

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-994

PHARMACOLOGY REVIEW



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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: 21-994
SERIAL NUMBER: 000
DATE RECEIVED BY CENTER: 11/21/2005
PRODUCT: Travatan[®]Z
INTENDED CLINICAL POPULATION: Reduction of elevated intraocular pressure (IOP) in patients with open angle glaucoma or ocular hypertension
SPONSOR: Alcon Universal Ltd., P.O Box 62, Bosch 69, CH-6331 Hunenberg, Switzerland
Authorized US Agent: Alcon Laboratories, Inc., 6201 South Freeway, Fort Worth, TX 76134-2009
DOCUMENTS REVIEWED: Vol. 4.1-4.4
REVIEW DIVISION: Division of Anti-Infective and Ophthalmology Products (HFD-520)
PHARM/TOX REVIEWER: Zhou Chen, MD, PhD
PHARM/TOX SUPERVISOR: Terry Peters, DVM
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Date of review submission to Division File System (DFS): March 2, 2006

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability

An "approval" is recommended for this NDA application.

B. Recommendation for nonclinical studies

No recommendation is necessary.

C. Recommendations on labeling

No recommendation is necessary. The proposed labeling is acceptable.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

Travoprost is approved as Travatan[®] in 2001 for the reduction of IOP in patients with open angle glaucoma or ocular hypertension. In the current NDA application, the sponsor proposed a new benzalkonium chloride-free (BAC-free) formulation. The sponsor indicated that benzalkonium chloride in IOP-lowering medications had been implicated in exerting a deleterious effect on the conjunctiva that resulted in altered postoperative wound healing. In nonclinical studies, the new formulation, Travatan[®] Z, showed a similar toxicity profile as the marketed formulation, Travatan[®]. The drug showed a low irritation potential when administered topically to the rabbit eye. Regarding ocular absorption, the new formulation seems to have a lower absorption.

B. Pharmacologic activity

Travoprost (AL-6221), an isopropyl ester derivative of the free acid AL-5848, is believed to be hydrolyzed to the free acid by ester hydrolase enzymes located in the cornea and appears in the aqueous humor as the free acid. AL-5848 is a highly selective and potent agonist at the prostanoid FP receptor (PGF₂ α receptor) with a K_i of 52 nM and a functional potency (EC₅₀) of 4 nM. In animal studies, travoprost produced a dose-related reduction of IOP, and once daily dosing with travoprost lowered IOP to a similar degree as BID dosing.

C. Nonclinical safety issues relevant to clinical use

No safety issues were raised comparing the Travatan[®] Z formulation with the marketed formulation.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

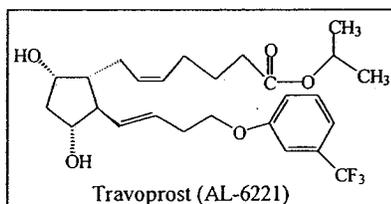
2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 21-944
Review number: 000
Sequence number/date/type of submission: 000/November 18, 2005/Commercial NDA
Information to sponsor: Yes () No (X)
Sponsor and/or agent: Alcon Universal Ltd., P.O Box 62, Bosch 69, CH-6331 Hunenberg, Switzerland
Authorized US Agent: Alcon Laboratories, Inc., 6201 South Freeway, Fort Worth, TX 76134-2009
Manufacturer for drug substance: The Dow Chemical Company, 1803 Building, Midland, Michigan 48674 as well as Mitchell Cotts Chemicals, P.O. Box 6, Steanard Lane, Mirfield, West Yorkshire WF14 8QB, UK

Reviewer name: Zhou Chen, M.D., Ph.D.
Division name: Anti-Infective and Ophthalmology Products
HFD #: HFD-520
Review completion date: March 1, 2006

Drug:

