

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204822Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review for NDA 204822

Date	April 8, 2014
From	William M. Boyd, M.D.
Subject	Cross-Discipline Team Leader Review
NDA #	204822
Applicant	Alcon Laboratories, Inc.
Date of Submission	July 15, 2014
PDUFA Goal Date	May 15, 2014
Type of Application	505(b)(1)
Name	IZBA (travoprost ophthalmic solution) 0.003%
Dosage forms / Strength	Topical ophthalmic solution
Proposed Indication(s)	Indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension
Recommended:	Recommended for Approval

1. Introduction

Travoprost is the isopropyl ester prodrug of a FP prostaglandin receptor agonist. It belongs to the pharmacological class of PGF₂ α agonists. Prostaglandin analogues are believed to lower intraocular pressure by increasing the outflow of aqueous humor via trabecular meshwork and uveoscleral pathways.

The purpose of this development program was to create a new formulation of travoprost that would maintain the IOP-lowering efficacy achieved with Travatan with lower drug exposure. The new formulation with a 0.003% concentration travoprost represents a 25% reduction from the currently approved travoprost 0.004%.

For equivalence trials, efficacy can be established if the difference in mean IOP between treatment groups is within ± 1.5 mm Hg at all post-baseline timepoints; and within ± 1 mm Hg at the majority of post-baseline timepoints. This requirement for equivalence has been used for the approval of numerous IOP lowering products.

2. Background

There are several topical treatments for lowering intraocular pressure in patients with open angle glaucoma and ocular hypertension. These treatments include beta-adrenergic antagonists (beta-blockers), alpha-adrenergic agonists, parasympathomimetic (miotic) agents, carbonic anhydrase inhibitors, and prostaglandin analogs.

Drug Products with Approved NDAs

Pharmacologic Class/ Applicant	Tradename	Established Name
Alpha-2 agonists		
Alcon	Iopidine	Apraclonidine
Allergan, Inc.	Alphagan/ Alphagan P	brimonidine tartrate
Beta-adrenergic antagonists		
Alcon	Betoptic/ Betoptic S	betaxolol hydrochloride
Novartis	Ocupress	carteolol hydrochloride
Allergan	Betagan	levobutanol hydrochloride
Bausch & Lomb	Optipranolol	metipranolol
Vistakon	Betimol	timolol hemihydrate
Aton Pharma	Timoptic	timolol maleate
Ista	Istalol	timolol maleate
Aton Pharma	Timoptic XE	timolol maleate gel forming solution
Carbonic Anhydrase Inhibitors		
Duramed Pharmaceuticals	Diamox	acetazolamide
Sandoz, Inc.	N/A	methazolamide
Topical Carbonic Anhydrase Inhibitors		
Alcon	Azopt	brinzolamide
Merck	Trusopt	dorzolamide hydrochloride
Cholinergic agonist		
Alcon	Pilopine HS	pilocarpine hydrochloride gel
Alcon	Isopto Carpine	pilocarpine hydrochloride
Prostaglandin Analogues		
Allergan	Lumigan	bimatoprost
Pharmacia	Xalatan	latanoprost
Alcon	Travatan/Travatan Z	travoprost
Merck	Zioptan	tafluprost
Sympathomimetics		
Allergan	Propine	dipivefrin hydrochloride
Combination Products		
Merck	Cosopt/Cosopt PF	dorzolamide hydrochloride/timolol maleate
Allergan	Combigan	brimonidine tartrate/timolol maleate
Alcon	BetopticPilo	betaxolol hydrochloride/pilocarpine hydrochloride
Alcon	Simbrinza	Carbonic anhydrase inhibitor/alpha-agonist
Other		
Sucampo Pharma Americas, Inc.	Rescula	unoprostone isopropyl

The first travoprost-containing product to be developed was Travoprost 40 µg/mL solution preserved with benzalkonium chloride (BAK). This product, marketed as Travatan, received FDA approval in March 2001 and EU marketing authorization in November 2001. The original indication was for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular

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hypertension who were intolerant of other IOP-lowering medications or insufficiently responsive to another IOP-lowering medication. The product indication was expanded to include approval for first-line therapy in the EU in April 2003 and in the USA in August 2010.

Travoprost 40 µg/mL solution preserved with sofZia (also known as SofZia-preserved Travoprost Ophthalmic Solution, 0.004%, Travatan BAK-free and Travatan Z) was approved in the USA in September 2006 and is also marketed in Canada and Japan. Travoprost 40 µg/mL solution preserved with polyquaternium-1 (also known as PQ-preserved travoprost 0.004% ophthalmic solution and Travatan APS) was approved by EMA in November 2010 and is marketed in approximately 60 countries worldwide.

The clinical development plan for Travoprost 0.003% Solution includes one Phase 3 safety and efficacy study (C-11-034). This safety and efficacy study was designed to demonstrate the equivalence of Travoprost 0.003% Solution to Travoprost 0.004% BAK, with both dosed once daily in the evening in patients with open-angle glaucoma or ocular hypertension.

3. CMC

From the two CMC Reviews finalized 3/18/14 and 5/13/14:

NDA 204822 has provided adequate CMC information to assure the identity, strength, purity and quality of the drug product. The Drug Master Files (DMF (b) (4) and DMF (b) (4)) for the travoprost drug substance supporting this NDA are adequate.

