CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207926Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	207926
Priority or Standard	Standard
Submit Date(s)	7/11/14
Received Date(s)	7/11/14
PDUFA Goal Date	5/11/2015
Division / Office	DTOP/OAP
Reviewer Name(s)	William M. Boyd, M.D.
Review Completion Date	12/10/2014
Established Name	Phenylephrine Hydrochloride Ophthalmic Solution
(Proposed) Trade Name	None
Therapeutic Class	alpha-1 adrenergic receptor agonist
Applicant	Akorn, Inc.
Formulation(s)	topical ophthalmic solution
Dosing Regimen	One drop of the 2.5% or 10% solution instilled at 3 – 5 minute intervals up to a maximum of 3 drops
Indication(s)	Dilate the pupil
Intended Population(s)	2.5% or 10% used in adults and pediatric patients ≥ 1 year; 2.5% used in pediatric patients < 1 year

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

NDA 207926 is recommended for approval with the revised labeling identified in this review. The submitted literature references contained in this submission support the use of phenylephrine hydrochloride ophthalmic solution 2.5% in adults and pediatric patients and the use of phenylephrine hydrochloride ophthalmic solution 10% in adults and pediatric patients over one year in age to dilate the pupil. Phenylephrine hydrochloride ophthalmic solution 10% is not recommended for approval for use in pediatric patients less than 1 year old.

1.2 Risk Benefit Assessment

NDA 207926 has been submitted as a 505(b)(2) application. 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.

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. (holder of another phenylephrine new drug application).

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

Ocular adverse reactions include stinging on instillation, temporary blurred vision, 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.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no proposed risk management actions except the usual post-marketing collection and reporting of adverse experiences associated with the use of drug product.

1.4 Recommendations for Postmarket Requirements and Commitments

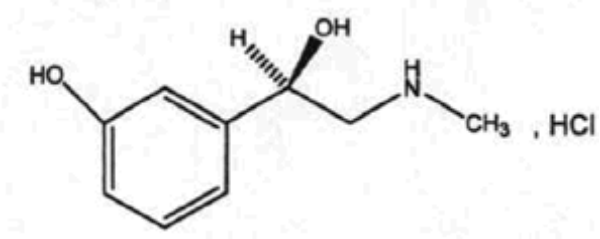
There are no recommended Phase 4 clinical study commitments.

2 Introduction and Regulatory Background

Phenylephrine hydrochloride is an alpha-1 adrenergic agonist drug that is used in ophthalmology mainly for its mydriatic effect. Pharmacologic pupil dilation can be achieved by stimulating the iris dilator muscle with a sympathomimetic agent (e.g., phenylephrine) and/or by inhibiting the sphincter muscle with an antimuscarinic (anticholinergic) eye drop (e.g., tropicamide). Often agents to do both are applied.

2.1 Product Information

Chemical structure of phenylephrine hydrochloride



Chemical Name: (R)-3-hydroxy-α[(methylamino)methyl]benzenemethanol hydrochloride.

Molecular Formula: $C_9H_{13}NO_2$-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	(b) (4)	
Monobasic Sodium Phosphate, (b) (4)	USP		
Phosphoric Acid	NF	pH Adjusting Agent	Q.S to adjust target pH to 6.5
Sodium Hydroxide (b) (4)	NF		
Water for Injection	USP	(b) (4)	
(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	(b) (4)	
Monobasic Sodium Phosphate, (b) (4)	USP		
Phosphoric Acid	NF	pH Adjusting Agent	Q.S to adjust target pH to 6.5
Sodium Hydroxide (b) (4)	NF		
Water for Injection	USP	(b) (4)	
(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)	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) 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

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 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

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)	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

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

2.2 Tables of Currently Available Treatments for Proposed Indications

Phenylephrine Hydrochloride Ophthalmic Solution, USP 2.5% and 10% (NDA 203510) was approved on 3/21/2013 to dilate the pupil.

Cyclomydril (NDA 011663) was a combination ophthalmic solution of phenylephrine hydrochloride 1% and cyclopentolate hydrochloride 0.2% approved for the production of mydriasis. The application was withdrawn after the applicant submitted and received approval of an ANDA (ANDA 84-300) for the same product.

