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APPLICATION NUMBER:

204822Orig1s000

<u>SUMMARY REVIEW</u>

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Renata Albrecht, MD
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	NDA 204822 N/A
Related IND	IND 51000 (see footnote 1)
Applicant Name	Alcon Laboratories, Inc. (Alcon)
Application Type	505(b)(1)
Date of Submission	7/15/2013 (standard review)
PDUFA Goal Date	5/15/2014
Proprietary Name / **Established (USAN) Name**	IZBA Travoprost ophthalmic solution
Dosage Forms / Strength	Solution / 0.003%
Preservative	Polyquaternium-1 0.001% (POLYQUAD®)
Route of Administration	Topical ophthalmic
Therapeutic Class	Prostaglandin
Proposed Indication(s)	Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension
Dosage Regimen	One drop in the affected eye(s) once daily in the evening
How Supplied	Travoprost 0.003% Solution will be packaged in a polypropylene oval bottle with a natural color polypropylene dispensing plug and a turquoise polypropylene closure.
Action/Recommended	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Jennifer Harris, William Boyd 2/3/2014
CDTL Review	William Boyd, Wiley Chambers 5/14/2014
Statistical Review	Solomon Chefo, Yan Wang, Dionne Price 3/27/2014
Pharmacology Toxicology Review	Andrew McDougal, Lori Kotch 4/3/2014
CMC Review	Fuqiang Liu, Rapti Madurawe 3/18/2013, 5/13/2014
Quality Microbiology Review	Vinayak Pawar, John Metcalfe 10/28/2013
Biopharmaceutics Review	Houda Mahayni, Angelica Dorantes 8/21/2013
Office of Compliance	Acceptable
Clinical Pharmacology Review	Yongheng Zhang, Philip Colangelo 12/13/2013
OPDP/DPDP	Christine Corser 3/31/2014
OSI/DGCPC	Roy Blay, Janice Pohlman, Kassa Ayalew 3/14/2014
OSE/DMEPA Proprietary Name	Kellie Taylor/Karen Townsend 2/19/2014 Rachna Kappor, Yelena Maslov 2/10/2014
OSE/DMEPA	Rachna Kapoor, Yelena Maslov 3/4/2014
OSE/DDRE	N/A
OSE/DRISK	N/A
Project Manager	Judit Milstein

OND=Office of New Drugs
CDTL=Cross-Discipline Team Leader
OSI/DGCPC=Office of Scientific Investigations/Division of Good Clinical Practice Compliance
OPDP/DPDP=Office of Prescription Drug Promotion/Division of Prescription Drug Promotion
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management

Signatory Authority Review Template

1. Introduction

Alcon has submitted NDA 204822 for IZBA (travoprost ophthalmic solution) 0.003%. This represents a new (lower) concentration and formulation of travoprost, containing a different preservative (polyquaternium-1, POLYQUAD®), compared to Alcon's previously approved product, Travatan (travoprost ophthalmic solution) 0.004% containing benzalkonium chloride (BAK) and Alcon's Travatan Z (travoprost ophthalmic solution) 0.004% containing an ionic buffered system *sof*Zia® (boric acid, propylene glycol, sorbitol, zinc chloride).

The application includes the results of one randomized, double-masked clinical trial C-11-034 demonstrating bioequivalence between IZBA and Travatan, as well as information on CMC, pharmacology/ toxicology, clinical pharmacology.

To support the approval of this formulation, the applicant provides a brief overview of their drug development program for travoprost, including their dose ranging studies (C-96-52 and C-97-02) of concentrations ranging from 0.00009% to 0.006%, and Phase 3 studies that evaluated concentrations of 0.0015% and 0.004%. (b) (4) [redacted]

The current application does not raise any novel regulatory issues or areas of concern. The review team recommends approval of the application. The CDTL review provides an overall summary of the application, and further details are provided in the primary reviews for this NDA.

2. Background

Glaucoma is a life-long progressive disease that is characterized by irreversible damage to the optic nerve and corresponding loss of visual field. One of the primary risk factors is elevated intraocular pressure (IOP). The reduction and control of elevated IOP in open-angle glaucoma and ocular hypertension is usually managed by chronic, long-term topical ocular therapy.

Travatan (travoprost ophthalmic solution) 0.004% (NDA 021257) was approved on March 16, 2001; the product contains benzalkonium chloride (BAK) 0.015% as preservative. The indication for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension was limited to patients who did not tolerate or respond to available IOP lowering agents because of the adverse reactions of iris pigmentation changes, given the uncertainly of the long-term consequences of these findings (skin/eyelid

(b) (4) [redacted]

pigmentation and eyelash changes were also noted). On August 31, 2010, the indication was revised to remove these limitations based on NDA 21257/S018, which contained follow up data of travoprost-treated patients for multiple years showing the eyelash changes could be reversible while iris pigmentation was not. The follow-up and post-marketing information did not identify reports of pigmentary glaucoma or melanoma, which had been a potential concern.

In April 2010, Alcon, Inc., announced that it would no longer make/market/distribute Travatan. However, Travatan Z (which contains a different preservative) will continue to be available.[2] A search of the Alcon web site shows that the package insert for Travatan is still available on http://www.alcon.com/eye-care-products/ (accessed 4/25/2014), along with the Travatan Z product labeling.

Travatan Z (NDA 021994) 0.004%, preserved with *sof*Zia® (boric acid, propylene glycol, sorbitol, zinc chloride) was approved September 21, 2006.

NDA 204822 is for a 25%-reduced concentration of travoprost (0.003%) and the preservative polyquaternium-1 (POLYQUAD).

A formulation of travoprost 0.004% containing the POLYQUAD preservative was approved by the European Medicines Agency (EMA) in November 2010 and marketed in about 60 countries, according to the applicant. [redacted] (b) (4) the IZBA product is [redacted] (b) (4) the EMA approved formulation.