Travoprost drug substance is manufactured by:

(b) (4)

DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT:

Travoprost Ophthalmic solution, 0.003% is a sterile, isotonic, buffered, preserved aqueous solution formulated for topical application. The inactive components include boric acid, hydrochloric acid, mannitol, polyoxyethylene hydrogenated castor oil 40 (HCO-40), Polyquaternium-1 (POLYQUAD), propylene glycol, sodium hydroxide, sodium chloride and purified water. HCO-40 excipient follows the JPE monograph which is of better quality than the HCO-40 USP Monograph. The applicant's NDA 21257 and NDA 21994 also use JPE quality HCO-40, (b) (4). POLYQUAD at the same concentration of 0.001% is used in some of Alcon's other

commercial drug products including Brimonidine Tartrate Ophthalmic Solution, 0.15% (NDA 21764). The preservative, POLYQUAD, is tested according to the same specifications that have been approved for Travoprost 0.004% PQ in Europe.

The package system is (b) (4) for travoprost containing products. This package system is comprised of a 4 mL (2.5mL (u) (s) fill) and 7.5 mL (5 mL (b) (4) fill) natural color (b) (4) polypropylene (b) (4) oval bottle with a natural color polypropylene (PP) dispensing plug and a turquoise color polypropylene closure. All primary packaging components will be sterilized by (b) (4). Tamper evidence is provided by a (b) (4) shrink band which, when heated, shrinks to conform around the neck and closure area of the bottle.

**Table 3.2.P.1-1 Composition of Travoprost 0.003% Solution
 (Formulation Identification Number 119592)**

Component	% w/v	mg/ml	Function	Quality Reference
Travoprost (AL-6221)	0.003 a	0.03 a	Active	In-House b
Polyoxyethylene Hydrogenated Castor Oil 40 (HCO-40)	(b) (4)	(b) (4)	(b) (4)	JPE c
Propylene Glycol				USP
Boric Acid				NF
Mannitol				USP
Sodium Chloride				USP
Polyquaternium-1 Solution d (eq. to Polyquaternium-1)				0.001
Hydrochloric Acid and /or Sodium Hydroxide	Adjust pH to 6.8	Adjust pH to 6.8	pH Adjustment	NF
			pH Adjustment	NF
Purified Water	(b) (4)	(b) (4)	(b) (4)	USP

a (b) (4)

b Travoprost will be tested to the approved specifications for TRAVATAN.

c JPE = Japanese Pharmaceutical Excipients. The Ph. Eur. (Macrogolglycerol Hydroxystearate) tests for heavy metal, alkalinity and appearance of solution will be substituted for the corresponding JPE tests. In addition, the following (supplemental) tests from the Ph. Eur. Monograph will be applied: free ethylene oxide, dioxan and iodine value. This is the same compendial designation and specification as approved for TRAVATAN).

d Polyquaternium-1 = POLYQUAD = polyquat = polidronium chloride. (b) (4)
 (u) (s)

PROPOSED SPECIFICATIONS:

Table 3.2.P.5.1-1 Regulatory Acceptance Specifications for Travoprost 0.003% Solution (FID 119592)

Test	Specification
Travoprost Identity (UHPLC) ^a	Positive
Travoprost Identity (TLC) ^a	Positive
Travoprost Assay (UHPLC)	(b) (4) % Label
Travoprost Degradation Products (UHPLC) (b) (4)	NMT (b) (4) % of active NMT (b) (4) % of active NMT (b) (4) % of active NMT (b) (4) % of active
Total Travoprost Degradation Products	NMT (b) (4) % of active
Unrelated Impurities (UHPLC) (b) (4)	NMT (b) (4) ppm NMT (b) (4) ppm NMT (b) (4) ppm NMT (b) (4) ppm
Unspecified Impurities (UHPLC) Any Single Unspecified Impurity Total Unspecified Impurities	NMT (b) (4) ppm NMT (b) (4) ppm
Boric Acid Identity (HPIC) ^a	Positive
Boric Acid Assay (HPIC)	(b) (4) % Label
Polyquaternium-1 (Polyquad) Identity (Spectrophotometric) ^a	Positive
Polyquaternium-1 (Polyquad) Assay (Spectrophotometric)	(b) (4) % Label
pH (Potentiometric)	(b) (4)
Osmolality (Freezing Point Depression)	(b) (4) mOsm/kg
Appearance (Visual): Color Clarity Particles/Particulates Precipitate	Colorless to Light Yellow (b) (4) NMT Ph. Eur. II (b) (4) None
Particulate Matter (Microscopy or HIAC)	NMT (b) (4) particles/mL \geq (b) (4) μ m NMT (b) (4) particles/mL \geq (b) (4) μ m NMT (b) (4) particles/mL \geq (b) (4) μ m
Sterility ^b	Meets USP requirements
Bacterial Endotoxins ^a	< (b) (4) EU/mL

^a Release test only.

^b Sterility testing will not be routinely conducted on production lots except at release. However, if tested, samples will comply with USP Requirements.

NMT = Not more than

FACILITIES INSPECTIONS:

The overall recommendation from the Office of Compliance is “Acceptable” in EES.

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**FDA CDER EES
 ESTABLISHMENT EVALUATION REQUEST
 DETAIL REPORT**

Application:	NDA 204822/000	Action Goal:	
Stamp Date:	15-JUL-2013	District Goal:	16-MAR-2014
Regulatory:	15-MAY-2014		
Applicant:	ALCON LABS INC 6201 SOUTH FREEWAY FORT WORTH, TX 761342099	Brand Name:	TRAVOPROST OPHTHALMIC SOLUTION
		Estab. Name:	
		Generic Name:	TRAVOPROST OPHTHALMIC SOLUTION
Priority:	5	Product Number; Dosage Form; Ingredient; Strengths	
Org. Code:	590		001; SOLUTION; TRAVOPROST; .003%

Application Comment:

FDA Contacts:	F. LIU	Prod Qual Reviewer		3017961469
	V. PAWAR	Micro Reviewer	(HFD-805)	3017961587
	N. BHANDARI	Product Quality PM		2404023815
	J. MILSTEIN	Regulatory Project Mgr	(HFD-590)	3017960763
	R. MADURAWA	Team Leader		3017961408

