

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-257

ADMINISTRATIVE DOCUMENTS



PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA Number: N 021257
Trade Name: TRAVATAN(TRAVOPROST OPHTHALMIC SOLUTION)
Generic Name: TRAVOPROST OPHTHALMIC SOLUTION
Supplement Number: 000 **Supplement Type:** N
Dosage Form:
Regulatory Action: AP **Action Date:**
COMIS Indication: LOWERING OF INTRAOCULAR PRESSURE IN PATIENTS WITH POAG/OHT

Indication #1: 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.

Label Adequacy: Does not apply
Formulation Needed: No new formulation is needed
Comments (if any)

Lower Range	Upper Range	Status	Date
0 years	16 years	Waived	

Comments: The sponsor has requested a waiver for 0 to 12 year old patients. They have proposed studies of 12 to 16 year old patients to gain exclusivity. Since the adverse events found with this medication make it inappropriate for use in the pediatric population, the agency has denied this proposal.

This page was last edited on 3/8/01

Signature

/S/
○

Date

March 8, 2001

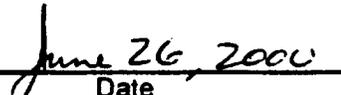
**APPEARS THIS WAY
ON ORIGINAL**

Item 16. DEBARMENT STATEMENT

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



Scott Krueger
Senior Director, Regulatory Affairs



Date

**APPEARS THIS WAY
ON ORIGINAL**

Deputy Division Director's Memorandum for NDA 21-257

NDA #21-257

March 13, 2001

Name: Travatan (travaprost ophthalmic solution)

Sponsor: Alcon Universal, Ltd.

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

Related Drugs: Xalatan (latanoprost ophthalmic solution) NDA 20-597
Rescula (isopropyl unoprostone ophthalmic solution) NDA 21-214
Lumigan (bimatoprost ophthalmic solution) NDA 21-275

Post-marketing Studies:

With the introduction of prostaglandin analogues for ophthalmologic use, adverse events related to pigmented tissues have been described. In an effort to better understand these events and their potential consequences, post-marketing studies have been requested for each New Drug Application that displays these properties.

In Alcon's response to the agency's approvable letter, Alcon committed to conduct a study to evaluate the potential pigmentation in the trabecular meshwork in patients undergoing a trabeculectomy after at least two years of treatment with Travatan and to conduct (or continue current studies) to evaluate the long-term effects of increased pigmentation.

These commitments are consistent with the commitments of the other new drug applications displaying pigmentation properties. Consistent with the approval letters for the other products, the proposed approval letter for this product does not specify these commitments.



Wiley A. Chambers, M.D.
Deputy Division Director

MEETING MINUTES

MEETING DATE: March 5, 2001 **TIME:** 3 p.m. **LOCATION:** Teleconference

HFD-550 Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products

NDA 21-257

DRUG: Travatan (travoprost ophthalmic solution) 0.004%

Indication: 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 measurement over time) to another intraocular pressure lowering medication.

SPONSOR/APPLICANT: Alcon Universal

TYPE of MEETING: Pre-Approval Safety Conference

ODE V OFFICE PARTICIPANTS:

Robert DeLap

REVIEW DIVISION PARTICIPANTS:

Wiley Chambers, William Boyd, Lucious Lim, Michael Puglisi, Jennifer Harris, Joanne Holmes, Raphael Rodriguez

OPDRA PARTICIPANTS:

Julie Beitz, Anne Trontell, Renan Bonnel, Claudia Karwoski, Patrick Guinn

Serious Adverse Events To Be Monitored By OPDRA:

1. Cardiac events
2. Deaths

Additional Comments:

The major safety concerns with this class of drugs are changes in patients' pigmented tissues, which may be permanent. It is unclear at this time what impact these changes may have. Long term follow-up studies, to be performed by the sponsor, have been requested by the Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products. The Division does not see a need for either OPDRA or the sponsor to assess whether Travatan is being prescribed as first line therapy (versus the indicated second-line use). Dr. Chambers believes the potential risks of changes in melanocytes and melanosomes have been sufficiently communicated to practitioners.

