CENTER FOR DRUG EVALUATION AND RESEARCH

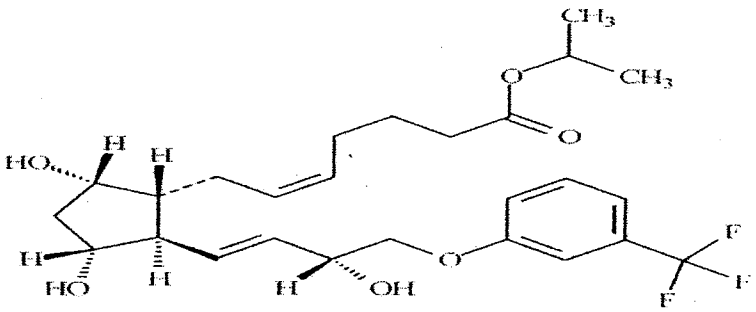
APPLICATION NUMBER:

21-994

MEDICAL REVIEW

CLINICAL REVIEW

Application Type	NDA 21-994
Submission Number	000
Submission Code	Original
Letter Date	11/18/05
Stamp Date	11/21/05
PDUFA Goal Date	09/21/06
Reviewer Name	Martin P. Nevitt, M.D., M.P.H.
Review Completion Date	5/09/06
Established Name	travoprost ophthalmic solution 0.004%
(Proposed) Trade Name	Travatan Z
Therapeutic Class	Prostaglandin $F_{2\alpha}$ analogue
Applicant	Alcon Research, Ltd. 6201 South Freeway P.O. Box 19534 Fort Worth, TX 76134-2099 817-551-4933 Angela C. Kothe, OD, PhD Associate Director, Regulatory Affairs
Priority Designation	S
Structure	$C_{26}H_{35}F_3O_6$



Dosing Regimen	One drop in the affected eye(s) once-daily in the evening
Indication	Reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension who are intolerant of intraocular lowering medications or are insufficiently responsive (failed to achieve target IOP determined after multiple measurements over time) to another intraocular pressure lowering medication
Intended Population	Patients 18 years or older with open angle glaucoma or ocular hypertension

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

From a clinical perspective, NDA 21–994 is recommended for approval for the treatment of elevated intraocular pressure (IOP) in patients with open angle glaucoma or ocular hypertension who are intolerant of intraocular lowering medications or insufficiently responsive (failed to achieve target IOP determined after multiple measurements over time) to another intraocular pressure lowering medication.

The submitted bioequivalence trial (study C-04-17) supports approval of Travatan Z, aka Travatan BAC-free. Travatan Z was developed for those patients who may be intolerant of the preservative benzalkonium chloride.

Study C-04-17 was a multicenter, phase 3 safety and efficacy trial. This safety/efficacy study was designed to demonstrate bioequivalence of Travatan Z (the BAC-free formulation of travoprost ophthalmic solution, 0.004%) to the marketed formulation of travoprost ophthalmic solution, 0.004% (Travatan), with both dosed once-daily in the evening in patients with open-angle glaucoma or ocular hypertension.

The primary efficacy endpoint, mean intraocular pressure, is demonstrated to be equivalent when comparing travoprost ophthalmic solution, 0.004% (Travatan Z), to the previously approved drug, travoprost ophthalmic solution, 0.004% (Travatan). Equivalence is defined as the two sided 95% confidence interval being less than 1.5 mmHg at each direct group comparison over multiple times over a three month period and being less than 1.0 mmHg for the majority of direct group comparisons. Travatan (NDA 21-257) was first approved in March 2001 for the reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension who are intolerant of intraocular lowering medications or are insufficiently responsive (failed to achieve target IOP determined after multiple measurements over time) to another intraocular pressure lowering medication.

The recommended dosing regimen is one drop in the affected eye(s) once daily in the evening.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

No additional clinical trials or postmarketing surveillance studies are required.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Established Name	travoprost ophthalmic solution, 0.004%
(Proposed) Trade Name	Travatan Z
Therapeutic Class	Prostaglandin $F_{2\alpha}$ analogue

Glaucoma is a disease characterized by optic nerve damage and visual field loss often associated with increased intraocular pressure (IOP). IOP is an important risk factor for developing open angle glaucoma. Ocular hypertension is a condition characterized by increased IOP in the absence of identifiable optic nerve damage and visual field loss.

In this clinical trial, reduction in IOP was the proposed primary efficacy endpoint studied in patients with open angle glaucoma or ocular hypertension. The proposed indication for this drug product was for the reduction of intraocular pressure in male or female patients, 18 years or older, with open angle glaucoma or ocular hypertension who are intolerant of intraocular lowering medications or are insufficiently responsive (failed to achieve target IOP determined after multiple measurements over time) to another intraocular pressure lowering medication.

The protocol for study C-04-17 was submitted to the FDA in July 2004 for Special Protocol Assessment to confirm the appropriateness of the clinical study design, analysis plan, selection of comparative agent and total number of patients to be included in the study. With this prior FDA agreement, a single multicenter clinical trial (study C-04-17) comparing travoprost ophthalmic solution, 0.004% (Travatan Z) with travoprost ophthalmic solution, 0.004% (Travatan) would be acceptable as clinical support if travoprost ophthalmic solution, 0.004% (Travatan Z) demonstrated equivalence to travoprost ophthalmic solution, 0.004% (Travatan).

Study C-04-17 was a multicenter, double masked, randomized, parallel-group, active control design with the following scheduled visits: Screening/Eligibility with a washout phase, and exam visits at week 2, week 6, and month 3. The study objectives were to evaluate the safety and efficacy of Travantan Z given once daily at 8 PM compared with Travatan also given once daily at 8 PM. Additional safety and secondary parameters examined were visual acuity, ocular signs (cornea, iris/anterior chamber, lens, aqueous flare and inflammatory cells), ocular hyperemia, dilated fundus parameters (vitreous, retina/macula/choroids, optic nerve, cup/disc ratio), automated perimetry, endothelial cell density and adverse events.

1.3.2 Efficacy

The primary measure of efficacy was mean IOP at 8 AM, 10 AM and 4 PM at exam visits on weeks 2 and 6, and month 3. If only one of a patient's eyes was dosed, the dosed eye was selected for analysis; if both of a patient's eyes were dosed, the worse evaluable eye was selected for analysis.

The demographic characteristics between the two treatment groups (Travatan Z and Travatan groups) showed no significant differences. The efficacy results of the trial demonstrated there were no statistically significant differences between the 2 treatment groups at any follow-up timepoint for mean IOP at each visit and at each time interval. The new formulation, Travatan Z, demonstrated equivalence to Travatan in IOP lowering ability.

1.3.3 Safety

The most frequently reported adverse events ($\geq$ 5% in either treatment group) were ocular hyperemia and ocular pruritis. A similar adverse event profile was observed comparing the most common adverse events observed in the Travatan Z and Travatan groups.

Common ocular adverse events occurring at an incidence of 2.0% to 5.5% in the Travatan Z group versus the Travatan group included ocular pruritus (5.5% vs. 3.5%), ocular discomfort (3.8% vs. 1.4%), foreign body sensation (2.6% vs. 1.2%) and ocular pain (2.3% vs. 1.4%). All of these events occurred at slightly higher incidences in the Travatan Z group than in the Travatan group; however, individual characteristics of these adverse events were similar between treatment groups. Decreased visual acuity and dry eye occurred at a slightly higher incidence in the Travatan group than the Travatan Z group, (both adverse events occurring at 2.0% vs. 1.7 %, respectively.)

Few serious adverse events were reported in the clinical trial. None of the events were ocular, and none were considered to be related to the study medications. There were two deaths reported during the clinical trial both occurring in the Travatan Z group but were not related to treatment; one patient died from multiple myeloma and another from septic shock. Other serious, non-fatal adverse events all unrelated to therapy were reported for 12 patients. This included 9 elderly patients with exposure to Travatan Z and 3 elderly patients with exposure to Travatan. Overall, although there was a higher incidence of serious adverse events in the Travatan Z group, none of these events were related to therapy and no common factors were noted in the non-fatal serious adverse events reported which would indicate a safety concern for Travatan Z.

Additionally, no safety concerns were identified based upon an analysis of change from baseline for visual acuity, ocular signs (cornea, iris/anterior chamber, lens, aqueous flare and inflammatory cells), ocular hyperemia, dilated fundus parameters (vitreous, retina/macula/choroids, optic nerve), cup/disc ratio, visual fields and endothelial cell density measurements in either treatment group in the overall safety population, adult population, or elderly population.

1.3.4 Dosing Regimen and Administration

Dose-response efficacy has been studied previously with travoprost, the active ingredient in Travatan and Travatan Z, in concentrations of 0.004% and 0.0015% in NDA 21-257. Although both concentrations demonstrated efficacy in lowering IOP, travoprost 0.004% lowered IOP more than travoprost 0.0015%. The amount of IOP reduction produced by travoprost 0.004% (7-

8 mmHg) as compared to travoprost 0.0015% (6-7 mmHg) was not statistically and clinically significant. Travoprost 0.004% was granted approval on March 2001 (NDA 21-257).

The recommended dosing regimen is one drop in the affected eye(s) once daily in the evening.

1.3.5 Drug-Drug Interactions

There were no important drug-drug interactions noted that would affect the product's clinical use.

1.3.6 Special Populations

No overall differences in safety or effectiveness have been observed between elderly and adult patients.

No patients with hepatic or renal impairment were studied.

There are no adequate and well-controlled studies in pregnant woman. It is not known whether this drug or its metabolites are excreted in human milk; although in an animal study of lactating rats radiolabeled travoprost and/or its metabolites were excreted in milk.

Safety and effectiveness in pediatric patients have not been established.

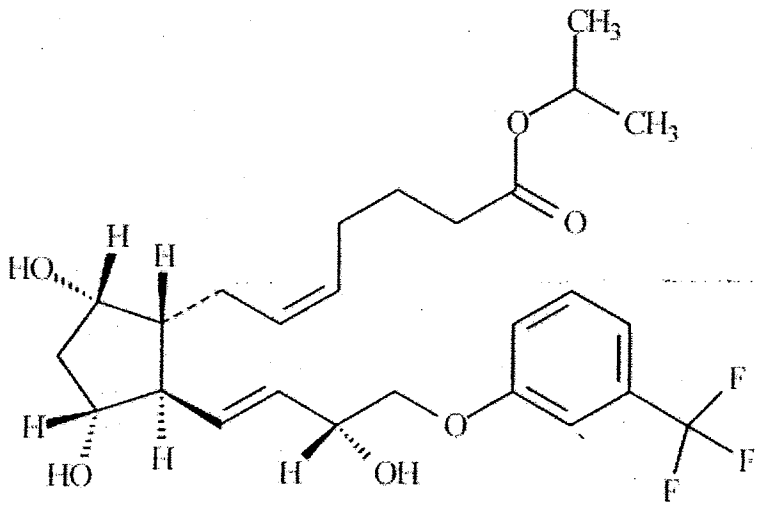
Reviewer's comments:

Travoprost ophthalmic solution, 0.004% in NDA 21-257 (Travatan), was evaluated in patients with hepatic impairment and also renal impairment in clinical trials. No clinically relevant changes in hematology, blood chemistry or urinalysis data were observed in these patients.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Established Name	travoprost ophthalmic solution, 0.004%
(Proposed) Trade Name	Travatan Z
Therapeutic Class	Prostaglandin $F_{2\alpha}$ analogue
Formulation	$C_{26}H_{35}F_3O_6$



Proposed Indication	Reduction of intraocular pressure (IOP) in patients 18 years or older with open angle glaucoma or ocular hypertension who are intolerant of intraocular lowering medications or are insufficiently responsive (failed to achieve target IOP determined after multiple measurements over time) to another intraocular pressure lowering medication

Composition of Travatan Z (FID[a] 107047)

Component	Percent W/V	Compendial Designation	Purpose
Travoprost (AL06221)	0.004 [b]	Non-Compendial	Active
Polyoxyl 40 Hydrogenated Castor Oil (HCO-40)		JPE Alternate: Alcon Global Monograph	
Propylene Glycol		USP	
Boric Acid		NF	
Sorbitol		NF	
Zinc Chloride		USP	
Sodium Hydroxide and/or Hydrochloric Acid		NF NF	
Purified Water		USP	

[a] FID = formulation identification number
[b] Adjust to based on purity of the raw material
[c] The combination of and provide the capacity. Preservation of the drug product in the container is achieved by the

Reviewer's Comments:

The Travatan Z formulation contains the same active ingredient in the same concentration previously approved in Alcon's Travatan (travoprost ophthalmic solution) 0.004% (NDA 21-572). The preservative benzylkonium chloride (BAC) has been removed.

