)

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					
SUBMITTED TO OC	(b) (4)				(b) (4)
OC RECOMMENDATION	(b) (4)			ACCEPTABLE	(b) (4)

4. Nonclinical Pharmacology/Toxicology

From the original Pharmacology/Toxicology Review: Approval is recommended.

This is a 505(b)(2) NDA for Phenylephrine Hydrochloride Ophthalmic Solution 2.5% and 10%, as a mydriatic agent. Akorn's proposed formulation has been marketed without prior FDA approval under the brand name AK-Dilate® since 1993.

Akorn did not conduct or sponsor any nonclinical studies for this application. Akorn's relied on studies from the published literature to support the safety of phenylephrine hydrochloride using the intended ocular dosing regimen.

Akorn provided a list of published nonclinical studies in which their AK-Dilate® formulation was used. In all but one of these studies, phenylephrine was used as a mydriatic to allow examination of the eye or to conduct procedures on the eye. Neither toxicity nor a lack of efficacy (mydriasis) was reported in regard to the use of phenylephrine in these studies. However, the objective of these studies was not to evaluate the safety and/or efficacy of phenylephrine, and it may be the case that these parameters were not directly assessed in these studies.

Phenylephrine is an α 1-adrenergic receptor agonist and, in the eye, acts as a potent vasoconstrictor and mydriatic agent by constricting the arterioles in the conjunctiva and the radial muscle of the iris. The safety profile of phenylephrine is well known based on the extensive clinical experience.

The nonclinical studies summarized by the sponsor to support systemic safety include the repeat-dose toxicity, genotoxicity, and carcinogenicity studies conducted by the National Toxicology Program. In addition, the existent marketing experience provides support for the systemic safety of the intended clinical ocular doses.

Phenylephrine hydrochloride is available under a variety of trade names as a solution for injection (10 mg/ml; max single dose is 1 mg IV), as tablets (10 mg), as various oral combination products (5-40 mg), and as various nasal spray solutions (0.125%, 0.25%, 0.5%, and 1.0%)³. As a stand-alone product (e.g. Sudafed), the maximum recommended oral dose for adults is 60 mg/day (1 mg/kg based on a 60 kg body weight). Higher oral doses (80 mg/day or 1.33 mg/kg) are recommended in combination products (e.g., with guaifenesin). These doses are 2.85 to 3.80-fold the highest intended clinical dose, assuming 100% absorption after ocular administration (3 drops/eye at 10% and a 35 μ L drop administered bilaterally = 21 mg or 0.35 mg/kg).

5. Clinical Pharmacology/Biopharmaceutics

From the original Clinical Pharmacology Review:

The Office of Clinical Pharmacology, Division of Clinical Pharmacology IV has reviewed the submission, and it is acceptable from a clinical pharmacology perspective.

The applicant did not conduct any clinical pharmacology related studies and requested the waiver of evidence of in vivo bioavailability or bioequivalence. In accordance with the 21 CFR §320.22(b)(1), Clinical pharmacology will grant the waiver of evidence of in vivo bioavailability or bioequivalence to this NDA.

From the original Biopharmaceutics Review:

The Biopharmaceutics team is of the opinion that for good cause, the requirement for the submission of evidence of in vivo bioavailability or bioequivalence can be waived, because the proposed drug product is an ophthalmic product intended only for local therapeutic effect. Therefore, the Biopharmaceutics team recommends that the biowaiver request be granted.

From the Biopharmaceutics perspective, NDA 207926 Phenylephrine ophthalmic solution 2.5% and 10% is recommended for approval.

6. Sterility Assurance

Phenylephrine Hydrochloride Ophthalmic solution, 2.5% and 10%, is a topical, ophthalmic preparation of the active ingredient in a buffered, preserved, aqueous solution in a multidose dropper bottle. The drug product is preserved with benzalkonium chloride (0.01%).

Product Quality Microbiology recommends approval.

7. Clinical/Statistical - Efficacy

From the original Medical Officer Review:

The primary support for efficacy for Phenylephrine Hydrochloride Ophthalmic solution 2.5% and 10% ophthalmic solution comes from the studies listed in Section 5.1: Suwan-Apichon, et al. 2010, Gambill, et al. 1967, Haddad, et al. 1970, Chawdhary, et al, 1984 and Yospaiboon, et al. 2004 and from the Pediatric Study by Sindel, et al. 1986.