Trade name: Travatan®Z
Generic name: Travoprost ophthalmic solution, 0.004%
Code name: AL-6221
Chemical name: (Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(1E,3R)-3-hydroxy-4-[(α , α , α -trifluoro-m-isopropyl-tolyl)oxy]-1-butenyl]cyclopentyl]-5-heptenoate
CAS registry number: 157283-68-6
Molecular formula/molecular weight: C₂₆H₃₅F₃O₆; MW=500.55
Structure:



Relevant INDs/NDAs/DMFs: DMFc _____, IND 51,000; NDA 21-257

Drug class: PGF_{2 α} analogue

Intended clinical population: Reduction of elevated intraocular pressure (IOP) in patients with open angle glaucoma or ocular hypertension

Clinical formulation:

Ingredient	Travoprost Ophthalmic Solution, 0.004%		
	% (w/v)	Compendial designation	Purpose
Travoprost	0.004	Non-compendial	Active ingredient
Polyoxyl 40 Hydrogenated Castor Oil (HCO-40)		JPE	
Propylene Glycol		USP	
Boric Acid		NF	
Sorbitol		NF	
Zinc Chloride		USP	
NaOH and/or HCl, Adjust		NF	
Purified Water		USP	

Route of administration: Ocular, topical

Proposed use: 1 drop (25 µl) per eye, once daily (Total dose could be 2 µg/patient/day or 0.04 µg/kg for a 50 kg adult)

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Studies reviewed within this submission:

Pharmacology:

All pharmacology studies were reviewed under NDA 21-257 (Travatan®). For detailed review information, please check pharmacology/toxicology review of NDA 21-257.

Pharmacokinetics:

TDOC-0001791: Ocular bioavailability comparison of two travoprost formulations in New Zealand White rabbits: Travatan® and Travatan® BAC-free
 Other PK studies were reviewed under NDA 21-257. For detailed review information, please check pharmacology/toxicology review of NDA 21-257.

Toxicology:

TDOC-0003457: One-day topical ocular irritation evaluation of Travatan® BAC-free ophthalmic solution in rabbits

TDOC-0003351: One-day exaggerated topical ocular irritation evaluation of Travatan® BAC-free (travoprost, 0.004%) ophthalmic formulations (FIDs 107670 and 107074) in New Zealand White rabbits

TDOC-0003456: Three month topical ocular irritation and toxicity study of Travatan® BAC-free in New Zealand White rabbits

012-30-0101: Two week topical ocular irritation toxicity evaluation of _____ ophthalmic solution in New Zealand White rabbits

051-30-0601: One month topical ocular irritation and systemic toxicity evaluation of AL-6221 (travoprost) _____ impurity using New Zealand rabbits

Other toxicity studies were reviewed under NDA 21-257. For detailed review information, please check pharmacology/toxicology review of NDA 21-257.

Studies not reviewed within this submission:

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

Travoprost (AL-6221), an isopropyl ester derivative of the free acid AL-5848, is believed to be hydrolyzed to the free acid by ester hydrolase enzymes located in the cornea and to appear in the aqueous humor as the free acid. AL-5848 is a highly selective and potent agonist at the prostanoid FP receptor (PGF₂α receptor) with a K_i for binding to the FP receptor of 52 nM and a functional potency (EC₅₀) of 4 nM. In animal studies, travoprost produced a dose-related reduction of IOP, and once daily dosing with travoprost lowered IOP to a similar extent as BID dosing.

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 (October 2000).

2.6.3 PHARMACOLOGY TABULATED SUMMARY

Not applicable

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

In an ocular bioavailability comparison study conducted in NZW rabbits, Travatan[®] BAC-free formulation (Travatan[®] Z) provided lower intraocular concentrations and AUC values of active AL-5848 compared to Travatan[®]. The reason is not clear. It is possible that benzalkonium chloride may facilitate resorption of AL-5848 from the tear through the corneal epithelium.

[**Reviewer's comments:** Several PK studies were conducted with ^3H -labeled drug. Usually ^{14}C is preferred because ^3H incorporates into body fluids easily and the accuracy of PK parameters is affected.]