Multiple products are approved and available which contain either tropicamide, or cyclopentolate to dilate the pupil. These products inhibit the sphincter muscle but do not stimulate the pupil dilating muscle.

2.3 Availability of Proposed Active Ingredient in the United States

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 was 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%, are currently being marketed and supplied in the United States for use as a mydriatic (NDA 203510).

Multiple products containing the combination of phenylephrine hydrochloride and promethazine hydrochloride in an oral syrup or solution are approved. A tablet containing phenylephrine hydrochloride and ibuprofen is also approved.

2.4 Important Safety Issues with Consideration to Related Drugs

There have been rare reports of serious cardiovascular reactions, including ventricular arrhythmias and myocardial infarctions in patients using phenylephrine 10%. These episodes, some fatal, have usually occurred in patients with pre-existing cardiovascular diseases. For this reason, 10% phenylephrine should not be used in patients known to have these risk factors. If phenylephrine is needed to be instilled in these patients, phenylephrine 2.5% should be considered.

A significant elevation in blood pressure is rare but has been reported following conjunctival instillation of recommended doses of phenylephrine 10%. The risk is less with phenylephrine 2.5%. Caution should be exercised in infants of low body weight, and patients with hypertension, hyperthyroidism. The post-treatment blood pressure of these patients, and any patients who develop symptoms, should be carefully monitored.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

(b) (4) The primary difference between formulations is that the Akorn product does not contain boric acid 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	• 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	• 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	• 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	• Monobasic Sodium Phosphate [redacted] USP • Dibasic Sodium Phosphate [redacted] 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.

2.6 Other Relevant Background Information

Phenylephrine hydrochloride has been used in hundreds of clinical trials since its introduction into the marketplace over 70 years ago. From this large volume of clinical trials, several studies that were designed as randomized, masked studies and that contain statistical analysis are reviewed in Sections 5.0 and 6.0 of this Medical Officer's review.

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.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This New Drug Application is being submitted as a 505(b)2 application. Akorn, Inc. certified that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Reference literature reports, surveys, and articles cited in this review are representative of the published literature. There is no evidence that these references refer to trials not conducted in accordance with acceptable clinical ethical standards.

3.2 Compliance with Good Clinical Practices

Reference literature reports, surveys, and articles cited in this review are representative of the published literature. There is no evidence that these references refer to trials not conducted in accordance with acceptable clinical ethical standards.

3.3 Financial Disclosures

This is a 505(b)(2) 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.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

See Section 2.1.

4.2 Clinical Microbiology

There are no clinical microbiology issues or reviews for this product. It is not an anti-infective.

4.3 Preclinical Pharmacology/Toxicology

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

Phenylephrine is an alpha1-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.

4.4 Clinical Pharmacology

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), the clinical pharmacology reviewer agrees with the waiver of evidence of in vivo bioavailability or bioequivalence to this NDA because it is self-evident.

4.4.1 Mechanism of Action

Phenylephrine is an alpha receptor sympathetic agonist used in ocular diagnostic, therapeutic or surgical procedures due to its vasoconstrictor and mydriatic action. Phenylephrine possesses predominantly α-adrenergic effects. In the eye, phenylephrine acts locally as a potent vasoconstrictor and mydriatic, by constricting ophthalmic blood vessels and the radial muscle of the iris.

4.4.2 Pharmacodynamics

The ophthalmologic usefulness of phenylephrine is due to its rapid effect; maximal mydriasis occurs in 60-90 minutes with recovery after 5-7 hours.

4.4.3 Pharmacokinetics

The systemic exposure following topical administration of phenylephrine has not been studied. A higher systemic absorption is expected for the 10% solution than the 2.5% solution, and when the corneal barrier function is compromised.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 5.1: 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	Statistical Tests
Suwan-Apichon, et al. (2010)	Diabetic subjects with Darkly Pigmented Irides / 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. (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. (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)	Healthy Caucasian subjects/ N=15 (7 F and 8 M)/ 12-38 yrs; mean age=26.4 yrs 9 subjects had blue 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	For each group, means and standard deviations for the amount of maximal mydriasis (mm) were provided. No formal statistical comparison was performed in the

Studies	Population/Sample size/Age	Arms (Sample size)	Comment	Measurement/ Endpoint	Statistical Tests
	3 subjects had hazel irides 3 subjects had brown irides			the two eyes returned back to baseline.	article.
Haddad, et al. (1970)	**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.

