

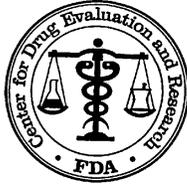
**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204200Orig1s000

204200Orig2s000

STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 204200
Drug Name: Adrenaline (epinephrine)
Indication(s): Induction of mydriasis during cataract surgery
Applicant: JHP Pharmaceuticals
Submitted Date: 03/08/2012
PDUFA Date: 09/07/2012
Review Priority: Priority
Biometrics Division: DBIV
Statistical Reviewer: Yunfan Deng, Ph.D.
Concurring Reviewer: Yan Wang, Ph.D.
Medical Division: Division of Transplant and Ophthalmology Products
Clinical Team: Wiley Chambers, M.D, Deputy Director
Project Manager: Judit Milstein

Keywords:
505 (b)2, Mydriasis

Memorandum to File

This NDA is a 505 (b)2 submission based on historical evidence. This NDA seeks the approval of Adrenaline (epinephrine) for the induction of mydriasis in cataract surgery. The Applicant submitted three peer reviewed publications to support the efficacy of this indication. The statistical reviewer focuses on reviewing these three publications for efficacy evaluation; for safety evaluation, please see the medical reviewer's review.

Conclusion and Recommendations

The study results in all of the three papers showed some evidence of effect for epinephrine in maintaining mydriasis in cataract surgery. Although the Applicant seeks approval of epinephrine for the induction of mydriasis in cataract surgery, the statistical reviewer recommends the drug be approved for **maintenance** of mydriasis in cataract surgery instead. In addition, without any raw data submitted, the reviewer cannot verify the p-values reported in these publications; therefore, the statistical reviewer does not recommend reporting any p-values in the clinical study section of the labeling.

Background

Adrenaline® (epinephrine injection, USP) has been available on the market for over 100 years. The product has been continuously marketed under the Adrenalin® trademark by Parke-Davis, King Pharmaceuticals, and JHP Pharmaceuticals. Currently approved epinephrine products include Epipen® and Twinject® auto-injectors for emergency treatment of allergic reactions (Type I) and numerous epinephrine containing anesthetic solutions. Epipen® and Twinject® are approved for anaphylaxis to stinging insects (e.g., order Hymenoptera, which includes bees, wasps, hornets, yellow jackets and fire ants) and biting insects (e.g., triatoma, mosquitos), allergen immunotherapy, foods, drugs, diagnostic testing substances (radiocontrast media) and other allergens, as well as idiopathic anaphylaxis or exercise-induced anaphylaxis.

Regardless of surgical technique, cataract surgery requires that the pupil be maximally dilated until the intraocular lens has been inserted. Pupil constriction during surgery increases the risk for damage to the iris, incomplete cortical or nuclear removal, and posterior capsule rupture with or without loss of vitreous, and loss of all or part of the lens nucleus into the posterior segment. Surgically induced miosis commonly occurs during cataract extraction procedures, due to mechanical manipulation of the iris. Difficulty in maintaining mydriasis during cataract surgery is significantly more pronounced in patients with diabetes, in patients receiving alpha-1 antagonist receptor blockers and in infants.

Epinephrine has been used off-label for maintenance of mydriasis in cataract surgery – maintaining the pupil to be dilated during surgery. According to previous discussion with the Agency, a clinical review for such ophthalmic indication is required for approval.

Mydriasis is produced by adrenergic sympathetic activity stimulating the dilator pupillae muscles of the iris. Epinephrine directly stimulates the dilator pupillae, but when the drug is applied to the

conjunctiva it does not penetrate in sufficient quantity to have a mydriatic effect. Therefore, preoperative mydriasis is usually achieved with a topical agent with better penetration of the cornea. During surgery, particularly following manipulation of the iris, the pupil tends to contract. However, once the anterior segment is opened, epinephrine solution can be injected or infused directly into the anterior chamber to directly stimulate the dilator pupillae.

In this NDA 505(b)2 submission, the Applicant submitted three publications that based on prospective studies for supporting the efficacy of adrenaline (epinephrine) for maintaining mydriasis in cataract surgery.