2.2 Currently Available Treatment for Indications

There are currently available numerous topical treatments for open angle glaucoma and ocular hypertension either as first or second line therapy. These treatments include Beta-adrenergic antagonists (beta-blockers), Adrenergic agonists, Parasympathomimetic (miotic) agents, Carbonic anhydrase inhibitors and Prostaglandin analogues.

2.3 Availability of Proposed Active Ingredient in the United States

Travoprost is the active ingredient in the currently approved product Travatan (travoprost ophthalmic solution 0.004%).

The following table provides a comparison of the previously approved formulation of Travatan (travoprost ophthalmic solution, 0.004%) with Travatan Z (travoprost ophthalmic solution, 0.004%).

Comparison of Compositions of Travatan Z and Travatan

Component	% of Composition	
	Travatan Z	**Travatan**
Travoprost	0.004	Same
Benzalkonium Chloride	-	0.01%
HCO-40	[redacted]	
Boric Acid		
Disodium Edetate		
Zinc Chloride		
Tromethamine		
Sorbitol		
Mannitol		
Propylene Glycol		
Sodium Hydroxide and/or Hydrochloric Acid		
Purified Water		

Reviewers' comments:

The clinical study forming the basis of this NDA, is a bioequivalence trial that compared Travatan (travoprost ophthalmic solution, 0.004%) with Travatan Z (travoprost ophthalmic solution, 0.004%).

In addition to removal of benzalkonium chloride (BAC), the formulation was modified to remove disodium edetate (EDTA) and mannitol and to include propylene glycol, zinc chloride and sorbitol. The concentration of boric acid is also [redacted] from [redacted]. Save for the absence of BAC, the changes are considered relatively minor, relate to known excipients of ophthalmic preparations, and do not pose a concern with regard to ocular toxicity or local tolerance.

2.4 Important Issues With Pharmacologically Related Products

There have been no additional safety issues raised with this class of agents outside of those identified in this review.

In an effort to maintain effective IOP reduction while enhancing tolerability, Travatan Z ophthalmic solution has been developed. This new formulation will provide improved tolerability for those patients who are intolerant of benzalkonium chloride (BAC) used in ophthalmic medications.

Reviewer's comments:

The class effects for the prostaglandin analogues, including travoprost ophthalmic solution, 0.004% have been reported to include changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the iris and the periorbital tissue (eyelid) and increased pigmentation and growth of eyelashes. These changes may be permanent.

2.5 Presubmission Regulatory Activity

The protocol for study C-04-17 was submitted to the FDA in July 2004 for Special Protocol Assessment to confirm the appropriateness of the clinical study design, analysis plan, selection of comparative agent and total number of patients to be included in the study.

Based on this review the following changes to the study protocol and/or agreements were made:

- The Division agreed that Travatan would be an appropriate control group
- The Division agreed that 300 patients per treatment arm followed for 3 months would be an adequate number of patients to support the efficacy and safety of Travantan Z (Travatan BAC-free)
- The Division recommended patients with particularly thick corneas be excluded because applanation tonometry may not accurately reflect changes in intraocular pressure in these patients (with pachymetry measurements included at baseline exam)
- Endothelial cell density measurements were added at baseline and exit at selected sites

2.6 Other Relevant Background Information

The sponsor has not submitted any international labeling regarding approval or pending approval for Travatan Z.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

NDA 21-994 is recommended for approval pending CMC review.

3.2 Animal Pharmacology/Toxicology

In nonclinical studies, the formulation Travatan Z showed a similar toxicity profile as the marketed formulation Travatan. The drug product showed a low irritation potential when administered topically to the rabbit eye. Studies with impurities including [redacted] and [redacted] showed no biologically relevant toxicity.

The NDA is approvable from a nonclinical perspective.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The submitted clinical study report and protocol for study C-04-17 and relevant literature reports were reviewed. The submitted study report forms the basis for the majority of this application.

The application was submitted in paper and electronic format.

A PubMed electronic literature search was performed to supplement the review, and no new information was found.

4.2 Tables of Clinical Studies

Phase 3 Glaucoma/Ocular Hypertension Study Utilized in M.O. Safety and Efficacy Review

Study ID	# Study Center Location	Study Period Total Enrollment /Target Enrollment	Study Design Type	Study Treatment	Study Objective	# Patients by arm	Duration of treatment	M/F mean age (range) Race	Diagnosis Inclusion Criteria	Safety Variables
C-04-17	48 centers USA	Oct. 2004 to June 2005 Total enrollment N=690 Target enrollment N=600	Randomized, multi-center, double-masked, parallel, active control	Travatan BAC-free (Travatan Z) Travatan	Compare the safety and IOP-lowering efficacy of Travatan BAC-free to Travatan in patients with open-angle glaucoma or ocular hypertension	Travatan BAC-free N=344 Travatan N=346	3 months	M 320 F 370 56.8% 63.1 yrs. (18-94)	Patients ≥ 18 yrs. Of either sex and of any race diagnosed with open angle glaucoma (with or without pseudoexfoliation or pigment dispersion component) or confirmed ocular hypertension	Extent of exposure, adverse events, visual acuity, ocular signs, ocular hyperemia, dilated fundus, automated perimetry, endothelial cell density

M = Male, F = Female; yrs = years, IOP = intraocular pressure

Reviewer's Comments:

The design of the clinical trial and the number of centers is acceptable.

4.3 Review Strategy

The submitted clinical study report and protocol for study C-04-17 and relevant literature reports were reviewed. The submitted study report forms the basis of this application.

The entire application was submitted in electronic and paper format.

4.4 Data Quality and Integrity

The medical officer has reviewed all Case Report Forms for discontinued subjects in study C-04-17. There were no problems noted with data quality and integrity.

4.5 Compliance with Good Clinical Practices

The data was reviewed for consistency with other applications in this class. No special methods were used.

All trials were conducted under the review of approved Institutional Review Board committees. Investigators used an informed consent form that was appropriate for the trial.

4.6 Financial Disclosures

The applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on *Financial Disclosure by Clinical Investigators.*

There is no evidence to suggest that the results of the studies were impacted by any financial payments.

5 CLINICAL PHARMACOLOGY

All Pharmacology studies were submitted under NDA 21-257. For detailed pharmacology study reviews, please see Review and Evaluation of Pharmacology and Toxicology Data for NDA 21-257.

5.1 Pharmacokinetics

Absorption:
Travoprost is absorbed through the cornea and is hydrolyzed to the active free acid. Data from four multiple dose pharmacokinetic studies (totaling 107 subjects) have shown that plasma concentrations of the free acid are below 0.01 ng/ml (the quantitation limit of the assay) in two-thirds of the subjects. In those individuals with quantifiable plasma concentrations (N=38), the mean plasma C_{max} was 0.018 ± 007 ng/ml (ranged 0.01 to 0.052 ng/mL) and was reached within 30 minutes. From these studies, travoprost is estimated to have a plasma half-life of 45 minutes. There was no difference in plasma concentrations between Days 1 and 7, indicating steady-state was reached early and that there was no significant accumulation.

Metabolism:
Travoprost, an isopropyl ester prodrug, is hydrolyzed by esterases in the cornea to its biologically active free acid. Systemically, travoprost free acid is metabolized to inactive metabolites via beta-oxidation of the α(carboxylic acid) chain to give the 1,2-dinor and 1,2,3,4-tetranor analogs, via oxidation of the 15-hydroxyl moiety, as well as via reduction of the 13,14 double bond.

Elimination:
The elimination of travoprost free acid from plasma was rapid and levels were generally

below the limit of quantification within one hour after dosing. The terminal elimination halflife of travoprost free acid was estimated from fourteen subjects and ranged from 17 minutes to 86 minutes with the mean half-life of 45 minutes. Less than 2% of the topical ocular dose of travoprost was excreted in the urine within 4 hours as the travoprost free acid.

5.2 Pharmacodynamics

Not studied.

5.3 Exposure-Response Relationships

Not applicable to this application.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The proposed indication is for the reduction of intraocular pressure in male or female patients, 18 years old or more, with open angle glaucoma or ocular hypertension.

6.1.1 Methods

The submitted clinical study report and protocol for study C-04-17 were reviewed.

The entire application was submitted in electronic and paper format.

A PubMed electronic literature search was performed to supplement the review, and no new information was found.

6.1.2 General Discussion of Endpoints

Reduction in IOP was the efficacy parameter studied in patients with open angle glaucoma or ocular hypertension.

The primary efficacy endpoint for study C-04-17 was the mean IOP measured using Goldmann applanation tonometry at 8 AM, 10 AM, and 4 PM at the Week 2, Week 6 and Month 3 visits. Results for the Intent-To-Treat group which included all randomized patients and the per protocol populations were provided in the current NDA.

If only one of a patient's eyes was dosed, the dosed eye was selected for analysis; if both of a patient's eyes were dosed, the worse evaluable eye was selected for analysis.

6.1.3 Study Design

Clinical development of Travatan Z is based on the body of work that had been compiled for approval of Travatan. This included two Phase 2 pivotal clinical trials (as well as dose-response studies, an adjunctive-use study, and clinical pharmacology and pharmacokinetic studies).