Following topical ocular administration of ^3H -AL-6221 in rabbits, the drug was absorbed into the eye with highest concentrations noted in the anterior tissues (iris-ciliary body and aqueous humor; T_{max} : 1-2 hr). In most ocular tissues, the drug was rapidly eliminated with half-life of 0.4-2.6 hr. In both rabbit and monkey studies, systemic exposure to the drug was very low after topical ocular administration.

The extent of binding of the drug to rat, monkey and human plasma proteins was similar at approximately 80%. Over the concentration range of 0.01 to 100 ng/ml, the percent of bound drug for these species was independent of drug concentration.

Systemically, travoprost free acid was rapidly and extensively oxidized to inactive metabolites. Biotransformations included β -oxidation of the α (carboxylic acid) chain to give 1,2,3,4-tetranor analogs, oxidation of the 15-hydroxyl moiety, as well as reduction of the 13,14 double bond. The metabolites identified included 1,2,3,4-tetranor-13,14-dihydro-15-oxo-AL-5848, 1,2-dinor-13,14-dihydro-15-oxo-AL-5848, 1,2,3,4-tetranor-15-oxo-AL-5848 and 1,2-dinor-15-oxo-AL-5848.

In rats, rabbits and dogs following intravenous administration of ^3H -AL-6221, plasma concentrations of radioactivity decreased in a biphasic manner with half-lives for radioactivity elimination of 35, 48 and 26 hr for rats, rabbits and dogs, respectively. In rats, 95% of a subcutaneous radiolabeled dose was eliminated within 24 hours. The major route of elimination was via the bile (61%).

Only one ocular bioavailability comparison study was submitted with this NDA package. All other PK studies were submitted under NDA 21-257. For detailed reviews for these PK studies, please see Review and Evaluation of Pharmacology and Toxicology Data for NDA 21-257 (October 2000).

2.6.4.2 Distribution

TDOC-0001791: Ocular bioavailability comparison of two travoprost formulations in New Zealand White rabbits: Travatan[®] and Travatan[®] BAC-free

The purpose of this study was to determine the relative ocular bioavailability of AL-5848, the pharmacologically active metabolite of travoprost, in male New Zealand White rabbits following a single topical ocular administration (30 μl) of Travatan[®] ophthalmic solution to the right eye and Travatan[®] BAC-free to the left eye. Aqueous humor and iris-ciliary body were sampled from 6 rabbits per time point at 0.25, 0.5, 1, 2, 4, and 6 hr after dosing. AL-5848 concentrations were determined using validated HPLC/MS/MS procedures with a lower limit of quantitation (LLOQ) of _____ ng/g for iris-ciliary body and _____ ng/ml for aqueous humor.

The results of this study (see table below) showed that in both aqueous humor and iris-ciliary body, the C_{max} and AUC values for Travatan[®] BAC-free were lower than those for Travatan[®]. Travatan[®] BAC-free provided lower intraocular concentrations of active AL-5848 compared to Travatan[®]. The reason of the lower intraocular uptake of AL-5848 from Travatan[®] BAC-free is not clear. It is possible that benzalkonium chloride facilitates resorption of AL-5848 from the tear through the corneal epithelium. In clinical studies, Travatan[®] containing 0.002%, 0.004% and 0.006% travoprost provided similar IOP-lowering effects. The sponsor indicated that the BAC-free formulation might provide similar IOP-lowering effects to Travatan[®] in human patients.