Publication 1: Intraocular Adrenaline Maintains Mydriasis during Cataract Surgery (Corbett MC and Richards AB, 1994)

In this randomized controlled study, 70 patients (33 men, 37 women) undergoing routine extracapsular cataract extraction were allocated to receive intraocular irrigation with or without epinephrine diluted to 1:1,000,000 (1 µg/mL). Mydriatic drops (cyclopentolate 1% and phenylephrine 10%) were administered to each patient during the hour preceding surgery. Patients received an average of 40 mL (40 µg) of epinephrine during irrigation. Irrigation fluid first entered the eye through the anterior capsulotomy needle, when the rate of flow was slow. After expression of the nucleus, a faster flow was used during irrigation aspiration of the soft lens matter.

Pupil diameters were measured by a blinded observer at the following time points;

- Before instillation of the mydriatic drops
- Before anesthesia
- Before surgery
- At 10, 20, and 30 minutes after start of surgery

Measurements were also taken in relation to specific surgical events: before and after expression of the nucleus, and after irrigation aspiration of the soft lens matter.

The mean pupil diameters at each time point for each treatment group (with or without epinephrine) were compared using an unpaired Student's T test. To aid this analysis, a pupil diameter of > 5 mm was prospectively determined to be the clinically relevant minimum diameter for miosis not to increase the difficulty of the surgical procedure.

The following figure shows the mean pupil diameters recorded during surgery for both treatment groups. Pupil diameters were similar between the two groups at the baseline, before anaesthesia (pre-anaes), and before surgery (pre-surg). Pupil diameters were larger in the epinephrine treated group at 20 minutes and 30 minutes into surgery.

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Note: ***p-value<0.001, **p-value<0.01 reported in the paper.

The following figure shows the mean pupil diameters recorded according to stage of surgery for both treatment groups. The adrenaline entering the eye through the anterior capsulotomy needle helped to resist the miosis induced by expression of the nucleus (7.1 vs 6.5 mm) and the mydriasis maintained during irrigation aspiration was much greater in the treated group (6.6 vs 6.0 mm).



Note: **p-value<0.01 reported in the paper.

Reviewer's remark: The above results showed that the pupil size was larger in the epinephrine group compared with the no epinephrine group during the surgery. However, the reviewer cannot verify p-values presented in the above two figures from the publication since the raw data are not available.

The following table presents the percentage of patients with pupil diameters of less than 5 mm at intervals during the surgery.

Time or Stage of Surgery	Without Epinephrine N=43	With Epinephrine N=27	Difference (95% CI) **	p-value for Chi-Square Test*	p-value for Fisher's Exact Test*
Before expression	0%	0%			
Before aspiration	7 (16%)	0%	16% (2.2%, 30.3%)	0.0271	0.0382
After aspiration	9 (21%)	2 (7%)	14% (-5.2%, 32.2%)	0.1302	0.1835
10 minutes	4 (9%)	1 (4%)	5.6% (-8.7%, 19.8%)	0.3760	0.6421
20 minutes	9 (21%)	1 (4%)	17% (0.1%, 34.3%)	0.045	0.0764
30 minutes	9 (21%)	3 (11%)	10% (-10.2%, 29.8%)	0.2887	0.3466

* Statistical Reviewer's calculation

** Statistical Reviewer's calculation: 95% Confidence Intervals (CI) based on asymptotic confidence limits with continuity correction

Reviewer's remark: The percentage of eyes in which the pupil diameter became less than 5 mm was less in the epinephrine group compared with the no epinephrine group during the surgery. The paper reported a p-value <0.001 based on the numbers presented in columns 2 and 3 in the above table. However, the reviewer cannot verify this p-value. The p-values produced by the reviewer are in the range 0.0271 to 0.6421.

Publication 2: The Effect of Intracameral Adrenaline Infusion on Pupil Size, Pulse Rate and Blood Pressure during Phacoemulsification (Liou S-W and Yang C-Y, 1998)

This randomized study evaluated the efficacy and safety of intraocular irrigation with 1:1,000,000 epinephrine during phacoemulsification. Forty-two subjects were enrolled; the study group (30 eyes) received epinephrine in balanced salt solution (BSS), while in the control group (12 eyes), BSS alone was used. Pupil size was measured before phacoemulsification, before irrigation/aspiration and after irrigation/aspiration. Data were analyzed with the unpaired Student's t test. It appears that the study was not blinded.

The following table presents the pupil size over time in both treatment groups. According to the paper, these results showed that pupil size remained constant in the patients receiving I/A with 1:1,000,000 epinephrine but progressively shrinking in the control group.

