CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206289Orig1s000

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/BLA Number:	206289 [505(b)(2) application]
Drug Name:	Atropine sulfate Ophthalmic solution USP 1%
Indication(s):	To produce cycloplegia and mydriasis For the treatment of amblyopia
Applicant:	Akorn, Inc
Date(s):	Received 10/23/13
	PDUFA goal date 4/30/14
Review Priority:	Priority
Biometrics Division:	Division of Biometrics IV
Statistical Reviewer:	Joy Mele, M.S.
Concurring Reviewers:	Yan Wang, Ph.D.
	DBIV Team Leader
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Clinical Team:	Wiley Chambers, M.D.
	Primary clinical reviewer and Deputy Division Director
Project Manager:	Christina Marshall

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1 EXECUTIVE SUMMARY

The applicant, Akorn, has submitted a 505(b)(2) application to support approval of atropine sulfate ophthalmic solution 1%. The reference drug for this application is atropine sulfate injection manufactured by Hospira. Atropine ophthalmic solution is presently marketed under Grandfather status by several companies and is not a FDA-approved, labeled product.

Published literature (Appendix 5.1) submitted with the application was considered inadequate by the clinical reviewer, Dr. Wiley Chambers. Dr. Chambers selected eight publications to support indications for mydriasis, cycloplegia and amblyopia and these publications are the focus of this review. Only summary data reported in these publications were available for statistical review.

Six publications provided results for cycloplegia and/or mydriasis (b) (4) Therefore four publications (Table 3.1.1; Barbee, 1957; Ebri, 2007; Marron, 1940; Wolf,1946) provide results to support indications for cycloplegia and mydriasis. In the four studies described in these publications, 229 children and adults were given atropine 1%.

The mydriasis effect and the cycloplegia effect of atropine 1% was consistent across a broad subject population with the majority of subjects showing dilation of 6 mm or more and minimal accommodation from light stimulation. These effects were generally comparable or better than what was observed for a variety of controls.

One study of the four studies (Ebri) was a randomized, controlled study that provided statistical evidence of the effect of atropine 1% compared to cyclopentolate and tropicamide plus cyclopentolate. Atropine was significantly more effective than either control at increasing dilation and reducing residual accommodation ($p<0.03$, Table 3.1.3).

Atropine 1% for the treatment of amblyopia was studied by the Pediatric Eye Disease Group in a randomized, blinded study of 193 children. About 90% of subjects completed 17 weeks on study although only about 55% completed on randomized treatment. About one-third of the subjects required a more intensive treatment regimen than the randomized regimen (e.g. atropine was increased from weekend use to daily use). The results for this study slightly favored patching over atropine for improving acuity but the confidence interval on the difference was within the non-inferiority boundary of 5 letters defined a priori (treatment difference for patching-atropine of +1.2 with confidence interval of -0.7 to +3.1).

Overall there is sufficient data from five publications chosen by the FDA reviewer to support indications for mydriasis (pupil dilation) and cycloplegia and for the treatment of amblyopia.

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2 INTRODUCTION

2.1 Overview

Atropine Sulfate Ophthalmic Solution 1% is used to produce cycloplegia and mydriasis and is used for the treatment of amblyopia. This product has been on the market as an unapproved, grandfathered product under the Food, Drug and Cosmetic Act of 1938 and has been produced by Akorn since 1995. Atropine Sulfate injection, 0.05% and 0.1% was approved for Hospira, Inc. in 2001. Akorn intends to rely on the labeling for Atropine Sulfate injection as evidence of safety for Akorn's formulation of Atropine Sulfate ophthalmic solution, 1%, for ophthalmic use.

This NDA is a 505(b)(2) application that depends solely on publication data to support three indications; cycloplegia, mydriasis and treatment of amblyopia.

Cycloplegia is paralysis of the ciliary muscle of the eye; this paralysis reduces accommodation of the eye to see different distances, i.e. reduces focus, causes blurriness. A measure of cycloplegia is residual accommodation which may be measured in diopters (the reciprocal of focal length in meters). Accommodation is decreased due to cycloplegia.

Mydriasis is dilation of the pupil due to either disease or a drug. Pupil dilation is measured in mm and either pupil size or percentage of subjects with pupils larger than 5 or 6 mm is an acceptable endpoint.