Pediatric Efficacy Study

Author – date	Title	Description a) Design b) Efficacy c) Safety
Sindel, et al. 1986	Comparison of the Pupillary 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 > 6 mm c) Blood pressure and heart rate change significantly less in group C

5.2 Review Strategy

The July 11, 2014, submission was submitted electronically. Subsequent amendments were also submitted in electronically. All literature reports were reviewed.

A literature search conducted by this reviewer failed to identify any additional literature references which were contrary to the information provided or referenced by Akorn, Inc. in this application for this indication.

5.3 Discussion of Individual Studies/Clinical Trials

Three studies [Suwan-Apichon, et al. 2010; Yospaiboon, et al. 2004; Chawdhary, et al. 1984] were randomized, double-blind, parallel-group comparisons. One study in pediatric subjects [Sindel, 1986], was a randomized, partially blinded, 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.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

6.1.1 Methods

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 9.2 of this review for a list of these literature articles.

6.1.2 Demographics

Key Efficacy Studies

	Gambill study	Haddad study		Chawdhary study	Yospaiboon study	Suwan-Apichon, study
Number of Subjects	15	8 (Group 1) First Phase of Study**	24 (Group 2)	40	564	100
Gender						
Male	8	NR	NR	NR	248	58
Female	7	NR	NR	NR	316	42
Age						
Range in years	12 - 38	21- 53	All > 50	20 - 40	5 - 87	21-78
mean	26.4	NR	NR	NR	51.1	54.2
Iris color						
Blue	9	3	NR	-	-	-
Hazel	3	2	NR	-	-	-
Brown	3	3	NR	40	564	100

*NR – not reported
** Group 1 subjects confirmed a dose response curve from 0.1% up to 10% phenylephrine. The dose response began to plateau off at 5% phenylephrine with a complete plateau established at 10% phenylephrine.

Reviewer's comments:
Various reports and observations by clinicians have demonstrated that light colored irides dilate more easily with phenylephrine. Therefore, to study the mydriatic effect of phenylephrine in clinical trials many investigators enrolled a majority of subjects with dark colored irides (the more difficult cases) to demonstrate the dilation effect of the drug. While not preferred, this is acceptable.

6.1.3 Subject Disposition

The efficacy results are based on the all randomized patients enrolled in the studies. The effect of topical phenylephrine hydrochloride ophthalmic solution 2.5% and 10% occurs within minutes; therefore all subjects that were randomized and enrolled into the studies were evaluated.

6.1.4 Analysis of Primary Endpoint(s)

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 (± 0.35)	3.57 (± 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)	
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	4.1 ± 0.2	5.8 ± 0.3	4.2 ± 0.3	7.2 ± 0.8	4.3 ± 0.3	7.7 ± 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)			
Amount of maximal pupil mydriasis (mm)*	Baseline Pupil (OD)	Maximal Pupil (OD)	Baseline Pupil (OS)	Maximal Pupil (OS)	Baseline Pupil (OD)	Maximal Pupil (OD)	Baseline Pupil (OS)	Maximal Pupil (OS)
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 ± 1.0	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.

Reviewer's comments:
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.

6.1.5 Analysis of Secondary Endpoints(s)

Not applicable.

6.1.6 Other Endpoints

Not applicable.

6.1.7 Subpopulations

The overall age range of patients from the key efficacy studies was 5-87 years. Neonates were evaluated separately for safety and efficacy. Based on a comparison across studies, the effectiveness results do not appear to vary with age.

In general, more females than males participated in these studies. None of the studies examined the effects of gender on the effectiveness outcome.

None of the demographic factors described appeared to correlate with any specific efficacy outcome.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

See Section 6.1.4 of this review. The studies support a dosing regimen of 2.5% and 10% phenylephrine solution instilled at 3 – 5 minute intervals up to a maximum of 3 drops per eye in patients aged 1 or older and 2.5% phenylephrine in pediatric patients < 1 year old.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Pupil movement is generally seen within 15 minutes, maximal mydriasis between 20 to 90 minutes, and recovery after 3 to 8 hours.