AL-5848 concentrations in rabbit ocular tissues treated with Travatan and Travatan BAC-free

(mean ± SD)	Aqueous humor			Iris-ciliary body		
	Travatan	Travatan BAC-free	%*	Travatan	Travatan BAC-free	%
C _{max} (ng/g or ml)	14.7±3.6	10.2±3.0	69	5.27±1.69	4.08±1.56	77
T _{max} (hr)	2	1		1	1	
AUC _{0-∞} (ng-hr/g or ml)	48.8±3.0	30.0±1.7	61	17.7±1.1	13.7±0.9	77

* Percentage of the values for Travatan

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

Not applicable

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

Many ocular and systemic toxicity studies were conducted under NDA 21-257. Topical ocular administration of travoprost in monkeys resulted in an increased palpebral fissure, noted clinically as “big eye”, and increased iridal pigmentation. In a 6-month rat study with repeated daily subcutaneous administration of travoprost, treatment-related mortalities were noted at 100 µg/kg (600 µg/m²). Microscopic bone changes (endosteal fibrosis and hyperostosis) were noted at doses > 30 µg/kg (180 µg/m²). These doses were approximately 121-fold above the highest human daily dose (1.48 µg/m²). Therefore, travoprost was generally considered as safe and well tolerated.

Two one-day studies and one three-month ocular toxicity study in NZW rabbits were included in this NDA submission. In these studies, BAC-free formulation was compared with the marketed Travatan[®]. Both formulations showed similar safety profiles with a very low ocular irritation potential. No biologically relevant toxicity was noted.

2.6.6.2 Single-dose toxicity

TDOC-0003457: One-day topical ocular irritation evaluation of Travatan[®] BAC-free ophthalmic solution in rabbits

Key study findings: Travatan® BAC-free ophthalmic solution showed a low ocular irritation potential and elicited minimal to moderate discomfort in the treated eyes. Similar findings were also seen in the marketed drug Travatan®.

Document #: TDOC-0003457

Protocol #: N-04-137

Study Aim: To determine the ocular irritation potential of Travatan® BAC-free ophthalmic solution in NZW rabbits following an exaggerated one-day dosing regimen

Compound/Vehicle: Travatan® BAC-free ophthalmic solution vehicle (group 1), Travatan® BAC-free ophthalmic solution (Lot #: 04-37157-1, Group 2) and. Travatan® (marketed drug, Lot #: 50393F, Group 3)

Ingredient (% w/v)	BAC-free vehicle	Travatan BAC-free
Lot #	04-37331-1	04-37157-1
AL-6221		0.004
Polyoxyl 40 hydrogenated castor oil		
Boric Acid, NF		
Sorbitol, NF		
Propylene glycol, USP		
Zinc chloride, USP		
NaOH, NF and/or HCl, NF		
Purified H ₂ O		

Dose & Route: Two drops (30 µl each)/eye, right eyes, every 30 min for a total of 10 applications

Animals: New Zealand White rabbits, 4-month old, weighing 3.0-3.4 kg, 3/sex/group

Study Location: Alcon Laboratory, Inc., 6201 South Freeway, Fort Worth, TX 76134

Compliance with GLP/QAU: Yes

Study Initiation: 8/30/2004

Study Design: Test articles or vehicle was applied to the right eye (two 30 µl drops) of each rabbit every 30 min for a total of 10 applications. The left eye served as the untreated control. The day of dosing was designated as Day 1.

Observations and times:

Mortality, morbidity, and daily observations: 2x/day

Biomicroscopic examination: Pretest and Days 1 (one hr after the last dose), 2, 3, and 4

Ocular comfort examination: After the 1st and last doses on Day 1

Body weight: Pretest and Day 4

Results:

Mortality and clinical observations: No deaths occurred and no remarkable clinical signs were noted.

Slit lamp biomicroscopy examination: Conjunctival congestion data are summarized in the table below. On Day 1 at one hr after the last dosing, moderate conjunctival congestion (score = 2) in the right eye was noted in 1/6 vehicle control rabbits, 2/6 rabbits in BAC-free group, and 3/6 rabbits in marketed Travatan® group. In addition, rabbits in marketed Travatan® group also showed moderate conjunctival congestion on Day 3 (1/6), and minimal conjunctival discharge on Day 3 (1/6). All other ocular parameters evaluated

were unremarkable throughout the study. It seemed that Travatan[®] BAC-free treated animals did not show additional biomicroscopical findings beyond the levels in control and Travatan[®] treated animals.

