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APPLICATION NUMBER:

207926Orig1s000

PHARMACOLOGY REVIEW(S)

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: 207-926

Supporting document/s: 1

Applicant's letter date: 7-11-2014

CDER stamp date: 7-11-2014

Product: Phenylephrine Hydrochloride Ophthalmic Solution
USP, 2.5% and 10%

Indication: Pupil dilation

Applicant: Akorn, Inc.

Review Division: Transplant and Ophthalmology Products

Reviewer: María I. Rivera, PhD

Supervisor/Team Leader: Lori E. Kotch, PhD

Division Director: Renata Albrecht, MD

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Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 207-926 are owned by Akorn or are data for which Akorn has obtained a written right of reference. Any information or data necessary for approval of NDA 207-926 that Akorn does not own or have a written right to reference constitutes published literature. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 207-926.

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1 Executive Summary

1.1 Introduction

This is a 505(b)(2) NDA for Phenylephrine Hydrochloride Ophthalmic Solution 2.5% and 10%, USP as a mydriatic agent. Akorn's proposed formulation has been marketed without prior FDA approval under the brand name AK-Dilate[®] since 1993. Recently, the FDA approved a phenylephrine hydrochloride ophthalmic solution (NDA 203-510; approved March 22, 2013) at the same concentrations and for the same indication as proposed by Akorn.

1.2 Brief Discussion of Nonclinical Findings

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

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

Given the long history of clinical use of phenylephrine for both ophthalmic and systemic use, the more than 20 years of clinical experience with Akorn's AK-Dilate[®], and the recent approval of the 505(b)(2) NDA 203-510 for the same concentrations of active ingredient and dosing regimen, nonclinical has no objection to the approval of this NDA.

1.3 Recommendations

1.3.1 Approvability

Approval is recommended.

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

Applicant-Proposed language:

8.1 Pregnancy

(b) (4) Animal reproduction studies have not been conducted with topical phenylephrine. It is also not known whether phenylephrine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Phenylephrine hydrochloride should be given to a pregnant woman only if clearly needed.

8.3 Nursing Mothers

It is not known whether this drug is excreted in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when phenylephrine hydrochloride ophthalmic solution 2.5% and 10% is administered to a nursing woman.

Reviewer's recommended edits: None

13 NONCLINICAL TOXICOLOGY

(b) (4)

Reviewer's recommended edits:

Removal of this section is recommended to be consistent with the label of NDA 203-510 (Paragon Biotech's Phenylephrine Hydrochloride 2.5% and 10%; approved 3-21-2013), NDA 205-388 (Omero's Phenylephrine hydrochloride 1%/ketorolac tromethamine 0.3%; approved on 5-30-2014) and NDA 203-826 (West Ward Pharm Corp's Phenylephrine Hydrochloride IV Injection; approved on 12-20-2012). These approved NDAs are for short-term use.

2 Drug Information

2.1 Drug

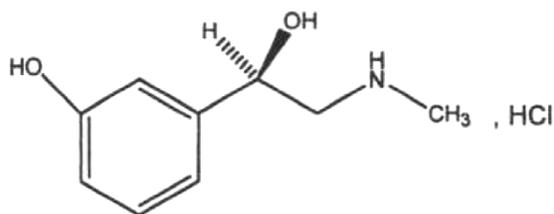
CAS Registry Number: 61-76-7

Generic Name: Phenylephrine Hydrochloride

Chemical Name: Benzenemethanol, 3-hydroxy- α -[(methylamino)methyl]-,hydrochloride, (*R*)-, or (*-*)-*m*-Hydroxy- α - [(methylamino)methyl]benzyl alcohol hydrochloride

Molecular Formula/Molecular Weight: C₉H₁₃NO₂•HCl/203.67 g/mol

Structure or Biochemical Description



Pharmacologic Class: α -1 adrenergic receptor agonist

2.2 Relevant INDs, NDAs, BLAs and DMFs

- NDA 203-510 Phenylephrine Hydrochloride Ophthalmic Solution 2.5% and 10% (Paragon BioTeck, Inc; approved 2013)

2.3 Drug Formulation

The unit composition for Phenylephrine Hydrochloride Ophthalmic Solution, 2.5% is shown in Table 1. The composition of Phenylephrine Hydrochloride Ophthalmic Solution, 10% is the same as that of Phenylephrine Hydrochloride Ophthalmic Solution, 2.5% with the exception that the content of phenylephrine hydrochloride is 100.0 mg/mL instead of 25.0 mg/mL.