There are currently multiple topical products in several classes available for the reduction of IOP, including beta-adrenergic antagonists (beta-blockers), alpha-adrenergic agonists, parasympathomimetic (miotic) agents, carbonic anhydrase inhibitors, prostaglandin analogs, and some combination products. A complete list is included in the Medical Officer's Review and CDTL Review.

3. CMC

For details, see the CMC, Quality Microbiology and Biopharmaceutic reviews.

Briefly, the product is a sterile ophthalmic solution containing travoprost 30 µg/mL, polyoxyethylene hydrogenated castor oil 40 (HCO-40),[3] sodium chloride, propylene glycol, boric acid, mannitol, polyquaternium-1 solution 0.001 (POLYQUAD, preservative),[4] hydrochloric acid and/or sodium hydroxide and purified water. The concentration of POLYQUAD (0.01 mg/mL) in the travoprost 0.003% solution is essentially the same as that approved for some ophthalmic demulcent products and marketed IOP-lowering eye drops in the US (Brimonidine Tartrate Ophthalmic Solution, 0.15%), EU (TRAVATAN® PQ) and

[2] http://glaucoma.emedtv.com/travatan/travatan.html
http://myeyepod.blogspot.com/2010/06/travatan-discontinued.html
[3] Polyoxyethylene hydrogenated castor oil 40 (HCO-40) is covered by JPE (Japanese Pharmacopeia of Excipients) and is also used in approved products under NDA 21257 and NDA 21994.
[4] POLYQUAD at the same concentration of 0.001% is used in several of Alcon's other commercial drug products including Brimonidine Tartrate Ophthalmic Solution, 0.15% (NDA 21764) and Diclofenac Sodium Ophthalmic solution, 0.1% (NDA 20809).

(b) (4) (DUOTRAV® PQ). Further details on the formulation and specifications can be found in primary reviews.

The product is intended for multi-dose topical administration. The package system is comprised of a 4 mL (contain 2.5 ml of solution) and 7.5 mL (containing 5 mL of solution) polypropylene oval bottle with a (b) (4) mm natural color polypropylene dispensing plug and a (b) (4) mm turquoise polypropylene closure. This is said to be (b) (4) for travoprost products.

All primary packaging components are 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. A carton will be used for the secondary packaging.

Drug product specifications include identification, assay and impurities for travoprost, leachates, assay for boric acid and POLYQUAD, and physical measurements, e.g., particulates, color, clarity, etc. The microbiological attributes include sterility and bacterial endotoxins.

The reviewers determined that the applicant met regulatory expectations for testing of primary packaging integrity, preservative effectiveness test validation, validating the sterilization process for the manufacturing equipment, validating the performance of process simulations in support of the (b) (4) manufacture of the drug product, and validating the process used for sterilization of the manufacturing equipment for the performance of process simulations in support of the (b) (4) manufacture of the drug product.

All stability results at the long term storage conditions through 52 weeks, accelerated conditions through 26 weeks, and stressed conditions through 6 weeks are acceptable for 2.5 mL/4mL and 5 mL/7.5 mL bottle configurations. Therefore, a shelf-life of 18 months (78 weeks) is granted for both container closure sizes (2.5 mL/4 mL and 5 mL/7.5 mL bottles) when stored at 2°C to 25°C.

Pursuant to 21 CFR §320.22 (b) (1), the Applicant requested a waiver from the requirements for submission of in vivo bioavailability or bioequivalence data for this topical solution; the biowaiver was granted.

The reviewers note that NDA 204822 has provided adequate CMC information to assure the identity, strength, purity and quality of the drug product. Labeling has been finalized. The overall recommendation from the Office of Compliance is Acceptable.

<u>*Comment:*</u>
I concur with the conclusions reached by the chemistry reviewers regarding the acceptability of the manufacturing of the drug product. Manufacturing site inspections were acceptable. There are no outstanding CMC issues to preclude approval.

4. Nonclinical Pharmacology/Toxicology

For details, see the Pharmacology/Toxicology Review. A brief summary it provided below.

The applicant conducted nonclinical studies in support of the original travoprost drug development program that were reviewed previously.

The applicant conducted one 3-month topical ocular toxicity and irritation study to support the travoprost 0.004% POLYQUAD (PQ) formulation (approved in Europe) in New Zealand White (NZW) rabbits which was submitted in this NDA 204822. There were four arms: vehicle three times daily (TID), travoprost 0.002% TID, travoprost 0.004% twice daily (BID), and travoprost 0.012% BID. Conjunctival congestion and discharge were seen with the highest dose, but no gross or microscopic findings in the tissues examined. This study along with the other non-clinical testing of travoprost and data on the preservative (PQ) are considered to support approval.

The labeling parallels the Travatan Z product and the reviewer recommends updating the labeling to use travoprost free acid plasma concentrations to extrapolate human equivalent doses (HED), a more conservative approach to update Sections 8.1 and 13.1. Travoprost, an isopropyl ester prodrug, is hydrolyzed by esterases in the cornea to its biologically active free acid.

Comment:
I concur with the conclusions reached by the pharmacology/toxicology reviewers to recommend approval. Labeling revisions have been incorporated in labeling. There are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

Travoprost belongs to the pharmacological class of prostaglandin F2α receptor agonists. It is absorbed through the cornea and is hydrolyzed to the active free acid. Travoprost free acid is a relatively selective FP prostanoid receptor agonist which is believed to reduce intraocular pressure by increasing the outflow of aqueous humor via trabecular meshwork and uveoscleral outflow.

Pharmacokinetic studies demonstrated very low systemic plasma levels following topical administration of travoprost 0.004% BAK with concentrations in most samples from 5 multiple-dose studies being less than a sensitive assay's quantitation limit of 10 pg/mL. In studies in patients with renal impairment and hepatic impairment, no clinically relevant changes in hematology, chemistry, or urinalysis lab data were reported.