Amblyopia is a condition where vision is impaired however the eye appears to be normal; this condition is often referred to as "lazy eye". The effect of a drug product on amblyopia is measured by the improvement in visual acuity.

Using PubMed, the applicant identified several hundred publications. Based on relevance of study objectives and results, completeness of information and quality (i.e. well-controlled, blinded, randomized and balanced designs), the applicant selected six publications to support efficacy of atropine for their 505(b)(2) application. Those six publications are summarized in Appendix 5.1.

Dr. Wiley Chambers, the deputy director of the Division of Transplant and Ophthalmic Products, performed a search of the literature and selected eight publications appropriate for review of the effectiveness of atropine solution in the treatment of amblyobia and to produce mydriasis and cycloplegia. These eight studies are listed in Table 2.1.1 on the following page. These studies are the focus of this review.

Two studies were selected by both FDA and the applicant; Ebri 2007 and Wolf 1946.

Five studies may support the indications of pupil dilation and cycloplegia; Barbee 1957, Chia 2012, Ebri 2007, Marron 1949 and Wolf 1946. Two studies may support only the indication of cycloplegia; Kawamoto 1997 and Stolovitch 1992. The indication of treatment of amblyopia may be supported by one study published by the Pediatric Eye Disease Group in 2008.

Of the studies described in the eight publications (see Table 2.1.1 on following page), three (Chia 2012, Ebri 2007 and Pediatric Eye Disease Group 2008) were randomized clinical trials. Note that there is a randomized study for each of the proposed indications. These studies can provide the most statistically robust results. The other studies provide important descriptive data to support the randomized studies.

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Table 2.1.1 Publications selected by the FDA clinical reviewer (Dr. W. Chambers) to support 3 indications for atropine 1% (See Appendix 5.2 for a listing of the references.)

Study	Indication	Design	Arms (# of subjects)
Barbee 1957	Pupil dilation Cycloplegia	Non-randomized Double-blind	Atropine 1% Plus 9 other agents Total of 300 pts
Chia 2012	Pupil dilation Cycloplegia	Randomized Double-blind	Atropine 0.5% (161) Atropine 0.1% (155) Atropine 0.01% (84)
Ebri 2007	Pupil dilation Cycloplegia	Randomized Parallel groups	Atropine 1% (79) Cyclopentolate 1% +Tropicamide 0.5% (78) Cyclopentolate 1% (76)
Marron 1940	Pupil dilation Cycloplegia	Non-randomized	Atropine 1% (107) Scopolamine 0.5% (21) Homatropine 5% (25)
Wolf 1946	Pupil dilation Cycloplegia	Non-randomized Open label	Atropine 1% 15 eyes (13) Methylatropine 1% 23 eyes(21) Homatropine 1% 7 eyes (7)
Kawamoto 1997	Cycloplegia	Sequential groups	Atropine 0.5% (<6yrs old) or 1% (6 and older) Cyclopentolate 1% Total of 51 children
Stolovitch 1992	Cycloplegia	Subject own control /comparison to baseline	Atropine 1% (36)
Pediatric Eye Disease Group 2008	Amblyopia	Randomized Parallel groups Blinded assessment	Atropine 1% (95) Patching (98)

The main body of this review (Section 3) is divided by indication into two sections to describe the efficacy data; one section for mydriasis and cycloplegia and one for amblyopia.

2.2 Data Sources and Quality

The full NDA can be accessed in the FDA electronic document room at the following link: \\CDSESUB1\evsprod\NDA206289\206289.enx. The information provided in the NDA was very limited.

This review was dependent on the publications chosen by the FDA clinical reviewer. No data was submitted for this 505(b)(2) application. Summary statistics were provided in the publications and these statistics serve as the basis for the statistical review.

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3 STATISTICAL EVALUATION

3.1 Studies supporting indications for cycloplegia and mydriasis

The FDA clinical reviewer selected five publications that described studies demonstrating mydriasis (pupil dilation) and cycloplegia due to atropine treatment and two publications that demonstrated cycloplegia alone (Table 3.1.1).