See Appendix of this CDTL review for a list of these literature articles.

Efficacy studies using the consensual light reflex to demonstrate phenylephrine's ability in producing mydriasis

Gambill, et al. 1967 Study and Haddad, et al. 1970 Study – Group 2

The purpose of the Gambill 1967 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. 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.

The purpose of the Haddad 1970 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. 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.

Gambill Study
(10% phenylephrine)

	All Subjects (N=15)	Light Irides (N=9)	Dark Irides (N=6)
Amount of maximal pupil mydriasis (mm)*			
Mean	2.42	2.69	2.01

*Measured with infrared pupillography to evaluate the difference in pupil size between treated and untreated eyes of a subject when a light stimulus is applied to the eyes in dim illumination.

Haddad Study – Group 2

	1.0 % phenylephrine (N=12)	10% phenylephrine (N=12)
Amount of maximal pupil mydriasis (mm)*		
Mean and SD	3.4 (\pm 0.35)	3.57 (\pm 0.02)

*Measured with infrared pupillography to evaluate the difference in pupil size between treated and untreated eyes of a subject when a light stimulus is applied to the eyes in dim illumination.

The degree of mydriasis was determined by measuring the difference in pupillary responses of the two eyes to a light stimulus when the drug has been instilled in only one eye. Normally both pupils constrict equally when one eye alone is stimulated.

These studies demonstrate that the eyes dosed with phenylephrine remain dilated approximately 2.5 – 3.5 mm more than the contralateral eye when stimulated by a light reflex. These results confirm the ability of phenylephrine to dilate the pupil.

Efficacy studies comparing various concentrations of phenylephrine to produce mydriasis

Chawdhary, et al. 1984 Study, Yospaiboon, et al. 2004 Stud, and Suwan-Apichon, et al. 2010 Study

The purpose of the Chawdhary 1984 study was to study the effects of various dilutions of phenylephrine hydrochloride ophthalmic solution in terms of effective mydriasis and cardiovascular effects in an Indian population having brown irides. Subjects were divided into 4 groups of 10 patients each. Fresh aqueous solutions of phenylephrine hydrochloride were 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. Pupillary sizes at 2, 4, 6, 8, 10, 15, 20, 30, 50 and 70 minute were measured.

The purpose of the Yospaiboon 2004 study was to compare the safety and efficacy of phenylephrine 2.5% versus 10% on pupillary dilation for dark irides. 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. Pupillary measurement was performed immediately before 1% tropicamide, 30 minutes after 1% tropicamide (before 10% or 2.5% phenylephrine) and 30 minutes after 10% or 2.5% phenylephrine. Systolic and diastolic blood pressure and heart rate were also measured before and 30 minutes after 10% phenylephrine or 2.5% phenylephrine.

The purpose of the Suwan-Apichon 2010 study was to compare the safety and efficacy of phenylephrine 2.5% versus 10% on pupillary dilation for dark irides. This was a randomized, double-blind, dose-controlled trial in which 100 diabetic subjects, 50 per group, were assigned at random to receive either 2.5% or 10% phenylephrine 30 minutes after topical administration

of 1% tropicamide to both eyes. Digital images of the pupil were taken before and 30 minutes after tropicamide and 30 minutes after phenylephrine. Systolic and diastolic blood pressure and heart rate were recorded before and 30 minutes after phenylephrine.