No pharmacokinetic studies with travoprost 0.003% Solution were conducted.
The applicant requested a waiver from the requirements for submission of in vivo bioavailabililty or bioequivalence data; this request was accepted. Clinical equivalence was shown in Study C-11-034. No labeling revisions are proposed.

Comment:
I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewers to recommend approval. There are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical-Efficacy

For details, see the Clinical and Statistical reviews. A brief summary is provided below.

This new formulation and concentration of travoprost is supported by Study C-11-034, a Phase 3, double masked, randomized multicenter trial, comparing the IZBA product to the approved Travatan product. The study was conducted at 60 centers (52 in US, 8 in Europe) and 864 patients were enrolled, 442 randomized to travoprost 0.003% (IZBA) and 422 to travoprost 0.004% (Travatan). Randomization was stratified by site and IOP (24-27 mmHg or 28-36 mmHg). Patients were dosed once-daily in the evening. The objective was to show the two products were equivalent; this was achieved by showing the 2-sided 95% CI for the difference in IOP between treatment groups was within ± 1.5 mmHg at each of the 3 time points measured at each of the three visits and the majority of the CIs (>50%) were be within ± 1 mmHg. IOP measurements were done at 8AM, 10AM and 4PM at Week 2, Weeks 6 and Month 3. The study design, endpoints, and analysis are consistent with the design of other applications for this indication; the duration of the study is acceptable because of safety data on higher concentrations.

Within the ITT analysis set, the majority of subjects in the study were Caucasian (72.4%), female (59.7%), 65 years of age and older (55.8%; overall mean age = 65.2 years, range 21 to 92 years), had brown eyes (60.3%) and a diagnosis of open-angle glaucoma (69.1%).

Based on the results of the study, all mean differences in measurements for the two products were within ± 1 mmHg margin (and thus also within the ± 1.5 mmHg margin). The mean reduction from baseline (25-27 mmHg) ranged from about 7 to 8 mmHg in each treatment group. Approximately 53% of patients were able to achieve IOP less than 18 mmHg at the 4PM visit measurement; fewer patients (35% to < 50%) achieved this target at the 8AM and 10AM visits, although the largest decrease in IOP from baseline was seen at the 8AM measurement. Approximately half the patients were able to achieve a 30% reduction from baseline. The mean IOP at each visit are provided in the table below.

Comparison of Mean IOP (mmHg) at Baseline, Week 2, Week 6, and Month 3 (ITT Analysis Set)

		Travoprost 0.003% (N=442)		Travatan (N=418)		Mean Difference (a) (b) (95% CI)
Visit	Time Point	N	Mean (SE)	N	Mean (SE)	
Baseline	8 AM	442	26.9 (0.12)	418	27.1 (0.14)	-0.2 (-0.5, 0.2)
	10 AM	442	25.4 (0.13)	418	25.6 (0.15)	-0.2 (-0.6, 0.2)
	4 PM	442	24.6 (0.14)	418	24.8 (0.16)	-0.2 (-0.6, 0.2)
Week 2	8 AM	442	19.4 (0.16)	416	19.5 (0.17)	-0.1 (-0.5, 0.3)
	10 AM	442	18.6 (0.16)	416	18.6 (0.16)	-0.0 (-0.4, 0.4)
	4 PM	442	18.0 (0.16)	416	18.3 (0.16)	-0.3 (-0.7, 0.1)
Week 6	8 AM	439	19.3 (0.16)	413	19.3 (0.17)	-0.0 (-0.4, 0.4)
	10 AM	440	18.5 (0.16)	413	18.6 (0.17)	-0.1 (-0.5, 0.3)
	4 PM	440	18.0 (0.16)	413	18.1 (0.17)	-0.2 (-0.6, 0.2)
Month 3	8 AM	432	19.2 (0.17)	408	19.3 (0.18)	-0.1 (-0.5, 0.3)
	10 AM	432	18.3 (0.17)	408	18.6 (0.18)	-0.3 (-0.7, 0.1)
	4 PM	431	18.0 (0.16)	408	18.0 (0.17)	0.0 (-0.4, 0.4)

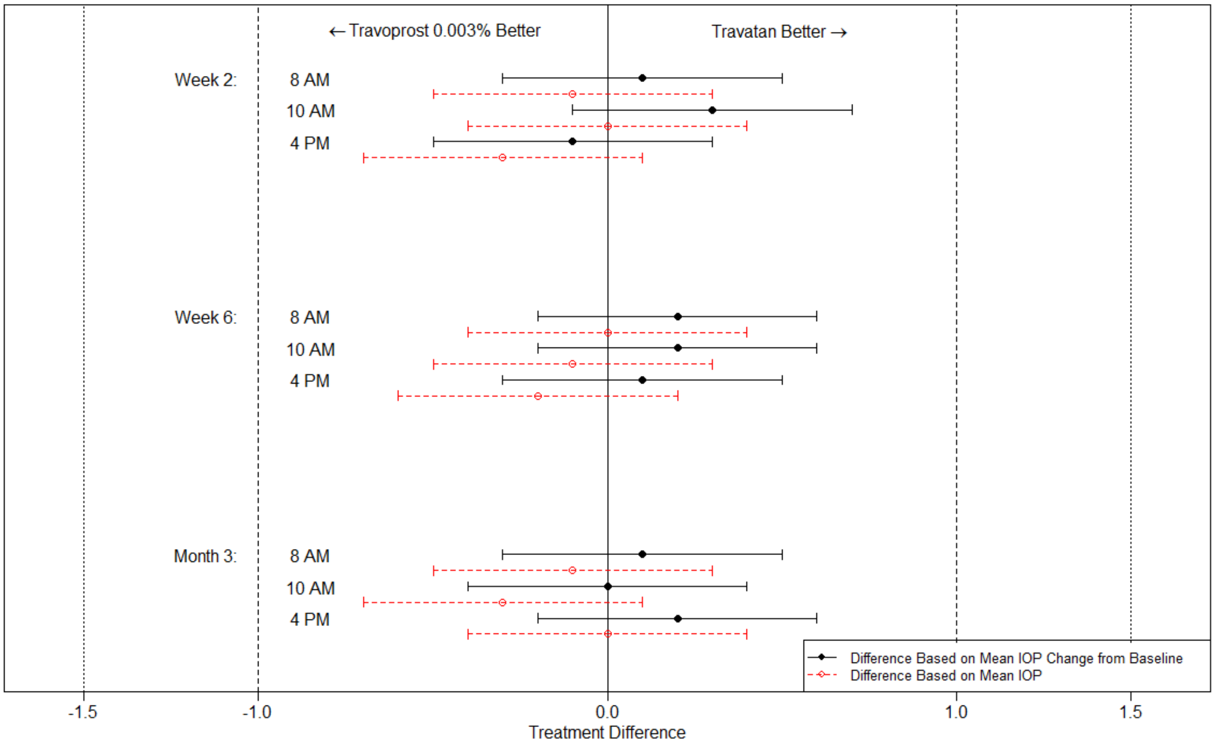
SE = Standard Error; CI = Confidence Interval
(a) Estimates for Week 2, Week 6, and Month 3 visits based on least squares mean derived from a statistical model that accounts for correlated IOP measurements within patient where site and 8 AM baseline IOP stratum are in the model
(b) Estimates for Baseline visit at each time points were based on two sample independent t-test procedure
Source: FDA Statistical Review