Table 3.1.1 Design of studies measuring responses of mydriasis and/or cycloplegia to atropine 1% ophthalmic solution

Study	Design	Arms (# of subjects)	Atropine Dosing	Responses	Subject Population
Studies that measured cycloplegia and mydriasis					
Barbee 1957	NR, DB Placebo controls	Atropine 1% Plus 7 other agents & 2 placebo controls 30 pts/arm: 10 white, blue-eyed subj 10 white, brown-eyed subj 10 black, brown-eyed subj.	3 drops given in one eye	40' after drops Dilation measured with a ruler Change in accommodation measured with Snellen rating card	Aged 16-60 yrs No ocular disease Black and white subjects Blue and brown eyed
Chia 2012	R, DB	Atropine 0.5% (161) Atropine 0.1% (155) Atropine 0.01% (84)	1 drop nightly for 2 years	Myopia progression	Aged 6-12 yrs Myopic refraction of ≥ 2D
Ebri 2007	R, P	Atropine 1% (79) Cyclopentolate 1% +Tropicamide 0.5% (78) Cyclopentolate 1% (76)	1 drop 3x daily for 3 consecutive days	Dilation measured with a ruler Residual Accom. measured with retinoscopy (diff. subtracting near from far)	Aged 4-15 yrs Nigerian All brown eyed Presented with eye complaint
Marron 1940	NR groups of subjects for each drug	Atropine 1% (107) Scopolamine 0.5% (21) Homatropine 5% (25)	1 drop 3x daily for 3 consecutive days +1 drop AM of exam	Dilation measured with a pupillometer Accom. measured with a Prince's rule Did not report residual accom.	Aged 15-40 yrs U. of Chicago Students & faculty with eye complaint
Wolf 1946	NR Open label Incomplete Crossover	Atropine 1% 15 eyes (13) Methylatropine 1% 23 eyes (21) Homatropine 1% 7 eyes (7)	1 drop	Dilation measured with a pupillometer Accom. measured with newsprint on a slide. Resid accom measured as a ratio	Aged 16-37 yrs
Studies that measured cycloplegia only					
Kawamoto 1997	Sequential groups Cyclopentolate then Atropine	Atropine 0.5% (<6yrs old) or 1% Cyclopentolate 1% Total of 51 children	2x daily for 7 days	Refraction measured with autorefkeratometer	Aged 3-15yrs Japanese Most hyperopes (far-sighted)
Stolovitch 1992	Subject own control /comparison to baseline	Atropine 1% (36)	1 drop 3x on one day +1 drop AM of exam & repeated	Refraction measured with retinoscopy	Aged 5mos-11yrs Hyperopic Caucasian children in TelAviv

DB=Double-blind SB=Single-blind P=Parallel groups R=Randomized NR=Non-randomized

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With the exception of the Chia study, all 6 other studies used a 1% ophthalmic solution of atropine. The Chia study studied atropine doses of 0.5%, 0.1% and 0.01% for the long-term treatment (2 years in this study) of myopia. Myopia is a condition of the eye where it is difficult to see objects far away; distant objects look blurry. This condition is also called nearsightedness. The authors concluded the lowest dose tested (0.01%) was comparable to doses of 0.5% and 0.1% in slowing progression of myopia. Myopia was seen to be improved without any notable dilation or change in accommodation. This study does not provide data to support the use of the 1% dose of atropine for dilation and cycloplegia. (b) (4)

The 6 other studies were 1 day to 7 days in length and were designed to measure cycloplegia and /or mydriasis (dilation); these studies can provide statistical data that support the indications of mydriasis and cycloplegia. The quality of these 6 studies varied considerably; only one (Barbee) explicitly stated it was double-blind and only one (Ebri) explicitly stated that subjects were randomized to treatment. Because most studies did not include a randomized comparator, the emphasis here is on descriptive statistics of the effect of atropine 1%.

The subject populations for the six studies together include children (ages 5 months to 18) and adults (ages 19-60). Three studies (Ebri, Kawamoto and Stolovitch) included only children. Subgroup analyses were not done by age in these studies. Only one study (Barbee) performed analyses by eye color and by race. All subjects in the Ebri study were brown-eyed. Eye color was not mentioned in most publications. The geographic location of the studies was not mentioned in all publications; the Marron study was conducted in Chicago, Kawamoto in Japan, Stolovitch in Israel and Ebri in Nigeria. In some studies, subjects presented with eye complaints while in others subjects with no known problems were entered.

Overall the subject populations were quite varied and suggest that generalizing the results of these six studies to a broad population could be possible.

