CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208151Orig1s000

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 #:	208151
Drug Name:	Isopto (atropine sulfate ophthalmic solution) 1%
Indication(s):	Mydriasis Cycloplegia Amblyopia (b) (4)
Applicant:	Alcon research ltd
Date(s):	Stamp date: February 12, 2016 PDUFA date: December 12, 2016
Review Priority:	Standard
Biometrics Division:	DBIV
Statistical Reviewer:	Abel Tilahun Eshete, PhD
Concurring Reviewers:	Yan Wang, PhD
Medical Division:	Ophthalmology
Clinical Team:	Medical Reviewer: Wiley Chambers, MD
Project Manager:	Michael Puglisi

Keywords: Cycloplegia, Mydriasis Amblyopia, Dilation, Light accommodation

Table of Contents

LIST OF TABLES

SUMMARY

The applicant selected a total of fifteen publications to support the efficacy of atropine for their 505(b) (2) application that depends solely on publication data to support the efficacy of atropine sulfate ophthalmic solution 1% for four indications: (1) cycloplegia, (2) mydriasis, (3) (b) (4) (4) amblyopia (Table 1 and Table 2). Dr. Wiley Chambers, the deputy director of the Division of Transplant and Ophthalmic Products, has also performed a literature search and selected thirteen publications. Seven of the thirteen publications identified by Dr. Chambers are the same publications included in the applicant's submission (Table 3).

Note that the thirteen publications identified by Dr. Wiley Chamber were reviewed by the FDA clinical and statistical reviewers in the medical division of transplant and ophthalmology products (DTOP) for another NDA two years ago. DTOP has concluded that these publications provided sufficient evidence of efficacy of atropine for the following three indications: (1) cycloplegia, (2) mydriasis, and (3) penalization of the healthy eye in the treatment of amblyopia. (b) (4)

The statistical reviewer for the current NDA, Dr. Abel T. Eshete, has reviewed the relevant publications identified by both the applicant and Dr. Wiley Chambers and did not identify any major statistical issues. He concluded that there is sufficient statistical evidence in the publications to support the proposed indications of mydriasis and cycloplegia and treatment of amblyopia. However, because the statistical reviewer was not able to determine whether the atropine evaluated in the publications is similar to the to-be-marketed product, the final determination for the approval of the product is deferred to the clinical review team.

Table 1: Applicant's Selection of Published Clinical Efficacy Studies of Atropine as a Cycloplegia and Mydriasis Agent

Reference	Study Design	Study Objectives	No. of Subjects	Dosing Regimen
Celebi 1999	Prospective	To compare the **cycloplegic** effect of atropine versus cyclopentolate	32 (ages 5–10 yrs)	Atropine 1% 3 times daily for 3 days; single morning instillation on 4th day versus cyclopentolate HCl 1% (3 times in 15 min)
Ebri 2007	Randomized	To compare the effectiveness of atropine and 2 other **cycloplegic** agents	233 (ages 4–15 yrs)	Atropine 1%; cyclopentolate 1%; cyclopentolate 1% and tropicamide 0.5%
Liu 2012	Prospective, self-matched pairs control	To compare the effectiveness of **cycloplegia** between atropine and cyclopentolate	80 (ages 4–9 yrs)	Atropine 1% 3 times daily for 3 days; cyclopentolate 1% (3 times in 15 min)
Caruba 2006	Randomized, prospective, single masked	To compare atropine eye drops and inserts in terms of quality of preoperative **mydriasis**	51 (ages not specified)	Eye drop (atropine 1%, diclofenac 0.1%, tropicamide 0.5%, phenylephrine collyrium 10%,); Insert (atropine 1%, diclofenac collyrium 0.1%, and Mydriasert®)
McCormick 2006	Randomized, assessor masked, controlled	To compare pledget sponge to conventional repeated atropine drop administration for inducing **mydriasis**	56 (Adults)	Atropine 1%; proxymetacaine 0.5%; tropicamide 1%;phenylepherine 2.5%; 2 drops or sponge to lower conjunctival fornix
Barbee 1957	Prospective, Double-masked, Placebo-controlled	To compare the effect of 10 different treatments for inducing **mydriasis and cycloplegia**	300 (ages 16-60 yrs)	3 drops in one eye

Source: Table 2.7.3.1.1-1 from NDA 2.7.3 Summary of Clinical Efficacy.

Table 2: Applicant's Selection of Published Clinical Efficacy Studies of Atropine (b) (4) for the Treatment of Amblyopia

Reference	Study Design	Study Objectives	No. of Subjects	Dosing Regimen
(b) (4)				
Pediatric Eye Disease Investigator Group 2008	Randomized, multicenter	To compare patching with atropine in the treatment of moderate **amblyopia**	193 (ages 7–12 yrs)	1% atropine each weekend day versus patching 2 hrs per day
Repka 2014	Randomized, multicenter	To report visual acuity at 15 years of age in patients who were younger than 7 years when enrolled in a trial for moderate **amblyopia**	419 with 188 long-term follow-up (ages 2–7 yrs at enrollment, 14–17 yrs at completion)	1% atropine 1 drop daily or patching 6 hrs/day
Foley-Nolan 1997	Single masked, single center	To compare visual acuity outcomes between atropine penalization or occlusion therapy in patients with **amblyopia**	36 (ages 2.5 to 9 years)	One drop of 1% atropine daily each morning

Pediatric Eye Disease Investigator Group 2005	Randomized, multicenter	To evaluate the effectiveness of optical correction versus patching plus near visual activities and atropine for treatment of **amblyopia** in children aged 7 to 17 years. (Only children between the ages of 7-12 were treated with atropine.)	404 (ages 7-17)	1 drop daily of 1% atropine sulfate for the sound eye
Tejedor 2008	Randomized, Single center	To compare the efficacy and sensory outcome of pharmacologic and optical penalization in the treatment of moderate to mild **amblyopia**.	31 (ages 2-10)	1% atropine twice weekly when interocular acuity difference was present and once weekly for maintenance therapy

Source: Table 2.7.3.1.1-2 from NDA 2.7.3 Summary of Clinical Efficacy.

Table 3: List of Publications Selected by the Clinical Reviewer

Study	Indication	Design	Arms (# of subjects)
Barbee 1957	Pupil dilation Cycloplegia	Non-randomized Double-blind	Atropine 1% Plus 9 other agents Total of 300 patients
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 their own control/comparison to baseline	Atropine 1% (36)

Pediatric Eye Disease Group 2008	Amblyopia	Randomized Parallel groups Blinded assessment	Atropine 1% (95) Patching (98)
[redacted] (b) (4)			

Source: Table 5.3 from clinical review (page 14) by Dr. Wiley Chambers (dated in DARRTS on September 13, 2016)

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

/s/

ABEL T ESHETE
11/08/2016

YAN WANG
11/08/2016
I concur.