Overall Recommendation: ACCEPTABLE on 04-APR-2014 by R. SAFAAI-JAZI () 3017964463
 PENDING on 03-SEP-2013 by EES_PROD

**FDA CDER EES
 ESTABLISHMENT EVALUATION REQUEST
 DETAIL REPORT**

Establishment: CFN: 1610287 FEI: 1610287
 ALCON RESEARCH, LTD.
 6201 SOUTH FWY
 FORT WORTH, TX 761342099

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Establishment Comment: DRUG PRODUCT MANUFACTURING/TESTING FACILITY. ALCON HAS APPLIED QBD PRINCIPLES IN THE MANUFACTURING PROCESS, SPECIFICALLY TO DETERMINE THE POTENTIAL CRITICAL VARIABLES, INCLUDING MATERIAL ATTRIBUTES AND PROCESS PARAMETERS. (on 02-AUG-2013 by N. BHANDARI (j) 2404023815)

Profile: STERILE LIQUID (EXCLUDE SUSPENSIONS & EMULSIONS) OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					
SUBMITTED TO OC	03-SEP-2013				BHANDARIN
SUBMITTED TO DO	09-SEP-2013	10-Day Letter			WILLIAMSJU
DO RECOMMENDATION INSPECTION OF MAY 2013	26-NOV-2013			ACCEPTABLE	JMARTIN1
OC RECOMMENDATION	01-DEC-2013			ACCEPTABLE	SAFAAIJAZIR

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Establishment: CFN: (b) (4) FEI: (b) (4)
 (b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Establishment Comment: DRUG SUBSTANCE MANUFACTURER (on 26-JUL-2013 by N. BHANDARI () 2404023815)

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
<u>Reason</u>					
SUBMITTED TO OC	03-SEP-2013				BHANDARIN
OC RECOMMENDATION	03-SEP-2013			ACCEPTABLE	WILLIAMSJU

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**FDA CDER EES
 ESTABLISHMENT EVALUATION REQUEST
 DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)
 (b) (4)
 DMF No: AADA:
 Responsibilities: DRUG SUBSTANCE MANUFACTURER
 Establishment Comment: DRUG SUBSTANCE MANUFACTURER (on 03-SEP-2013 by N. BHANDARI () 2404023815)
 Profile: NON-STERILE API BY CHEMICAL SYNTHESIS OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
<u>Reason</u>					
SUBMITTED TO OC	03-SEP-2013				BHANDARIN
SUBMITTED TO DO CMS/EES/FACTS SHOWING ADDRESS AT	03-SEP-2013	GMP Inspection		(b) (4)	WILLIAMSJU
ASSIGNED INSPECTION TO IB LAST CSN INSPECTION WAS IN 2004	06-SEP-2013	Product Specific and GMP Inspection			MROSE
INSPECTION SCHEDULED	26-NOV-2013		(b) (4)		BSEEMAN
INSPECTION PERFORMED This comprehensive inspection of (b) (4) (b) (4) was conducted as part of CDER's IOG Work Plan for FY'13, in accordance with the CPs 7346.832 and 7356.002F under FACTS ID # (b) (4) The products covered during this inspection were Travoprost (NDA 204-822) and (b) (4) The profiles covered were CSN.			(b) (4)		Robert.Martin1
(b) (4)					
The prior FDA inspection was conducted from (b) (4) as part of OIG's FY'04 work plan in accordance to Compliance Programs 7356.002F and 7346.832 under FACTS ID# (b) (4) At the conclusion of the inspection no FDA 483 "Inspectional Observations" was issued to the firm. The inspection was classified as NAI.					
At the conclusion of the inspection no FDA 483 "Inspectional Observations" was issued to the firm however, the following items were discussed with the management team: (b) (4) Prior to the conclusion of the inspection, the management team provided documentation and commitments to address this issue.					
DO RECOMMENDATION	28-MAR-2014			ACCEPTABLE	PHILPYE
OC RECOMMENDATION	01-APR-2014			ACCEPTABLE	SAFAAJAZIR

4. Nonclinical Pharmacology/Toxicology

From the original Pharmacology/Toxicology Review finalized 4/3/14:

The nonclinical studies previously conducted to support travoprost 0.004% also support this NDA for travoprost 0.003%.

From the recommended labeling:

There are no adequate and well-controlled studies of IZBA (travoprost ophthalmic solution) 0.003% administration in pregnant women. Malformations were observed in rats at doses that were 1500 times higher the maximum recommended human ocular dose (MRHOD) based on estimated C_{max} values for the active free acid. Embryoletality and decreased fetal/neonate viability were observed in mice at subcutaneous doses 9-fold higher than the MRHOD based on estimated C_{max} for the active free acid. IZBA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Travoprost was teratogenic in rats, at an intravenous (IV) dose up to 10 mcg/kg/day (1500 times the MRHOD), evidenced by an increase in the incidence of skeletal malformations as well as external and visceral malformations, such as fused sternebrae, domed head and hydrocephaly. Travoprost did not produce malformations in rats at IV doses up to 3 mcg/kg/day (470 times the MRHOD), or in mice at subcutaneous doses up to 1 mcg/kg/day (9 times the MRHOD). Travoprost produced an increase in post-implantation losses and a decrease in fetal viability in rats at IV doses of 10 mcg/kg/day (1500 times the MRHOD) and in mice at subcutaneous doses of 1 mcg/kg/day (9 times the MRHOD).

In the offspring of female rats that received travoprost subcutaneously from Day 7 of pregnancy to lactation Day 21 at doses of ≥ 0.12 mcg/kg/day (3.2 times the MRHOD), the incidence of postnatal mortality was increased, and neonatal body weight gain was decreased. Neonatal development was also affected, evidenced by delayed eye opening, pinna detachment and preputial separation, and by decreased motor activity.