Pupil Size	Before Phaco	After Phaco	After I/A
Epinephrine (N=30)	8.06 ± 0.637	8.00 ± 0.633	8.03 ± 0.623
Placebo (N=12)	7.79 ± 0.567	5.96 ± 1.340	5.54 ± 1.364
p-value*		<0.00001	<0.00001

* p-values reported in the paper.

Reviewer's remark: The above results showed that the pupil size was larger in the epinephrine irrigation group compared with the placebo irrigation group during phacoemulsification.

The summary statistics with p-values were presented in the paper (showed in the above table). However, due to limited information provided in this paper (the paper didn't specify the

variability reported was standard deviation or standard error) and there are no raw data submitted, the reviewer cannot verify these p-values.

Publication 3: Maintenance of Mydriasis with One Bolus of Epinephrine during Phacoemulsification (Liou S-W and Chen C-C, 2001)

Reviewer's remark: In this study epinephrine was delivered differently from the previous two studies. For this study, epinephrine was injected one single dose into the anterior chamber prior to phacoemulsification. For the previous two studies, epinephrine was delivered by intraocular irrigation during the surgery.

A total of 60 consecutive patients undergoing cataract surgery were randomly allocated to 5 treatment groups receiving a single bolus injection of epinephrine at dilutions of

- 1:25,000
- 1:50,000
- 1:100,000
- 1:200,000
- 1:400,000

in 0.1 mL of balanced salt solution (BSS) respectively. In addition, a control group of 10 patients received the same volume of injection of BSS only. The single injection was made into the anterior chamber directly over the pupil. It appears that the study was not blinded.

Pupil size were measured just prior to incision at surgery, one minute after the intracameral injection of epinephrine, after phacoemulsification and after irrigation/aspiration (I/A). The following table presents the pupil size over time for all treatment groups.

	N	Pupil Size			
		Pre-Incision	Post-Injection	Post-Phaco	Post-I/A
Control	10	6.9 ± 0.5	7.1 ± 0.5	5.5 ± 0.4	5.0 ± 0.4
Epi 1:25000	11	7.2 ± 0.5	7.7 ± 0.5	8.0 ± 0.6*	8.1 ± 0.6*
Epi 1:50000	13	7.2 ± 0.6	7.9 ± 0.7	8.1 ± 0.8*	8.0 ± 0.5*
Epi 1:100000	10	6.3 ± 0.4	7.3 ± 0.5	7.7 ± 0.7*	7.8 ± 0.6*
Epi 1:200000	14	6.4 ± 0.5	7.4 ± 0.6	7.5 ± 0.7*	7.7 ± 0.6*
Epi 1:400000	12	6.0 ± 0.6	6.9 ± 0.6	6.9 ± 0.9*	6.8 ± 0.2*

* p-values < 0.05 compared with control as reported in the paper.

Reviewer's remark: The above results showed that the pupil size was larger in the all epinephrine injection groups compared with the placebo group after phacoemulsification and after irrigation/aspiration (I/A). However, due to limited information provided in this paper (the paper didn't specify the variability reported was standard deviation or standard error) and there are no raw data submitted, the reviewer cannot verify the p-values reported.

Conclusion

Based on the results of these three publications, there is some evidence to support the efficacy for epinephrine in maintaining mydriasis in cataract surgery. All three papers reported p-values that were less than 0.05 for difference endpoints comparing epinephrine group with placebo control group; however, due to limited information provided in the papers and there are no raw data submitted, the reviewer cannot verify these p-values.

Labeling Recommendation

Although the Applicant seeks approval of epinephrine for the induction of mydriasis in cataract surgery, the statistical reviewer recommends the drug be approved for **maintenance** of mydriasis in cataract surgery instead.

For the publication titled “Intraocular Adrenaline Maintains Mydriasis during Cataract Surgery” by Corbett MC and Richards AB in 1994, based on the data reported in the paper, the reviewer cannot reproduce the p-values claimed by the authors. For the other two publications, due to limited information provided in the submitted papers and there are no raw data submitted, the reviewer cannot verify the p-values reported in these papers. Therefore, the statistical reviewer does not recommend reporting any p-values in the clinical study section of the labeling.