6.1.10 Additional Efficacy Issues/Analyses

None.

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

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 below. See Appendix 9.2 of this review for a list of these literature articles.

Authors	Study title	a) Design b) Efficacy data c) Safety data
Allinson 1990	Reversal of Mydiasis/ 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 ± 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 demercarium 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 mydriatic 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.

7.1.2 Categorization of Adverse Events

Reference literature reports, surveys, and articles cited in this review are representative of the published literature. They are adequate to make a determination of the safety of the 2.5% and 10% phenylephrine hydrochloride concentrations. There is no evidence that these references refer to trials not conducted in accordance with acceptable clinical ethical standards.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Pooling of data across various studies was not informative given the variety of studies performed, i.e., case report studies, non- randomized studies, randomized studies, etc.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

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.

Phenylephrine ophthalmic solution 2.5% results in an acceptable increase of heart rate and blood pressure; due to these increases the higher dose of phenylephrine ophthalmic solution 10% is not recommended in infants less than 1 year old. See Section 7.4.5 of this review.

7.2.2 Explorations for Dose Response

The dose response curve for mydriasis flattens above the 2.5% concentration with little difference between 5% and 10% concentrations (Haddad, et al 1979). The efficacy difference between the 5% and 10% concentrations is not statistically significant. The optimal dose range appears to be 2.5% to 10%. In general, a subject should receive a dose by instillation, every 3-5 minutes until the desired mydriasis is obtained to a maximum of 3 drops.

7.2.3 Special Animal and/or In Vitro Testing

Phenylephrine hydrochloride 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.

Given the extensive use of phenylephrine in humans, additional animal / in vitro testing is not required.

7.2.4 Routine Clinical Testing

Additional clinical testing is not required.

7.2.5 Metabolic, Clearance, and Interaction Workup

Metabolic and clearance studies were not performed.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Refer to Section 2.4.

7.3 Major Safety Results

7.3.1 Deaths

No deaths were reported due to the use of topical ophthalmic phenylephrine solution.

7.3.2 Nonfatal Serious Adverse Events

Several authors describe the potential for 10% phenylephrine to exacerbate vasoconstrictive conditions and cardiovascular conditions following topical ophthalmic use. Marked elevation of blood pressure, tachycardia, ventricular arrhythmias, myocardial infarction, and subarachnoid hemorrhage are reported as rare reactions following topical ocular instillation. Four cases of worsening of visual loss in subjects with non-arteritic ischemic optic neuropathy after 2.5% phenylephrine plus 0.5% or 1% tropicamide was used in a dilated fundus exam have been reported.

7.3.3 Dropouts and/or Discontinuations

Not applicable.

7.3.4 Significant Adverse Events

Ophthalmic use of phenylephrine occasionally causes 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 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.

7.3.5 Submission Specific Primary Safety Concerns

See Section 2.4 and Section 7.3.4.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

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.

7.4.2 Laboratory Findings

Not applicable. See Section 7.4.3.

7.4.3 Vital Signs

There is a potential for 10% phenylephrine to cause an increase in blood pressure particularly systolic blood pressure and to increase or decrease HR. There is evidence that 2.5% is less likely to cause an increase in BP or HR and for this reason is generally preferred in the elderly and the very young.

7.4.4 Electrocardiograms (ECGs)

ECG findings were not reported.

7.4.5 Special Safety Studies/Clinical Trials

Special safety studies were performed in neonates in the Sindel, et al. 1986 Study and the Borromeo-McGrail, et al. 1973 Study. See Section 6.1.4.3 of this review for a more detailed discussion of Sindel 1986.

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 ± 9.3tt	+3.0 ± 6.0
Diastolic	+15.9 ± 7.8*	+19.5 ± 14.2*	+5.4 ± 7.6ttt	+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

Reviewer's comments:
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

Reviewer's comments:
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.

7.4.6 Immunogenicity

Not applicable.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

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.

7.5.2 Time Dependency for Adverse Events

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.

7.5.3 Drug-Demographic Interactions

The risk of severe hypertension is greatest in infants less than 1 year old receiving instillations of 10% phenylephrine hydrochloride solutions.