Two-year carcinogenicity studies in mice and rats at subcutaneous doses of 10, 30, or 100 mcg/kg/day did not show any evidence of carcinogenic potential. However, at 100 mcg/kg/day, male rats were only treated for 82 weeks, and the maximum tolerated dose (MTD) was not reached in the mouse study. The high dose (100 mcg/kg) corresponds to exposure levels over 400 times (for the mouse) and 700 times (for the rat) of the human exposure at the maximum recommended human ocular dose (MRHOD) of 0.03 mcg/kg, based on estimated plasma C_{max} for active free acid. Travoprost was not mutagenic in the Ames test, mouse micronucleus test or rat chromosome aberration assay. A slight increase in the mutant frequency was observed in one of two mouse lymphoma assays in the presence of rat S-9 activation enzymes.

Travoprost did not affect mating or fertility indices in male or female rats at subcutaneous doses up to 10 mcg/kg/day [40times the MRHOD based on estimated plasma C_{max} for active

free acid. At 10 mcg/kg/day, the mean number of corpora lutea was reduced, and the post-implantation losses were increased. These effects were not observed at 3 mcg/kg/day (12 times the MRHOD).

5. Clinical Pharmacology/Biopharmaceutics

From the original Clinical Pharmacology Review finalized 12/13/13

For the current NDA, the proposed product is similar to the one approved by EMA (0.004% with polyquarternium-1), except that the strength is lowered to 0.003%. The proposed dosage and indication for the new product is the same as that FDA-approved for TRAVATAN and TRAVATAN Z: once-daily topical ocular therapy for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension. The applicant has not conducted any additional clinical pharmacology studies and requested a waiver from the requirements for submission of in vivo bioavailability or bioequivalence data. To support the NDA, the applicant conducted a therapeutic equivalence Phase 3 Study C-11-034 (Travoprost 0.003% vs. Travoprost 0.004% BAK, i.e., TRAVATAN, N=864 patients).

The Applicant's request for a waiver from the requirements for submission of in vivo bioavailability/bioequivalence data is acceptable based on the consideration that the differences in formulation between TRAVATAN and Travoprost ophthalmic solution 0.003% (Polyquarternium-1 as the preservative) are not expected to influence the limited systemic availability of travoprost, based on the therapeutic bioequivalence established by Alcon Study C-11-034 (Travoprost 0.003% vs. Travoprost 0.004% BAK, i.e., TRAVATAN, N=864 patients).

In conclusion, no substantial review and labeling update (with respect to Section 12.3 Pharmacokinetics) are needed for this NDA from a clinical pharmacology perspective. The submission is approvable from a clinical pharmacology perspective.

6. Sterility Assurance

From the original Product Quality Microbiology Review finalized on 10/28/13:

There are no microbiology deficiencies identified.

Container-Closure and Package integrity – The packaging system is [REDACTED] (b) (4) for travoprost containing products. The container closure integrity [CCI] of the packaging system has been validated. For each of three validation runs (20 test samples, 2 positive controls and 2 negative controls each), the challenged units [immersion in microbial suspension containing (b) (4) CFU/mL of *Escherichia coli*] were negative for growth.

Preservative Effectiveness – The results of preservative effectiveness test validation studies for 0.004% Ophthalmic Solution (AL-6221, (b) (4)) containing Polyquaternium-1 as preservative were presented. These results include the mean values for triplicate plates for three separate tests for each of the five test microorganisms. Triplicate samples from the same lot were tested. Using standard plate count techniques, they were able to enumerate gram-positive (*S. aureus*) and gram-negative (*P. aeruginosa* and *E. coli*) vegetative bacteria, yeast (*C. albicans*) and mold (*A. niger*) at a (b) (4). A minimum detection limit of < (b) (4) CFU/mL is established for these organisms. The validity of a preservative effectiveness assay was established by demonstrating that low levels ((b) (4) CFU/mL for bacteria and yeast and (b) (4) CFU/mL for mold) of challenge organism can be detected and enumerated in test product using appropriate sampling techniques and outgrowth media containing necessary neutralizers (inactivators). The minimum detection levels are established as < (b) (4) CFU/mL for *S. aureus*, *P. aeruginosa*, *E. coli*, *C. albicans*, and *A. niger*.

The applicant meets the regulatory expectations for validating the process used to test integrity of the primary packaging system and the effectiveness of Polyquaternium-1 as a preservative in the drug product.