MEETING MINUTES – Pre-Approval Safety Conference

Record of Telephone Conversation Conference

Date: February 16, 2001
RE: NDA No: NDA 21-257
Product Name: Travatan (travoprost) sterile ophthalmic solution, 0.004%
Firm Name: Alcon Universal, Ltd
6201 South Freeway, Fort Worth, TX 76134

Internal Telecon participants: Bonnie Dunn, Linda Ng (DNDCIII/ONDC), Pat Alcock, Bruce Hartman, Brenda Uratani, (Office of Compliance), David Beltran (investigator/Dallas District Office) and Richard Rodriguez (Director of Compliance Branch in the Dallas District). Pat Alcock initiated the call.

Background.

Allan Fenselau, chemistry reviewer for this NDA, had raised questions about the irregularities in a set of submitted data, concerning the Series 3 study for unpouched product. BDunn has forwarded this information to PAlcock. PAlcock decided to set up a telephone conference with the investigator in the Dallas District Office who was conducting an inspection of the manufacturing site for another application.

Content.

PAlcock informed BDunn and LNg that David Beltran started an investigation of Alcon's Fort Worth's site on February 15, 2001. Both OC and the Dallas District Office have received AFenselau's email, which provided information on inconsistencies on a submitted set of stability data for the Series 3 unpouched stability study. DBeltran gave a status report of his findings. DBeltran was able to ascertain that for new molecular entities, Alcon's R & D handles the stability studies, and used the pouched product. The ASPEX, manufacturing group, in another building, pulled some product (one lot of two different strengths). And did a special project to evaluate the stability of the unpouched. Alcon did perform a Special Project to evaluate unpouched. When the R&D group said that they needed to perform an unpouched study, the manufacturing group told them they had these data for these studies. DBeltran said he looked at the data, and there were no discrepancies. DBeltran also informed the Alcon that these kinds of incidences create credibility problems and the two groups should be talking to each other and their regulatory affairs staff. DBeltran's conclusion was that there were no data integrity problem, and no FDA Form 483 was issued. DBeltran also stated that the media fill and monitoring system corrections have been implemented.

PAlcock also added that the OAI Alert (red line in EES) would be taken off for all other Alcon, Fort Worth site supplements.

cc: NDA 21-257
HFD-550/Division File
HFD-550/MPuglisim
HFD-830/BDunn
HFD-550/LNg
HFD-550/AFenselau
HFD-550/WChambers
HFD-324/PAlcock & Bhartman & BUratani

MEMORANDUM OF A TELEPHONE CONVERSATION

Date: 28-FEB-01
Submission: NDA 21-257

Between: Scott Krueger, Alcon Laboratories, Inc.
And others (only the above participated in discussion)
And: Allan Fenselau, Ph.D., Review Chemist Linda Ng, Ph.D., Chemistry Team Leader
HFD-550/HFD-830
Phone: 301-827-2511 Fax: 301-827-2531

Subject: Discussion of issues from review of NDA 21-257 faxed on 22-FEB-01,
specifically the issues of the drug product regulatory specification and analysis of
substances related and unrelated to travoprost

On Wednesday February 28 at approximately 9:15am we called Scott Krueger of Alcon and other company representatives to discuss the items faxed to them on the previous day. The discussion was focused on the **boldfaced** items in the recommended regulatory specification attached to the end of this memorandum. The first issue to be discussed was the acceptance criteria for the three package extractables—all degradants of the antioxidant used in the manufacture of the polypropylene components (plugs and bottles). It was pointed out to Alcon that the limited analytic data reveal levels of the impurities [redacted] during 13-20 months of storage at 25°C. After 13-20 months at 40°C the levels of [redacted]

[redacted] Furthermore, the only study with possible relevance on the biological qualification of these substances is the Phase III clinical study. These studies appear to have used materials that, after 78-104 weeks, contained [redacted]

[redacted] The levels at the time of use were not reported. These values as such do not approximate the recommended value of [redacted] Finally, as noted in the application, this oval DROP-TAINER system is a new primary package for Alcon and has not been previously marketed. Consequently, little is known about the problems that can arise from its greater use by greater numbers of patients—a situation that requires a cautionary approach to setting acceptance criteria for impurities associated with the packaging.

