Deputy Division Director Review
NDA 204-200, Original - 2

Date	September 6, 2012
From	Wiley A. Chambers, M.D.
NDA #	204200 Original-2
Applicant	JHP Pharmaceuticals, LLC
Date of Submission	March 7, 2012
PDUFA Goal Date	September 7, 2012
Proprietary Name / Established (USAN) names	Adrenalin (epinephrine injection, USP) 1 mg/mL
Dosage forms / Strength	Solution containing 1 mg/mL
Proposed Indication(s)	Induction and maintenance of mydriasis during intraocular surgery
Recommended:	Recommended for Approval

1. Introduction

Adrenaline (epinephrine injection, USP) has been available on the market for over 100 years without an approved new drug application. Epinephrine injection is marketed by a number of different manufacturers, the particular product which is the subject of this application has been marketed under the Adrenalin trademark by Parke-Davis, followed by King Pharmaceuticals, and JHP Pharmaceuticals.

This is a 505(b)(2) application which lists EpiPen, held by Meridian, as the reference listed drug, although it is unclear that the applicant has actually relied on any Agency finding in relation to EpiPen. The labeling as currently proposed relies entirely on published literature for the clinical and non-clinical sections, and on product specific information for the product description.

2. Background

FDA has discussed with JHP, the regulatory status of their marketed, unapproved, Adrenalin (epinephrine injection, USP). A Pre-Investigational New Drug Application (PIND) file was opened on March 11, 2011, for this product (PIND 111712). A New Drug Application for Adrenalin (epinephrine injection, USP) 1 mg/mL submitted March 7, 2012, and initially contained two proposed indications (b) (4)

Since the two indications are being reviewed by two different review divisions, the application has been administratively split into:

- Original 1- Emergency treatment of severe acute anaphylactic reactions (b) (4)
- Original 2- Induction of mydriasis during cataract surgery.

The mydriasis indication received a priority review designation (six month review clock); there are no approved drug products for the induction and maintenance of mydriasis during cataract surgery that can be given after an incision is made into the cornea.

3. Product Quality

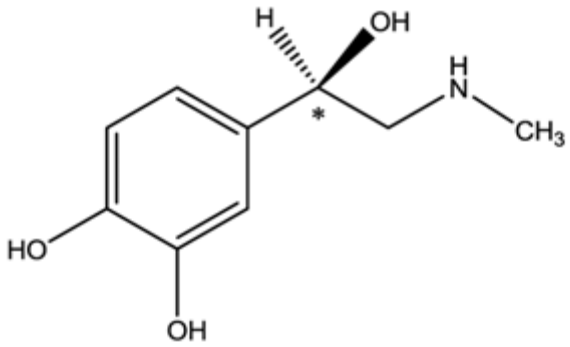
PHARMACOLOGIC CATEGORY: Sympathomimetic catecholamine

DOSAGE FORM: Injection (solution containing 1 mg/mL)

STRENGTH/POTENCY: 1 mg/mL

ROUTE OF ADMINISTRATION: Intraocular

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
1,2-Benzenediol, 4-[1-hydroxy-2-(methylamino)ethyl]-, (R) (USP)
(-)-3,4-Dihydroxy-α-[(methylamino)methyl]benzyl alcohol (CAS)
R-1-(3,4-dihydroxyphenyl)-2-methylaminoethanol (BP)



Molecular Formula

$C_9H_{13}NO_3$

Relative Molecular Mass

183.20

Formulation (b) (4)

Ingredient	Grade	Function	Batch Quantity	Unit Formula
Epinephrine	USP	Active	(b) (4)	
Sodium Chloride	USP	Tonicity adjustor	(b) (4)	9.0 mg
Sodium Metabisulfite	NF	Antioxidant	(b) (4)	1.0 mg
(b) (4) Hydrochloric Acid	USP	(b) (4)	(b) (4)	
Water for Injection	USP	(b) (4)	(b) (4)	

Drug Product Specifications:

Test	Specification 1 mL Release	Specification 1 mL Stability (b) (4)
Description		
Assay		
(b) (4)		
Individual Unidentified Impurity		
Total Impurities		
Identification		
pH		
Sodium Bisulfite		
Total Acidity		
Color & Clarity		
Sterility		
Particulate Matter		
Bacterial Endotoxin		

As of the date of this review, the ONDQA reviewer recommends a Complete Response based on the following:

> "The major drug product degradants [redacted] The proposed acceptance criterion for total impurities is NMT [redacted] This is unprecedented for a FDA approved drug product.
>
> Some of the analytical methods [redacted] cannot accurately measure the actual level of impurities through the whole reporting range and the level of quantification limits for the methods are far above the ICH reporting threshold (0.1%). The analytical method for sodium bisulfite (antioxidant) can not accurately measure the sodium bisulfite level within the range proposed in the specification. These methods are not acceptable.
>
> Due to the deficiencies noted above, the identity, strength, quality, purity, and potency of the drug product cannot be adequately assured per CFR 314.50(ii)(a). Therefore, this NDA is recommended for "COMPLETE RESPONSE" from a CMC perspective."