Many studies have reviewed the safety of phenylephrine and some authors have excluded subjects with a history of cardiovascular conditions from their studies based on the known and expected risks of using sympathomimetic drugs in such subjects.

7.5.4 Drug-Disease Interactions

None.

7.5.5 Drug-Drug Interactions

The potential for interaction exists with other drugs administered topically and systemically.

Interaction with topical anticholinergic cycloplegic drugs eg : tropicamide, cyclopentolate hydrochloride, homatropine hydrobromide, or scopolamine hydrobromide and has been shown to be synergistic, resulting in a greater mydriasis. The two drugs are frequently used together for that reason.

The cardiac and pressor effects of phenylephrine are potentiated by prior administration of monoamine oxidase (MAO) inhibitors because the metabolism of phenylephrine is reduced. The potentiation is greater following oral administration of phenylephrine than after parenteral administration of the drug because reduction of the metabolism of phenylephrine in the intestine results in increased absorption of the drug. Topical ocular administration may be regarded as similar to parenteral because of the rapid direct absorption into the blood of the superior vena cava and the heart (McEvoy 2007). Tricyclic antidepressants (e.g., imipramine) or guanethidine may also potentiate the vasopressor effects of phenylephrine. The mydriatic response to phenylephrine may be decreased in patients receiving levodopa (McEvoy 2007).

Rarely, administration of phenylephrine to patients who have received cyclopropane or halogenated hydrocarbon general anesthetics that increase cardiac irritability and seem to sensitize the myocardium to phenylephrine may result in arrhythmias. The manufacturer states that vasopressors should be used only with extreme caution or not at all with these general anesthetics. However, in usual therapeutic doses, phenylephrine is much less likely to produce arrhythmias than is norepinephrine or metaraminol (McEvoy 2007).

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Human carcinogenicity studies were not performed. Carcinogenicity studies with phenylephrine hydrochloride have been completed in mice at doses up to 2500 ppm in feed and in rats at doses up to 1250 ppm in feed. Phenylephrine hydrochloride demonstrated no carcinogenic effect in male or female mice and rats.

7.6.2 Human Reproduction and Pregnancy Data

It is not known whether phenylephrine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Phenylephrine ophthalmic solution, 2.5% and 10% should be given to a pregnant woman only if clearly needed.

7.6.3 Pediatrics and Assessment of Effects on Growth

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.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Rebound miosis has been reported in elderly patients one day after receiving phenylephrine ophthalmic solution, and re instillation of the drug produced a lesser mydriatic effect.

Topical overdosing is unlikely since the excess spills onto the face. However, repeated instillation may be dangerous particularly in those with cardiovascular disease.

7.7 Additional Submissions / Safety Issues

Akorn, Inc. submitted a 120-Day Safety Report Update for Phenylephrine Ophthalmic Solution 2.5% and 10% on December 3, 2014. . The time period covered by this report is July 11, 2014 through December 02, 2014. Akorn did not conduct any clinical studies and there is no new safety information to report during this period.

8 Postmarket Experience

A market review of phenylephrine sales in the US in 2010 showed that approximately 15 million mL of eye drops were purchased. This volume equates to approximately 100 million patient exposures annually.

In a FDA Adverse Event Reporting System (FAERS) Standard Case Series Summary Report run December 14, 2012, for “Phenylephrine ophthalmic,” the following events were identified:

Preferred Term	Count Of Events	Percent Of Total Cases
TOXIC ANTERIOR SEGMENT SYNDROME	20	15.38%
INFLAMMATION	16	12.31%
EYE DISORDER	15	11.54%
IRIDOCYCLITIS	14	10.77%
BRADYCARDIA	8	6.15%
DRUG EFFECT PROLONGED	7	5.38%
APNOEA	6	4.62%
CYANOSIS	6	4.62%
BLINDNESS	5	3.85%
CORNEAL ABRASION	5	3.85%
EYE PAIN	5	3.85%
MYDRIASIS	5	3.85%
VISUAL IMPAIRMENT	5	3.85%
DIZZINESS	4	3.08%
ENDOPHTHALMITIS	4	3.08%
HYPERTENSION	4	3.08%
HYPOTENSION	4	3.08%
MALAISE	4	3.08%
NECROTISING COLITIS	4	3.08%
VISION BLURRED	4	3.08%
CARDIAC ARREST	3	2.31%
CONJUNCTIVITIS	3	2.31%
DRUG INEFFECTIVE	3	2.31%