IOP Change from Baseline (mmHg)

*One subject had missing data at 8 AM at Week 6; one subject had missing data at 4 PM at Month 3.

		IZBA				TRAVATAN			
Visit		N	8 AM	10 AM	4 PM	N	8 AM	10 AM	4 PM
Week 2	Mean	442	-8.0	-7.3	-7.1	416	-8.1	-7.5	-7.1
	95% CI		(-8.3, -7.7)	(-7.6, -7.0)	(-7.4, -6.8)		(-8.4, -7.8)	(-7.8, -7.2)	(-7.4, -6.8)
Week 6	Mean	440*	-8.1	-7.4	-7.2	413	-8.3	-7.5	-7.2
	95% CI		(-8.4, -7.9)	(-7.6, -7.1)	(-7.5, -6.9)		(-8.7, -8.0)	(-7.9, -7.2)	(-7.5, -6.9)
Month 3	Mean	432*	-8.2	-7.5	-7.1	408	-8.4	-7.6	-7.3
	95% CI		(-8.6, -7.9)	(-7.9, -7.2)	(-7.4, -6.8)		(-8.7, -8.1)	(-7.9, -7.2)	(-7.7, -7.0)

The following figure shows the treatment difference based on mean IOP (red lines) and based on mean IOP change from baseline (black line) for the ITT analysis set.



Dots represent point estimates of treatment difference in mean IOP change from baseline; Horizontal lines represent 95% Confidence Intervals
Source: FDA Statistical Review, Figure 6

As shown in the figure above, the statistical reviewer noted that based on both efficacy measures, the equivalence criterion of the two-sided 95% CIs for the treatment differences to be within ±1.5 mmHg was successfully met. However, the point estimates for the treatment differences based on the two efficacy measures were in differing directions; analysis based on the primary endpoint of mean IOP measure slightly favored travoprost 0.003% while analysis based on the mean IOP change from baseline efficacy measure slightly favored Travatan. As noted in the statistical review, the mean IOP changes from baseline at each on-therapy visit and assessment time point are generally a more meaningful measure of efficacy than comparing the mean IOP measurements, since the former accounts for any baseline imbalances.

Comment:
In summary, study C-11-034 met the pre-defined criteria for efficacy. I concur with the recommendation for approval by the clinical and statistical reviewers. The Clinical Studies section adequately summarizes the study design and efficacy outcomes.

NDA 21257 - Travatan 0.004% Background

To understand some of the background on the travoprost 0.004% drug development and findings from previously-reviewed clinical trials of the control drug, Travatan, the clinical review for NDA 21257, dated 11/15/2000 (DARRTS) was consulted.[5] The original NDA

[5] http://www.accessdata.fda.gov/drugsatfda_docs/nda/2001/21257_Travatan_medr_P1.pdf (accessed 4/24/2014)

21257 review included results from five controlled trials examining different concentrations of travoprost in patients with open-angle glaucoma or ocular hypertension; the characteristics of these trials are presented in the table below.

Protocol Number	Study Design	Treatment Duration	Treatment Groups	Dosing	No. Sites	No. Subjects Randomized
Dose-Response C-97-02 US	Triple-masked, randomized, placebo-controlled	28 days	AL-6221 0.001% AL-6221 0.002% AL-6221 0.004% AL-6221 0.006% AL-6221 Vehicle	1 drop p m. OU 1 drop p m. OU 1 drop p m. OU 1 drop p m. OU 1 drop p m. OU	9	227 (1:1:1:1)
Efficacy/Safety C-97-71 US	Triple-masked, randomized, active-controlled	12 months	AL-6221 0.0015% AL-6221 0.004% Timoptic 0.5% Xalatan 0.005%	1 drop p m. OU 1 drop p m. OU 1 drop BID OU 1 drop p m. OU	44	801 (1:1:1:1)
Efficacy/Safety C-97-72 US	Triple-masked, randomized, active-controlled	6 months	AL-6221 0.0015% AL-6221 0.004% Timoptic 0.5%	1 drop p m. OU 1 drop p m. OU 1 drop BID OU	44	605 (1:1:1)
Efficacy/Safety C-97-73 US & Canada	Triple-masked, randomized, placebo-controlled	6 months	AL-6221 0.0015% AL-6221 0.004% AL-6221 Vehicle (all dosing adjunctive to Timoptic 0.5%)	1 drop p m. OU 1 drop p m. OU 1 drop p m. OU 1 drop BID OU	46	427 (1:1:1)
Efficacy/Safety C-97-79 EU & Australia	Triple-masked, randomized, controlled	9 months	AL-6221 0.0015% AL-6221 0.004% Timoptic 0.5%	1 drop p m. OU 1 drop p m. OU 1 drop BID OU	64	573 (1:1:1)

The efficacy results from these studies indicate that concentrations of 0.0015% to 0.006% resulted in clinically acceptable reduction in IOP, and in most of these trials the numeric differences <u>between</u> products in mmHg IOP reduction did not reach a clinically significant difference.