Chawdhary Study
 N=40

Mean and standard deviation of pupil size in mm at maximal dilation

	1.25 % phenylephrine (N=10)		2.5 % phenylephrine (N=10)		5 % phenylephrine (N=10)		10% phenylephrine (N=10)	
	Baseline Pupil	Maximal Pupil	Baseline Pupil	Maximal Pupil	Baseline Pupil	Maximal Pupil	Baseline Pupil	Maximal Pupil
Amount of maximal pupil mydriasis (mm)*								
Mean and SD	4.1 ± 0.2	5.8 ± 0.3	4.2 ± 0.3	7.2 ± 0.7	4.3 ± 0.3	7.6 ± 0.2	4.2 ± 0.3	8.2 ± 0.3

Yospaiboon Study*
 N=564

Mean and standard deviation of pupil size in mm at maximal dilation

	2.5 % phenylephrine (N=271)				10% phenylephrine (N=293)			
	Baseline Pupil (OD)	Maximal Pupil (OD)	Baseline Pupil (OS)	Maximal Pupil (OS)	Baseline Pupil (OD)	Maximal Pupil (OD)	Baseline Pupil (OS)	Maximal Pupil (OS)
Amount of maximal pupil mydriasis (mm)*								
Mean and SD	4.5 ± 1.0	7.2 ± 1.0	4.3 ± 0.9	7.1 ± 1.1	4.4 ± 1.1	7.6 ± 1.0	4.3 ± 0.9	7.6 ± 1.0

* All eyes had also received one drop of 1% tropicamide

Suwan-Apichon Study
 N=100

Mean and standard deviation of pupil size in mm at maximal dilation

	Mean Pupil Diameter			
	2.5%		10%	
	R	L	R	L
Baseline	4.73 ± 1.09	4.66 ± 1.04	4.97 ± 0.94	4.87 ± 0.89
Tropic 1%	6.46 ± 0.74	6.45 ± 0.75	6.56 ± 0.78	6.50 ± 0.77
Phenyl	7.05 ± 0.71	7.05 ± 0.72	7.40 ± 0.72	7.39 ± 0.72
Phen-Trop	0.59 ± 0.45	0.59 ± 0.42	0.83 ± 0.40	0.79 ± 0.53

These results confirm the ability of phenylephrine to dilate the eye. Baseline pupillary dilation ranged from 4.1 to 4.4 mm while after instillation of phenylephrine pupillary dilation ranged from 7.0 to 8.2 mm.

Efficacy study in newborns demonstrating phenylephrine’s ability to produce mydriasis

Sindel, et al. 1986 Study

The purpose of the Sindel 1986 study was to compare the safety and efficacy of the combination of mydriatic drops (phenylephrine 2.5% plus 0.5% tropicamide plus 0.5% cyclopentolate) with two other combinations of mydriatic drops (phenylephrine 2.5% plus 1.0% tropicamide, and phenylephrine 1.0% plus 1.0% tropicamide) in preterm infants.

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 was available to perform the measurements. 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 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.

Sindel Study
(N=34)

	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)	
Age at study (days)	53.9		52.9		52.3		54.0	
Birth weight (grams)	1022 ± 226		1115 ± 281		1110 ± 317		980 ± 155	
Amount of maximal pupil mydriasis (mm)*	Baseline Pupil	Maximal Pupil	Baseline Pupil	Maximal Pupil	Baseline Pupil	Maximal Pupil	Baseline Pupil	Maximal Pupil
Mean and SD	2.8 ±0.8	7.4 ±0.5	3.0 ± 0.6	7.3 ± 0.4	2.9 ± 0.6	7.1 ±0.6	2.9 ± 0.2	2.9 ±0.2

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.

Efficacy studies demonstrating phenylephrine’s ability to produce mydriasis with Akorn’s formulation

The efficacy data for phenylephrine in general is being supplemented with additional literature reports of studies conducted using Akorn’s formulation. These studies are summarized in Table 14 below. While these reports do not provide specific data on the extent of mydriasis produced by the Akorn phenylephrine solution, the product was found to be effective in producing the extent of mydriasis desired by the authors. See Appendix 9.2 of this review for a list of these literature articles.

These five (5) literature studies were reviewed. Although these reports do not provide specific data on the extent of mydriasis produced by the Akorn phenylephrine solution, the product was found to be effective in producing the extent of mydriasis required by the authors. There are no reports of lack of efficacy with the Akorn product in these studies.

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% +proparacaine, 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: Module 2.7.3.

Summary Efficacy Statement

The submitted literature references contained in this submission support the efficacy of phenylephrine hydrochloride ophthalmic solution 2.5% and 10% in adults and pediatric patients.