Table 3.1.2 on the following page provides a summary of the results for both dilation and cycloplegia. There was a great deal of variability in the way results were presented in the publications so this reviewer made an effort to select results that would allow one to assess the consistency of response to atropine 1% across the studies. The results for dilation were consistently reported in mm. The results for residual accommodation were reported in mm, in diopters, as a difference from baseline and as a ratio of baseline.

Four studies (Barbee, Ebri, Marron and Wolf) showed that mean dilation due to atropine treatment ranged from 6.5 to 8.3 mm with the majority of subjects having values above 6 mm. Some other drugs (scopolamine and homatropine) had slightly larger values for dilation as seen in one study by Marron. Maximum dilation usually occurred within an hour and was maintained. The Barbee study showed no differences between the races and eye colors studied with all groups showing mean dilation values greater than 6 mm.

Cycloplegia was measured in all six studies listed in Table 3.1.2. The first four studies listed provided results for accommodation and/or residual accommodation while the last 2 studies (Kawamoto and Stolovitch) only provided results for refraction. According to the FDA clinical reviewer, refraction is not a good measure of the efficacy of a product to produce cycloplegia. Therefore the emphasis here is on the cycloplegia results from the first 4 studies listed in Table 3.1.2. There was no consistency in how cycloplegia was reported with differing definitions for residual accommodation as noted in Table 3.1.1. However, regardless of the measure, smaller values indicate more cycloplegia.

In three of the 4 studies (Barbee, Ebri and Wolf) accommodation or residual accommodation was less than what was seen in controls (recall that smaller values for accommodation indicate more cycloplegia); atropine then was nominally more effective in causing cycloplegia than the controls in those studies (placebo, cyclopentolate alone, cyclopentolate with tropicamide, methylatropine and homatropine).

Age and eye color can impact accommodation. No studies had subgroup results by age but the data from Ebri shows that atropine is effective in children while Barbee, Marron and Wolf showed effectiveness in adults. Barbee studied groups of subjects defined by race (white and black) and eye color (brown and blue) and showed no differences in cycloplegia between these groups. It should be noted that the publication does not indicate whether subjects in these categories were randomized to treatment stratifying on eye color and race so it is not clear whether the comparisons are of randomized groups.

Data from these studies consistently showed that recovery from cycloplegia was slowest with atropine compared to several different ophthalmic drugs.

Table 3.1.2 Mydriasis and/or cycloplegia results for studies of atropine 1% ophthalmic solution
Mydriasis (dilation) is measured by pupil diameter and cycloplegia is measured by accommodation (A) or residual accommodation (RA)

Study	Dilation Results for Atropine 1%	Dilation Results for Control or other arm	Cycloplegia Results for Atropine 1%	Cycloplegia Results for Control or other arm
Barbee 1957	Mean baseline ~4mm Mean posttrt ~6.5 mm No difference among races and eye colors. (Fig 1)	All 7 other agents had mean dilation greater than 6 mm. One agent, scopolamine, had a mean value>atropine	Change in pupil size (A) close to zero (Fig 2 bottom) A after treatment<0.1 mm	All other active agents had values >atropine (thereby the other agents are less effective)
Ebri 2007	100% had dilation ≥ 6mm	For cyclopentolate, 53% had dilation ≥ 6mm For cyclopentolate +0.5%Tropicamide, 94% had dilation ≥ 6mm	100% had RA 0-0.5 D Mean RA 0.04 D Sign. Lower RA than other agents p<0.0001	For cylcopentolate, 54% had RA 0-0.5 D Mean 0.63 D For cyclopentolate +0.5%Tropicamide, 71% had RA 0-0.5 D Mean 0.36 D
Marron 1940	Average full dilation of 7.9 mm By 40 minutes	For scopolamine, average full dilation of 8 mm For Homatropine, average full dilation of 8 mm	Average minimum A of 1.9 D (ratio RA ~0.16 from Fig 3) Full effect after 4 drops/fell within 30’	For scopolamine, minimum A of 1.6D (ratio RA ~0.18) For Homatropine, minimum A of 1.6D (ratio RA ~0.18)
Wolf 1946	Average full dilation of 8.3 mm	For Methylatropine, average full dilation of 7.7 mm For Homatropine, average full dilation of 5.9 mm	Mean RA of 0.21 (ratio)	For Methylatropine, Mean RA of 0.29 (ratio) For Homatropine, Mean RA of 0.55 (ratio)
Kawamoto 1997	NA	NA	Mean refraction <6yrs +3.55 D >7yrs +2.60 D	For Cyclopentolate, Mean refraction <6yrs +2.89 D >7yrs +1.83 D
Stolovitch 1992	NA	NA	Mean refraction ~3D	NA

D=diopters

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The results of statistical tests to compare atropine to a control were scant in all 5 publications. Most publications reported only means without any measures of variation so no analyses could be performed by this reviewer from that summary data. For example, Barbee reported significant differences ($p<0.001$, t-tests) for dilation and for cycloplegia for atropine compared to placebo but only provided means and so this reviewer could not verify their results.