One clinical trial, study C-04-17, is provided in this Medical Officer's review. The information from this clinical study follows:

Principle Investigators and Patients Enrolled
Study C-04-17

Principal Investigator	Center Number	City and State	Number Enrolled
Jason Bacharach, M.D.	2434	Petaluma, CA	9
Howard S. Barnebey, M.D.	2195	Seattle, WA	0
Stanley Jay Berke, M.D.	3962	Lynbrook, NY	9
Michael S. Berlin, M.D.	4082	Los Angeles, CA	2
Andre J Cottingham, M.D.	3349	San Antonio, TX	0
E. Randy Craven, M.D.	1236	Littleton, CO	11
Jung T. Dao, M.D.	3920	Phoenix, AZ	0
William F. Davitt, M.D.	3802	El Paso, TX	15
Douglas D. Day, M.D.	2348	Atlanta, GA	40
Efraim Duzman, M.D.	3785	Irvine, CA	15
Richard M. Evans, M.D.	553	San Antonio, TX	24
Catherine T. Fitzmorris, M.D.	4034	Metairie, LA	6
Ronald Frenkel, M.D.	2137	Stuart, FL	14
Mark S. Gorovoy, M.D.	2583	Fort Myers, FL	4
Thomas T. Henderson, M.D.	3420	Austin, TX	3
Bret A. Hughes, M.D.	2433	Detroit, MI	1
Jane Hughes, M.D.	3664	San Antonio, TX	20
Martin Kaback, M.D.	962	Slingerhills, NY	10
Gregory Katz , M.D.	3731	Ypsilanti, MI	6
Michael Kottler, M.D.	355	Salt Lake City, UT	10
Joseph Krug, Jr., M.D.	2439	Charlotte, NC	0
Bradley Kwapiszeski, M.D.	3112	Shawnee Mission, KS	18
Richard Lewis, M.D.	649	Sacramento, CA	4
Jeffrey Lozier, M.D.	3678	San Diego, CA	22
Eugene McLaurin, M.D.	4011	Memphis, TN	18
Katherine Ochsner, M.D.	1011	Wilmington, NC	15
James Peace, M.D.	3627	Inglewood, CA	20
Bernard Perez, M.D.	3720	Tampa, FL	6
Ravi Reddy, M.D.	3853	Henderson, NV	26
Tushina Reddy, M.D.	3925	Las Vegas, NV	20
Ned Reinstein, M.D.	2448	Tulsa, OK	13
Alan Robin, M.D.	648	Baltimore, MD	0
Michael Rotberg, M.D.	1393	Charlotte, NC	17
Kenneth Sall, M.D.	1806	Artesia, CA	36
Paul Schacknow, M.D.	3270	Lake Worth, FL	2
Howard Schenker, M.D.	1939	Rochester, NY	29
Stephen Scoper, M.D.	1238	Norfolk, VA	27
Elizabeth Sharpe, M.D.	731	Mt. Pleasant, SC	11

Principal Investigator	Center Number	City and State	Number Enrolled
Robert Shields, M.D.	589	Denver, CO	9
Shannon Smith, M.D.	1892	Nacogdoches, TX	7
Emil Stein, M.D.	3851	Las Vegas, NV	10
Robert Stewart, M.D.	271	Houston, TX	20
Michael Tepedino, M.D.	3626	High Point, NC	5
Stuart Terry, M.D.	415	San Antonio, TX	19
Robert Thomas, M.D.	3919	Phoenix, AZ	2
George Thorne, M.D.	2353	Austin, TX	26
Jonathan Stanwood Till, M.D.	2467	Salem, VA	4
Nikhil Wagle, M.D.	4012	Davenport, IA	5
Thomas Walters, M.D.	1007	Austin, TX	21
Mark Weiss, M.D.	394	Tulsa, OK	31
Robert Williams, M.D.	2128	Louisville, KY	8
David Wirta, M.D.	2600	Newport Beach, CA	40

Reviewer's comments:

It is preferred to have at least 10 subjects per center to allow for an interaction analysis.

Inclusion Criteria:

1. Patients of either sex and any race, 18 years of age or older diagnosed with open angle glaucoma (with or without pseudoexfoliation or pigment dispersion component) or ocular hypertension were screened for the study.
2. Patients must have met the following IOP entry criteria in at least one eye:
   - For each qualifying eye, the mean IOP must have been 24 to 36 mmHg at 8 AM on both Eligibility Visits 1 and 2.
   - For each qualifying eye, the mean IOP must have been 21 to 36 mmHg at 10 AM and 4 PM on both Eligibility Visits 1 and 2.
   - The mean IOP in either eye at **any** timepoint during Eligibility Visits 1 and 2 must not have been greater than 36 mmHg.
   - The mean IOP was the average of two IOP measurements in the same eye.
   - The same eye(s) must have qualified at both Eligibility Visits 1 and 2.
3. Only patients who satisfied all informed consent requirements were to be included in the study.
4. Patients who wore contact lenses were allowed to participate in the study provided that the contact lenses were removed before instillation of study medication, and that the patient waited a minimum of 15 minutes following drug instillation before re-inserting the lenses. In addition, patients must have been willing to discontinue soft contact lens wear for at least seven (7) days or hard contact lens wear for at least twenty-eight (28) days prior to pachymetry and endothelial cell photography. Patients who wore contact lenses were instructed to wear or bring their glasses with them on study visit days.

5. Patients using nonprescription and/or prescription topical ophthalmic and/or systemic non-ocular hypotensive medications (except for those in the Exclusion Criteria) were included in the study.

EXCLUSION CRITERIA

1. Females of childbearing potential (those who were not surgically sterilized or postmenopausal) were excluded from participation in the study if they met any one of the following conditions:
   - They were currently pregnant or,
   - They had a positive result on the urine pregnancy test at the Screening Visit or,
   - They intended to become pregnant during the study period or,
   - They were breast-feeding or,
   - They were not using highly effective birth control measures:
   - Hormonal - oral, implanted, or injected contraceptives;
   - Mechanical - spermicide in conjunction with a barrier such as a condom or diaphragm or IUD
2. Patients with any form of glaucoma other than open-angle glaucoma (with or without a pigment dispersion or pseudoexfoliation component) or ocular hypertension were excluded from the study.
3. Patients who were currently on therapy or were on therapy with another investigational agent within 30 days prior to the Screening visit were exclude from the study.
4. History of chronic or recurrent severe inflammatory eye disease (i.e., scleritis, uveitis, herpes keratitis) in either eye excluded the patient from the study.
5. History of ocular trauma within the past six months in either eye excluded the patient from the study.
6. History of ocular infection or ocular inflammation within the past three months in either eye excluded the patient from the study.
7. History of clinically significant or progressive retinal disease such as retinal degeneration, diabetic retinopathy, or retinal detachment in either eye excluded the patient from the study.
8. History of any other severe ocular pathology (including severe dry eye) in either eye, that precluded the administration of a topical prostaglandin analogue excluded the patient from the study.
9. Intraocular surgery within the past six months in either eye as determined by patient history and/or examination excluded the patient from the study.
10. Ocular laser surgery within the past three months in either eye as determined by patient history and/or examination excluded the patient from the study.
11. Any abnormality preventing reliable applanation tonometry of either eye excluded the patient from the study.
12. Patients with best-corrected visual acuity worse than 0.6 logMAR score in either eye excluded the patient from the study.
13. Patients with angle grade less than Grade 2 in either eye, as measured by

gonioscopy (extreme narrow angle with complete or partial closure) excluded the patient from the study.

14. Patients with a cup/disc ratio greater than 0.80 (horizontal or vertical measurement) in either eye excluded the patient from the study.
15. Patients with severe central visual field loss in either eye were excluded from the study. Severe central visual field loss was defined as a sensitivity of less than or equal to 10 dB in at least two of the four visual field test points closest to the point of fixation.
16. Use of any additional topical or systemic ocular hypotensive medication during the study excluded the patient from the study.
17. Patients who could not safely discontinue all glucocorticoid medications administered by any route were excluded from the study. Patients must have washed out of chronic glucocorticoid medications for at least four weeks, or intermittent glucocorticoid therapy for at least two weeks prior to the Eligibility 1 visit, and must have been able to remain off these medications for the duration of the study
18. Patients with less than 30 days stable dosing regimen before the Screening visit of any medications or substances administered by any route and used on a chronic basis that may affect IOP, including but not limited to, beta-blocking agents were excluded from the study.
    Note: Patients must have been on a stable dosing regimen of medications for at least thirty(30) days prior to the Screening visit and must not have changed the dosing regimen during the eligibility period. Any change in dosage or addition of such medication(s) during the study must have been documented in the patient's chart.
19. History or other evidence of severe illness or any other conditions which would make the patient, in the opinion of the investigator, unsuitable for the study excluded the patient from the study.

Study Plan

The primary objective of this study was to compare the safety and efficacy of TRAVATAN BAC-free (Travatan Z) to that of TRAVATAN administered once daily in patients with open-angle glaucoma or ocular hypertension. The study was conducted in two phases: Phase 1 (Screening/Eligibility Phase) and Phase 2 (Treatment Phase). Phase 1 of the study was the Screening/Eligibility Phase which consisted of a Screening visit, IOP lowering medication washout, followed by two Eligibility visits. Phase 2 consisted of on therapy visits up to three months on masked medication.

This study was prospectively designed to provide primary efficacy results based on data collected at Week 2, Week 6, and Month 3 visits. All enrolled patients were followed for up to three months for both safety and efficacy.

Efficacy Endpoint

The primary efficacy parameter was mean IOP at 8 AM, 10 AM and 4 PM. Study visits were planned at Week 2, Week 6, and Month 3. If only one of a patient's eyes was dosed, the dosed eye was selected for analysis. If both of a patient's eyes were dosed, the worse

evaluable eye was selected for analysis.

Hypothesis tests were performed using a repeated measures analysis of variance. For the test of equivalence, a two-sided 95% confidence interval for the treatment group difference at each visit and time point was constructed based on the repeated measures analysis of variance. Primary inference for the test of equivalence was based upon the per protocol data set, and confirmed with the intent-to-treat data set. There was no multiplicity adjustment needed since results across all study visits and times were required to satisfy the ±1.5 mmHg equivalence criterion.

An additional clinical requirement was that the majority of confidence limits must have been within ±1.0 mmHg. There was no multiplicity argument affecting this additional criterion because this assessment was carried out subsequent to the formal statistical test mentioned above.

Descriptive statistics were calculated for IOP, IOP change from baseline, and IOP percent change from baseline. Mean IOP change from baseline was also estimated using a repeated measures analysis of variance.

Reviewer's Comments:

Refer to section 6.1.4 for a review of the primary efficacy endpoint.

Schedule of Visits and Measurements

Activity	Screen	Eligibility 1			Eligibility 2			Week 2 ± 1 day			Week 6 ± 3 days			Month 3 (Exit) ± 3 days or early Discontinue		
		8 AM	10 AM	4 PM	8 AM	10 AM	4 PM	8 AM	10 AM	4 PM	8 AM	10 AM	4 PM	8 AM	10 AM	4 PM
Informed Consent[1]	X															
Demographics	X															
Medical History	X															
Inclusion/Exclusion	X															
Concomitant Meds/General Health	X	X			X			X			X			X		
Urine Pregnancy Test[2]	X													X		
Hyperemia[3]					X	X	X	X	X	X	X	X	X	X	X	X
Visual Acuity[4]	X	X			X			X			X			X		
Ocular signs[3,5]	X	X			X			X			X			X		
Flare/Cells					X			X			X			X		
IOP[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dilated Fundus[3]	X															X
Gonioscopy	X															
Automated Perimetry[7]	X													X		
Pachymetry					X											
Endothelial Cell Density[8]					X									X		
D/C Curr. IOP ↓ Med.	X															
Dispense Study Med.							X			X			X			
Adverse Events								X	X	X	X	X	X	X	X	X
Collect Study Med.																X
Exit Patient																X

[1] Must be signed/dated before study procedures are performed.