8. Safety

From the original Medical Officer Review:

A review of the published literature shows there are a substantial number of publications describing the safety of the use of phenylephrine hydrochloride for topical ophthalmic use at concentrations ranging from 1 % to 10%. Key safety articles with their summaries are listed in the following table.

See Appendix of this CDTL review for a list of these literature articles.

Cross-Discipline Team Leader Review
 William M. Boyd, M.D.
 NDA 207926
 Phenylephrine Hydrochloride Ophthalmic Solution, 2.5% and 10%

Authors	Study title	a) Design b) Efficacy data c) Safety data
Allinson 1990	Reversal of Mydriasis/ Dipiprazole	a) 50 subjects, within subject, randomized Dipiprazole treatment eye. All eyes received 1% Trop and 2.5% PE. b) 5mm mydriasis on T+PE (p=0.01<0.05) Reduced post D by over 3 mm in two hours and completely in 24 hrs. c) BP and Pulse, IOP. No sig diff. No data given
Brown 1980	Lack of Side Effects From Topically Administered 10% Phenylephrine Eyedrops A Controlled Study	a) Controlled, Double masked. PE 10% n=100, Trop 1% n=50 b) 3 drops 2 mins apart in both eyes. No data on efficacy. c) No difference between the PE and T on DBP, SBP or Pulse
Samantary 1975	Systemic effects of topical phenylephrine (10%)	a) 10% PE c) They found elevations of 10-40 mmHg SBP and 10=-30mmHg of SBP
Chowdhary 1984	Mydriasis-use of Phenylephrine (a dose response concept)	a) 10%, 5%, 2.5% 1.25% (N=10/group) Double masked. Dose response/controlled b) Mydiatic dose response. .Sig diff ? between 2.5% and 1.25% c) safety is dose related. 2.5% and 1.25% had no effect on pulse and BP whereas 10% and 5% did. .More so with 10% and at 6-8 mins.
Chin 1994	PE eye drops in ophthalmic surgery – a clinical study of cardiovascular effects.	a) Double masked. Saline (n=30), 2.5% (n=29) and 10% (n=30)PE and mydriacyl. undergoing cataract surgery 50% were hypertensive b) No efficacy data c) Higher BP in the PE groups more sig in 10% than 2.5% more significant in non hypertensives . 10.3% of 10% and 3% on 2.5% required hypotensive treatment.
Filho 2007	Cardiovascular and papillary effects of topical Ophthalmic 2.5% and 10% in healthy volunteers. In Portuguese with an English abstract	a) Case controlled randomized crossover study of 2.5% and 10% PE in 28 HV's b) Stat sig difference in mydiatic effect p=OD 0.015/ OS 0.028 c) no difference in safety
Malhotra 1998	Comparison of cardiovascular effects of 2.5% and 10% PE during ophthalmic surgery	a) N=54. DM, Randomized. 0.25% or 10% PE and 1% Trop. In subjects without CV disease history. c) both cause an increase in SBP 14.1 – 18.9 mmHg but no SSD between them
Symons 1997	Letter to the Editor With response from Tanner.	Review publication a) Comparison of BP and pulse 10% phenylephrine plus 1% tropicamide (n=126) vs a 1% tropicamide (n=14) b) No data on mydriasis presented c) No difference in mean BP but significant difference on the percent of subjects with 30mm Hg fluctuation in BP.