The second issue was the need to include testing of [redacted] is present at levels comparable to those reported for [redacted] and consequently, should not be eliminated from the regulatory specification. The reason for its exclusion provided by Alcon during the 22-FEB-01 teleconference was that [redacted] does not elute from the [redacted] column under the conditions that they employ. This argument is unacceptable for excluding a test from the regulatory specification. Alcon was going to look into applying a satisfactory method to correct this problem and provide an estimate on the time needed to validate the new procedure.

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The final issue concerned the reporting of analytical data for travoprost-unrelated and unspecified substances. It was recommended that a new category has been created: "Unspecified Substances" with two entries "Any Single Unspecified Substance" with a limit of [redacted] and "Total Unspecified Substances" with a limit of [redacted]. "Unrelated Substances" include three specified substances [redacted] and no "Total Unrelated Substances." The combination of these two categories will permit satisfactory evaluation of the levels of both unspecified travoprost-related and unrelated substances.

Alcon wanted to take some time to consider these matters, but would provide a response later in the day.

cc: NDA 21-257
Division File
HFD-550/M.Puglisi
HFD-550/WChambers
HFD-550/AFenselau
HFD-550/LNg
HFD-830/C-wChen

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ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

MEMORANDUM OF A TELEPHONE CONVERSATION

Date: 22-FEB-01

Submission: NDA 21-257

Between: Scott Krueger, Alcon Laboratories, Inc.

Danny Dunn, Ph.D.

And others (list to be provided by Alcon; only the above participated in discussion)

And: Allan Fenselau, Ph.D., Review Chemist Linda Ng, Ph.D., Chemistry Team Leader
HFD-550/HFD-880

Phone: 301-827-2545 Fax: 301-827-2531

Subject: Discussion of issues from review of NDA 21-257 faxed on 22-FEB-01,
specifically the issues of the drug product regulatory specification and analysis of
substances related and unrelated to travoprost

On Thursday February 22 at approximately 4:15pm we called Scott Krueger of Alcon and other company representatives to discuss the items faxed to them earlier in the day. The items of particular interest are the three listed at the end of this memorandum. The first question that was discussed involved clarification on the methods used to determine the identity of chromatographic peaks as either related or unrelated to travoprost. Alcon indicated that extensive studies from standard as well as accelerated stability studies had permitted isolation and identification of the travoprost degradation products (in the product formulation) and package extractables/leachables and vehicle degradants from placebo formulation. The firm's feeling was that these studies had identified all of the impurities of significance for inclusion in the drug product regulatory specification. However, no clear-cut response could be provided for how they would handle a situation with an anomalous peak that exceeds [redacted] label claim for travoprost: Is it travoprost-related or -unrelated? If the impurity were to be arbitrarily designated as unrelated, serious deficiencies in safety analysis could arise. The option of listing as part of the regulatory specification all presently-known impurities that are related and unrelated to travoprost was to be considered by Alcon. With regard to the values for acceptance criteria in the recommended drug product regulatory specification, they understood the concern for including a category of "Any Single Unspecified Related Substance" with a limit of [redacted]. They responded that the use of such low levels of drug substance [redacted] should allow a higher limit with no increase in safety risk. We indicated that we would discuss this matter with the medical reviewers. Alcon inquired about the recommended limits for the unrelated substances and were informed that these quantities were based on the limited stability study data. These matters were to be evaluated by Alcon, and a response would be available by the end of February.

cc: NDA 21-257
Division File
HFD-550/M.Puglisi
HFD-550/WChambers
HFD-550/AFenselau
HFD-550/LNg
HFD-830/C-wChen