[2] Pregnancy test required on all female patients of childbearing potential. The patient should follow the manufacture's procedure in the package insert for this product.

[3] Must be scored according to the grading criteria outlined in Definition of Terms.

[4] Best corrected logMar scale.

[5] Slit lamp exam must be performed prior to IOP measurements or instillation of the fluorescein agent.

[6] All IOP measurements should be ± 30 minutes of the required time.

[7] Automated Perimetry if not performed at Screening, may be performed between Screening and Eligibility 2 Visit. Visual fields must be reliable prior to dispensation of medications.

[8] Take endothelial cell photos (at selected sites only). Baseline photos may be taken any time between the Eligibility 1 and Eligibility 2 Visits.

Patient Population

Patient Group	Enrolled		Evaluable for Analysis/ Discontinued	
	Travatan Z Number of Patients	Travatan Number of Patients	Travatan Z Number of Patients	Travatan Number of Patients
Safety: N = 690 **Discontinued**	344	346	344 0	346 0
ITT: N = 679 **Discontinued**	338	341	332 6	336 5
PPP: N = 661 **Discontinued**	322	339	300 22	332 7

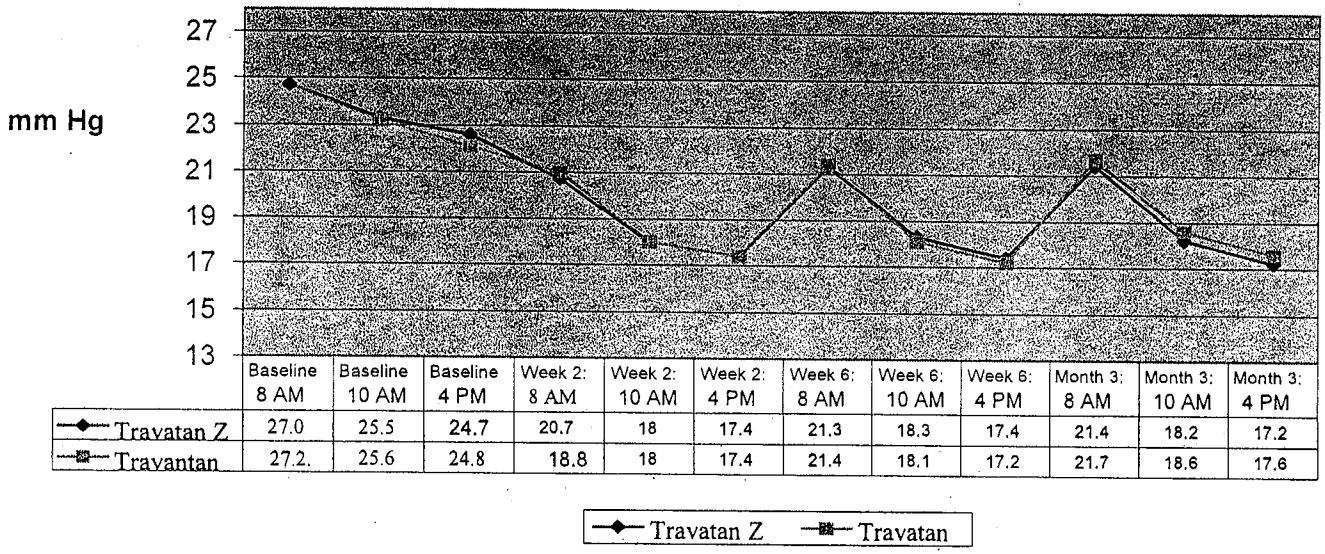
Reviewer's Comments:

The ITT population provides the basis of the primary efficacy data set. Case report forms for discontinued patients were reviewed by the medical officer.

All 690 patients received study medication and all were included in the safety analysis. Of the 690 randomized patients, 11 were discontinued from the study prior to collection of any on therapy study visit data; therefore, 679 patients were evaluable for and included in the intent-to-treat analysis. Twenty-nine patients were excluded from the per protocol analysis, which included the 11 patients above with no on-therapy study visit data and 18 patients due to protocol violations. The additional 18 exclusions were due to inclusion criteria violations (n=1), exclusion criteria violations (n=6), use of contraindicated concomitant medications (n=6), non-qualifying IOP (n=4), and an errant repeat of the first eligibility visit (n=1).

6.1.4 Efficacy Findings

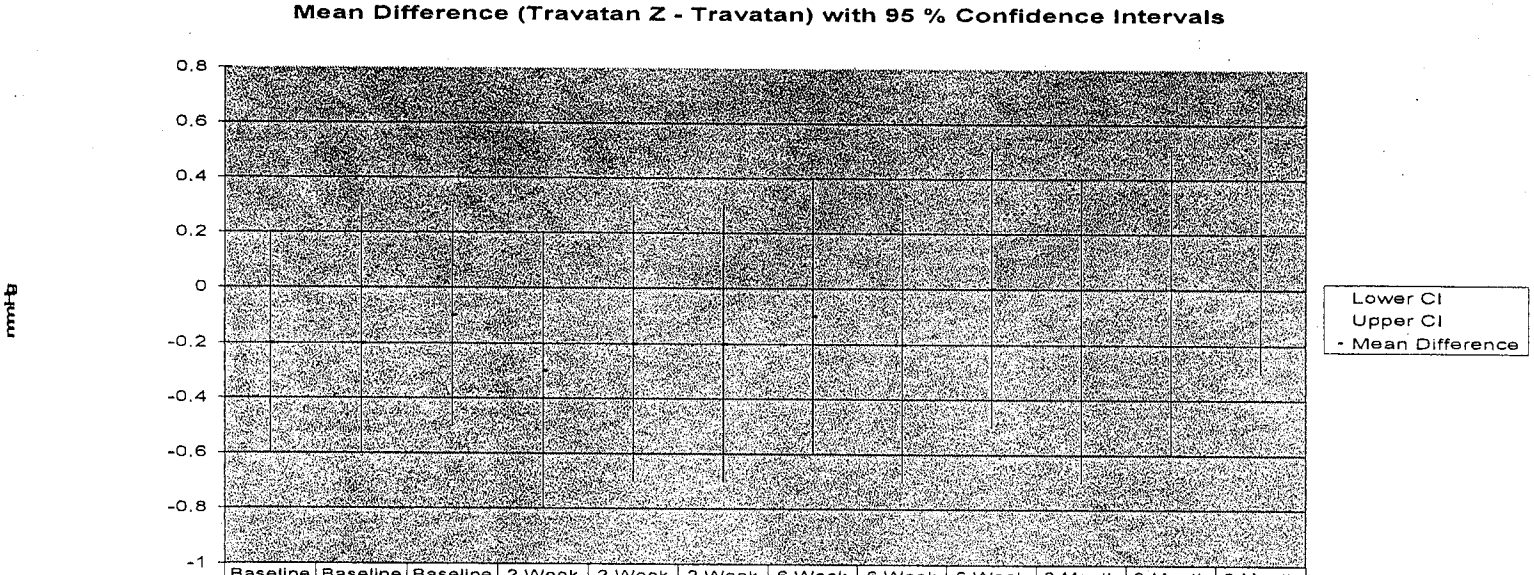
Mean IOP per Visit and Time (ITT)



	Baseline 8 AM	Baseline 10 AM	Baseline 4 PM	Week 2: 8 AM	Week 2: 10 AM	Week 2: 4 PM	Week 6: 8 AM	Week 6: 10 AM	Week 6: 4 PM	Month 3: 8 AM	Month 3: 10 AM	Month 3: 4 PM
Travatan Z	27.0	25.5	24.7	20.7	18	17.4	21.3	18.3	17.4	21.4	18.2	17.2
Travantan	27.2.	25.6	24.8	18.8	18	17.4	21.4	18.1	17.2	21.7	18.6	17.6

Reviewer's Comments:

IOP, the primary efficacy endpoint, is based on the mean IOP. There were no statistically significant differences between the 2 treatment groups at any follow-up timepoint. This new formulation, Travatan Z, demonstrated equivalence to Travatan for the primary endpoint. Equivalence is defined as the two sided 95% confidence interval being less than 1.5 mmHg at each direct group comparison over multiple times over a three month period and being less than 1.0 mmHg for the majority of direct group comparisons.



	Baseline 8 AM	Baseline 10 AM	Baseline 4 PM	2 Week 8 AM	2 Week 10 AM	2 Week 4 PM	6 Week 8 AM	6 Week 10 AM	6 Week 4 PM	3 Month 8 AM	3 Month 10 AM	3 Month 4 PM
Lower CI	-0.6	-0.6	-0.5	-0.8	-0.7	-0.7	-0.6	-0.7	-0.5	-0.7	-0.6	-0.3
Upper CI	0.2	0.3	0.3	0.2	0.3	0.3	0.4	0.3	0.5	0.4	0.5	0.7
- Mean Difference	-0.2	-0.2	-0.1	-0.3	-0.2	-0.2	-0.1	-0.2	0	-0.2	0	0.2

Reviewer's Comments:

The mean IOP of the two treatment arms at baseline is comparable. During follow-up, the mean change from baseline IOP of the Travatan Z group was found to be equivalent to the Travatan group. (i.e., the 95% confidence interval crosses zero at all timepoints measured).

6.1.5 Clinical Microbiology

This drug is not an antimicrobial. Not applicable.

6.1.6 Efficacy Conclusions

The primary efficacy endpoint demonstrates Travatan Z to be equivalent to Travatan in IOP lowering. Equivalence is defined as the two sided 95% confidence interval being less than 1.5 mmHg at each direct group comparison over multiple times over a three month period and being less than 1.0 mmHg for the majority of direct group comparisons.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The submitted clinical study report and protocol for study C-04-17 were reviewed. The submitted study report was reviewed and forms the basis of this application.

The entire application was submitted in electronic and paper format.

A PubMed electronic literature search was performed to supplement the review and no new information was found.

The medical officer has reviewed the Case Report Forms for discontinued subjects in the study (C-04-17).

The data was reviewed for consistency with other applications in this class. No special methods were used.

All trials were conducted under the review of approved Institutional Review Board committees. Investigators used an informed consent form that was appropriate for the respective trials.

7.1.1 Deaths

Two deaths were reported during the study, both of which occurred in elderly patients with exposure to Tavatan Z (septic shock coded as shock; multiple myeloma coded as carcinoma).

Reviewer's comments:

These two events were assessed as being unrelated to the study drug. Agree.

7.1.2 Other Serious Adverse Events

Serious Adverse Events
Number (%) of Patients
Either Treatment Group

Adverse Event	Travatan Z N=344 N (%)	Travatan N = 346 N (%)
Overall	11 (3.1%)	3 (0.9%)
Death (carcinoma; shock)	2 (0.6%)	0 (0.0%)
Bone disorder (spinal stenosis)	2 (0.6%)	0 (0.0%)
Kidney calculus	1 (0.3%)	0 (0.0%)
Carcinoma	1 (0.3%)	1 (0.3%)
Dehydration	1 (0.3%)	1 (0.3%)
Cholelithiasis	1 (0.3%)	0 (0.0%)
Heart Failure	1 (0.3%)	0 (0.0%)
Supraventricular tachycardia	1 (0.3%)	0 (0.0%)
Surgical procedure (prostatectomy)	1 (0.3%)	0 (0.0%)
Infection	0 (0.0%)	1 (0.3%)

Few serious adverse events were reported in the clinical trial. None of the events were ocular, and none were considered by the investigators to be related to the study medications.