Authors	Study title	a) Design b) Efficacy data c) Safety data
Yospaiboon 2004	Randomized Double-blind Study of Phenylephrine 2.5% vs 10% on papillary dilatation	a) Phenylephrine 2.5% (n=293) vs phenylephrine 10% (n=271). Both groups received 1% tropicamide. b) Phenylephrine 10% more effective than 2.5% with significant difference between groups for the amount of additional dilatation after tropicamide p<0.001 c) Significant difference on pulse rate p=0.005 but not SBP or DBP.
Lansche RK 1966	Systemic reactions to topical epinephrine and phenylephrine	Case reports of 2 subjects 40F had a headache and passed out after 2% epinephrine, 57M experienced increased BP and HR and fainting after a single drop of 10% phenylephrine . Contributing factors discussed.
Fraunfelder 1978.	Possible adverse effects from topical ocular 10% phenylephrine	
Solosky 1972	Hypertension following 10% phenylephrine ophthalmic.	3 case reports of subjects of subjects experiencing increased BP (69F, 3mth F, 62 M)
Wilensky 1973	Acute Systemic Hypertension after conjunctival instillation of Phenylephrine Hydrochloride	Case report: BP went from 150/100 to 270/170 after proparacaine one drop and three drops 10% phenylephrine
McReynolds 1956	Hazards of use of sympathomimetic drugs in ophthalmology	Acute subarachnoid hemorrhage in a 35 yo. A cotton wick soaked in 10% phenylephrine inserted in lower cul de sac to induce dilatation and separate posterior synechiae. BP went from 118/68 to 230/130 and had subarachnoid bleed.
Heath 1939	Use of phenylephrine hydrochloride (neo-synephrine Hydrochloride) in ophthalmology	Reported BP unaltered in 40%, lowered in slightly in about 58% and slightly increased in 2% (Criterion was \pm 4mm Hg was no change) N=60.
Biggs 1959	The effect of sympathomimetic drugs upon the amplitude of accommodation	Phenylephrine 10% administered intensively caused only a slight recession of the near point. No effect was noted at dosage levels which the clinician might employ for refraction purposes.
Becker 1959	The effect of phenylephrine hydrochloride on the miotic treated eye.	In normal subjects phenylephrine 10% produced mydriasis and had little or no effect on the IOP of eyes treated with miotics. In subjects with glaucoma on demerarium bromide 0.25% phenylephrine 10% caused a very slight increase in IOP.
Borromeo-McGrail 1973	Systemic hypertension following ocular administration of 10% phenylephrine in the neonate.	a) Double –masked comparison of phenylephrine 10% (n=3) and phenylephrine 2.5% (n=4) in low birth weight infants. b) No efficacy data c) With phenylephrine 10% SBP up 12-16mmHg DBP up 10-14mmHg . Phenylephrine 2.5% had no effect
Barbee 1957	A comparative study of mydiatic and cycloplegic agents in human subjects without eye disease.	10% phenylephrine produced similar mydriasis in blue brown and black eyes. Although numerically the mydriasis was less in black eyes.
Martha Meyer 1980	Phenylephrine hydrochloride in Pharmacology of Ocular Drugs	Review of the safety issues.

Authors	Study title	a) Design b) Efficacy data c) Safety data
Pless 2003	Topical phenylephrine may result in worsening of visual loss when used to dilate pupils in patients with vaso-occlusive disease of the optic nerve.	Report on 4 patients with non-arteritic ischemic optic neuropathy who experienced acute worsening of visual function after phenylephrine used for fundus exam. 45 mins to 12 hrs later. All on 2.5% phenylephrine plus 0.5-1.0% tropicamide.
Alpay 2010	The local vasoconstriction of infant's skin following instillation of mydriatic eye drops.	Two case reports in neonates of extensive blanching of the skin after 2.5% phenylephrine Suggests reducing drop size and wiping away excess.
Lee 1958	The influence of epinephrine and phenylephrine on Intraocular Pressure.	Patients with OAG and normals IOP effect variable Studied phenylephrine 1% and 10%.
Sindel 1986	A comparison of the papillary and cardiovascular effects of various mydriatic agents in preterm infants.	a) Randomized, A. Phenylephrine 2.5% tropicamide 1.0% (n= 10) B. Phenylephrine 2.5% tropicamide 0.5% (n=10) C. phenylephrine 1.0% tropicamide 1.0% (n=10) D. Saline (n=4) b) Mydriasis in groups A and B was not different. Group C was less in bright light but still >6mm c) BP and HR changes significantly less in group C
Vaughan 1973	Ventricular arrhythmias after topical vasoconstrictors.	Case report of an 8 yo under GA for squint surgery. 4-5 drops 10% phenylephrine sent BP up 100/60 to 190/120 HR slowed. Multiple premature ventricular contractions.

Exposure

From the Table of publications listed in Section 7.1.1 addressing the safety of phenylephrine topically applied to the eye, at least 1229 subjects were exposed to phenylephrine of which 630 received phenylephrine 10%.