Mean Score of Conjunctival Congestion in Rabbits

Group	Females	Right eyes					Left eyes				
		Pretest	Day 1	Day 2	Day 3	Day 4	Pretest	Day 1	Day 2	Day 3	Day 4
1	Mean	0	1.0	0.3	0.3	0	0	0.7	0	0	0
	Incidence	0/3	2/3	1/3	1/3	0/3	0/3	2/3	0/3	0/3	0/3
2	Mean	0	1.3	0.3	0.7	0.3	0.3	0.3	0	0	0.3
	Incidence	0/3	3/3	1/3	2/3	1/3	1/3	1/3	0/3	0/3	1/3
3	Mean	0	1.7	0.3	0	0	0.3	0	0.3	0.3	0
	Incidence	0/3	3/3	1/3	0/3	0/3	1/3	0/3	1/3	1/3	0/3
Group	Males										
1	Mean	0.3	0.3	0.3	0.7	0.3	1.0	0.7	0.3	0	0.3
	Incidence	1/3	1/3	1/3	2/3	1/3	3/3	2/3	1/3	0/3	1/3
2	Mean	0.7	1.3	0.3	0	0	0.7	0.7	0.3	0	0.3
	Incidence	2/3	3/3	1/3	0/3	0/3	2/3	2/3	1/3	0/3	1/3
3	Mean	0.7	1.3	0.3	1.0	0.3	0.7	0	0	1.0	0.3
	Incidence	2/3	3/3	1/3	2/3	1/3	2/3	0/3	0/3	3/3	1/3

Ocular comfort evaluation: The scores were 2.00, 2.33, and 1.66 for vehicle, BAC-free, and marketed Travatan[®] groups, corresponding to minimal discomfort, minimal-moderate discomfort, and minimal discomfort, respectively.

Body weights: Normal.

In summary, New Zealand White rabbits were topically treated with vehicle, Travatan[®] BAC-free ophthalmic solution and Travatan[®] ophthalmic solution 10 times a day for one day and observed for 4 additional days. Travatan[®] BAC-free ophthalmic solution showed a low ocular irritation potential and minimal to moderate discomfort in the treated eye. Similar findings were seen in animals treated with vehicle alone and the marketed Travatan[®] ophthalmic solution.

TDOC-0003351: One-day exaggerated topical ocular irritation evaluation of Travatan[®] BAC-free (travoprost, 0.004%) ophthalmic formulations (FIDs 107670 and 107074) in New Zealand White rabbits

Key study findings: No significant ocular irritation and toxicity was seen with Travatan[®] BAC-free ophthalmic formulations tested in this study under exaggerated dosing conditions.

Document #: TDOC-0003351

Protocol #: N-05-042

Study Aim: To determine the acute topical ocular irritation potential of various BAC-free ophthalmic vehicles containing travoprost in NZW rabbits following an exaggerated one-day dosing regimen

Compound/Vehicle: Two Travatan[®] BAC-free ophthalmic formulations and one vehicle (see table below). Lot 04-38249-1 (FID 107047) was the same as the proposed clinical formulation.

Ingredient (% w/v)	Vehicle for FID 107670	Travatan® BAC-free	Travatan® BAC-free
FID #	108555	107670	107047
Lot #	05-40085-1	05-40084-1	04-38249-1
AL-6221		0.004	0.004
Polyoxyl 40 hydrogenated castor oil			
Boric Acid, NF			
Sorbitol, NF			
Propylene glycol, USP			
Zinc chloride, USP			
NaOH, NF and/or HCl, NF			
Purified H ₂ O			

Dose & Route: One drop (30 µl)/eye, right eyes, every 30 min for a total of 10 applications (Two drops were given for the first three applications.)