- Protocol C-97-02 (US) was a 5 arm study comparing four concentrations of travoprost (0.001%, 0.002%, 0.004% and 0.006% - all dosed once daily for 28). The concentrations that achieved the greatest IOP lowering effect were 0.002%, 0.004% and 0.006%. The ocular adverse events profile for these doses is presented below in Section 8. Safety.
- Protocol C-97-71 was a 4 arm study, 12 months in duration, and compared travoprost 0.0015% QD and 0.004% QD with Timoptic 0.5% BID and Xalatan 0.005% (QD) – to keep the trial masked, patients had bottles marked “morning” for 8AM and “evening” for 8PM). The reviewer notes that both the 0.0015% and 0.004% travoprost and Xalatan 0.005% demonstrate similar ability to lower IOP over time (12 months), and IOP was lower with these drugs than with Timoptic 0.5%, although the difference was not considered to be a clinically significant amount.
- Protocol C-97-72 was similar in design, minus the Xalatan control arm and of 6 months duration. Both 0.0015% and 0.004% travoprost demonstrated similar ability to lower IOP over time (6 months), and IOP was lower with these drugs than with Timoptic 0.5%, although the difference was not considered to be a clinically significant amount.

- Protocol C-97-73 was a 3 arm study of 6 month duration; all patients received Timoptic 0.5% and either travoprost 0% (vehicle), 0.0015% or 0.004%. Both travoprost containing arms demonstrated similar ability to lower IOP over time (6 months), and IOP was lower with these drugs than with Timoptic 0.5% alone. The additional IOP lowering of both combinations was considered a clinically significant amount (around 4 to 5 mmHg).
- Protocol C-97-79 was a 3-arm study of 9 months duration comparing travoprost 0.0015% and 0.004% to Timoptic 0.5%. Reduction in IOP was comparable for travoprost 0.0015% and Timoptic 0.5% and statistically superior for travoprost 0.004% over time (9 months). The difference was not considered a clinically significant amount.

8. Safety

For further details, the Clinical and Statistical Reviews should be consulted. A brief summary is provided below.

The safety database for this application from Study C-11-034 consisted of 442 IZBA treated patients and 421 Travatan treated patients, the median time of drug exposure was 91 days and 90 days, respectively, the mean time of exposure was 89 days and 88 days, respectively and 332 IZBA and 301 Travatan patients were treated for >87 days.

The safety profiles between IZBA (travoprost 0.003%) and Travatan in study C-11-034 were similar. There were no deaths reported; serious adverse events were reported in 5 (1.1%) patients on IZBA and 7 (1.7%) on Travatan. Ten vs. 14 patients discontinued treatment due to adverse reactions (3 vs. 4), patient decision (3 vs. 3), noncompliance (1 vs. 0), loss to follow up (2 vs. 1), inadequate IOP control (0 vs. 5) and other (1). The following patients discontinued due to visual adverse events:

- IZBA: 66/F due to eye irritation, eye pruritis; 67/F due to conjunctival hyperemia, photophobia, vision blurred
- Travatan: 51/F ulcerative keratitis; eyelid edema, ocular hyperemia; conjunctivitis allergic, ocular hyperemia.

30.3% of subjects in the travoprost 0.003% group and 32.3% of subjects in the Travatan group experienced at least 1 treatment-emergent AE. The table of common adverse reactions is presented below.

Adverse Events Reported at a Rate of ≥ 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)
Eyelash thickening/growth#	4 (0.9)	5 (1.2)
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
Source: Medical Officer Review and
Section 2.7.4 Summary of Clinical Safety, Table 2.7.4.7-4

The applicant's study report 5.3.5.1 for C-11-034 documents baseline eye color of patients, but (using the search "iris" and "iris pigment") does not report any iris pigmentation findings or discuss iris pigmentation. The following table mentions the iris in context of iris/anterior chamber. The only mention of iris pigmentation in the clinical study report (CSR) is found in the approved Travatan product labeling included in the CSR. Pigmentation is discussed later in this section.

Table 12.5.2-2 Number and Percentage of Patients with Ocular Signs Changes from Baseline to Any Visit – C-11-034

	Trav 0.003%			TRAVATAN		
Ocular Signs	**Total**	**N**	**(%)**	**Total**	**N**	**(%)**
Cornea	**442**	8	(1.8)	**420**	10	(2.4)
Iris/Anterior Chamber	**442**	1	(0.2)	**420**	1	(0.2)
Lens	**442**	4	(0.9)	**420**	5	(1.2)
Eyelids/Conjunctiva	**442**	13	(2.9)	**420**	21	(5.0)
Aqueous Flare	**425**	0	(0.0)	**405**	2	(0.5)
Inflammatory Cells	**425**	2	(0.5)	**405**	2	(0.5)

Trav 0.003% = Travoprost 30 µg/mL eye drops, solution preserved with POLYQUAD
TRAVATAN = Travoprost 40 µg/mL eye drops, solution preserved with BAK
Baseline = Eligibility 2 (8 AM) Visit
Change in ocular signs is defined as a one unit or more increase from baseline to any visit for either study eye compared to the same eye at baseline.
Source: application section 5.3.5.1 for C-11-034, 12.5.2. OCULAR SIGNS

Selected adverse reactions are further discussed below. The clinical review for NDA 21257 was also consulted to learn about the safety findings in the earlier clinical trials of travoprost. The adverse event tables from the Medical Officer Review of NDA 21257 dated 11/15/2000 for ocular adverse events are reproduced on the following pages.