Since the use of phenylephrine ophthalmic drops 2.5% and 10%, is for examinations and surgical procedures there are no data on long term exposure and safety.

Deaths

No deaths were reported due to the use of topical ophthalmic phenylephrine solution in the randomized, controlled clinical trials utilized to establish the safety and efficacy of the drug product. There are case reports of death with the use of phenylephrine applied topically for other indications.

Common Adverse Events

Since the use of phenylephrine ophthalmic drops 2.5% and 10%, is for single dose examinations and procedures there are no data on long term exposure and safety.

Phenylephrine is a sympathomimetic and systemic absorption of eye drops is known to occur via the nasal mucosa, cornea, and conjunctiva. Within minutes of application ocular reactions including eye pain and stinging on instillation, temporary blurred vision, photophobia, and conjunctival sensitization may occur.

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.

Ophthalmic use of phenylephrine can occasionally cause systemic sympathomimetic effects such as palpitation, tachycardia, premature ventricular contractions, occipital headache, pallor or blanching, trembling or tremors, increased perspiration, and hypertension. In one patient, hypertension was reported to be severe enough to cause subarachnoid hemorrhage followed insertion of a cotton wick saturated with 10% phenylephrine hydrochloride in the lower conjunctival cul-de-sac.

Systemic effects occur only rarely after topical application of solutions containing 2.5% or less of phenylephrine hydrochloride to the conjunctiva but are more likely to occur if the drug is instilled after the corneal epithelium has been damaged (e.g., by trauma or instrumentation) or permeability is increased by tonometry, inflammation, surgery of the eye or adnexa, or topical application of a local anesthetic; when the eye or adnexa are diseased; or when lacrimation is suppressed such as during anesthesia. The risk of severe hypertension is greatest in infants receiving instillations of 10% phenylephrine hydrochloride solutions.

Drug- Specific Safety Explorations

Special safety studies were performed in neonates in the Sindel 1986 Study and the Borromeo-McGrail 1973 Study.

Sindel Study
(N=34)

	Group A Phenylephrine 2.5% and 1% tropicamide (N=10)	Group B Phenylephrine 2.5% and 0.5% tropicamide (N=10)	Group C Phenylephrine 1.0% and 1.0% tropicamide (N=10)	Group D Saline only (N=4)
Age at study (days)	53.9	52.9	52.3	54.0
Birthweight (grams)	1022 ± 226	1115 ± 281	1110 ± 317	980 ± 155
Maximum change in blood pressure and heart rate after eye drops instilled				
Blood pressure (%)				
Systolic	+14.9 ± 9.6*	+17.2 ± 12.5**	+7.1 ± 10.1	-0.8 ± 6.9
Mean	+17.1 ± 10.4*	+22.8 ± 17.4**	+7.7 ± 9.3 ^{tt}	+3.0 ± 6.0
Diastolic	+15.9 ± 7.8*	+19.5 ± 14.2*	+5.4 ± 7.6 ^{ttt}	+0.8 ± 10.6
Heart rate (%)	+6.0 ± 6.1*	+10.0 ± 10.6*	+4.4 ± 5.2	+2.1 ± 2.0

*p < 0.02 vs. baseline

**p < 0.01 vs. baseline

^{tt} A vs. C p=0.04, B vs C p=0.02

^{ttt} A vs. C p=0.007, B vs. C p=0.01

Phenylephrine ophthalmic solution 2.5% results in an acceptable increase of heart rate and blood pressure in neonates.

Borromeo-McGrail 1973 Study

Borromeo-McGrail 1973 was a randomized, masked study comparing pupillary dilating capabilities and associated cardiovascular effects of phenylephrine hydrochloride ophthalmic solution 2.5%, 10% and saline in 12 neonates under 1 month of age and weighing from 907 gm to 2,438 gm. Formal pupillary measurements were not made or recorded, the article states, "...all patients who received either 2.5% or 10% phenylephrine had full pupillary dilatation within 25 to 30 minutes. The time of onset and degree of dilatation was not related to the concentration of phenylephrine used."

A separate group of eight low birth weight infants was studied in an open phase with 10% phenylephrine ophthalmic instillation. In this phase, the observer was aware that 10% phenylephrine drops had been instilled.