Reviewer's Comments:

No serious adverse events were reported for more than 1% in any treatment group.

7.1.3 Dropouts and Other Significant Adverse Events

Listing of Patients by Investigator Who Discontinued The Study

Investigator	Patient	TX Group	Reason
2137	1164	Travatan Z	Adverse event allergic reaction
2434	1406	Travatan Z	Adverse event conjunctivitis / uveitis
2448	1511	Travatan Z	Adverse event iritis / follicles conjunctival
2137	1154	Travatan Z	Adverse event eye pain
1939	1052	Travatan Z	Adverse event palpitations
2600	1684	Travatan Z	Adverse event carcinoma
2353	1323	Travatan Z	Adverse event lung carcinoma / shock
1011	762	Travatan Z	Protocol violation – investigator inappropriately repeated eligibility visit
1393	904	Travatan Z	Protocol violation – patient did not meet inclusion/exclusion criteria
2128	1104	Travatan Z	Protocol violation – patient did not meet inclusion/exclusion criteria
2128	1108	Travatan Z	Protocol violation – patient did not meet inclusion/exclusion criteria
3664	2019	Travatan Z	Patient decision –unrelated to an adverse event
3853	3262	Travatan Z	Protocol violation – patient did not meet inclusion/exclusion criteria
1939	1055	Travatan	Adverse event eye pain / hyperemia eye
3112	1711	Travatan	Adverse event eye pain / hyperemia eye
1806	0974	Travatan	Adverse event iritis
1806	0970	Travatan	Inadequate control of IOP
0394	0276	Travatan	Adverse event dermatitis
2448	1508	Travatan	Adverse event infection (viral upper respiratory infection)
2348	1287	Travatan	Inadequate control of IOP
2353	1301	Travatan	Inadequate control of IOP
2353	1323	Travatan	Inadequate control of IOP
962	608	Travatan	Protocol violation – patient did not meet inclusion/exclusion criteria
2128	1103	Travatan	Protocol violation – patient did not meet inclusion/exclusion criteria

7.1.3.1 Overall profile of dropouts

Patients	Travatan Z N (%)	Travatan N (%)
Total Randomized	344 (100%)	346 (100%)
Completed Study	331 (96.2%)	335 (96.8%)
Discontinued:	13 (3.8%)	11 (3.2%)
Adverse Event	7 (2.0%)	5 (1.4%)
Protocol Violation	5 (1.5%)	2 (0.6%)
Personal Reasons	1 (0.3%)	0 (0.0%)
Lack of Efficacy	0 (0.0%)	4 (1.2%)

Reviewer's Comments:

Overall, 24 patients (3.5%) were discontinued from the study which included 13 patients (3.8%) with exposure to Travatan Z and 11 patients (3.2%) with exposure to Travatan. Discontinuation rates and reasons for discontinuation were similar between the two groups.

7.1.3.2 Adverse events associated with dropouts

The adverse event rate was similar comparing Travatan Z to Travatan, 2.0% and 1.4%, respectively.

Reviewer's comments:

Overall, no common factors were noted in reported adverse events resulting in patient discontinuation which would indicate a safety concern for either Travatan Z or Travatan.

7.1.3.3 Other significant adverse events

Refer to section 7.1.2.

7.1.4 Other Search Strategies

Case Report Forms for all discontinued subjects were reviewed by the Medical Officer.

7.1.5

Number (%) of Patients with Adverse Events Reported by ≥ 1 % of Patients Either Treatment Group

BODY SYSTEM Preferred Term	Travatan Z N = 344 N (%)	Travatan N = 346 N (%)
OVERALL	132 (38.3%)	132 (38.1%)
OCULAR		
Hyperemia eye	22 (6.4%)	31 (9.0%)
Pruritis Eye	19 (5.5%)	12 (3.5%)
Discomfort eye	13 (3.8%)	5 (1.4%)
Visual acuity decreased	6 (1.7%)	7 (2.0%)
Dry eye	6 (1.7%)	7 (2.0%)
Foreign body sensation	9 (2.6%)	4 (1.2%)
Pain eye	8 (2.3%)	5 (1.4%)
Keratitis	6 (1.7%)	4 (1.2%)
Corneal staining	1 (0.3%)	4 (1.2%)
Vision decreased	4 (1.2%)	1 (0.3%)
Accidental injury	4 (1.2%)	4 (1.2%)
NONOCULAR		
BODY AS A WHOLE		
Cold syndrome	4 (1.2%)	14 (4.0%)
Allergy	5 (1.5%)	6 (1.7%)
Infection	5 (1.5%)	1 (0.9%)
Flu syndrome	4 (1.2%)	2 (0.6%)
Headache	1 (0.3%)	1 (1.2%)
CARDIOVASCULAR		
Hypertension	4 (1.2%)	7 (2.0%)
ENDOCRINE		
Diabetes mellitus	3 (0.9%)	6 (1.7%)
METABOLIC & NUTRITIONAL		
Hypercholesterolemia	6 (1.7%)	4 (1.2%)
MUSCULOSKELETAL		
Arthritis	4 (1.2%)	-
RESPIRATORY		
Brochitis	2 (0.6%)	4 (1.2%)

Reviewer's Comments:

The most frequently reported event (≥ 6% in either treatment group) was ocular hyperemia occurring at an overall incidence of 6.4% in the Travatan Z group and 9.0% in the Travatan

group. Ocular hyperemia in this case is an expected class effect of prostaglandin analogue use and is generally thought to be a cosmetic issue.

Based upon a review of the common adverse events no safety concerns were identified. A similar adverse event profile was observed between the Travatan Z and Travatan groups.

7.1.5.1 Eliciting adverse events data in the development program

Adverse events were assessed at each scheduled visit (Day 0 through Month 3) and at any unscheduled visit. Duration, investigator's perceived relationship between event and study drug, action(s) taken and outcome were recorded on the Adverse Event form.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

All adverse events wee coded using a modified COSTART dictionary and received independent causality assessments from the study investigator and medical monitor.

7.1.5.3 Incidence of common adverse events

Refer to section 7.1.5. There is only one clinical trial; therefore there is no pooled data.

7.1.5.4 Common adverse event tables

Refer to section 7.1.5. There is only one clinical trial; therefore there is no pooled data.

7.1.5.5 Identifying common and drug-related adverse events

Refer to section 7.1.5.

7.1.5.6 Additional analyses and explorations

Not applicable. There were no additional analyses and explorations performed regarding adverse events.

7.1.6 Less Common Adverse Events

Refer to section 7.1.5.

7.1.7 Laboratory Findings

Not applicable. Clinical laboratory data (hematology, chemistry, urinalysis) were not collected in this study.

7.1.7.1 Overview of laboratory testing in the development program

Not applicable. Clinical laboratory data (hematology, chemistry, urinalysis) were not collected in this study.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Not applicable. Clinical laboratory data (hematology, chemistry, urinalysis) were not collected in this study.

7.1.7.3 Additional analyses and explorations

Not applicable. Clinical laboratory data (hematology, chemistry, urinalysis) were not collected in this study.

7.1.7.4 Special assessments

Not applicable. Clinical laboratory data (hematology, chemistry, urinalysis) were not collected in this study.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Not applicable. Vital signs (heart rate and blood pressure) data were not collected in this study.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

Not applicable. Based on the fund of knowledge regarding this group of therapeutics, no ECGs were performed.

7.1.10 Immunogenicity

Not applicable. The drug product is not expected to induce immunogenicity.

7.1.11 Human Carcinogenicity

In nonclinical studies, the new formulation, Travatan Z, showed a similar toxicity profile as the

marketed formulation Travatan.

7.1.12 Special Safety Studies

No safety concerns were identified based upon an analysis of change from baseline for visual acuity, ocular signs (cornea, iris/anterior chamber, lens, aqueous flare and inflammatory cells), ocular hyperemia, dilated fundus parameters (vitreous, retina/macula/choroids, optic nerve), cup/disc ratio, visual fields and endothelial cell density measurements in either treatment group in the overall safety population, adult population, or elderly population.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Not applicable. This is not a therapeutic class with known abuse potential or apparent withdrawal potential.

7.1.14 Human Reproduction and Pregnancy Data

There are no adequate and well-controlled studies in pregnant women. Travatan Z should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

It is not known whether this drug or its metabolites are excreted in human milk, although a study in lactating rats demonstrated that radiolabeled travoprost and/or its metabolites were excreted in milk.

7.1.15 Assessment of Effect on Growth

Safety and effectiveness in pediatric patients has not been established.

7.1.16 Overdose Experience

No information is available on overdosage of Travatan Z or Travatan during clinical trials in adults.

7.1.17 Postmarketing Experience

Travatan Z is not currently marketed in any country. However, Travatan (travoprost ophthalmic solution, 0.004%) is currently registered in over 75 countries.

Review of spontaneous post-marketing reports confirms the overall safe use of Travatan. No reaction term has been reported with a frequency which could suggest a product related problem. Travatan is well-tolerated and safe for use as indicated, based upon a review of spontaneous post-marketing reports of adverse events.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The clinical study report, clinical protocol and literature reports were reviewed. The entire application was submitted in electronic and paper format.

Modules 1, 2 and 5 were reviewed in depth.

Refer to Section 4.2 for a table of the clinical study.

7.2.1.1 Study type and design/patient enumeration

Data from one phase 3 clinical study has been submitted in support of this NDA. Refer to Section 4.2 for a table of the clinical study.

7.2.1.2 Demographics

Demographics for All Randomized Patients in Study C-04-17

Travatan Z N= 344; Travatan N= 346

Category	Treatment Group			
	Travatan Z		Travatan	
	N	%	N	%
Sex				
Male	154	44.8	166	48.0
Female	190	55.2	180	52.0
Age Class				
< 65 yrs	183	53.2	164	47.4
≥ 65 yrs	161	46.8	182	52.6
Race				
Black	67	19.5	64	18.5
Caucasian	226	65.7	241	69.7
Asian	4	1.2	2	0.6
Hispanic	46	13.4	37	10.7
Other	1	0.3	2	0.6
Iris Color				
Brown	193	56.1	182	52.6
Hazel	53	15.4	51	14.7
Green	22	6.4	14	4.0
Blue	71	20.6	97	28.0
Grey	5	1.5	2	0.6
Diagnosis (Study Eye)				
Ocular Hypypertension	134	39.0	133	38.4
Open-Angle Glaucoma	202	58.7	206	59.6
Open-Angle Glaucoma with Pigment Dispersion	6	1.7	6	1.7
Open-Angle Glaucoma with Pseudoexfoliation	2	0.6	1	0.3

Reviewer's Comments:

There were no significant differences between treatment groups in baseline demographic characteristics.

7.2.1.3 Extent of exposure (dose/duration)

Duration of Exposure by Scheduled Visit for All Randomized Patients

Exam Visit	Travatan Z	Travatan	Total
Day 0	344	346	690
Week 2	6	5	11
Week 6	5	4	9
Month 3 or more	313	337	670

Reviewer's Comments:

The mean duration of treatment exposure was similar in both groups. For the Travatan Z group mean duration of treatment exposure was 87.7 days. For the Travatan group mean duration of treatment exposure was 88.1 days.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

The medical reviewer conducted a PubMed electronic literature search to supplement the submitted review of the literature. There was no significant new information found in the published literature.