Only a portion of the search is presented here. Many of the counted events are unrelated to the sole use of phenylephrine hydrochloride ophthalmic solution; they appear to be associated with ocular conditions for which topical phenylephrine was used diagnostically or therapeutically to dilate the pupil, e.g. toxic anterior segment syndrome, inflammation, iridocyclitis, etc.

9 Appendices

9.1 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.

9.2 Literature Review/References

EFFICACY

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

Eyeson-Annan, Hirst Battistuttat , Green Ophthalmology 1998; 105 (4): 726-32.

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.

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

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

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

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

Paggiarino DA, Brancata LJ, Newton RE. The Effects of Pupil Size and Accomodation of Sympathetic and Parasympatholytic Agents. Ann Ophthalmol, 1993;25:244-253.

Sindel BD, Baker MD, Maisels MJ, Weinstein J. A Comparison of the Pupillary and Cardiovascular Effects of Various Mydriatic Agents in Preterm Infants. J Ped Optha and Strabismus. 23(6); 273-6 Nov 1986.

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

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.

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

SAFETY

Allinson RW, Gerber DS, Bieber S, Hodes BL. Reversal of Mydriasis by Dapiprazole. Ann Ophtalmol 1990: 22; 131-138.

Alpay A, Ermis B, Ugurbas SC, Battal F, Sagdik HM. The local vasoconstriction of infant's skin following instillation of mydriatic eye drops. Eur J Clin Pharmacol. 2010 Nov;66(11):1161-4. Epub 2010 Sep 11.

Barbee RF, Smith WO. A Comparative Study of Mydriatic and Cycloplegic Agents In Human Subjects Without Eye Disease. Am. J. Ophthalmology 1957 Nov: 44 (5 part 1) 617-22.

Biggs RD, Alpern M, Bennett DR. The Effect of Sympathomimetic Drugs Upon the Amplitude of Accommodation. AJO 1959 :48 (1 part 2) p169-72.

Becker B, Gage T, Kolker AE, Gay AJ. The Effect of Phenylephrine Hydrochloride on the Miotic-Treated Eye. Am J Ophthalmol;1959; 48: 313-21.

Borromeo-McGrail V, Bordiuk JM, Keitel H. Systemic Hypertension Following Ocular Administration of 10% Phenylephrine in the Neonate. Pediatrics 1973; 53: 1032-6.

Brown MM, Brown GC, Spaeth GL. Lack of Side Effects From Topically Administered 10% Phenylephrine Eyedrops. Arch Ophthalmol .1980 ,98; 487.

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

Chin KW, Law NM, Chin MK. Phenylephrine Eye Drops in Ophthalmic Surgery – A Clinical Study on Cardiovascular Effects. Med J Malaysia Vol 49.Jun 1994.

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.

Fraunfelder FT, Scafidi AF:. Am J Ophthalmol 85:447, 1978.

Heath P. Neosynephrine: Some Uses and Effects in Ophthalmology. Arch Ophth. 16:839 Nov 1936.

Lansche RK. Systemic Reactions to Topical Epinephrine and Phenylephrine. Am J Ophth 1966 61: 95.

Lee PF. The Influence of Epinephrine and Phenylephrine on Intraocular Pressure. AMA Archives of Ophthalmology Vol 60: Nov 1958. 863-7.

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

Martha Meyer S, Fraunfelder FT. Phenylephrine Hydrochloride. Ophthalmology 1980; 87:1177-1180.

McReynolds WU, Havener WH, Henderson JW. Hazards of the Use of Sympathomimetic Drugs in Ophthalmology. Arch Ophthalmol 1956;56:176-9

Pless M, Friberg TR, Semin Ophthalmol.2003 Dec;18 (4) :218-21.

Samantary S, Thomas A: Indian J Ophthalmol 23:16-17, 1975.