Pigmentation

Prostaglandins are associated with various known toxicities: iris pigmentation (probably irreversible), eyelid pigmentation, eyelash growth and changes. The above table does not include any reports of increased pigmentation, and information on eye lash changes was found in Section 2.7.4 Summary of Clinical Safety, Table 2.7.4.7-4.

Based on the review of NDA 21257 it appears pigment changes may be detected in 1 to 3 months, but are more likely to be found in studies of longer duration (6 to 12 months) at higher rates. In NDA 21257, for example, photographs were taken to assess iris pigment changes and eyelash changes. This helps explain the paucity of reports from the 3 month study above.

- In Study C-97-71 over the 12 month course of the study and showed greater iris pigmentation with travoprost (3.7% - 5.7% patients) and Xalatan (5.9% patients) compared to Timoptic 0.5% (0 patients). Eyelash photographs taken over the 12 month course of the study resulted in reports of changes (color, length, density, thickness) in travoprost (47.1–62.7% of patients), Xalatan (29% of patients) and Timolol (2.4% of patients).
- In Study C-97-72, no patients (0/172) treated with travoprost 0.001% and 2/166 (1.2%) patients treated with travoprost 0.004% developed iris pigmentation by 6 months. Eyelash changes were seen in 41.9% to 57.8% travoprost patients and 2.3% Timoptic patients.
- In Study C-97-73, no patients treated with travoprost 0.001% or 0.004% developed iris pigmentation by 6 months. Eyelash changes were seen in 40.9% to 56.3% of patients on travoprost and none on Timoptic 0.5%.
- In Study C-97-79, greater iris pigmentation with travoprost (4% to 5.1% patients) compared to Timoptic 0.5% (0 patients). Eyelash photographs taken over the 12 month course of the study resulted in reports of changes (color, length, density, thickness) in travoprost (67.4% to 76.8% of patients) and Timolol (3% of patients).

The reviewer noted, "*Whether these changes are purely cosmetic or have safety related issues have not been determined.*" At the time of the original approval, these changes raised concern whether excess pigmentation in the iris could result in pigmentary glaucoma or the melanocytes could give rise to melanoma. Therefore a limited indication was approved in 2001.

Ocular 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. Earlier clinical trials required investigators to grade ocular redness of each treated eye, compared to baseline and standard photographs. The reported hyperemia rates included any patient with an increase of 1 or more in their graded ocular redness using a scale from 0 to 3 units, as well as patient and/or physician reports of hyperemia. The current trial did not include a required grading of hyperemia for each patient. The reporting rate of hyperemia for this trial includes only patient and/or physician reports of hyperemia.

Conjunctival Hemorrhage

In the current Study C-11-034 there is only 1/422 patients (0.2%) who developed conjunctival hemorrhage on IZBA compared to 6/421 (1.4%) on Travatan. Because of the difference seen between the rate of conjunctival hemorrhage in this study, the rates of (sub)conjunctival hemorrhage reported in previous studies with travoprost 0.004% were examined.

Subconjunctival hemorrhage was reported in approximately 1.5% of patients in studies C-97-71 and C-97-72; it was also reported with the vehicle and 0.001% product in C-97-02, and not reported with travoprost 0.004% in C-97-02, C-97-73 and C-97-79. While the lower rate seen in the IZBA arm is encouraging, as shown below, in at least half of the previous studies with Travatan 0.004%, subconjunctival hemorrhage was not reported. A second study would be important to corroborate this finding.

Conjunctival hemorrhage in travoprost 0.004%

Study #	Conjunctival hemorrhage Rate
Study C-97-02	0/48
Study C-97-71	3/200 (1.5%)
Study C-97-72	3/201 (1.5%)
Study C-97-73	0/145 (with timolol)
Study C-97-74	0/197
Total	6/801 (0.8%)

<u>Table of Adverse Reactions from MO Review of NDA 21257</u>

Protocol C-97-02 (NDA 21257)

**Frequency and Incidence of Ocular Adverse Events
Occurring at Rates Greater than 1%**

Coded Adverse Event	AL-6221				
	0.001% N=47	**0.002% N=44**	**0.004% N=48**	**0.006% N=43**	**Vehicle N=45**
	N (%)	N (%)	N (%)	N (%)	N (%)
All Events	12 (25.5)	20 (45.5%)	18 (37.5)	25 (58.1)	8 (17.8)
OCULAR					
Hyperemia Eye	3 (6.4)	8 (18.2)	3 (6.3)	11 (25.6)	
Flare	2 (4.3)			1 (2.3)	
Pruritus Eye	1 (2.1)	5 (11.4)	5 (10.4)	5 (11.6)	1 (2.2)
Cataract	1 (2.1)				
Discomfort Eye	1 (2.1)		1 (2.1)		2 (4.4)
Dry Eye	1 (2.1)	1 (2.3)	1 (2.1)	4 (9.3)	2 (4.4)
Hem Subconjunctival	1 (2.1)				1 (2.2)

Staining Corneal	1 (2.1)		1 (2.1)	4 (9.3)	1 (2.2)
Surgical/Medical Proc	1 (2.1)				
Vision Change	1 (2.1)				
Browache			1 (2.1)		
Conjunctivitis		1 (2.3)		1 (2.3)	
Corneal Abrasion				1 (2.3)	
Discharge Eye Nos				1 (2.3)	
Eye Fatigue		1 (2.3)			
Foreign Body Sensation		1 (2.3)	1 (2.1)	1 (2.3)	1 (2.2)
Keratitis				1 (2.3)	
Pain Eye		2 (4.5)	1 (2.1)	4 (9.3)	
Photophobia		2 (4.5)	1 (2.1)	3 (7.0)	
Spasm Lid				1 (2.3)	
Tearing			2 (4.2)	1 (2.3)	
Vision Blurred				1 (2.3)	
Vision Decreased				1 (2.3)	
NON-OCULAR	See original review for information				