Memorandum

Date January 31, 2001

From CSO, Investigations and Preapproval Compliance Branch
DMPQ, HFD-322

Subject Recommendation
NDA 21-257 Travoprost Ophthalmic Solution

To Bonnie Dunn
Deputy Division Director, DNDC III

Firm: Alcon Laboratories, Inc.
6201 South Freeway
PO Box 1959, Fort Worth
TX 76134-2099
CFN: 1610287

We have completed our review of the inspection report that covered the subject application. The inspection was performed October 12 through 27, 2000 and resulted in a district recommendation to withhold approval. Based on the subsequent responses and new data submitted by the firm (December 26, 2000 and January 11, 2001), the Division of Manufacturing and Product Quality (DMPQ) does not concur with this recommendation.

Alcon has submitted a response to the district's Warning Letter issued on November 13, 2000. This response adequately addressed deficiencies except for that concerning media fill. The FDA investigator found that the firm had been discarding media fill units collected during intervention and not documented the number of discarded units. The DMPQ, the Dallas District and the review microbiologists had two teleconferences with the firm December 18, 2000 and January 10, 2001.

With regard to outstanding issues on media fills, the firm agreed with FDA's assessment and expectation that all media fill units produced during the manual intervention steps should be incubated. Even though these intervention units may not be counted as part of the overall media fill calculation, any contaminated units in this group should be reported and justified as to the cause of contamination. In addition, DMPQ stated the conditions for removing media fill units during intervention could not be arbitrary. The removal of media fill units should be specified in detail in the SOP and documented in the Batch Production Record with respect to the type of intervention, duration of intervention and the number of units removed for that particular intervention.

NDA 21-257
Alcon Laboratories Inc., Fort Worth, TX

According to the firm's responses, Alcon has conducted new media fills using the modified protocol accounting for the units removed during manual intervention. Three successful media fill were performed on Filling line D. As per DMPQ review of the firm's responses, DMPQ has found the firm's corrective action and the new data satisfactory. Dallas District may still wish to conduct re-inspection at Alcon to verify the firm's corrective action and responses to the Warning Letter dated November 17, 2000. This can be done during a post-approval process validation inspection.

Should you have any questions, please contact me at (301) 827-7267.

/s/

Brenda Uratani, Ph.D.

cc:

HFD-324 R/F

HFR-SW100

HFD-322 B Uratani

Concur: P Alcock *PA 1/3/01*

WORD:\Alcon

**APPEARS THIS WAY
ON ORIGINAL**

MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION CENTER
FOR DRUG EVALUATION AND RESEARCH

EVALUATION OF CLINICAL INVESTIGATOR INSPECTIONS.

DATE: January 23, 2001

NDA 21-257

HFD 550

SPONSOR: Alcon Universal

Product: Travatan (travoprost ophthalmic solution)

Chemical

Type: 1

Potential:

P

Indications: For the lowering of intraocular pressure in patients with chronic open angle glaucoma or ocular hypertension.

Project

Manager: Michael Puglisi

Medical

Officer: Lim Lucious

I. Background:

These routine inspections were part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which NDA 21-257 approval may be based and to assure that the rights and welfare of the human subjects of those studies were protected. These inspections were conducted in accordance with CP 7348.811, Clinical Investigators, in addition to concentrate in comparing source documents, case report forms (CRFs), and data listings in regard to primary endpoints, adverse drug events reporting and discontinued subjects in these protocols. Sites selected in corroboration between HFD-550 Division medical officer, Dr. Lucious and DSI reviewer, Dr. Jose Carreras.

Name	City	Protocol	CL
Robert L. Shields, M.D.	Denver, Colorado	#C-97-72	VAI
William A. Pilchard, M.D.	Shawnee Mission, Kansas	#C-97-72	NAI
Cecil Beehler, M.D.	Fort Myers, Florida	#C-97-71	NAI
Alcon Research	Fort Worth, Texas	#C97-71	NAI*

Key to Classifications

NAI = No deviation from regulations

VAI = Minor Deviation(s) from regulations

* Based on communications with the District Office Inspector. EIR has not been reviewed.