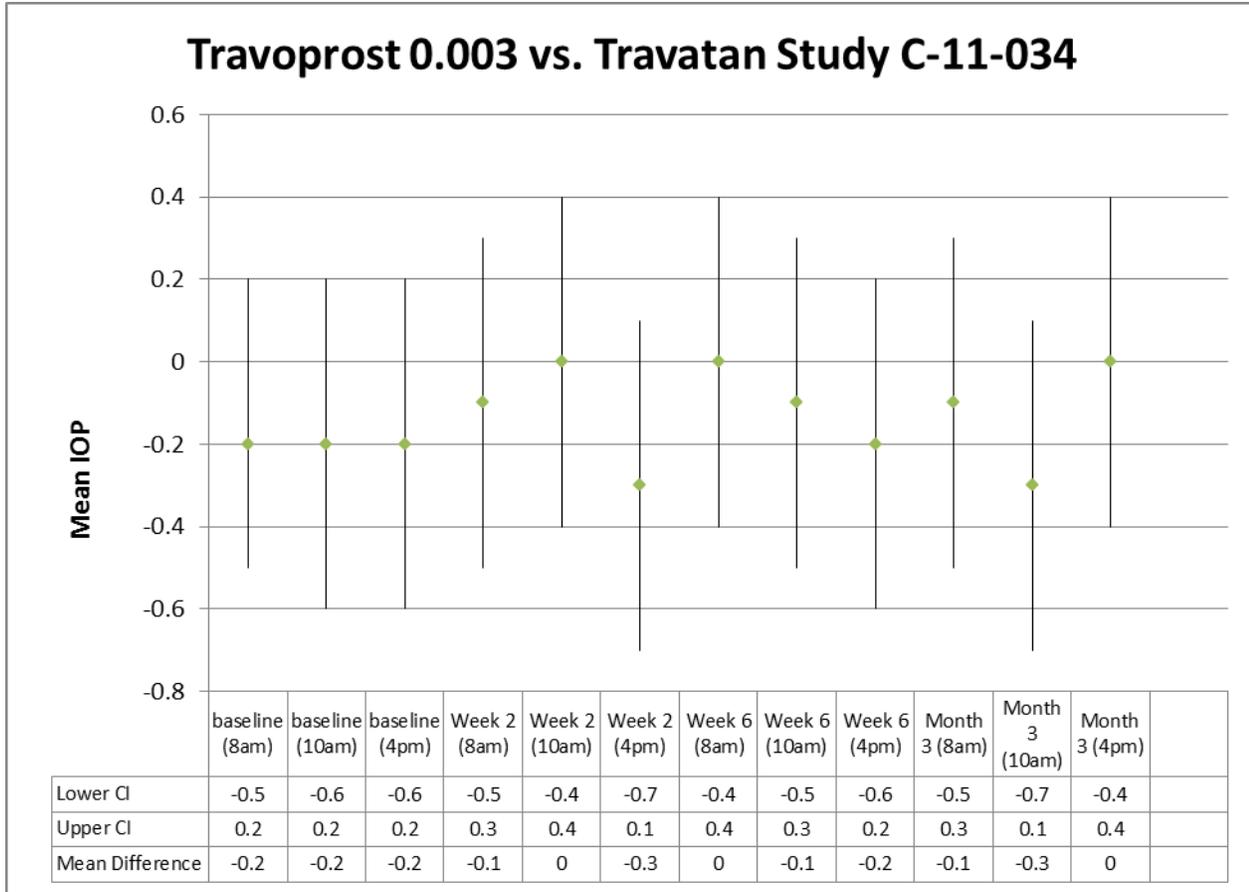
7. Clinical/Statistical - Efficacy

From the original Medical Officer Review dated 2/3/14:

This application contains a single bioequivalence study to support the approval of travoprost 0.003% for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension. The submitted clinical study report and clinical protocol related to Study C-11-034 were reviewed in depth.

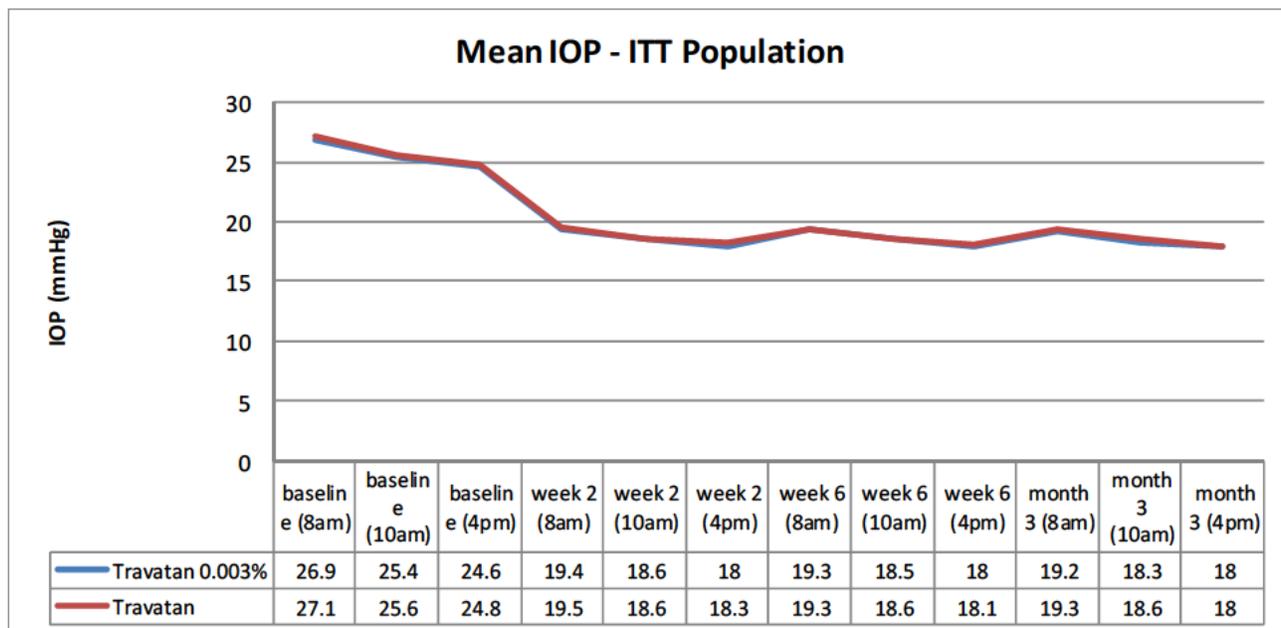
This was a multicenter, double-masked, randomized, active-controlled, two-arm, parallel group, equivalence study designed to evaluate the safety and efficacy of Travoprost 0.003% Solution relative to Travoprost 0.004% (i.e. Travatan) in adult patients with open-angle glaucoma or ocular hypertension. This study consisted of 6 visits conducted during two sequential phases: the Screening/Eligibility phase, which included a Screening Visit and 2 Eligibility Visits, and the treatment phase, which included 3 on therapy visits (conducted at Week 2, Week 6, and Month 3). Enrolled patients were randomized (1:1) at the second Eligibility Visit to 1 of the 2 study drugs and instructed to instill 1 drop of the assigned study drug in both eyes, once daily for 3 months. Evaluations of safety and efficacy were performed at selected time points (8 AM, 10 AM, and 4 PM) during study visits conducted at Week 2, Week 6, and Month 3.