I disagree with these recommendations for the following reasons:

1. *[redacted] The USP assay for epinephrine does not distinguish between the isomers of epinephrine. The total impurity limit for Adrenaline [redacted] is proposed to be [redacted] because the Agency required JHP to include [redacted] the total impurities. [redacted] The limit for each of the individual impurities for Adrenaline is [redacted] The assay specification for epinephrine is set [redacted] Specifications have been included in the Adrenaline application [redacted]*

2. *The inability of the analytical methods to quantitate [redacted] are not relevant. The assay cannot quantitate the amount [redacted]*

(b) (4)

3. *The product is labeled as epinephrine* (b) (4) *The difference in biologic activity between the two isomers is not clear, both have pharmacologic activity. As reported by Patil et al in Molecular Geometry and Adrenergic Drug Activity, Pharmacologic Reviews, 1975; 26(4):323-392., Cushny reported in 1926 that the (+) form was 1/12 as active as the (-) form in raising blood pressure. Rowland and Potter in Steric structure activity of various adrenergic agonists, Current Eye Research, 1981; 1(1):25-35, describe d-epinephrine as having equal or greater effects than l-epinephrine in rabbit eyes with topical administration although weaker cardiovascular effects. As suggested by Patil et al, Chirality. 2008; 20:529-543, the differences are probably due to the receptor sites. There is little evidence to suggest that there is a difference in clinical efficacy for the proposed ocular and systemic indications, particularly in the eye.*

In my opinion, the proposed specifications are acceptable. Due to the small volume and expected dilution prior to use, it is unlikely that the current specifications will lead to any ocular harm (b) (4)

4. Nonclinical Pharmacology/Toxicology

The nonclinical safety assessment of Adrenalin for ocular use relied on reports obtained from the literature. All of the effects seen in animals were due to the expected pharmacologic and supra-pharmacologic actions of epinephrine. No unexpected nonclinical effects of epinephrine have been reported.

5. Clinical/Statistical - Efficacy

Induction and maintenance of the mydriasis, as the phrase is used in this review and proposed labeling of the drug product is considered one indication. Pupillary dilation in response to direct application of epinephrine intracamerally occurs within seconds but without continued administration rapidly wears off. The phrase "induction and maintenance" is meant to describe an increase in pupillary diameter over the diameter that would have occurred during the entire intraocular surgical procedure as long as the drug product is continuing to be administered.

APPEARS THIS WAY ON ORIGINAL

The main support for efficacy is from the following publications:

Study	Authors	Title	Doses Studied	Number of Patients
1	Liou and Chen, 2001	Maintenance of Mydriasis with One Bolus of Epinephrine Injection During Phacoemulsification	0.1 mL injection, 1:25,000; 1:50,000; 1:100,000; 1:200,000; 1:400,000	70 patients; Mean Age 69 (55-83); 10 control; 11 group 1; 13 group 2; 10 group 3; 14 group 4; 12 group 5
2	Corbett and Richards, 1994	Intraocular adrenaline maintains mydriasis during cataract surgery	1:1,000,000 epinephrine in intraocular irrigation fluid	70 patients; Mean Age 75
3	Gimbel, 1988	The Effect of Treatment with Topical Nonsteroidal Anti-inflammatory drugs with and without Intraoperative Epinephrine on the Maintenance of Mydriasis during Cataract Surgery	1:1,666,667 epinephrine in intraocular fluid; 6 treatment groups; Ocufen plus epinephrine, Ocufen without epinephrine; Indocid plus epinephrine, Indocid without epinephrine; Placebo with epinephrine; Placebo without epinephrine	216 patients randomly distributed between 6 groups (approx 36 per group)
4	Liou and Chen, 1998	The Effect of Intracameral Adrenaline Infusion on Pupil Size, Pulse Rate, and Blood Pressure During Phacoemulsification	1:1,000,000 epinephrine in intraocular irrigation fluid	42 eyes (30 with 0.25 mL added to 250 mL BSS Plus), 12 control eyes (BSS Plus)
5	Backstrom and Behndig, 2006	Redilation with intracameral mydriatics in phacoemulsification surgery	1:1,666,667 epinephrine in intraocular fluid in epinephrine group. Additional 150 microliters of 1.5% in Intracameral mydriatic (ICM)group	80 patients; Mean Age 76; 30 eyes epi+ ICM; 30 eyes epi + no-ICM; 10 eyes no-epi + ICM; 10 eyes no-epi + no-ICM.
6	Duffin, Pettit and Straatsma, 1983	Maintenance of Mydriasis with Epinephrine During Cataract Surgery	1:16,000 to 1:96,000	55 patients, Mean Age 72 (range 55 to 93)