The Ebri publication was the exception with proportions reported for outcomes for all randomized groups. The Ebri study showed that atropine was significantly more effective than cyclopentolate alone ($p<0.00001$) or cyclopentolate with tropicamide ($p=0.03$) in dilating the pupil 6 mm or more and also in reducing residual accommodation ($p<0.0001$ for both comparisons) (Table 3.1.3).

Table 3.1.3 Reviewer's dilation and cycloplegia results for the Ebri study

	Atropine 1%	Control	Trt Difference A-C
% dilation ≥ 6 mm	70/70 (100%)	Cyclopentolate 40/76 (53%) Cyclo+Trop 72/77 (94%)	+47% (CI 36%, 59%) +6.5% (CI 0.8%, 15%)
% with residual accommodation 0-0.5 D	70/70 (100%)	Cyclopentolate 41/76 (54%) Cyclo+Trop 55/77 (71%)	+46% (CI 35%, 57%) +29% (CI 19%, 40%)

In summary, four publications (Barbee. Ebri, Marron and Wolf) provided evidence that atropine 1% is effective at increasing dilation and decreasing accommodation in broad populations. One study (Ebri) provided strong statistical evidence of the effectiveness of atropine 1% compared to cyclopentolate 1% or tropicamide 0.5% plus cyclopentolate 1% for dilation and cycloplegia.

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3.2 Study supporting an indication for treatment of amblyopia

A trial[1] conducted by the Pediatric Eye Disease Investigator Group entered 193 children with amblyopia at 39 centers. Children aged 7 to 12 years (mean of 9) were randomized to atropine 1% (n=95) or patching (n=98) stratifying on visual acuity in the amblyopic eye and center. In the sound eye, patching was to be done 2 hours a day or atropine 1% was to be given on both weekend days. (Patching is the treatment standard for amblyopia.) Treatment was to be continued for 17 weeks; if vision improved but the amblyopia had not resolved, treatment continued and children were tested every 8 weeks. Follow-up visits were planned for Week 5 and Week 17. If acuity was not increased by 5 letters or more by the Week 5 visit, patching was increased to 4 hours daily or atropine was given daily.

About 90% of randomized subjects completed the study (Table 3.2.1). About 1/3 of subjects had their treatment regimen increased in each arm. By Week 17, 54% of atropine-treated subjects and 58% of patched subjects were still taking the randomized regimen.

Table 3.2.1 Subject disposition

	Atropine 1%	Patching
Randomized	95 (100%)	98 (100%)
Trt switched at Week 5 visit	2 (2%)	2 (2%)
Trt increased at Week 5 visit	32 (34%)	31 (32%)
Completed 5 weeks	89 (94%)	91 (93%)
Completed 17 weeks	88 (93%)	84 (86%)
Completed on Rand. Trt.[1]	51 (54%)	57 (58%)

[1]Subjects who remained on weekend atropine or 2 hour patching. Note the percentages of 54% and 58% are based on the full randomized population, not the completers. The authors used the completers for this computation.

The primary outcome in this study is visual acuity at Week 17 in the amblyonic eye which was measured in letters using the E-ETDRS test. A score of 85 letters corresponds approximately to 20/20 vision. The tester was blinded to treatment. The window for the Week 17 response went from Week 13 to Week 26; measures outside that window were not included in the analysis.

The authors used an analysis of covariance model with baseline acuity as a covariate to analyze the treatment difference for acuity at Week 17; their stated goal was to show equivalence between the two treatments where equivalence was defined by a 95% confidence interval that excluded a difference of 5 letters or greater in favor of either treatment.

The treatment arms were comparable at baseline for acuity in the amblyonic eye and the sound eye (see Table 3.2.2 on the following page).