Table 1: Unit Composition for Phenylephrine Hydrochloride Ophthalmic Solution, 2.5%

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)

2.4 Comments on Novel Excipients

None

2.5 Comments on Impurities/Degradants of Concern

None

2.6 Proposed Clinical Population and Dosing Regimen

- For patients 1 year of age and older, one drop of Phenylephrine Hydrochloride Ophthalmic Solution, USP 2.5% or 10% at 3 to 5 minute intervals up to a maximum of 3 drops per eye
- In pediatric patients less than 1 year of age, one drop of Phenylephrine Hydrochloride Ophthalmic Solution, USP 2.5% instilled at 3 to 5 minute intervals up to a maximum of 3 drops per eye

2.7 Regulatory Background

A pre-IND meeting (Pre-IND 121700) was held on 3-14-2014. The Division agreed the applicant could rely on published literature for the nonclinical information sections of the NDA.

3 Studies Submitted

3.1 Studies Reviewed

No studies were conducted.

3.2 Studies Not Reviewed

Not applicable

3.3 Previous Reviews Referenced

NDA 203-510 - Phenylephrine Hydrochloride Ophthalmic Solution 2.5% and 10%

4 Pharmacology

Phenylephrine is an α 1-adrenergic receptor agonist and, in the eye, acts as a potent vasoconstrictor and mydriatic agent by constricting the arterioles in the conjunctiva and the radial muscle of the iris. The safety profile of phenylephrine is well known based on the extensive clinical experience. The sponsor provided a review article that, in addition to the pharmacological properties, summarizes the indications, contraindications, and reported side effects after ocular instillation of phenylephrine 2.5% or 10%¹. Some excerpts are presented below:

¹ Meyer SM and Fraunfelder FT. 3. Phenylephrine Hydrochloride. Ophthalmology, 87(11): 1177-80 (1980)

- Local adverse reactions to phenylephrine include transient pain, release of pigment into the aqueous (aqueous floaters) with transient increase in intraocular pressure, and possible occlusion of structurally narrow angles.
- Use of phenylephrine in the eye may also cause headache or brow ache, blurred vision, lacrimation, reactive hyperemia, and transient keratitis.
- In patients more than 50 years of age, phenylephrine appears to alter the response of the pupillary dilator muscle so that rebound miosis may occur the day after the drug is administered.
- Phenylephrine 10% can be systemically absorbed, causing acute cardiovascular complications.
- Phenylephrine is generally contraindicated for ophthalmic use in patients with abnormally shallow anterior chambers or narrow-angle glaucoma and in those with known hypersensitivity to phenylephrine or other components of the commercially available solutions.
- Phenylephrine 10% is contraindicated in infants and in adults with cardiovascular disease.
- Side effects from topical instillation of phenylephrine, such as coronary occlusion, acute hypertension, and stroke, are uncommon, but can be serious and even lethal. The 10% concentration is more likely to cause significant adverse ocular reactions and should therefore be applied only in single-dosage situations or for short periods of time.

5 Pharmacokinetics/ADME/Toxicokinetics

No studies were cited or conducted.

6 General Toxicology

Akorn provided a list of 16 published nonclinical studies that used Akorn's AK Dilate[®] brand phenylephrine ophthalmic solution. All but one of the cited nonclinical studies used Akorn's AK-Dilate[®] formulation a mydriatic to allow examination of the eye or to conduct procedures on the eye. The concentrations of phenylephrine were 2.5% and 10% used in combination with tropicamide in 7 studies and cyclopentolate in 3 studies. The species were dogs (1 study), rabbits (5 studies), rat (3 studies) and mouse (7 studies). None of these studies reported a lack of a mydriatic effect or any toxicity considered related to phenylephrine. However, the objective of these studies was not to evaluate the safety and/or efficacy of phenylephrine, and these parameters may not have been directly assessed in these studies.