Jose A. Carreras, M.D.

cc:
NDA 21-257
Division File
HFD-47/Carrier

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ON ORIGINAL**

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ON ORIGINAL**

M. Puglisi

MEMORANDUM OF A TELEPHONE CONVERSATION

Date: 10-OCT-00
Submission: NDA 21-257

Between: Scott Krueger, Alcon Laboratories, Inc.
And: Allan Fenselau, Ph.D., Review Chemist
HFD-550/HFD-880
Phone: 301-827-2545 Fax: 301-827-2531

Subject: Questions on Review Status of NDA N 21-257,
specifically regarding Expiry Date for use on Label

On Tuesday October 10 at approximately 8:30am Scott Krueger of Alcon called to ask what, if any, decision had been made regarding the expiry dating that his firm could place on the product packaging for Travatan. Although this was the first time this question was directed at me, I fortunately had been kept up on this matter by both Mike Puglisi and Wiley Chambers. I indicated to him that inadequate and inappropriate information had been included with the submission to provide any firm response to his question. Using the analysis contained in the Attachment I was able to provide a response consistent with Item 8 in the attached analysis. However, I noted that much confusion presently existed about their intended packaging, which Mr. Krueger confirmed was a problem for him as well. He indicated that as of 10-OCT-00 they are uncertain about the packaging—namely, pouched or unpouched—and may withdraw their request for a Physician Sample size, since the Label Contents of 0.8mL would be insufficient to permit the full 4-week treatment that the marketing group has now recommended. I indicated that an amendment to clarify these matters is needed as soon as possible, since I have a review deadline coming up in less than one month. He was going to get corporate clarification and get back to us.

/S/ —
11-OCT-00

cc: NDA 21-257
Division File
HFD-550/M.Puglisi
HFD-550/WChambers
HFD-550/AFenselau
HFD-550/LNg
HFD-830/C-wChen

/S/ 10/11/00

**APPEARS THIS WAY
ON ORIGINAL**

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: March 9, 2000 **DUE DATE:** September 28, 2000 **OPDRA CONSULT #:** 00-0077

TO: Karen Midthun, M.D.
 Director, Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products
 HFD-550

THROUGH: Mike Puglisi, Project Manager
 HFD-550

PRODUCT NAME: Travatan
 (travoprost ophthalmic solution,
 0.0015%, 0.004%)

MANUFACTURER: Alcon Laboratories, Inc.
 Fort Worth, TX 76134

NDA #: 21-257

SAFETY EVALUATOR: Carol Pamer, R.Ph.

SUMMARY: In response to a consult from the Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products (HFD-550), OPDRA conducted a review of the proposed proprietary name "Travatan" to determine the potential for confusion with approved proprietary and generic names as well as pending names.

OPDRA RECOMMENDATION: From a safety perspective, OPDRA does not object to the use of the name "Travatan". See the checked box below. We have also made recommendations for labeling revisions.

- FOR NDA/ANDA WITH ACTION DATE BEYOND 90 DAYS OF THIS REVIEW**
 This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDAs from the signature date of this document. A re-review request of the name should be submitted via e-mail to "OPDRAREQUEST" with the NDA number, the proprietary name, and the goal date. OPDRA will respond back via e-mail with the final recommendation.
- FOR NDA/ANDA WITH ACTION DATE WITHIN 90 DAYS OF THIS REVIEW**
 OPDRA considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDAs from this date forward.
- FOR PRIORITY 6 MONTH REVIEWS**
 OPDRA will monitor this name until approximately 30 days before the approval of the NDA. The reviewing division need not submit a second consult for name review. OPDRA will notify the reviewing division of any changes in our recommendation of the name based upon the approvals of other proprietary names/NDAs from this date forward.