Published literature includes the above adequate and well controlled studies demonstrating the safety and efficacy of epinephrine when injected intracamerally or added to balanced salt solution during intraocular surgery. Intracameral epinephrine has been widely used for decades. While the company did not provide a systematic plan for reviewing the literature, independent searches have the literature have failed to provide any inconsistencies in the studies provided by the applicant. Studies 1-4 and 6 were included in the applicant's original submission. Study 5 was identified during an additional Medline search.

In randomized, controlled studies, patients undergoing routine cataract extraction were evaluated after receiving intraocular irrigation with or without epinephrine diluted up to 1:1,666,666 (0.6 mcg/mL). Patients have also been evaluated after receiving bolus intracameral injections of epinephrine diluted between 1:25,000 (40 mcg/mL) and 1:400,000 (2.5 mcg/mL).

In patients with similar pupil diameters at baseline, with or without the use of preoperative mydriatic agents, mydriasis was maintained better in the eyes receiving epinephrine by an average of one to two millimeters in pupil diameter. Pupil constriction to 5mm or less occurred more often in the patients not receiving epinephrine.

6. Safety

The safety profile was evaluated from the published literature, adverse events reported to the applicant during marketing of the product and a review of MedWatch reports. The potential adverse consequences of intracameral epinephrine when administered as intended (diluted into the ophthalmic irrigating solution) are difficult to evaluate because of the short onset of effect (seconds), short duration of effect (minutes) and the potentially confounding factors associated with using it as an admixture to balanced salt solution in intraocular surgery. There have been very few adverse reports to the Agency after millions of doses of used over decades.

As reported by Hull et al [*Am J Ophthalmol.* 1975 Feb;79(2):245-50] commercial epinephrine 1:1000 with its preservative sodium bisulfite damaged corneal endothelial function and ultrastructure in rabbit and monkey eyes with sodium bisulfite the source of the damage. Endothelial damage can be prevented with a 1:5000 dilution of commercially available epinephrine in 0.1% sodium bisulfite or freshly prepared epinephrine bitartrate 1:1000 with a bicarbonate Ringers.

Cakmak et. al. [*Cutaneous and Ocular Toxicology.* 2010; 29(1):41-49] reported the safe use of 1:100,000 dilution of sodium bisulfate preserved epinephrine. Their clinical trial evaluated the effects on the corneal endothelial cells in patients treated with or without 1:100,000 epinephrine and they did not detect any differences.

Bozkurt et. al. [*J Cataract Refract Surg* 2010; 36:1380–1384] performed a randomized clinical trial evaluating the safety of an intracameral 0.2 mL injection of 1:5000 epinephrine. The clinical trial focused on the macular safety and demonstrated no difference with or without epinephrine.

Wilson et al. [*J Cataract Refract Surg* 2007; 33:1325–1327] have reported on the safety of routine use of epinephrine [0.5 mL in 500 mL of 0.1% epinephrine] in pediatric patients. Included in this report is a case of intraoperative floppy-iris syndrome (IFIS) which occurred when the epinephrine was inadvertently left out of the irrigating solution.

Studies listed as numbers 2 and 4 measured mean pulse rate and blood pressure and showed no significance difference between patients receiving epinephrine and controls and there was no increased incidence of ventricular dysrhythmias in patients receiving epinephrine.

POSTMARKETING EXPERIENCE

The Office of Safety Evaluation provided a summary of the reported adverse events associated with the use of epinephrine when administered intracamerally. The cases have been reviewed. Each of the cases has multiple potentially contributing causes and all events listed above have also been reported with the use of balanced salt solution (BSS) without epinephrine. None of the reported cases suggest that the cause of the adverse event was related to epinephrine use.

7. Advisory Committee Meeting

No issues of safety or efficacy were identified during the review of this application which were believe to benefit from a presentation of this application to an Advisory Committee.

8. Labeling

NDA 204200 for Adrenalin (epinephrine injection, USP) 1 mg/mL, is recommended for approval for the induction and maintenance of mydriasis during intraocular surgery with the package insert labeling submitted by JHP Pharmaceuticals, LLC, on 9/5/2012.

8 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/

WILEY A CHAMBERS
09/07/2012