The nonclinical studies summarized by the sponsor to support systemic safety include the repeat-dose toxicity, genotoxicity, and carcinogenicity studies conducted by the National Toxicology Program². In addition, the existent marketing experience

² National Toxicology Program Technical Report No. 322, Toxicology and Carcinogenesis Studies of Phenylephrine Hydrochloride in F344/N Rats and B6C3F₁ Mice, NIH Publication No. 87-2578, January 1987, http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/tr322.pdf#search=phenylephrine%20hydrochloride

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

7 Genetic Toxicology

Studies conducted by the National Toxicology Program² demonstrated that phenylephrine was not mutagenic in *Salmonella typhimurium* (with or without S9 activation). Mutagenicity assessments using the mouse lymphoma L5178Y/TK^{+/-} assay were judged to be equivocal because the high doses of phenylephrine used were toxic to the cells and the results were not reproduced in a second study. A positive response was noted in the first trial without metabolic activation at the high dose of 1,500 µg/mL (relative total growth was 12.2%). Phenylephrine induced sister-chromatid exchange at ≥1500 µg/mL (-S9 fraction) but was negative for the formation of chromosomal aberrations in Chinese hamster ovary cells at doses up to 2,500 µg/mL (-S9 fraction) and 10,000 µg/mL (+S9 fraction).

8 Carcinogenicity

The applicant made reference to carcinogenicity studies conducted by the National Toxicology Program². Briefly, the carcinogenicity of phenylephrine was studied in two-year studies in mice and rats. The doses used were 0, 620, and 1,250 ppm phenylephrine in the diet in rats, and 0, 1,250, and 2,500 ppm in mice. There was no evidence of carcinogenicity in mice or rats. Based on the feed consumed, the maximum doses correspond to 50 mg/kg/day (rats) and 270 mg/kg/day (mice). The following non-neoplastic lesions were considered related to phenylephrine hydrochloride: chronic focal inflammation of the liver and perivascular cuffing of the lung at both doses in male and female rats, inflammation of the prostate at both doses in male rats, and focal cellular change in the liver in high-dose male mice.

(b) (4)

³ Clinical Pharmacology Online Index (FDA Library)

Removal of this section is recommended, consistent with the labels of NDA 203-510 (Phenylephrine Hydrochloride Ophthalmic Solution 2.5% and 10%; approved on March 2013), NDA 205-388 (Phenylephrine hydrochloride 1%/ketorolac tromethamine 0.3%; approved on May 2014) and NDA 203-826 (Phenylephrine Hydrochloride IV Injection; approved on December 2012). These FDA approved products are also indicated for short-term use. Given the single day use of the intended product (1 drop at 3-5 minute intervals up to a maximum of 3 drops per eye), lack of a reason for concern from the available genetic toxicity and carcinogenicity data, and long history of clinical use, the inclusion of these data in the label is not considered clinically relevant in this case.

9 Reproductive and Developmental Toxicology

Akorn cited three reproductive toxicology studies from the published literature conducted in cultured rat embryos or pregnant rats. The main findings from these studies are summarized in Table 2 (excerpted from the NDA).

Table 2: Cited Reproductive Toxicity Studies from the Published Literature

Author (Reference)	Design	Species	Dose/Duration	Route of Administration	Results
Fujinaga, et al., 1991	Cultured rat embryos	Rat embryos.	0-500 µg/mL.	In vitro exposure	Up to 52% incidence of in situ inversus at highest dose of 500 µg/mL.
Ugen, et al., 1986	Reproductive toxicity – effect on teratogenicity.	Rats, pregnant	Acetazolamide alone, phenylephrine alone or combination. Oral doses of 0 to 15 mg/kg of phenylephrine administered late day 10 or early day 11 of gestation.	Oral gavage.	Coadministration of phenylephrine (12.5 mg/kg) significantly increased the incidence of acetazolamide-induced right-forelimb ectrodactyly (determined on gestational day 20), but phenylephrine alone at doses of 7.5 to 15 mg/kg did not cause this lesion
Ugen, et al., 1987	Reproductive toxicity. Study of effect on uterine blood flow.	Rats, pregnant	phenylephrine at oral doses of 0 to 12.5 mg/kg of phenylephrine administered late day 10 or early day 11 of gestation.	Oral gavage.	Significant decrease in absolute and relative maternal cardiac output at doses of 7.5 and 12.5 mg/kg but not at doses of 0.3 or 2.5 mg/kg. Relative uterine blood flow also significantly decreased compared to control values at doses of 2.5, 7.5, and 12.5 mg/kg but not at 0.3 mg/kg

Note: The proper term is “situs inversus” not “in situ inversus” as presented in the table.