Analyses of Endpoints – Mean IOP



Source: NDA 204-822, Module 5, CSR for protocol C-11-034, Table 11.4.1.1-1.

The 95% confidence interval of the mean difference in IOP between Travatan (travoprost 0.004%) and travoprost 0.003% is within 1mmHg for all timepoints measured.



Source: NDA 204-822, Module 5, CSR for protocol C-11-034, Table 11.4.1.1-1.

Travatan (travoprost 0.004%) and travoprost 0.003% have similar IOP lowering ability throughout the trial. The mean reduction from baseline in IOP ranged from approximately 7 to 8 mmHg for both treatment groups.

Efficacy Summary Statement

Results from the phase 3 study C-11-034 submitted in this NDA demonstrated that travoprost 0.003% lowered IOP by approximately 7-8 mmHg and was equivalent to Travatan (travoprost 0.004%) in IOP-lowering efficacy as measured by mean IOP. The difference in mean IOP between travoprost 0.003% and Travatan was within 1mmHg at all post-baseline timepoints.

8. Safety

From the original Medical Officer Review dated 2/3/14:

The safety of this product is based on the 12 month results of a single phase 3 study: C-11-034 in conjunction with what is known about the adverse effects associated with the use of this class of drugs.

Overall Exposure at Appropriate Doses/Durations

Number and Percentage of Patients Exposed to Study Drug (Safety Population)

	Trav 0.003%		Travatan	
	N	(%)	N	(%)
1-15 Days	0	(0.0)	5	(1.2)
16-45 Days	7	(1.6)	4	(1.0)
46-87 Days	113	(25.6)	111	(26.4)
>87 Days	322	(72.9)	301	(71.5)

Trav 0.003% = Travoprost 30 µg/mL eye drops, solution preserved with Polyquad

Travatan = Travoprost 40 µg/mL eye drops, solution preserved with BAK

Source: NDA 204-822, Module 5, CSR for protocol C-11-034, Table 12.1-2.

Subject Disposition

Discontinuations – Safety Population

	Travoprost 0.003%	Travoprost 0.004%
Total	10	14
Adverse event	3	4
Patient decision	3	3
Noncompliance	1	0
Lost to follow-up	2	1
Inadequate IOP control	1	5
Other		1

Patients with Adverse Events Leading to Patient Discontinuation (Safety Set)

Treatment	Age/Sex	Adverse Event	Onset day
Travoprost 0.003%	66/F	eye irritation, eye pruritus	16
Travoprost 0.003%	44/F	myalgia	2
Travoprost 0.003%	67/F	conjunctival hyperemia, photophobia vision blurred	40 64
Travoprost 0.004%	62/F	dizziness, somnolence	4
Travoprost 0.004%	51/F	ulcerative keratitis	82
Travoprost 0.004%	72/F	eyelid edema headache ocular hyperemia	9 3 3
Travoprost 0.004%	61/F	conjunctivitis allergic, ocular hyperemia	1

Adverse Events

Adverse Events Reported at a Rate of $\geq 1\%$ (Safety Set) – Study C-11-034

	Travoprost 0.003% N=442	Travoprost 0.004% N=421
Coded Adverse Event	N(%)	N(%)
Eye disorders		
Ocular hyperemia	31 (7)	34 (8.1)
Conjunctival hyperemia	25 (5.7)	30 (7.1)
Eye pruritus	15 (3.4)	10 (2.4)
Eye irritation	10 (2.3)	6 (1.4)
Dry eye	7 (1.6)	7 (1.7)
Photophobia	4 (0.9)	5 (1.2)
Punctate keratitis	6 (1.4)	3 (0.7)
Conjunctival hemorrhage	1 (0.2)	6 (1.4)
Eye pain	3 (0.7)	4 (1.0)
Vision blurred	2 (0.5)	4 (1.0)
Vitreous floaters	2 (0.5)	4 (1.0)
Conjunctivitis allergic	-	4 (1.0)
Infections and infestations		
Upper respiratory tract infection	5 (1.1)	1 (0.2)
Musculoskeletal and connective tissue disorders		
Osteoarthritis	1 (0.2)	4 (1.0)

NDA 204-822, Module 5, CSR for protocol C-11-034, Table 14.3.1.5-1

The rate of adverse events were similar between travoprost 0.003% and Travatan with exception of conjunctival hemorrhage which was six (6) fold higher in the Travatan group, although not statistically different.

Hyperemia

In the NDA 21257 review, the reviewer notes that for studies C-97-71, C-97-72, C-97-73 and C-97-79 there is a statistically significant difference in ocular hyperemia among treatment groups ($p=0.0001$). A concentration-related increase in mean ocular hyperemia was observed between travoprost (AL-6221) 0.0015% and 0.004% compared to Timoptic 0.5%.