/S/
 Jerry Phillips, R.Ph.
 Associate Director for Medication Error Prevention
 Office of Post-Marketing Drug Risk Assessment
 Phone: (301) 827-3242
 Fax: (301) 480-8173

/S/ *8-18-00*
 Peter Hong, M.D.
 Director
 Office of Post-Marketing Drug Risk Assessment
 Center for Drug Evaluation and Research
 Food and Drug Administration

Office of Postmarketing Drug Risk Assessment (OPDRA)

HFD-400; Parklawn Building Room 15B-03

FDA Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: August 10, 2000

NDA NUMBER: 21-257

NAME OF DRUG: Travatan (travoprost ophthalmic solution, 0.0015% and 0.004%)

NDA HOLDER: Alcon Laboratories
Fort Worth, TX 76134

I. INTRODUCTION

This consult was written in response to a request from the Division Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products (HFD-550) for assessment of the tradename *Travatan*. This name was reviewed by the FDA CDER Labeling and Nomenclature Committee (LNC) in 1999 and found to be "acceptable" for use. The LNC noted two sound-alike, look-alike product names, Travasol and Ativan. These products were believed to have "low" and "medium" potential for confusion with *Travatan*.

Travatan (travoprost ophthalmic solution) is a selective agonist for the FP prostanoid receptor. This drug product is indicated for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension. It will be supplied as 0.0015% and 0.004% ophthalmic solutions in 0.8 mL professional sample and 2.5 mL packaging sizes. The recommended dose is one drop in the affected eye(s) once daily in the evening. *Travatan* may be used concomitantly with other topical ophthalmic drugs to lower intraocular pressure.

II. RISK ASSESSMENT

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts^{i,iii,iii} as well as several FDA databases^{iv} for existing drug names which sound alike or look alike to *Travatan* to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's (USPTO) Text and Image Database was also conducted^v. An Expert Panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted four (4) prescription analysis studies, to simulate the prescription ordering process.

A. EXPERT PANEL DISCUSSION

A group discussion was held by OPDRA to gather professional opinions on the safety of the proprietary name *Travatan*. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of OPDRA Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

Several sound-alike, look-alike names were identified by the Expert Panel. With most of these products, the differences in dosage forms and dosing schedules would distinguish these products from Travatan. One ophthalmic product was identified, Xalatan (latanoprost), that was noted to have some sound-alike qualities relative to Travatan.

TABLE 1

Product name	Dosage form(s), Generic name	Usual adult dose	Other
Travatan	Ophthalmic: 0.0025, 0.004% solution (travoprost)	One drop daily in affected eye(s) in the evening.	Alcon Pharmaceuticals
Xalatan	Ophthalmic: 0.005% solution (latanoprost)	One drop daily in affected eye(s), in the evening.	SA per OPDRA. Pharmacia & Upjohn
Teveten	Oral: 400, 600 mg tablets (eprosartan)	Oral: 600 mg once daily; 400-800 mg per day, in 1 or 2 divided doses.	L/A, S/A OPDRA
Travasol	Intravenous: varying concentrations (amino acid solution)	IV: mL per hour as specified.	S/A per LNC, OPDRA
Trovan	Oral: 100, 200 mg tablets (trovafloxacin)	IV: 100 – 300 mg once daily, followed by oral dosing. Oral: 100 – 200 mg once daily, for entire course of 7 to 14 days.	L/A per OPDRA
Triazolam	Oral: 0.125, 0.25 mg tablets (Halcion™)	Oral: 0.125 or 0.25 mg at bedtime.	L/A, S/A OPDRA
Travelab	Oral: 50 mg tablets (dimenhydrinate)	50 mg as needed to prevent vertigo, motion sickness.	S/A per OPDRA
		Frequently used, not all-inclusive.	**L/A (look-alike), S/A (sound-alike)

B. STUDY CONDUCTED BY OPDRA

1. Methodology

A study was conducted within FDA employing a total of 94 health care professionals (nurses, pharmacists, and physicians) to determine the degree of confusion of *Travatan* with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. This exercise was conducted in an attempt to simulate the prescription ordering process. An OPDRA staff member wrote prescriptions, each consisting of a combination of marketed and unapproved drug products and prescriptions for *Travatan* (see page 4). These written prescriptions were optically scanned and one prescription was delivered via email to each study participant. In addition, two OPDRA staff members recorded a verbal outpatient prescription that was then delivered to two groups of study participants via telephone voicemail. Each reviewer was then requested to provide an interpretation of the prescription via email.