7.2.2.1 Other studies

One phase 3 clinical trial (study C-04-17) was submitted in this NDA to support the approval for Travatan Z. In study C-04-17 Travatan Z was compared to Travatan. Travatan had been previously approved March 2001 in NDA 21-257.

7.2.2.2 Postmarketing experience

Travatan Z is not currently marketed in any country. However, Travatan (travoprost ophthalmic solution, 0.004%) is currently registered in over 75 countries.

In the time period between 01 November 2001 and 31 October 2004, there were [redacted] spontaneous adverse event reports meeting minimum reporting criteria associated with the use of Travatan worldwide. During this period [redacted] units were sold for an incidence of adverse of events of 0.0040%.

The postmarketing data is consistent with the safety profile from the clinical studies, and provides reassurance that no new safety issues have emerged with prolonged use.

7.2.2.3 Literature

The medical reviewer conducted a PubMed electronic literature search to supplement the submitted review of the literature. There was no significant new information found in the published literature.

7.2.3 Adequacy of Overall Clinical Experience

An adequate number of subjects, including adequate demographic subsets, were exposed to the drug product in a well-controlled, randomized, clinical trial. The doses and durations of exposure were adequate to assess safety for the intended use.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Not applicable. Refer to Pharmacology/Toxicology review.

7.2.5 Adequacy of Routine Clinical Testing

Not applicable. Clinical laboratory data (hematology, chemistry, urinalysis) were not collected in this study.

The methods and ophthalmologic tests used and their frequency were adequate to effectively monitor the subject population.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Not applicable. This data was not collected in this study.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The applicant's evaluation of potential adverse effects for this pharmacological class of drug is adequate.

7.2.8 Assessment of Quality and Completeness of Data

The submitted safety database appeared adequate and complete for the class of pharmacologic class of agents.

7.2.9 Additional Submissions, Including Safety Update

On March 15, 2006 the 120-day safety update report for Travatan Z was submitted.

There is no new safety information regarding Travatan BAC-free (travoprost ophthalmic ophthalmic solution), 0.004% since the original submission of November 18, 2005.

Reviewer's comments:

Acceptable. There are no new additional safety concerns.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

There were no statistically significant differences between 2 the treatment groups.

Reviewer's Comments:

Refer to comments to section 7.1.5 (Common Adverse Events).

7.4 General Methodology

7.4.1 See Section 7.1.5.

7.4.1.1 Pooled data vs. individual study data

Not applicable. This NDA is a single study phase 3 clinical trial.

7.4.1.2 Combining data

Not applicable. This NDA is a single study phase 3 clinical trial.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The recommended dosing regimen is one drop in the affected eye(s) once daily in the evening.

8.2 Drug-Drug Interactions

There were no important drug-drug interactions noted that would affect the product's clinical use.

8.3 Special Populations

No overall differences in safety or effectiveness have been observed between elderly and adult patients.

No patients with hepatic or renal impairment were studied.

There are no adequate and well-controlled studies in pregnant woman. It is not known whether this drug or its metabolites are excreted in human milk, although in an animal study of lactating rats radiolabeled travoprost and/or its metabolites were excreted in milk.

Safety and effectiveness in pediatric patients has not been established.

8.4 Pediatrics

No additional pediatric studies are planned. Refer to section 8.3.

8.5 Advisory Committee Meeting

Not applicable.

8.6 Literature Review

The medical reviewer conducted a PubMed electronic literature search to supplement the submitted review of the relevant information. There was no significant new information found in the published literature.

8.7 Postmarketing Risk Management Plan

Not applicable. The applicant did not submit a postmarketing risk management plan, nor is one needed.

8.8 Other Relevant Materials

The Division of Medication Errors and Technical Support (DMETS/DDMAC) (consult #: 05-0269 and 05-0269-1, 05-0269-2) had the following recommendations:

1. DMETS does not recommend the use of the proprietary "Travatan Z", "Travatan —", or "Travatan —"

Reviewer's comments:

Disagree. Even if the patient received Travatan instead of Travatan Z, the error is unlikely to be clinically significant.

2. DMETS recommends implementation of the label and labeling revisions outlined in Section III of this review to minimize potential errors with the use of this product.

Reviewer's comments:

Agree that sponsor revise the statement "FOR PROFESSIONAL USE ——— ' on carton/container labels so that it clearly denotes its status as a drug sample, e.g. "Sample," "Not for Sale," or "Professional Courtesy Package" [21 CFR 203.38(c)]. As currently written, "FOR PROFESSIONAL USE ——— does not indicate the bottle is a sample.

3. DDMAC finds the proprietary names "Travatan Z," "Travatan ——— ' and "Travatan ———," are acceptable from a promotional perspective.

Reviewer's comments:

Agree.

9 OVERALL ASSESSMENT

9.1 Conclusions

The bioequivalence trial (study C-04-17) supports approval of Travatan Z. The primary efficacy endpoint, mean intraocular pressure, demonstrated equivalence when comparing travoprost ophthalmic solution, 0.004% (Travatan Z), to the previously approved drug, travoprost ophthalmic solution, 0.004% (Travatan). Travatan (NDA 21-257) was first approved in March 2001.

9.2 Recommendation on Regulatory Action

From a clinical perspective, NDA 21–994 is recommended for approval for the treatment of elevated intraocular pressure (IOP) in patients with open angle glaucoma or ocular hypertension who are intolerant of intraocular lowering medications or insufficiently responsive (failed to achieve target IOP determined after multiple measurements over time) to another intraocular pressure lowering medication.

9.3 Recommendation on Postmarketing Actions

Not applicable. Further postmarketing actions are not required.

9.4 Labeling Review

Reviewer's commets:

Sponsor's label and the reviewer's labeling comments follow section 9.5.

9.5 Comments to Applicant

None. No postmarketing actions are recommended except completion of postmarketing studies agreed upon for NDA 21-257.

13 Page(s) Withheld

_____ Trade Secret / Confidential

X Draft Labeling

_____ Deliberative Process

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

/s/

Martin Nevitt
5/24/2006 10:00:30 AM
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NDA 21-994
Review # 2

Amendment

Submission date: 09/15/06
Review date: 09/19/06

Applicant:

Alcon Research, Ltd.
6201 South Freeway
Fort Worth, TX 76134-2099

Angela C. Kothe
Director, Regulatory Affairs
(817) 551-4933

Drug:

Travatan®Z (travaprost ophthalmic solution, 0.004%)

Pharmacologic Category:

Prostaglandin $F_{2\alpha}$ analogue

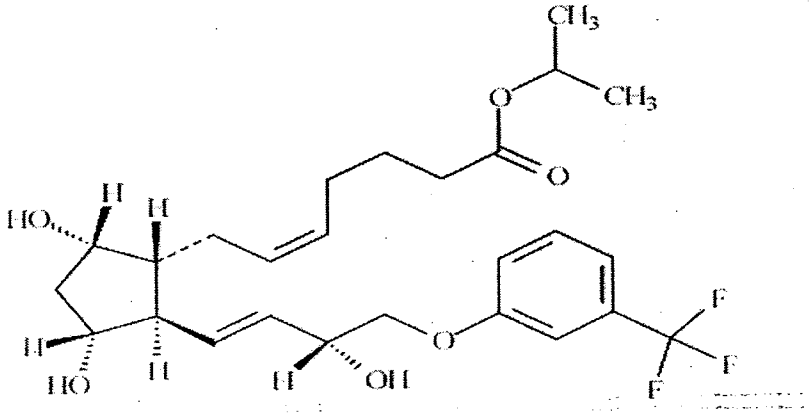
Submitted:

The sponsor has submitted the following revised labeling for the package insert and the carton/container on September 15, 2006, based on discussions with the agency.

TRAVATAN® Z
(travoprost ophthalmic solution) 0.004%
Sterile

DESCRIPTION

Travoprost is a synthetic prostaglandin $F_{2\alpha}$ analogue. Its chemical name is [1*R*-[1α(*Z*),2β(1*E*,3*R**),3α,5α]]-7-[3,5-Dihydroxy-2-[3-hydroxy-4-[3-(trifluoromethyl)phenoxy]-1-butenyl]cyclopentyl]-5-heptenoic acid, 1-methylethylester. It has a molecular formula of $C_{26}H_{35}F_3O_6$ and a molecular weight of 500.55. The chemical structure of travoprost is:



Travoprost is a clear, colorless to slightly yellow oil that is very soluble in acetonitrile, methanol, octanol, and chloroform. It is practically insoluble in water.

TRAVATAN® Z ophthalmic solution is supplied as sterile, buffered aqueous solution of travoprost with a pH of approximately 5.7 and an osmolality of approximately 290 mOsmol/kg. Each mL of TRAVATAN® Z contains: Active: travoprost 0.004%. Inactives: polyoxyl 40 hydrogenated castor oil, *sof*Zia™ (boric acid, propylene glycol, sorbitol, zinc chloride), sodium hydroxide and/or hydrochloric acid to adjust pH, and purified water, USP. Preserved in the bottle with an ionic buffered system, *sof*Zia™.

CLINICAL PHARMACOLOGY

Mechanism of Action

Travoprost free acid is a selective FP prostanoid receptor agonist which is believed to reduce intraocular pressure by increasing trabecular meshwork and uveoscleral outflow. The exact mechanism of action is unknown at this time.

Pharmacokinetics/Pharmacodynamics

Absorption:
Travoprost is absorbed through the cornea and is hydrolyzed to the active free acid. Data from four multiple dose pharmacokinetic studies (totaling 107 subjects) have shown that plasma concentrations of the free acid are below 0.01 ng/ml (the quantitation limit of the assay) in two-thirds of the subjects. In those individuals with quantifiable plasma concentrations (N=38), the mean plasma C_{max} was 0.018 ± 007 ng/ml (ranged 0.01 to 0.052 ng/mL) and was reached within 30 minutes. From these studies, travoprost is estimated to have a plasma half-life of 45 minutes. There was no difference in plasma concentrations

between Days 1 and 7, indicating that there was no significant accumulation.

Metabolism:
Travoprost, an isopropyl ester prodrug, is hydrolyzed by esterases in the cornea to its biologically active free acid. Systemically, travoprost free acid is metabolized to inactive metabolites via beta-oxidation of the α(carboxylic acid) chain to give the 1,2-dinor and 1,2,3,4-tetranor analogs, via oxidation of the 15-hydroxyl moiety, as well as via reduction of the 13,14 double bond.

Elimination:
The elimination of travoprost free acid from plasma was rapid and levels were generally below the limit of quantification within one hour after dosing. The terminal elimination half-life of travoprost free acid was estimated from fourteen subjects and ranged from 17 minutes to 86 minutes with the mean half-life of 45 minutes. Less than 2% of the topical ocular dose of travoprost was excreted in the urine within 4 hours as the travoprost free acid.

