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APPLICATION NUMBER:

207926Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

**OFFICE OF CLINICAL PHARMACOLOGY REVIEW
AMENDMENT**

NDA:	207-926
Submission Date(s):	July 11, 2014
PUDFA:	May 11, 2015
Drug	Phenylephrine hydrochloride
Product/Formulation; Strength(s)	Phenylephrine hydrochloride ophthalmic solution 2.5% and 10%
Primary Reviewer	Yongheng Zhang, Ph.D.
Team Leader	Philip Colangelo, Pharm D, Ph D
OCP Division	DCP4
OND Division	DTOP/OAP
Applicant	Akorn Inc., Lake forest, IL 60045
Proposed indication	To dilate the pupil
Dose and Administration	In patients 1 year of age or greater, apply one drop of either phenylephrine hydrochloride ophthalmic solution 2.5% or 10% every 3 to 5 minutes as required up to a maximum of 3 drops per eye per day
Submission Type	Type 7 ; 505(b)(2) ; Standard

SUMMARY

In the Clinical Pharmacology Review dated 11/07/2014, the 21 CFR §320.22(b)(1) was cited to support the decision of granting the waiver of evidence of in vivo bioavailability or bioequivalence to this NDA. However, an error was made in the content of the citation, specifically with respect to §320.22(b)(1)(ii). This amendment to the review is to correct this error, and the citation should have been listed as follows:

21 CFR §320.22(b)(1)

(b) "For certain drug products, the in vivo bioavailability or bioequivalence of the drug product may be self-evident. FDA shall waive the requirement for the submission of evidence obtained in vivo measuring the bioavailability or demonstrating the bioequivalence of these drug products. A drug product's in vivo bioavailability or bioequivalence may be considered self-evident based on other data in the application if the product meets one of the following criteria:

(1) The drug product:

(i) Is a parenteral solution intended solely for administration by injection, or an ophthalmic or otic solution; and

(ii) Contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application or abbreviated new drug application.

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/s/

YONGHENG ZHANG
12/08/2014

PHILIP M COLANGELO
12/08/2014

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

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Submission Type	Type 7 ; 505(b)(2) ; Standard

SUMMARY

Phenylephrine is an alpha-adrenergic receptor sympathetic agonist that has been used for more than 70 years to dilate the pupil in ocular diagnostic, therapeutic and surgical procedures. Phenylephrine hydrochloride ophthalmic solutions, 2.5% and 10%, are currently being marketed and supplied in the US for use as a mydriatic. One product (NDA 203,510) from Paragon Biotech Inc has recently been cleared by a FDA approval process via 505(b)(2) pathway. Similar to NDA 203,510, the current submission is also a literature-based NDA. The sponsor considers that the safety and efficacy of phenylephrine hydrochloride ophthalmic solution, 2.5% and 10%, have been well established. Therefore, it is unnecessary to conduct any additional clinical studies to support this NDA.

The sponsor 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) (see below), the reviewer grants the waiver of evidence of in vivo bioavailability or bioequivalence to this NDA.

21 CFR §320.22(b)(1)

(b) "For certain drug products, the in vivo bioavailability or bioequivalence of the drug product may be self-evident. FDA shall waive the requirement for the submission of evidence obtained in vivo measuring the bioavailability or demonstrating the bioequivalence of these drug products. A drug product's in vivo bioavailability or bioequivalence may be considered self-evident based on other data in the application if the product meets one of the following criteria:

(1) The drug product:

(i) Is a parenteral solution intended solely for administration by injection, or an ophthalmic or otic solution; and

(ii) contains an active ingredient in the same dosage form as a drug product that is the subject of an approved full new drug application or abbreviated new drug application.

RECOMMENDATIONS

The Clinical Pharmacology information provided by the Applicant in the NDA is acceptable and the reviewer recommends approval of Phenylephrine hydrochloride ophthalmic solution 2.5% and 10%.

The reviewer's proposed label changes in Appendix 1 should be forwarded to the sponsor.

Appendix 1. Proposed Labeling with Revisions

The following proposed labeling has been marked with revisions made by the Clinical Pharmacology Reviewer.

(underline = Clin Pharm reviewer's addition; ~~strike through~~ = Clin Pharm reviewer's deletion)

12. CLINICAL PHARMACOLOGY

12.3. 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. (b) (4)