Protocol C-97-71 (NDA 21257)

Frequency and Incidence of Ocular Adverse Events Occurring at Rates Greater than 1%

Coded Adverse Event	Al-6221 0.0015% N=205	AL-6221 0.004% N=200	Timoptic 0.5% N=200	Xalatan 0.005% N=196
	N (%)	N (%)	N (%)	N (%)
All Events	158 (77.1)	166 (83.0)	140 (70.0)	141 (71.9)
OCULAR				
Hyperemia eye	78 (38.0)	99 (49.5)	28 (14.0)	54 (27.6)
Visual Acuity Decrease	12 (5.9)	17 (8.5)	19 (9.5)	9 (4.6)
Discomfort Eye	11 (5.4)	15 (7.5)	15 (7.5)	5 (2.6)
Iris Discoloration	10 (4.9)	6 (3.0)		10 (5.1)
Pruritus Eye	8 (3.9)	15 (7.5)	4 (2.0)	12 (6.1)
Eye Disease	7 (3.4)	3 (1.5)	3 (1.5)	4 (2.0)
Cataract	6 (2.9)	5 (2.5)	3 (1.5)	
Pain Eye	6 (2.9)	16 (8.0)	3 (1.5)	7 (3.6)
Dry Eye	5 (2.4)	9 (4.5)	3 (1.5)	
Foreign Body Sensation	5 (2.4)	14 (7.0)		6 (3.1)
Keratitis	5 (2.4)	7 (3.5)	5 (2.5)	4 (2.0)
Cataract Nos	4 (2.0)	9 (4.5)	4 (2.0)	5 (2.6)
Inflammatory Cells Aqueous	4 (2.0)	4 (2.0)	4 (2.0)	
Vitreous Disease	4 (2.0)			
Aqueous Flare	3 (1.5)	3 (1.5)	3 (1.5)	
Hemorrhage Subconjunctival	3 (1.5)	3 (1.5)		8 (4.1)
Iritis	3 (1.5)			
Vision Abnormal	3 (1.5)	4 (2.0)		
Blepharitis		7 (3.5)		7 (3.6)
Conjunctivitis		4 (2.0)		
Retinal Pigment			3 (1.5)	
Surgical/Medical Proc		4 (2.0)		
Vitreous Detachment		3 (1.5)		
Photophobia		4 (2.0)	3 (1.5)	3 (1.5)
Vision Blurred		6 (3.0)	6 (3.0)	9 (4.6)

Visual Field Defect				3 (1.5)
Hemorrhage Retinal			5 (2.5)	
Pallor Optic Disc			3 (1.5)	
Retinal Disease				3 (1.5)
Tearing			4 (2.0)	3 (1.5)
NON-OCULAR –see original	review			

Protocol C-97-72 (NDA 21257)

Frequency and Incidence of Ocular Adverse Events Occurring at Rates Greater than 1%

Coded Adverse Event	**AL-6221 0.0015% N=202**	**AL-6221 0.004% N=201**	**Timoptic 0.5% N=202**
	N (%)	N (%)	N (%)
All Events	126 (62.4)	134 (66.7)	98 (48.5)
OCULAR			
Hyperemia Eye	59 (29.2)	86 (42.8)	18 (8.9)
Visual Acuity Decrease	9 (4.5)	10 (5.0)	9 (4.5)
Pruritus Eye	7 (3.5)	12 (6.0)	5 (2.5)
Keratitis	6 (3.0)	8 (4.0)	4 (2.0)
Discomfort Eye	5 (2.5)	5 (2.5)	9 (4.5)
Pain Eye	3 (1.5)	12 (6.0)	
Vision Blurred	6 (3.0)	5 (2.5)	6 (3.0)
Dry Eye	3 (1.5)	6 (3.0)	4 (2.0)
Foreign Body Sensation	4 (2.0)	6 (3.0)	
Conjunctivitis		3 (1.5)	3 (1.5)
Hemorrhage Subconjunctival	3 (1.5)	3 (1.5)	
Vision Decrease			4 (2.0)
Inflammatory Cells Aqueous		3 (1.5)	
Blepharitis		3 (1.5)	
Aqueous Flare		3 (1.5)	
Tearing		4 (2.0)	
Lid Margin Crusting		3 (1.5)	
NON-OCULAR	See original review for information		

Protocol C-97-73 (NDA 21257)

Frequency and Incidence of Ocular Adverse Events Occurring at Rates Greater than 1%

Coded Adverse Event	**Timoptic 0.5% + AL-6221**		
	0.0015% N=142	**0.004% N=145**	**Vehicle for AL N=139**
	N (%)	N (%)	N (%)
All events	83 (58.4)	84 (57.9)	60 (43.2)
OCULAR			
Hyperemia Eye	33 (23.2)	52 (35.9)	13 (9.4)
Inflammatory Cells Aqueous	7 (4.9)	6 (4.1)	
Discomfort Eye	7 (4.9)	7 (4.8)	3 (2.2)
Keratitis	7 (4.9)	3 (2.1)	5 (3.6)
Aqueous Flare	5 (3.5)	2 (1.4)	
Pruritus Eye	4 (2.8)	5 (3.4)	2 (1.4)
Visual Acuity Decrease	4 (2.8)	6 (4.1)	5 (3.6)