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTIONS
Outpatient: Travatan 0.004%, 1 gtt ou HS, 15 mL, 1 refill	Outpatient: Travatan 0.004%, put one drop in each eye at bedtime. Dispense 15 mLs, one refill.
Inpatient: D/C Travatan today	

2. Results

Results of this exercise are summarized below:

Study	No. of participants	# of responses (%)	"Travatan" response	Other response
Written: Outpatient	31	23 (74%)	1 (4%)	22 (96%)
Inpatient	31	22 (71%)	20 (91%)	2 (9%)
Verbal: Outpatient	16	10 (63%)	2 (20%)	8 (80%)
Outpatient	16	9 (56%)	5 (56%)	4 (44%)
Total	94	64 (68%)	28 (44%)	36 (59%)

Among participants in the two (2) written prescription studies, 24 of 45 respondents (53%) interpreted the name incorrectly. The incorrect name interpretations generally were phonetic variations of "Travatan".

Among participants in the two (2) verbal prescription studies, 12 of 19 respondents (63%) interpreted the name incorrectly. The incorrect name interpretations generally were phonetic variations of "Travatan".

C. SAFETY EVALUATOR RISK ASSESSMENT

In the Expert Panel Discussion, there were proprietary names of currently marketed U.S. products identified that were thought to have some sound-alike, look-alike qualities with respect to Travatan. *However, confusion of Travatan with these products seems unlikely, given the differences in dosage forms, strengths available, and routes of administration.* One ophthalmic product was identified, Xalatan (latanoprost), that was noted to have some sound-alike qualities relative to Travatan. The indication for use and recommended dosing of this product is the same as Travatan. However, prescriptions for Travatan must specify one of the desired strengths (e.g., 0.0015% and 0.004%), which differ from Xalatan (e.g., 0.005%). These features would likely serve to distinguish prescriptions for these products from the other.

We conducted prescription studies in an attempt to simulate the prescription ordering process. *In this exercise, there were no erroneous interpretations of this proprietary name with other U.S. marketed drug products.* However, there are limitations in the predictive value of these studies, primarily due to the sample size.

For these reasons, we do not object to the use of the proprietary name "Travatan".

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In this review of the container labeling, carton labels, and draft package insert for Travatan, OPDRA has attempted to focus on safety issues relating to possible medication errors. We have identified areas of possible improvement, in the interest of minimizing potential medication errors.

A. CONTAINER LABELS (0.8 mL, 2.5mL package size; 0.0015 and 0.004% solutions)

The name and strength of the product should have the most prominence on the labels. We note that you have highlighted the net quantity statements on the container labels with differentiating colors. This gives greater prominence to the net quantity statement, rather than the strength. OPDRA recommends differentiating the product strengths, rather than the net quantity.

B. CARTON LABELS (0.8 mL, 2.5mL package size; 0.0015 and 0.004% solutions)

Delete the World Wide Web address for the manufacturer, www.alconlabs.com, from the side panel, as this material is promotional in tone.

C. PACKAGE INSERT

We recommend utilizing "mcg", rather than "µg", throughout the package insert. The abbreviation "µg" is often misinterpreted as "mg".

IV. RECOMMENDATIONS

- A. OPDRA does not object to the use of the proprietary name "Travatan".
- B. We have made recommendations for labeling revisions to minimize potential errors with the use of this product.

OPDRA would appreciate feedback of the final outcome of this consult (e.g., copy of revised labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Carol Pamer, R.Ph. at 301-827-3245.

/S/

Carol Pamer, R.Ph.
Safety Evaluator
Office of Postmarketing Drug Risk Assessment (OPDRA)

Concur:

/S/

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Postmarketing Drug Risk Assessment (OPDRA)