The most noticeable difference in the early studies and the current Study C-11-034 is the lower rate of ocular hyperemia reported for both IZBA and Travatan; the reason for this difference is the methodology used to evaluate hyperemia:

- In confirmatory clinical trials involved in the development of Travoprost 0.004% preserved with BAK or sofZia (C-97-71, C-97-72, C-97-79, and C-04-17) adverse events were collected for any clinically relevant change, based on the clinical judgment of the study investigator, in an ophthalmic assessment measured during a clinical trial. Additional specific criteria were outlined in the protocols that required that an AE be reported by the study investigator. These clinical trials required investigators to grade ocular redness of each treated eye.¹ The reported hyperemia rates included patient and/or physician reports of hyperemia as well as any patient with an increase of 1 or more in their graded ocular redness.
- In clinical trial C-11-034, changes from baseline in an ophthalmic assessment measured during the clinical trial were reported as AEs for any clinically relevant change, based upon the clinical judgment of the study investigator. Adverse events for changes from baseline in an ophthalmic assessment measured during clinical trial C-08-40 (Travoprost 0.004% PQ) were also collected in the same manner as in C-11-034. These trials did not include a “required grading of hyperemia for each patient.” The reporting rate of hyperemia for these trials includes only patient and/or physician reports of hyperemia.

Safety Summary Statement

Overall, travoprost 0.003% was safe and well tolerated. The rate of adverse events was similar between travoprost 0.003% and Travatan. There was no significant difference between groups in the number of dropouts/discontinuations.

The most common adverse reaction observed in controlled clinical studies with travoprost ophthalmic solutions including IZBA was ocular hyperemia which was reported in 10 to 50% of patients depending on the methodology used to capture hyperemia. Up to 3% of patients discontinued therapy due to conjunctival hyperemia. Ocular adverse reactions reported at an incidence of 5 to 10% in these clinical studies included decreased visual acuity, eye discomfort, foreign body sensation, pain and pruritus.

Ocular adverse reactions reported at an incidence of 1 to 4% in clinical studies with travoprost ophthalmic solutions included abnormal vision, blepharitis, blurred vision, cataract, conjunctivitis, corneal staining, dry eye, iris discoloration, keratitis, lid margin crusting, ocular inflammation, photophobia, subconjunctival hemorrhage and tearing.

9. Advisory Committee Meeting

¹ Ocular hyperemia assessment was performed at 8AM, 10AM, 4PM at Eligibility 2 (baseline) examinations and any subsequent visits. A scale ranging from 0 to 3 units in 0.5 increments was used to assess ocular hyperemia. Clinically significant change from baseline in ocular hyperemia was defined as an increase of one or more units from the maximum hyperemia score recorded at any one time-point at the baseline

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This drug product did not present any new or problematic chemistry/manufacturing issues, preclinical issues, or clinical issues to warrant convening an FDA Advisory Committee Meeting.

10. Pediatrics

A full waiver request for pediatric studies has been submitted and accepted.

11. Other Relevant Regulatory Issues

DSI

A Division of Scientific Investigations (DSI) audit was requested. The study (C-11-034, entitled “A Multicenter, Double-Masked Study of the Safety and Efficacy of Travoprost Ophthalmic Solution, 0.003% Compared to TRAVATAN in Patients with Open-Angle Glaucoma or Ocular Hypertension”) was inspected in support of the indication. The clinical sites of Drs. Branch and Peace were selected for inspection because of their relatively high enrollments.

Name of CI, Location	Protocol #/ Site #/ # of Subjects	Inspection Dates	Final Classification
James D. Branch, M.D. 224 Town Run Lane Winston-Salem, NC 27101	C-11-034/ 3631/ 48	7-9 Jan 2014	NAI
James H. Peace, M.D. United Medical Research Institute 431-433 North Prairie Avenue Inglewood, CA 90301	C-11-034/ 3627/ 33	3-6 Dec 2013	NAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in Form FDA 483 or preliminary communication with the field;
EIR has not been received from the field or complete review of EIR is pending.

Data generated by these clinical sites and submitted by the sponsor appear adequate in support of the respective indication.

FINANCIAL DISCLOSURE

The applicant has examined its financial data regarding significant payments of other sorts made to all investigators in the studies and equity information as provided by the investigators, as defined in 21 CFR 54.2. There is no evidence to suggest that the results of the study were impacted by any financial payments.

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DMEPA

IZBA was found acceptable as a proprietary name by the Division of Medication Error Prevention and Analysis (DMEPA), and the applicant was notified in a formal letter dated 2/19/14.

DMEPA also provided recommendations on the packaging configuration and the package insert labeling.

DTOP agreed with the following recommendations for carton and container:

1. Place the route of administration “For Ophthalmic Use” on the principal display panel of the container label to highlight the route of administration. (b) (4)
2. Similarly, place the route of administration “For Ophthalmic Use ” on the principal display panel of the container label to highlight the route of administration.

DTOP did not agree with only capitalizing the first letter of the proprietary name. Alcon has trademarked IBZA, not Ibza. The law requires the route of administration (For Ophthalmic Use), but unless harm has actually been demonstrated we would not specify “For Ophthalmic Use Only.”

DDMAC

The Division of Drug Marketing, Advertising, and Communications (DDMAC) reviewed the proposed product labeling in a review dated 4/9/14.

OPDP Comment: We note that other prostaglandin analogue labels (such as Travatan Z and Lumigan) include a Warning and Precaution (W&P) regarding “Angle Closure, Inflammatory, or Neovascular Glaucoma.” Should a similar W&P be included in this IZBA label?

Current OND recommendations for labeling do not encourage the inclusions of Warnings and Precautions where no data is actually provided or known.

OPDP Comment: We note that the currently approved Travatan Z (travoprost 0.004%) reports an incidence of ocular hyperemia of 30% to 50%. We would just like to confirm that the additional IZBA clinical trial report an ocular hyperemia incidence of (b) (4) 0%.

The label describes the an incidence of ocular hyperemia from (b) (4) % in studies with travoprost ophthalmic solutions including IZBA. Differences may be due to method used to report hyperemia.

OPDP Comment: Should IZBA be included here [Section 6.1] as well? We are concerned that this statement could be used to suggest that these risks are not associated with IZBA. If applicable, we recommend including “IZBA” here.