Blepharitis	3 (2.1)	2 (1.4)	
Eye Disease	3 (2.1)		
Foreign Body Sensation	3 (2.1)	4 (2.8)	
Pain Eye	3 (2.1)	6 (4.1)	
Vision Blurred	3 (2.1)	3 (2.1)	2 (1.4)
Conjunctivitis	2 (1.4)	2 (1.4)	
Hemorrhage Retinal	2 (1.4)		
Iritis	2 (1.4)		
Surgical/Medical Proc	2 (1.4)		
Vitreous Disease	2 (1.4)		
Dry Eye		8 (5.5)	
Tearing		3 (2.1)	
Eye Fatigue		2 (1.4)	
Lid Disease		3 (2.1)	
Optic Nerve Disease			2 (1.4)
Photophobia		4 (2.8)	
Sticky Sensation		2 (1.4)	
Vision Abnormal			2 (1.4)
NON-OCULAR	See original review		

Protocol C-97-79 (NDA 21257)

Frequency and Incidence of Ocular Adverse Events Occurring at Rates Greater than 1%

Coded Adverse Event	**AL-6221 0.0015% N=190**	**AL-6221 0.004% N=197**	**Timoptic 0.5% N=186**
	N (%)	N (%)	N (%)
All Events	114 (60.0%)	133 (67.5%)	88 (47.3)
OCULAR			
Hyperemia Eye	50 (26.3)	69 (35.0)	15 (8.1)
Discomfort Eye	15 (7.9)	14 (7.1)	7 (3.8)
Pruritus Eye	7 (3.7)	15 (7.6)	3 (1.6)
Iris Discolor	10 (5.3)	7 (3.6)	
Visual Acuity Decrease	2 (1.1)		7 (3.8)
Cataract Nos	3 (1.6)	3 (1.5)	3 (1.6)
Foreign Body Sensation	5 (2.6)	3 (1.5)	
Vision Blurred	3 (1.6)		3 (1.6)
Dry Eye	3 (1.6)	4 (2.0)	
Pain Eye	3 (1.6)	4 (2.0)	
Conjunctivitis	2 (1.1)	3 (1.5)	2 (1.1)
Cataract			2 (1.1)
Optic Nerve Disease		4 (2.0)	
Blepharitis	3 (1.6)		
Inflammatory Cells Aqueous	3 (1.6)		2 (1.1)
Aqueous Flare	2 (1.1)		
Surgical/Medical Proc	2 (1.1)		
Retinal Disease	3 (1.6)		
Hair Disease		3 (1.5)	
Lid Disease			2 (1.1)
Meibomitis		3 (1.5)	
Tearing			2 (1.1)
Visual Field Defect			2 (1.1)
NON-OCULAR	See original review		

No new safety issues were identified in the November 5, 2013 120-day safety update for the marketed travoprost products. Of note, marketing of Travatan (NDA 21257) has been discontinued.

Comment:
I concur with the conclusions and recommendations for approval of the application by the clinical and statistical reviewers. The labeling has been revised and includes relevant safety information for travoprost from the broader development program, including the safety profile of travoprost when used for longer duration (current study was of 3-month duration).

9. Advisory Committee Meeting

This is a new formulation and lower strength of a marketed product. The application did not identify scientific issues for presentation and discussion at the Advisory Committee meeting.

10. Pediatrics

The Pediatric Review Committee agreed with the applicant's proposal that pediatric studies be waived.

11. Other Relevant Regulatory Issues

11.1 Office of Compliance Facility Inspections

Manufacturing facilities are acceptable.

11.2 Office of Scientific Investigation (OSI) Audits

Inspections of two investigators were completed and both were classified as NAI; their data are considered adequate to support the application.

11.3 Debarment certification

Alcon Research, Ltd. and its affiliated companies hereby certify that it did not and will not use in any capacity the service of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

11.4 Financial Disclosure

Five of 60 investigators disclosed financial arrangements with the applicant; these arrangements were judged not to impact the results of the clinical study. These five investigators enrolled (b) (4) subjects each, a total of (b) (4) of the 864 randomized to the trial.

11.5 Other Regulatory Issues

None

12. Labeling

- The proprietary name IZBA for travoprost ophthalmic solution 0.003% was found acceptable and the applicant notified via letter on 2/19/2014

- Physician labeling (PLR) has been finalized and input from the reviewers and consultants was discussed and incorporated as applicable. Based on the finalized IZBA labeling, supplement request letters will be sent to request that Travatan product labeling be updated
- Carton and immediate container labels have been finalized; input from reviewers and consultants was discussed and changes incorporated as applicable
- Patient labeling/Medication guide – these are not proposed for the current product

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

NDA [redacted] (b) (4) is recommended for approval.

- Risk Benefit Assessment

Glaucoma is a life-long progressive disease that is characterized by irreversible damage to the optic nerve and corresponding loss of visual field. One of the primary risk factor is elevated intraocular pressure (IOP). The reduction and control of elevated IOP in open angle glaucoma and ocular hypertension is usually managed by chronic, long-term topical ocular therapy.

There are currently multiple topical products in several classes available for the reduction of IOP, including beta-adrenergic antagonists (beta-blockers), alpha-adrenergic agonists, parasympathomimetic (miotic) agents, carbonic anhydrase inhibitors, prostaglandin analogs, and some combination products. A complete list is included in the Medical Officer's Review and CDTL Review.

The rationale behind developing the present formulation was to reduce the amount of active ingredient and change the preservative, with the goal of developing an effective product with a potentially improved safety profile.

One controlled, randomized, masked clinical trial was submitted that compared the approved Travatan (travoprost ophthalmic solution) 0.004% to IZBA. The results showed that the two products had comparable activity, met the pre-specified definitions of equivalence, and were able to reduce the IOP by 7 to 8 mmHg.

In this 3-month trial, the safety information was available in over 800 patients, over 400 on the IZBA product and over 300 with duration of treatment for 3 months. The safety profile was comparable. In this context, the labeling for this travoprost product will also include the broader experience gained from previous controlled clinical trials and marketing information, and adverse reactions associated with longer use.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

None

- Recommendation for other Postmarketing Requirements and Commitments

None

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

/s/

RENATA ALBRECHT
05/15/2014