[1] Pediatric Eye Disease Investigator Group. Patching vs. Atropine to Treat Amblyopia in Children Aged 7 to 12 Years. Arch Ophthalmol. 126(12):1634-1642, 2008.

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The visual acuity results at Week 17 favor patching over atropine but the difference is not significant and the confidence interval on the difference as computed by the authors shows that the treatments are equivalent based on the authors' criterion of excluding 5 letters from the confidence interval on the difference (-0.7 to +3.1, Table 3.2.2). When using cutoffs to assess acuity (better than 20/25 and 15 or more letters), a higher percentage (7-8%) of patched subjects showed improvement than atropine subjects, however the difference was not statistically significant. The publication included a cumulative distribution plot (Figure 2 in the publication) that illustrated the similarity between the groups; there were few extreme values suggesting the means well-represented the data (medians of about 71 from the plot).

Table 3.2.2 Baseline and Week 17 Outcomes

	Atropine 1%	Patching	Patching-Atropine[1] (1-sided 95% CI)
Baseline Acuity (letters)	n=95	n=98	
Amblyopic eye mean (SD)	62 (7)	62 (6)	
Sound eye mean (SD)	86 (3)	86 (4)	
Intereye difference	24 (7)	23.5 (7)	
Week 17 Visual acuity	n=88	n=84	
Mean letters at Week 17	69 (9)	71 (9)	+1.2 (-0.7, +3.1)
Mean change from baseline Wk17	+7.6 (7.5)	+8.6 (7.8)	
N (%) Better than 20/25	15 (17%)	20 (24%)	+7% (-3%, +17%)
N (%) ≥ 15 letters	15 (17%)	21 (25%)	+8% (-2%, +18%)

[1] Positive values favor patching. Authors used an analysis of covariance model with baseline acuity as a covariate.

The authors also looked at results by age, baseline acuity and cause of amblyopia. As for the overall results, results by subgroups showed slightly better acuity in the patching group than the atropine group.

The results of the trial conducted by the Pediatric Eye Disease Investigator Group demonstrated that both atropine 1% and patching were viable treatments for improving acuity in amblyopic eyes in children. The authors conducted sufficient analyses to show that the data is robust by performing subgroup analyses and by showing that the effects were maintained when subjects were followed up. From a statistical perspective, this trial supports an indication for treatment of amblyopia with atropine 1% in children 7 to 12 years old.

4 CONCLUSIONS

The results from four published studies (See Table 3.1.1, Barbee, Ebri, Marron and Wolf) demonstrated the effectiveness of atropine 1% to cause mydriasis (dilation) and cycloplegia (accommodation). These studies enrolled subjects ranging in age from 4 years to 60 years, of both sexes, with both light and dark eyes and with eyes diseased or not.

One published study by the Pediatric Eye Disease Investigator Group demonstrated that atropine 1% is effective in treating amblyopia in children 7 to 12 years.

There is sufficient statistical evidence in five publications chosen by the FDA clinical reviewer to support the proposed indications of mydriasis and cycloplegia and treatment of amblyopia.