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/s/

YONGHENG ZHANG
11/07/2014

PHILIP M COLANGELO
11/07/2014

BIOPHARMACEUTICS REVIEW			
Office of New Drug Quality Assessment			
Application No.:	NDA 207926		Reviewer: Banu Sizanli Zolnik, Ph.D.
Division:	Division of Transplant and Ophthalmic Products		
Applicant:	Akorn		Biopharmaceutics Team Leader (Acting): Okpo Eradiri, Ph.D.
Trade Name:	None proposed		Acting Biopharmaceutics Supervisor: Paul Seo, Ph.D.
Generic Name:	Phenylephrine HCL	Date Assigned:	7/17/2014
Indication	For dilation of pupil	Date of Review:	12/09/2014
Formulation/ Strength	Ophthalmic solution, 2.5% and 10%	Route of Administration	Ophthalmic
SUBMISSIONS REVIEWED IN THIS DOCUMENT			
Submission Dates	Date of informal/Formal Consult	Primary Review due in DARRTS	
Original submission 7/11/2014	NA	12/12/2014	
Type of Submission:	Original 505 (b)(2) Application		
Review Key Points:	<ul style="list-style-type: none"> ▪ The evaluation of the biowaiver request 		
SUMMARY OF BIOPHARMACEUTICS FINDINGS:			
Submission:			
<p>NDA 207926 submission for Phenylephrine Hydrochloride Ophthalmic Solution, USP, 2.5% and 10% is indicated for dilation of the pupil. Akorn has been marketing phenylephrine hydrochloride under "Grandfather" status since 1993. The Applicant is relying the literature-based clinical data in support of their application. There is an FDA-approved Phenylephrine HCl ophthalmic solution 2.5%, and 10% in the market (NDA 203510, approval date March 21, 2013, Paragon Biotech).</p>			
Review:			
<p>The Biopharmaceutics review is focused on the evaluation of the overall information/data supporting the approvability of the biowaiver request.</p> <p>Based on 21 CFR § 320.22 (e), 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 biowaiver request is granted. It is noted that this deferral is compatible with the protection of the public health.</p>			

RECOMMENDATION:

The ONDQA-Biopharmaceutics team has reviewed NDA 207926 submitted on July 11 2014. From the Biopharmaceutics perspective, NDA 207926 Phenylephrine ophthalmic solution 2.5% and 10% is recommended for **APPROVAL**.

Banu Sizanli Zolnik, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Okpo Eradiri, Ph.D.
Biopharmaceutics Team Leader (Acting)
Office of New Drug Quality Assessment

cc: P. Seo

BIOPHARMACEUTICS ASSESSMENT

1. BACKGROUND

Submission

Phenylephrine HCl is an alpha-1 adrenergic receptor agonist indicated to dilate the pupil. The Applicant has been marketing the product under “Grandfather” status since 1993. This NDA is a 505 (b) (2) submission and the Applicant is relying on literature based clinical studies in support of the approval of the application. The other FDA approved phenylephrine HCl product on the market (NDA 203510, approval date March 21, 2013, Paragon Biotech) also relied on the literature based clinical data in support of approval of their submission.

Review

The Biopharmaceutics review is focused on the evaluation of the overall data supporting the approval of a waiver for the submission of an in vivo bioavailability/bioequivalence study.

Drug Substance

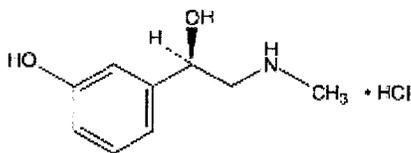


Figure 1: Structure of phenylephrine hydrochloride

Phenylephrine HCl is a white (b) (4) powder. It is freely soluble in water and in alcohol.

Drug Product

The proposed drug product is a sterile, clear, colorless topical mydriatic agent for ophthalmic use. Below is the composition information for 2.5% and 10% strengths.

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 (b) (4)
Dibasic Sodium Phosphate, (b) (4)	USP		
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 (b) (4)	USP		(b) (4)
(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 (b) (4)
Dibasic Sodium Phosphate, (b) (4)	USP		
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 (b) (4)	USP		(b) (4)
(b) (4)	(b) (4)		

The proposed formulation is qualitatively the same as the listed drug (NDA 203510) with the exception of presence of phosphoric acid in the proposed product whereas (b) (4) was used as a buffering agent in the approved product for the 2.5% strength. Per CMC reviewer, Dr. Mariappan Chelliah it is stated that “Although (b) (4) is listed as a pH adjusting reagent in Paragon’s phenylephrine hydrochloride ophthalmic solution (see NDA 203510) Paragon’s 10% solution does not require (b) (4) to adjust the pH. The high load of phenylephrine hydrochloride (100 mg/mL) likely lowers the pH below 6.5 such that only sodium hydroxide is required to adjust the pH. Akorn’s description of the formulation indicates use of sodium hydroxide alone to adjust the pH of the exhibits batches of both 2.5% and 10% solutions. However, phosphoric acid is still listed as a pH adjusting reagent so that it can be used as needed” (refer to CMC review for further information). Note that the approved Paragon Biotech’s 10% strength phenylephrine ophthalmic solution does not contain any boric acid.

Biowaiver request:

The Applicant requested a waiver of the requirement to submit evidence of in vivo BA/BE studies for their product. In support of their biowaiver request, the Applicant provided literature data showing low systemic levels of phenylephrine following ocular administration as shown in the table below.

Table 1. List of Pharmacokinetic studies described in this submission.