Borromeo-McGrail Study
Double-blind Phase
 N=12

All neonates < 1 month old, weighed 907 – 2,438 grams

	Phenylephrine 2.5% (N=4)	Phenylephrine 10% (N=3)	Normal Saline (N=5)
Blood pressure (%)			
Systolic	Unchanged	Increased 12 – 16 mm Hg (18% to 25%)	unchanged
Diastolic	Unchanged	Increased 10 – 14 mm Hg (22% to 50%)	unchanged
Heart rate	Unchanged	unchanged	unchanged
Respiratory rate	Unchanged	unchanged	unchanged

Borromeo-McGrail Study
Open label Phase
 N=8

All neonates < 1 month old, weighed 907 – 2,438 grams

	Phenylephrine 10% (N=8)
Blood pressure (%)	
Systolic	Increased 6 – 22 mm Hg (7% to 50%)
Diastolic	Increased 4 – 18 mm Hg (13% to 70%)
Heart rate	unchanged
Respiratory rate	unchanged

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

Safety Summary Statement

A review of the published literature shows there are a substantial number of publications describing the safety of the use of phenylephrine hydrochloride for topical ophthalmic use at concentrations ranging from 0.08 % to 10%.

The submitted literature references contained in this submission support the safe use of phenylephrine hydrochloride ophthalmic solution, 2.5% and 10% in adults and pediatric patients over one year in age to dilate the pupil. Phenylephrine hydrochloride ophthalmic solution 10% is not safe for use in pediatric patients less than 1 year old.

Systemic adverse reactions to phenylephrine hydrochloride ophthalmic solution are primarily cardiovascular due to its vasoconstriction activity and have been reported include palpitation, tachycardia, premature ventricular contractions, hypertension, syncope, myocardial infarction, arrhythmia and subarachnoid hemorrhage. These systemic adverse reactions are more frequent with the 10% solution and more frequent in patients with pre-existing cardiovascular diseases.

Ocular adverse reactions include stinging on instillation, temporary blurred vision and photophobia and conjunctival sensitization.

Akorn, Inc. submitted a 120-Day Safety Report Update for Phenylephrine Ophthalmic Solution 2.5% and 10% on December 3, 2014. There is no new safety information that would alter the safety conclusions of the original NDA submission.

9. Advisory Committee Meeting

No Advisory Committee Meeting was held. There were no new issues raised in the review of the application which were thought to benefit from an Advisory Committee Meeting.

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

BIOSTATISTICS

Per the original Biostatistics review:

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.

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).

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 (±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.

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

OPDP

The Office of Prescription Drug Products (DPDP) provided a labeling review of the proposed, clean, substantially complete version of the package insert.

Comment [CGC1]: OPDP Comment: We note that the ADVERSE REACTIONS section also lists, “conjunctival sensitization” as an ocular adverse reaction. We recommend including this here in the highlights for consistency with the full PI.

DTOP Comments: Disagree. All adverse reactions do not need to be included in the Highlights and this potential event is not considered serious and is very rare.

Comment [CGC3]: OPDP Comment: We note that another phenylephrine label (NDA 203510) lists that phenylephrine is contraindicated in patients with hypertension or thyrotoxicosis (emphasis added). We also note that the Highlights section of this proposed PI lists thyrotoxicosis as well. Should this drug also be contraindicated in patients with thyrotoxicosis? If so, please consider adding and revising the header of this Contraindication to communicate this (such as, “Cardiac and Endocrine Disease”).

DTOP Comments: The final draft label has been revised.

Comment [CGC4]: OPDP Comment: Is this description (i.e cardiovascular adverse reactions) necessary? OPDP is concerned that this language minimizes the potential risk. OPDP notes that this risk already communicates that the sentence references “some reports.” We recommend deleting “(b) (4)” and, if possible, disclosing the exact or approximate number of reports.

DTOP Comments: The final draft label has been revised.