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5 APPENDICES

5.1 Reviewer's summary of applicant's selected publications

Reference	Wolf 1946	Rosenbaum 1981	Hiatt 1983	Zetterstom 1985	Fan 2004	Ebri 2007
Sites/Country	1? US	? US	2 US	1 Sweden	1 Hong Kong	2 Nigeria
Design	OL NR	CO OL NR	CO NR	CO R SB	CO NR SB?	P R
Sample size Atropine Control	15 eyes (13 pts) M 23 eyes (21 pts) H 7 eyes (7 pts)	240 eyes (120 pts)	82 eyes (41 pts)	40 eyes (40 pts)	50 eyes (25 pts)	79 CT 78 C 76
Atropine concentration	1%	<1 yr 0.5% 1%	<2.5 yrs 0.5% 1%	0.5%	1%	1%
Control	Methylatropine 1%& Homatropine1%	Cyclopentolate 1%	Tropicamide 1%	Cyclopentolate 0.85% +Phenylephrine 1.5%	Tropicamide 1% + Phenylephrine 0.5% &Cyclopentolate1% + Tropicamide 1%	Cyclopentolate1% + Tropicamide .5% & only Cyclopentolate 1%
Atropine trt regimen	1 drop	3x a day for 3 days	2x a day for 2 days+ 1x morning of exam	2x a day for 3 days and AM of 4th day	2x a day for 3 days	3x a day for 3 days
Study population	Young adults	Estotropic young children	Children with esodeviation	Children w/ +2.5D hypermetropic	Children w/ hyper-opia>+2.5D in at least one eye	Children with dark eyes and an eye complaint
Age range % males	16-37 yrs NA	3mos-2yrs 45%	2 mos-5 yrs 49%	3-6 yrs NA	2-10 yrs 52%	4-15 yrs 42%
Endpoints for Mydriasis &/or Cycloplegia	Max Dilation Ratio Residual Accomod.	Retinoscopy (diopters) hyperopia	Refraction by retinoscopy	Refraction was determined by Heine Streak Retinoscope	Refraction by Topcon autorefractometer	Dilation Residual Accomod.
Details wrt blinding	NA	Examiner did not see control results prior to atropine trt	NA	Examiner was blinded to trt	Examiner was blinded to trt (however trt order was fixed)	Exam schedule unblinds the treatment assignment
Details wrt randomization	NA	NA	NA	Pts randomized to atropine or control 1st	NA	Randomized to 1 of 3 trts at each site
Details wrt stat. tests	Minimal incorrect stat test?	Minimal paired comparisons	Minimal results not clear	t-test for paired data Pearson's corr.	Repeated measures	Chi square test and ANOVA

Table created by reviewer. OL=open label R= randomized NR=not randomized CO=crossover SB=single blind P=parallel groups

5.2 References

Barbee, R. F., Smith W. O. Jr. A comparative study of mydriatic and cycloplegic agents; in human subjects without eye disease. Am J Ophthalmol. 44(5 Pt 1):617-22, 1957.

Chia A, Chua WH, Cheung YB, Wong WL, Lingham A, Fong A, Tan D. Atropine for the treatment of childhood myopia: safety and efficacy of 0.5%, 0.1%, and 0.01% doses (Atropine for the Treatment of Myopia 2). Ophthalmology. 119(2):347-54, 2012.

Ebri A, Kuper H, Wedner S. Cost-effectiveness of cycloplegic agents: results of a randomized controlled trial in Nigerian children. Invest Ophthalmol Vis Sci. 48(3):1025-31, 2007.

Kawamoto K, Hayasaka S. Cycloplegic refractions in Japanese children: a comparison of atropine and cyclopentolate. Ophthalmologica. 211:57–60, 1997.

Marron J. Cycloplegia and mydriasis by use of atropine, scopolamine, and homatropine-paradrine. Arch Ophthalmol. 23: 340-50, 1940.

Pediatric Eye Disease Investigator Group. Patching vs. Atropine to Treat Amblyopia in Children Aged 7 to 12 Years. Arch Ophthalmol. 126(12):1634-1642, 2008.

Stolovitch C, Loewenstein A, Nemmet P, Lazar M. Atropine Cycloplegia: How Many Instillations Does One Need? J Pediatr Ophthalmol Strabismus. 29:175-176, 1992.

Wolf AV, Hodge HC. Effects of atropine sulfate, methylatropine nitrate (metropine) and homatropine hydrobromide on adult human eyes. Arch Ophthal 36: 293-301, 1946.

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/s/

JOY D MELE
03/11/2014

YAN WANG
03/12/2014
I concur.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 206289 **Applicant: Akorn, Inc.** **Stamp Date: 10/23/13**

Drug Name: Atropine sulfate Ophthalmic solution USP 1% **NDA/BLA Type: 505(b)(2)**

EDR Location: \\CDSESUB1\evsprod\NDA206289\206289.enx

This NDA is a 505(b)(2) application that depends on published literature to support the efficacy and safety of atropine.

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

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)		X		No study reports or protocols. Studies are summarized in Module 2.7.3 Summary of Clinical Efficacy
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).		X		Data based on literature, no subgroup results
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).			X	505(b)(2) literature-based so no data

The results reported from the published literature were poorly summarized in the NDA. The applicant provided minimal discussion of how their application provides evidence of the efficacy and safety of atropine. Of the six studies provided, the most recent study of 233 patients (Ebri Ref#19) appears to provide the most complete data from a well-controlled, parallel study. A possible drawback to this study is that it is conducted in Nigeria with all dark-eyed children so generalization to a US diverse population may not be readily done. The publications for the other 5 studies provide some descriptive data that may be sufficient but they did not provide results from clearly defined statistical methods. A brief description of the designs for the 6 studies is contained in a table on the last page of this review. From a purely statistical perspective, this application does not provide sufficient information from two or more well-controlled studies to allow a statistical review; however, because the product has "grandfather" status, the descriptive data from 5 studies and the results from one well-controlled study may be sufficient. Based on the latter, this reviewer thinks the application is fileable if DTOP considers the selected six studies as representative of the data needed to approve the two indications proposed by the sponsor.