Source (N)	Formulation	Total Phenylephrine Dose (mg)	Mean Plasma Levels ^{a,b} (ng/mL)
Single Agent			
(Brown 1987) ^c (N=10)	2.5% aqueous	1.6	0.1 ^d
	10% aqueous	1.6	0.29 ^d
(Whitson, 1993) ^c (N=13)	10% aqueous	4.0	0.47 (0.00 – 0.80) ^e
	10% aqueous	12.0	0.55 (0.23 – 0.87) ^f 0.70 (0.35 – 1.48) ^g 0.86 (0.2 – 3.32) ^f
(Lynch, 1987) ^c (Preterm infants) (N=27)	2.5% aqueous	1.2	0.9
	2.5% aqueous	4.5	1.9
Phenylephrine and Tropicamide (0.5%)			
(Mouly, 2006) (N=18)	10% aqueous	30	< 0.5 ^h
Combination in Surgical Patients^h			
(Kumar, 1985) ^c (N=24)	2.5% aqueous	1.32 ⁱ	2.97 ± 1.37
	10% viscous	5.36 ^j	10.15 ± 7.87
(Kumar, 1986) ^c (N=30)	2.5% aqueous	1.32	3.15 ± 2.12
	2.5% viscous	1.34	2.12 ± 2.52

^aSamples collected 10 minutes after phenylephrine administration. Plasma levels are given as mean ± standard deviation or mean (range) where available.

^bAll studies referenced the same high performance liquid chromatography with fluorescent detection method to detect plasma phenylephrine levels.

^cThese studies had some authors in common.

^dIncomplete dataset. Results include only samples in which phenylephrine hydrochloride was detected.

^eResults for patients in which eyelids were closed after drop instillation.

^fResults for patients in which eyelids were not closed after drop instillation.

^gMeasurements began at 15 minutes after administering eye drops; limit of quantification for the assay is 0.5 ng/mL.

^hConcomitant topical mydriatic agents: 1% cyclopentolate hydrochloride and 0.25% scopolamine hydrobromide. Ophthalmic agents were instilled prior to the induction of general anesthesia.

ⁱDrop size not provided. Based on an estimated 0.66 mg/drop as in (Kumar, 1986).

^jDrop size not provided. Based on an estimated 2.68 mg/drop (calculated based on 0.67 mg/drop in a 2.5% viscous phenylephrine solution) (Kumar, 1986).

The literature data shows that systemic plasma levels of phenylephrine following either 2.5% or 10% strength ocular administration are low and in the range of 0.1-10 ng/mL with rapid elimination by 60 minutes. It is noted that phenylephrine systemic levels are much lower than oral administration (for example peak plasma concentration is reported to be 171-278 ng/mL following 7.4 mg phenylephrine tablet administration¹). Therefore the systemic levels of phenylephrine following ocular administration are unlikely to pose significant clinical safety issues.

It is the ONDQA-Biopharmaceutics team's view that the proposed product is an ophthalmic solution, intended only for local therapeutic effect and its low systemic absorption, per 21 CFR § 320.22 (e), 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 biowaiver request is granted.

¹ Bogner RL and Walsh JM. Sustained-release principle in human subjects utilizing radioactive techniques. J Pharm Sci 1964; 53(6):617-620

RISK ASSESSMENT TABLE

From Initial Quality Assessment			Review Assessment		
Product attribute / CQA	Factors that can impact the CQA	Risk Ranking*	Risk Mitigation Approach	Risk Evaluation [Acceptable/ Unacceptable]	Lifecycle Considerations/ Comments**
Solution	NA	L	NA	NA	NA

* Risk ranking applies to product attribute/CQA (L, M, H)

**Banu S.
Zolnik -S**

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Banu Sizanli Zolnik, Ph.D.
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Eradiri, Ph.D.**

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Okpo Eradiri, Ph.D.
Biopharmaceutics Team Leader (Acting)
Office of New Drug Quality Assessment

CLINICAL PHARMACOLOGY NDA FILEABILITY CHECKLIST

NDA: 207926
 Drug Name: Phenylephrine hydrochloride ophthalmic solution (2.5% and 10%)
 Applicant: Akorn Inc
 Indication: To dilate the pupil (b) (4)
 Submission Date: July 11, 2014
 Filing Date: September 9, 2014
 PDUFA Date: May 11, 2015
 OCP Primary Reviewer: Yongheng Zhang Ph. D.
 OCP Team Leader: Philip Colangelo Pharm. D., Ph.D.

Criteria for Refusal to File (RTF): This OCP checklist applies to NDA, BLA submissions and their supplements					
No	Content Parameter	Yes	No	N/A	Comment
1	Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			N/A	
2	Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)			N/A	
3	Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	Yes			Request for waiver of in vivo BA studies submitted
4	Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?			N/A	
5	Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?			N/A	
6	Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?			N/A	
7	Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?			N/A	
8	Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-	Yes			

	summary)?				
9	Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	Yes			
Complete Application					
10	Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	Yes			
<i>Fileability:</i> <i>Is the Clinical Pharmacology section of the application fileable?</i> <i>(if 'NO', please comment as to why it is not fileable)</i>		YES			

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/s/

YONGHENG ZHANG
08/19/2014

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