Clinical Studies
In clinical studies, patients with open-angle glaucoma or ocular hypertension and baseline pressure of 25–27 mm Hg, who were treated with TRAVATAN (travoprost ophthalmic solution) or TRAVATAN® Z (travoprost ophthalmic solution)dosed once-daily in the evening demonstrated 7- 8 mmHg reduction in intraocular pressure. In subgroup analysis of this study, mean IOP reduction in black patients was up to 1.8 mm Hg greater than in non-black patients. It is not known at this time whether this difference is attributed to race or to heavily pigmented irides.

In a multi-center, randomized, controlled trial, patients with mean baseline intraocular pressure of 24-26 mmHg on TIMOPTIC* 0.5% BID who were treated with travoprost 0.004% dosed QD adjunctively to TIMOPTIC* 0.5% BID demonstrated 6-7 mmHg reductions in intraocular pressure.

Travoprost ophthalmic solution, 0.004% has been studied in patients with hepatic impairment and also in patients with renal impairment. No clinically relevant changes in hematology, blood chemistry, or urinalysis laboratory data were observed in these patients.

INDICATIONS AND USAGE
TRAVATAN® Z ophthalmic solution is indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension who are intolerant of other intraocular pressure lowering medications or insufficiently responsive (failed to achieve target IOP determined after multiple measurements over time) to another intraocular pressure lowering medication.

CONTRAINDICATIONS
TRAVATAN® Z is contraindicated in patients with hypersensitivity to travoprost or any other ingredients in this product.

WARNINGS

Prostaglandin analogues, including travoprost ophthalmic solution, 0.004% have been reported to cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the iris and periorbital tissue (eyelid) and increased pigmentation and growth of eyelashes. These changes may be permanent.

Prostaglandin analogues, including travoprost ophthalmic solution, 0.004% may gradually change eye color, increasing the amount of brown pigmentation in the iris by increasing the number of melanosomes (pigment granules) in melanocytes. The long term effects on the melanocytes and the consequences of potential injury to the melanocytes and/or deposition of pigment granules to other areas of the eye are currently unknown. The change in iris color occurs slowly and may not be noticeable for months to years. Patients should be informed of the possibility of iris color change.

Eyelid skin darkening has been reported in association with the use of prostaglandin analogues, including travoprost ophthalmic solution, 0.004%.

Prostaglandin analogues, including travoprost ophthalmic solution, 0.004% may gradually change eyelashes in the treated eye; these changes include increased length, thickness, pigmentation, and/or number of lashes.

Patients who are expected to receive treatment in only one eye should be informed about the potential for increased brown pigmentation of the iris, periorbital and/or eyelid tissue, and eyelashes in the treated eye and thus heterochromia between the eyes. They should also be advised of the potential for a disparity between the eyes in length, thickness, and/or number of eyelashes.

PRECAUTIONS

General

There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the epithelial surface (see **Information for Patients**).

Patients may slowly develop increased brown pigmentation of the iris. This change may not be noticeable for months to years (see **WARNINGS**). Iris pigmentation changes may be more noticeable in patients with mixed colored irides, i.e., blue-brown, grey-brown, yellow-brown, and green-brown; however, it has also been observed in patients with brown eyes. The color change is believed to be due to increased melanin content in the stromal melanocytes of the iris. The exact mechanism of action is unknown at this time. Typically the brown pigmentation around the pupil spreads concentrically towards the periphery in affected eyes, but the entire iris or parts of it may become more brownish. Until more information about increased brown pigmentation is available, patients should be examined regularly and, depending on the situation, treatment may be stopped if increased pigmentation ensues.

TRAVATAN® Z ophthalmic solution should be used with caution in patients with a history of intraocular inflammation (iritis/uveitis) and should generally not be used in patients with active intraocular inflammation.

Macular edema, including cystoid macular edema, has been reported during treatment with prostaglandin $F_{2\alpha}$ analogues. These reports have mainly occurred in aphakic patients, pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema. TRAVATAN® Z should be used with caution in these patients.

TRAVATAN® Z has not been evaluated for the treatment of angle closure, inflammatory or neovascular glaucoma.

Information for Patients
Patients should be advised concerning all the information contained in the Warnings and Precautions sections. Patients should also be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures because this could cause the tip to become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

Patients also should be advised that if they develop an intercurrent ocular condition (e.g., trauma, or infection) or have ocular surgery, they should immediately seek their physician's advice concerning the continued use of the multi-dose container.
Patients should be advised that if they develop any ocular reactions, particularly conjunctivitis and lid reactions, they should immediately seek their physician's advice.

If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Two-year carcinogenicity studies in mice and rats at subcutaneous doses of 10, 30, or 100 µg/kg/day did not show any evidence of carcinogenic potential. However, at 100 µg/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 µg/kg) corresponds to exposure levels over 400 times the human exposure at the maximum recommended human ocular dose (MRHOD) of 0.04 µg/kg, based on plasma active drug levels.

Travoprost was not mutagenic in the Ames test, mouse micronucleus test and 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 µg/kg/day [250 times the maximum recommended human ocular dose of 0.04 µg/kg/day on a µg/kg basis (MRHOD)]. At 10 µg/kg/day, the mean number of corpora lutea was reduced, and the post-implantation losses were increased. These effects were not observed at 3 µg/kg/day (75 times the MRHOD).

Pregnancy: Teratogenic Effects

Pregnancy Category: C

Travoprost was teratogenic in rats, at an intravenous (IV) dose up to 10 µg/kg/day (250 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 was not teratogenic in rats at IV doses up to 3 µg/kg/day (75 times the MRHOD), or in mice at subcutaneous doses up to 1.0 µg/kg/day (25 times the MRHOD). Travoprost produced an increase in post-implantation losses and a decrease in fetal viability in rats at IV doses > 3 µg/kg/day (75 times the MRHOD) and in mice at subcutaneous doses > 0.3 µg/kg/day (7.5 times the MRHOD). In the offspring of female rats that received travoprost subcutaneously from Day 7 of pregnancy to lactation Day 21 at the doses of ≥ 0.12 µg/kg/day (3 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.

There are no adequate and well-controlled studies in pregnant women. TRAVATAN® Z should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

A study in lactating rats demonstrated that radiolabeled travoprost and/or its metabolites were excreted in milk. It is not known whether this drug or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TRAVATAN® Z ophthalmic solution is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

No overall differences in safety or effectiveness have been observed between elderly and other adult patients.

ADVERSE REACTIONS

The most common adverse event observed in controlled clinical studies with TRAVATAN (travoprost ophthalmic solution) 0.004% and TRAVATAN Z (travoprost ophthalmic solution) 0.004% was ocular hyperemia which was reported in 30 to 50% of patients. Up to 3% of patients discontinued therapy due to subconjunctival hyperemia.

Ocular adverse events reported at an incidence of 5 to 10 % in these clinical studies included decreased visual acuity, eye discomfort, foreign body sensation, pain and pruritis.

Ocular adverse events reported at an incidence of 1 to 4% in clinical studies with TRAVATAN or TRAVATAN Z included abnormal vision, blepharitis, blurred vision, cataract, cells, conjunctivitis, corneal staining, dry eye, eye disorder, flare, iris discoloration, keratitis, lid margin crusting, photophobia, subconjunctival hemorrhage, and tearing.

Nonocular adverse events reported at an incidence of 1 to 5% in these clinical studies were accidental injury, allergy, angina pectoris, anxiety, arthritis, back pain, bradycardia, bronchitis, chest pain, cold/flu syndrome, depression, dyspepsia, gastrointestinal disorder, headache, hypercholesterolemia, hypertension, hypotension, infection, pain, prostate disorder, sinusitis, urinary incontinence, and urinary tract infection.

DOSAGE AND ADMINISTRATION

The recommended dosage is one drop in the affected eye(s) once-daily in the evening. The dosage of TRAVATAN® Z ophthalmic solution should not exceed once-daily since it has been shown that more frequent administration of travoprost may decrease the intraocular pressure lowering effect.

Reduction of intraocular pressure starts approximately 2 hours after administration of travoprost. The maximum effect is observed 12 hours after administration and is maintained throughout the day.

TRAVATAN® Z may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

HOW SUPPLIED

TRAVATAN® Z (travoprost ophthalmic solution) 0.004% is a sterile, isotonic, buffered, preserved, aqueous solution of travoprost (0.04 mg/mL) supplied in Alcon's oval DROP-TAINER® package system.

TRAVATAN® Z is supplied as a 2.5 mL solution in a 4 mL and a 5 mL solution in a 7.5 mL natural polypropylene dispenser bottle with a natural polypropylene dropper tip and a turquoise polypropylene overcap. Tamper evidence is provided with a shrink band around the closure and neck area of the package.

2.5 ml fill in 4 mL bottle	**NDC** 0065-0260-25
5 mL fill in 7.5 mL bottle	**NDC** 0065-0260-05

Storage: Store at 2° - 25°C (36° - 77°F).

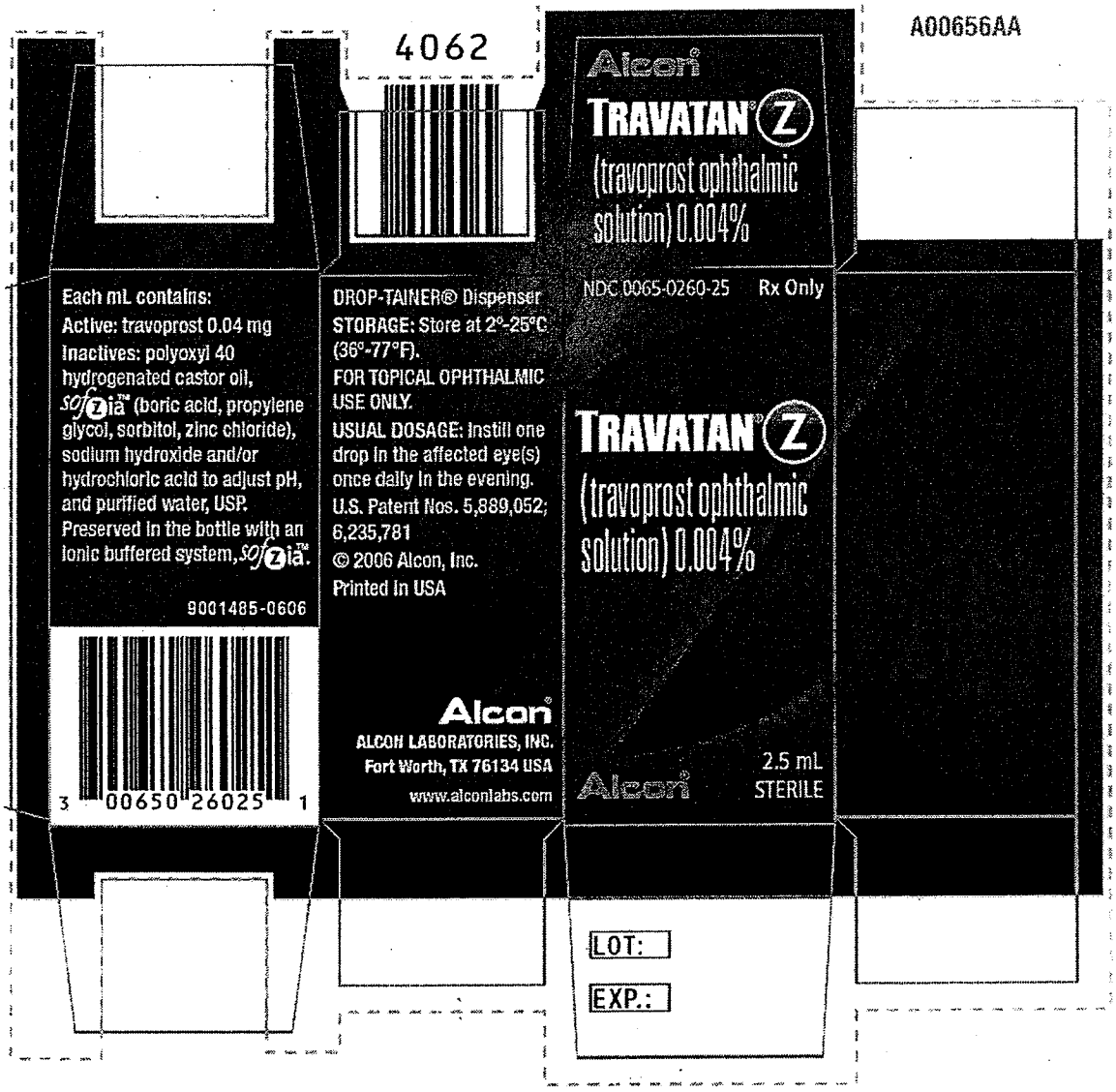
Rx Only

U.S. Patent Nos. 5,889,052 and 6,235,781

* TIMOPTIC is the registered trademark of Merck & Co., Inc.