Reference:

1. Corbett MC, Richards AB. Intraocular adrenaline maintains Mydriasis during cataract surgery. *Br J Ophthalmol.* 1994; 78:95-98
2. Liou SW and Yang CY. The effect of intracameral adrenaline infusion on pupil size, pulse rate and blood pressure during phacoemulsification. *J Ocular Pharmacol Ther.* 1998; 14(4):357-361
3. Liou SW, Chen CC. Maintenance of mydriasis with one bolus of epinephrine injection during phacoemulsification. *J Ocular Pharmacol Ther.* 2001; 17:249-253

SIGNATURES/DISTRIBUTION LIST

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Primary Statistical Reviewer

Concurring Reviewer:

Yan Wang, Ph.D
Statistical Team Leader:

cc:

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HFD-520/ Deputy Director: Wiley Chambers, M.D

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HFD-725/Biometrics Deputy Division Director: Daphne Lin, Ph.D

HFD-725/Biometrics Division Director: Mohammad Huque, Ph.D

HFD-700/Office of Biostatistics: Lillian Patrician

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/s/

YUNFAN DENG
08/06/2012

YAN WANG
08/06/2012
I concur.

REV-BIOMETRICS-02 (Review Noted (NAI))
NDA-204200
ORIG-1
Supporting Document 1
New/NDA
Form 3674
Submit Date: 03/07/2012 - FDA Received Date: 03/07/2012

Statistical confirmation of Phase III efficacy analyses is not required because proposed demonstration of efficacy is based on literature reviews rather than on trials submitted with data. Therefore there is no need for a formal filing review.

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/s/

ROBERT ABUGOV
04/12/2012
Filing Review NAI

STATISTICAL REVIEW AND EVALUATION: FILING REVIEW
(COMPLETED REVIEW FOR INTERNAL DISTRIBUTION ONLY)

NDA: 204200
Name Of Drug: Adrenaline (epinephrine)
Applicant: JHP Pharmaceuticals
Submission Date: March 07, 2012

Indication(s): Induction of mydriasis during cataract surgery
Number And Type Of Controlled Clinical Studies (By Indication): N/A

Statistical Reviewer: Yunfan Deng
Clinical Reviewer: Wiley Chambers
Project Manager: Judit Milstein

45 Day Meeting Date: April 11, 2012
Date Draft Review Expected: August 15, 2012
User Fee Date: September 06, 2012

The submission is a 505(b)2 submission based on historical evidence. The only available data is on scanned paper format of three peer reviewed publications.

<u>A. ORGANIZATION AND DATA PRESENTATION</u>	YES	NO	N/A
I. Is there a comprehensive table of contents with adequate indexing and pagination?	✓		
II. Are the original protocols, protocol amendments and proposed label provided			✓
III. Are patient profile listings (for <u>all</u> enrolled patients) provided in each study report?			✓
IV. Are adverse event listings by center and time of occurrence relative to enrollment date included?			✓
V. Have the data been submitted electronically?		✓	
a. If so, has adequate documentation of the data sets been provided?			
b. Do the electronic data appear to accurately represent the data described in the study reports?			
c. Can the data be easily merged across studies and indications?			
d. Are inclusion/exclusion and evaluability criteria adequately coded and described?			

<u>B. STATISTICAL METHODOLOGY</u>	YES	NO	N/A
I. Are all primary efficacy studies of appropriate design to meet basic approvability requirements, within current Divisional policy statements or to the extent agreed upon previously with the sponsor by the Division?			✓
II. For each study, is there a comprehensive statistical summary of the efficacy analyses which covers the intent-to-treat population, evaluable subject population			✓

and other applicable subgroups (age, gender, race, etc.)?

III. Based on the summary analyses of each study, do you believe:

✓

a. The analyses are appropriate for the type of data collected, the study design, and the study objectives (based on protocol objectives proposed labeling claims)?

b. Intent-to-treat and evaluable patient analyses are properly performed?

✓

c. Missing data has been appropriately handled?

✓

d. Any multiplicity issues (e.g., regarding endpoints, timepoints, or multiple dose groups) have been adequately addressed?

✓

e. If interim analyses were performed, were they planned in the protocol and were appropriate significance level adjustments made?

✓

IV. Were sufficient and appropriate reference included for novel statistical approaches?

✓

V. Are all of the pivotal studies complete?

✓

VI. Have safety data been comprehensively and adequately summarized?

✓

C. FILEABILITY CONCLUSIONS

From a statistical perspective, is this submission or indications therein, reviewable with only minor further input from the sponsor?

Yes, the submission is filable.

Yunfan Deng
Mathematical Statistician, DB IV

Concur: Yan Wang
Statistics Team Leader, DB IV

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

/s/

YUNFAN DENG
04/17/2012

YAN WANG
04/17/2012