Comment [CGC5]: OPDP Comment: We note that the approved label for another phenylephrine ophthalmic product (NDA 203510) states that these are “serious” cardiovascular adverse reactions, such as ventricular arrhythmias and myocardial infarction. The W&P in the NDA 203510 PI also explains that some of these episodes were fatal. We also note that the Highlights section of this proposed PI states, (b) (4)

We recommend revising the risk statement here to communicate the severity of this Warning and Precaution. Alternatively, if DTOP determines that this information is not pertinent for this product, we recommend revising the Highlights section for consistency with this W&P 5.2.

DTOP Comments: The final draft label has been revised.

Comment [CGC6]: OPDP Comment: We note that the approved label for NDA 203510 states, “Caution should be exercised in pediatric patients less than 5 years of age and patients with insulin dependent diabetes, hypertension, hyperthyroidism, generalized arteriosclerosis, or cardiovascular disease.” We also note that the Highlights states, “Caution in pediatric patients less than 5 years of age, and in patients with elevated blood pressure.” Should this statement appear here in the full PI as well? OPDP recommends either revising this section to include the information, or revising the Highlights section for consistency. OPDP defers to DTOP.

DTOP Comments: *The final draft label has been revised.*

Comment [CGC7]: OPDP Comment: Are these considered the most common adverse reactions associated with the drug? If so, please consider communicating this as well as including the incidence of each of these common adverse reactions.

DTOP Comments: *This is a 505(b)(2) application relying on published literature for safety and efficacy information for phenylephrine ophthalmic solution. Per the Labeling Review Tool, older products may not have an incidence rate for adverse reactions.*

Comment [CGC8]: OPDP Comment: We note that the approved label for NDA 203510 states that this maximal mydriasis occurs in 20 to 90 minutes (emphasis added). OPDP would just like to confirm that this time frame is correct for this phenylephrine product.

DTOP Comments: *The final draft label has been revised.*

DMEPA

The applicant chose not to submit a proprietary name for this drug product.

DMEPA provided a labeling review of the original carton and container labeling. DMEPA recommended changing the background color of the 2.5% solution to a more obvious red to prevent misidentification of the product as an anti-inflammatory. This product will be utilized almost exclusively in physician’s offices to dilate subjects prior to ocular examination; there is no perceived risk with misidentification of the product as an anti-inflammatory. The current color scheme is acceptable.

FINANCIAL DISCLOSURE

This is a 505(b)(2) supplemental application primarily based on literature. In accordance with 21 CFR Part 54, no financial disclosure is appropriate for this application. There are no “covered clinical studies” in this submission.

OSI

An Office of Scientific Investigations (OSI) audit was not requested. This is a 505(b)(2) supplemental application primarily based on literature.

12. Labeling

The labeling found in Appendix 2 (carton and Container labeling submitted on 12/16/14; package insert submitted on 1/14/15) is acceptable.

13. Recommendations/Risk Benefit Assessment

RECOMMENDED REGULATORY ACTION:

NDA 207926 for Phenylephrine Ophthalmic Solution, 2.5% and 10% is recommended for approval for dilation of the pupil.

Based on the published clinical literature, the information provided by the applicant supports the approval of this product for the approved indication, i.e. there is a positive benefit to risk ratio.

Systemic adverse reactions to phenylephrine hydrochloride ophthalmic solution are primarily cardiovascular due to its vasoconstriction activity. These systemic adverse reactions are more frequent with the 10% solution and more frequent in patients with pre-existing cardiovascular diseases.

Ocular adverse reactions include stinging on instillation, temporary blurred vision and photophobia and conjunctival sensitization.

The 10% solution is not recommended for use in infants less than 1 year old and patients with hypertension where the 2.5% solution should be used due the risk of increased systemic toxicity.

The benefits of using this drug product outweigh the risks for the above indication.

RECOMMENDATION FOR POSTMARKETING RISK MANAGEMENT ACTIVITIES:

There are no risk management activities recommended beyond the routine monitoring and reporting of all adverse events.

There are no recommended Postmarketing Requirements or Phase 4 Commitments.

Going forward, Akorn has committed to perform finished product release and stability testing of drug product as per revised drug product specifications (Effective Date: December 10, 2014) provided in a 12/14/16 submission.

Appendix 1

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/s/

WILLIAM M BOYD
01/15/2015

WILEY A CHAMBERS
01/15/2015