Sindel BD, Baker MD, Maisels MJ, Weinstein J. A Comparison of the Pupillary and Cardiovascular Effects of Various Mydriatic Agents in Preterm Infants. J Ped Optha and Strabismus. 23(6); 273-6 Nov 1986.

Solosko D, Smith RB. Hypertension Following 10 Per Cent Phenylephrine Ophthalmic. Anaesthesiology 1972; 36: 187-9.

Symons RCA, Walland MJ, Kaufman DV. Letter to the Editor. EYE 1997 11; 947-950.

Vaughan RW. Ventricular Arrhythmias After Topical Vasocontrictors. Anesth Analg 1973; 52:161-5.

Wilensky JT, Woodward HJ. Acute Systemic Hypertension After Conjunctival Instillation of Phenylephrine Hydrochloride. Am J Ophthalmol 1973; 76:156-7

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

AKORN FORMULATION STUDIES

Hardarson S and Stefánsson E. Oxygen saturation in central retinal vein occlusion. Am J Ophthalmol 150: 871-875, 2010.

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

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

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

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

9.3 Clinical Investigator Financial Disclosure Template

Not applicable. This is a 505(b)(2) 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.

9.4 Labeling Recommendations

Following are the labeling recommendations for the originally submitted (7/11/14) package insert and carton and container labeling.

13 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILLIAM M BOYD
01/08/2015

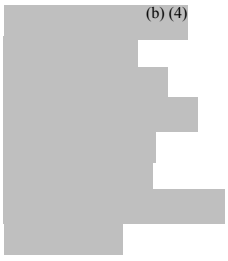
WILEY A CHAMBERS
01/09/2015

CLINICAL FILING CHECKLIST FOR NDA 207926

NDA/BLA Number: 207926 **Applicant:** Akorn, Inc. **Stamp Date:** July, 11, 2014

Drug Name: Phenylephrine Hydrochloride Ophthalmic Solution **NDA/BLA Type:** 505(b)(2)

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?			X	
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).				505(b)(2)
505(b)(2) Applications					
13.	If appropriate, what is the reference drug?	X			NDA 203510 – Phenylephrine Hydrochloride Ophthalmic Solution, 2.5% and 10% (b) (4) 

CLINICAL FILING CHECKLIST FOR NDA 207926

	Content Parameter	Yes	No	NA	Comment
14.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the referenced product(s)/published literature?	X			
15.	Describe the scientific bridge (e.g., BA/BE studies)				Literature reports provided describing the use of Akorn phenylephrine product in clinical trials
DOSE					
16.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			X	Literature provided in this 505(b)(2) application describe the standard concentrations and dosing and administration considered the standard of care for the use of this product
EFFICACY					
17.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication: Pivotal Study #2 Indication:	X			This is a 505(b)(2) application. Fourteen (14) literature articles are provided in support of efficacy.
18.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?				This is a 505(b)(2) application. Fourteen (14) literature articles are provided in support of efficacy. The literature includes descriptions of adequate and well-controlled trials.
19.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	This is a 505(b)(2) application.
20.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	This is a 505(b)(2) application.
SAFETY					
21.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			

CLINICAL FILING CHECKLIST FOR NDA 207926

	Content Parameter	Yes	No	NA	Comment
22.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
23.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
24.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			X	
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			
26.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?			X	This is a 505(b)(2) application.
27.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
28.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			X	This is a 505(b)(2) application.
OTHER STUDIES					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?			X	This is a 505(b)(2) application.
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?			X	This is a 505(b)(2) application.

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA 207926

	Content Parameter	Yes	No	NA	Comment
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	This is a 505(b)(2) application.
37.	Are all datasets to support the critical safety analyses available and complete?			X	This is a 505(b)(2) application.
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	This is a 505(b)(2) application.
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			X	This is a 505(b)(2) application.
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	This is a 505(b)(2) application.
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?			X	This is a 505(b)(2) application.

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ____YES____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

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

None identified.

William M. Boyd, M.D. August 25, 2014

Reviewing Medical Officer Date

Wiley Chambers, M.D. August 25, 2014

Deputy Division Director Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILLIAM M BOYD
08/27/2014

WILEY A CHAMBERS
08/28/2014