ALCON®
ALCON LABORATORIES, INC.
Fort Worth, Texas 76134 USA

Carton Label for 2.5 mL and 5 mL:



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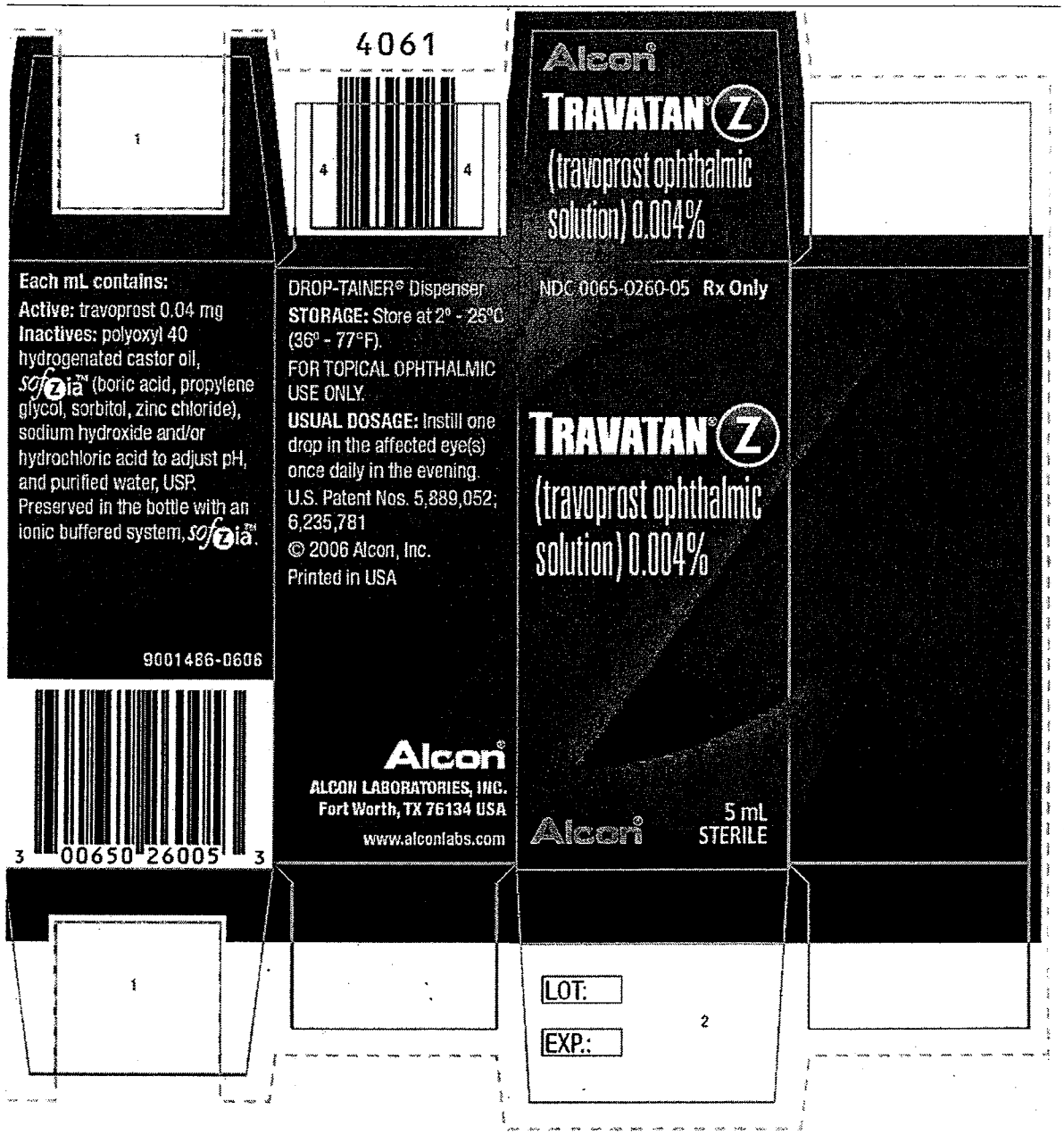

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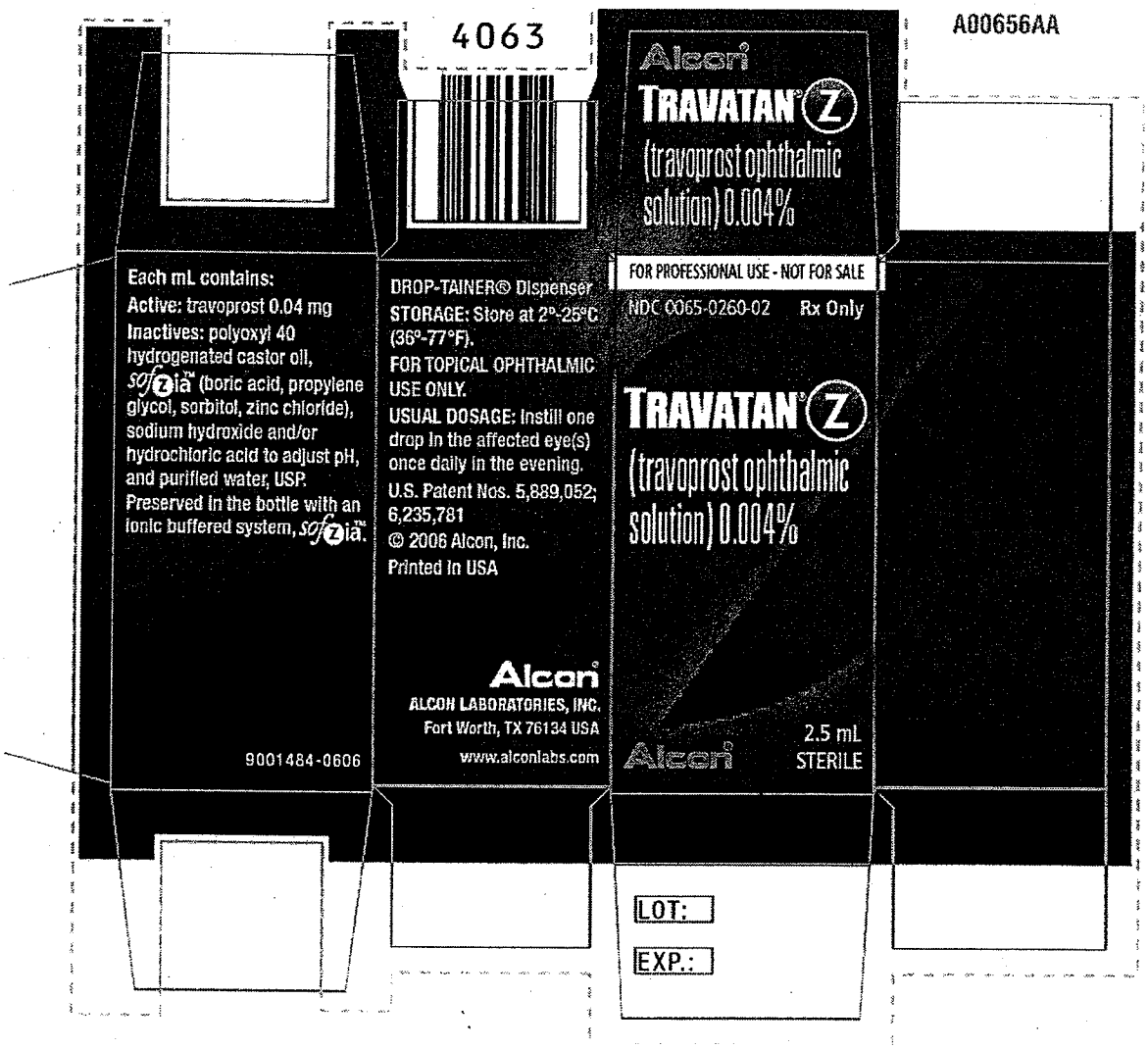
Carton Label for 2.5 mL Professional Sample:



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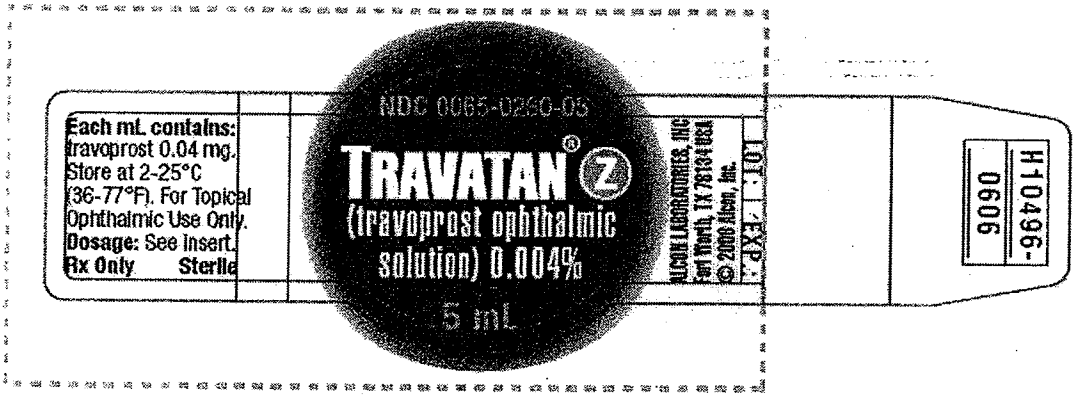
Container Label for 2.5 mL and 5 mL:



Container Label for 2.5 mL Professional Sample:

Reviewer's comments:

The sponsor has incorporated all agency labeling suggestions. The revisions to the package insert and the carton and container are acceptable.

Recommendation:

NDA 21-994 is recommended for approval with the revised labeling for the package insert and the carton/container.

Martin Nevitt, M.D., M.P.H.
Medical Officer

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/s/

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