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? _____Yes___

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

RTF_MAPP:http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM370948.pdf

File name: 5_Statistics Filing Checklist for a New NDA_BLA110207

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

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

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			Designs include both crossover and parallel designs. Most are not randomized nor blinded. Most of the studies would be considered unacceptable, from a statistical perspective. See comment above.
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.			X	No protocols for the 505(b)(2) NDA
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	Small single dose studies so IA not appropriate
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.		X		Inconsistent summary of safety data across 6 studies
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.		X		Only 1 study summarized patient disposition.

No statistical comments to be conveyed to the sponsor

Joy Mele

Reviewing Statistician Date

Yan Wang

Supervisor/Team Leader Date

File name: 5_Statistics Filing Checklist for a New NDA_BLA110207

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Table of six studies provided as evidence of efficacy of atropine ordered by date published

Reference	Wolf 1946	Rosenbaum 1981	Hiatt 1983	Zetterstom 1985	Fan 2004	Ebri 2007
Sites/Country	1? US	? US	2 US	1 Sweden	1 Hong Kong	2 Nigeria
Design	OL NR	CO OL NR	CO NR	CO R SB	CO NR SB?	P R SB?
Sample size Atropine Control	15 eyes (13 pts) M 23 eyes (21 pts) H 7 eyes (7 pts)	240 eyes (120 pts)	82 eyes (41 pts)	40 eyes (40 pts)	50 eyes (25 pts)	79 CT 78 C 76
Atropine concentration	1%	<1 yr 0.5% 1%	<2.5 yrs 0.5% 1%	0.5%	1%	1%
Control	1%Methylatropine & 1%Homatropine	1%Cyclopentolate	1%Tropicamide	0.85%Cyclopentolate +1.5%Phenylephrine	1%Tropicamide + 0.5%Phenylephrine &1%Cyclopentolate + 1%Tropicamide	1%Cyclopentolate + .5%Tropicamide & only 1% Cyclopentolate
Atropine trt regimen	1 drop	3x a day for 3 days	2x a day for 2 days+ 1x morning of exam	2x a day for 3 days and AM of 4th day	2x a day for 3 days	3x a day for 3 days
Study population	Young adults	Estotropic young children	Children with esodeviation	Children w/ +2.5D hypermetropic	Children w/ hyper-opia>+2.5D in at least one eye	Children with dark eyes and an eye complaint
Age range % males	16-37 yrs NA	3mos-2yrs 45%	2 mos-5 yrs 49%	3-6 yrs NA	2-10 yrs 52%	4-15 yrs 42%
Endpoints for Mydriasis &/or Cycloplegia	Max Dilation Ratio Residual Accomod.	Retinoscopy (diopters) hyperopia	Refraction by retinoscopy	Refraction was determined by Heine Streak Retinoscope	Refraction by Topcon autorefractometer	Dilation Residual Accomod.
Details wrt blinding	NA	Examiner did not see control results prior to atropine trt	NA	Examiner was blinded to trt	Examiner was blinded to trt (however trt order was fixed)	Exam schedule unblinds the treatment assignment
Details wrt randomization	NA	NA	NA	Pts randomized to atropine or control 1st	NA	Randomized to 1 of 3 trts at each site
Details wrt stat. tests	Minimal incorrect stat test?	Minimal paired comparisons	Minimal results not clear	t-test for paired data Pearson's corr.	Repeated measures	Chi square test and ANOVA

R=randomized NR=non-randomized DB=double blind SB=single blind OL=open label not blinded NI=non-inferiority
S=superiority CO=crossover P=parallel groups NA=not stated in the publication or not applicable

File name: 5_Statistics Filing Checklist for a New NDA_BLA110207

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/s/

JOY D MELE
02/27/2014

YAN WANG
02/28/2014