These studies were considered insufficient to characterize developmental or reproductive toxicity following phenylephrine administration. No original GLP-compliant nonclinical reproductive toxicity studies were conducted with phenylephrine.

The applicant has proposed the following language in the label, which is consistent with the labels of the approved phenylephrine hydrochloride products (the labels of NDA 203-510 (Phenylephrine Hydrochloride Ophthalmic Solution 2.5% and 10%; approved on March 2013) and NDA 203-826 (Phenylephrine Hydrochloride IV Injection; approved on December 2012).

8.1 Pregnancy

(b) (4) *Animal reproduction studies have not been conducted with topical phenylephrine. It is also not known whether phenylephrine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Phenylephrine hydrochloride should be given to a pregnant woman only if clearly needed.*

8.3 Nursing Mothers

It is not known whether this drug is excreted in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when phenylephrine hydrochloride ophthalmic solution 2.5% and 10% is administered to a nursing woman.

11 Integrated Summary and Safety Evaluation

This 505(b)(2) NDA seeks approval of Phenylephrine Hydrochloride Ophthalmic Solution 2.5% and 10%, USP as a mydriatic agent at the same dosage and route of administration (topical ocular) as that of the approved Phenylephrine Hydrochloride Ophthalmic Solution 2.5% and 10% (NDA 203-510).

Akorn, Inc. has not conducted or sponsored nonclinical studies to evaluate the safety of phenylephrine hydrochloride, and has relied on studies from the published literature.

Akorn provided a list of 16 published nonclinical studies that used their AK-Dilate[®] formulation. In all but one of these studies, phenylephrine was used as a mydriatic to allow examination of the eye or to conduct procedures on the eye. None of these studies reported any lack of a mydriatic effect or any toxicity considered related to phenylephrine. However, the objective of these studies was not to evaluate the safety and/or efficacy of phenylephrine, and these parameters may not have been directly assessed.

Given the long history of clinical use of phenylephrine for both ophthalmic and systemic use, the more than 20 years of clinical experience with Akorn's AK-Dilate[®], and the recent approval of the 505(b)(2) NDA 203-510 for the same concentrations of active ingredient and dosing regimen, nonclinical has no objection to the approval of this NDA.

CC list:

E. Lwin/PM
W. Boyd/MO

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/s/

MARIA I RIVERA
12/08/2014

LORI E KOTCH
12/08/2014

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 207926

Applicant: Akorn, Inc

Stamp Date: 7-11-2014

**Drug Name: Phenylephrine Hydrochloride NDA/BLA Type: 505(b)(2)
Ophthalmic Solution USP, 2.5% and 10%**

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

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		<p>Akorn's proposed formulation has been marketed without prior FDA approval under the brand name AK-Dilate[®] since 1993.</p> <p>All required elements are based on published literature or information in the label for the approved Phenylephrine Hydrochloride Ophthalmic Solution 2.5% and 10% (NDA 203-510) and Cyclomydril[®] (phenylephrine hydrochloride 1% and cyclopentolate hydrochloride 0.2%; ANDA 84-300).</p> <p>The published literature includes 16 reports of nonclinical studies in which AK-Dilate[®] was used to dilate the pupil to allow examination of the eye.</p>
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	n/a		See previous comment.
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	X		

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement
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PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	n/a		See previous comment.
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)			Defer to CMC for assessment of impurity issues that require P/T input.
11	Has the applicant addressed any abuse potential issues in the submission?	n/a		
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?	n/a		

n/a = Not applicable

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the pharmacology/toxicology 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.

María I Rivera, PhD

Reviewing Pharmacologist

Date

Lori E Kotch, PhD

Team Leader/Supervisor

Date

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement
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/s/

MARIA I RIVERA
08/06/2014

LORI E KOTCH
08/06/2014