The risks cited were seen with Travatan and Travatan Z, not with IZBA.

OPDP Comment: We note that the Travatan Z PI includes a section 8.6 titled, “Hepatic and Renal Impairment.” Should this information be included in this IZBA label as well?

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Current OND recommendations for labeling do not encourage the inclusions of Special Populations where no data is actually provided or known.

OPDP Comment: We note that the rest of the Clinical Studies section communicates the “Travoprost ophthalmic solution 0.003%” as “Travoprost 0.003%” not “IZBA.” For clarity, should this abbreviation be revised to “Travoprost 0.003%?”

The Clinical Studies Section has been revised to use consistent reference to the drug products.

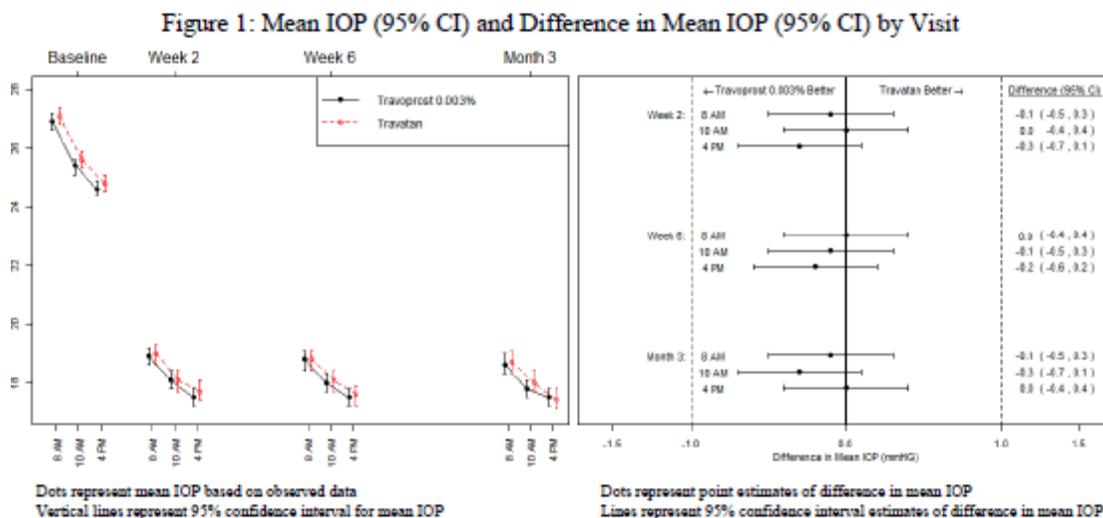
BIostatISTICS

Per the Biostatistics consultative review finalized 3/27/14:

In this submission, the applicant seeks approval of Travoprost ophthalmic solution 0.003% containing the preservative polyquaternium-1 (also known as PQ-preserved) for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension. Travoprost ophthalmic solution at a concentration 0.004% PQ is currently an approved product by the European Medicines Agency (EMA).

The primary evidence for the safety and efficacy of Travoprost solution 0.003% is based on a single Phase 3 trial (C-11-034). This trial was a multicenter, double-masked, randomized, active controlled, 2-arm, parallel group equivalence study. The study was designed to evaluate the safety and equivalence with respect to IOP-lowering efficacy of Travoprost 0.003% to Travoprost 0.004% BAK (preserved with benzalkonium chloride) in adult patients with open angle glaucoma or ocular hypertension. The active control arm, Travoprost 0.004% BAK (Travatan), received FDA approval in March 2001 and was marketed as Travatan.

As shown in Figure 1 below, overall, both treatment groups resulted in comparable IOP reductions at all visits and assessment time points; the point estimates for the mean IOP reductions ranged from 7.6 to 8.7 mmHg in the Travoprost 0.003% group and from 7.5 to 8.8 mmHg in the Travatan group. The highest IOP reduction in both treatment groups was observed at the 8 AM assessment time point.



12. Labeling

NDA 204822, IZBA (travoprost ophthalmic solution) 0.003% is recommended for approval for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension with the revised labeling found in the Appendix at the end of this CDTL review.

13. Recommendations/Risk Benefit Assessment

RECOMMENDED REGULATORY ACTION:

NDA 204822, IZBA (travoprost ophthalmic solution) 0.003% is recommended for approval for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension. The benefits of using this drug product outweigh the risks for the above indication.

RISK BENEFIT ASSESSMENT:

Travoprost 0.003% lowered IOP by approximately 7-8 mmHg and was equivalent to Travatan (travoprost 0.004%) in IOP-lowering efficacy as measured by mean IOP. The difference in mean IOP between travoprost 0.003% and Travatan was within 1mmHg at all post-baseline timepoints.

Overall, travoprost 0.003% was safe and well tolerated. The rate of adverse events was similar between travoprost 0.003% and Travatan. There was no significant difference between groups in the number of dropouts/discontinuations.

Based on the single trial submitted in this NDA, the risk/benefit profile of travoprost 0.003% is considered equivalent to Travatan and is therefore recommended for approval.

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Pharmacology/Toxicology, CMC, Biostatistics, Clinical, Clinical Pharmacology, and Product Quality Microbiology have recommended approval for this application.

RECOMMENDATION FOR POSTMARKETING RISK MANAGEMENT ACTIVITIES:

There are no risk management activities recommended beyond the routine monitoring and reporting of all adverse events.

There are no recommended Postmarketing Requirements or Phase 4 Commitments.

9 Page(s) of Draft Labeling have been Withheld in Full
as b4 (CCI/TS) immediately following this page

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

/s/

WILLIAM M BOYD
05/14/2014

WILEY A CHAMBERS
05/14/2014