Animals: New Zealand White rabbits, 4-9 months old, weighing 3.0-4.3 kg, 3/sex/group

Study Location: Alcon Laboratory, Inc., 6201 South Freeway, Fort Worth, TX 76134

Compliance with GLP/QAU: Yes

Study Initiation: 7/16/2005

Study Design: Drugs or vehicle was applied to the right eye of each rabbit every 30 min for a total of 10 applications. The left eye served as the untreated control. The day of dosing was designated as Day 1.

Group	N/sex	Observation days
1 untreated control	3	14
2 Vehicle	3	14
3 FID 107670 formulation	3	14
4 FID 107047 formulation	3	14

Observations and times:

Mortality, morbidity, and daily observations: Twice daily

Body weights: Weekly

Ophthalmic biomicroscopic examinations: Pretest, 1 and 24 hr after the last dose, and on Days 4, 7 and 14

Necropsy: After at least 14 days of observation. All animals were examined for external abnormalities.

Histopathology: Ocular tissues (eyes and adnexa) only

Results:

Clinical observations: No mortality occurred during the study. No toxicologically significant clinical signs were noted. Two Group 3 females and one Group 4 male had red (congested) right eyes on Day 1 which were thought to be treatment-related. The sponsor indicated exaggerated dosing was expected to cause some congestion in the travoprost-treated animals.

Body weights: No abnormal findings in body weights were noted.

Biomicroscopic evaluations: Corneal cloudiness, neovascularization, aqueous flare, light reflex abnormalities, and fluorescein staining were not seen in any of the treatment groups. Isolated incidences of iritis (one Group 1 male, right eye, and one Group 3 male, both eyes) were observed and were not considered as drug-related. Multiple incidences of

conjunctival congestion, swelling, and discharge were noted during the study and are described below.

Conjunctival congestion: Minimal conjunctival congestion (score = 1) was seen in all groups in both eyes during all observation time-points, indicating that the congestion might be spontaneous, or due to scratch or other stimulations but not drug-induced. At one hr after dosing, moderate conjunctival congestion (score = 2) was seen in the right eye in one Group 1 animal, two Group 3 animals, and three Group 4 animals. It seemed that animals receiving travoprost had a slightly higher incidence of moderate congestion and greater mean scores at one hr after dosing (see table below) when compared to controls. Moderate conjunctival congestion was also seen in both eyes approximately evenly across all control and treatment groups on Days 4, 7 and 14, suggesting that the congestion was not drug-related. Marked congestion (score = 3) was only seen in one Group 2 (vehicle control) male. The sponsor indicated that travoprost was known to cause hyperemia clinically and the increased incidence at one hr after dosing was not an unexpected finding.

Summary of Conjunctival Congestion (mean score and incidence)

group	sex		Right (treated) eyes						Left eyes					
			Pretest	1 hr	24 hr	Day 4	Day 7	Day 14	Pretest	1 hr	24 hr	Day 4	Day 7	Day 14
1	♀	mean	0.3	0	0	0	0.3	1.0	0.7	0.3	0	0.3	0.3	0
		incidence	1/3	0/3	0/3	0/3	1/3	2/3	2/3	1/3	0/3	1/3	1/3	0/3
1	♂	mean	0.7	1.0	0.3	0.3	0.7	1.3	0.3	0.7	0.7	0.7	1.0	1.7
		incidence	2/3	2/3	1/3	1/3	2/3	3/3	1/3	2/3	2/3	2/3	2/3	3/3
2	♀	mean	1.0	0.3	0.7	0.3	0.7	2.0	1.0	0	0	0.7	1.0	1.7
		incidence	3/3	1/3	2/3	1/3	2/3	3/3	3/3	0/3	0/3	2/3	3/3	3/3
2	♂	mean	0.7	0	0	1.0	0.7	1.3	0.3	0	0.3	0.3	1.0	1.0
		incidence	2/3	0/3	0/3	1/3	2/3	3/3	1/3	0/3	1/3	1/3	2/3	2/3
3	♀	mean	0	1.3	0.3	0	0.3	0.3	0.3	0.3	0.3	0.7	0.3	0.7
		incidence	0/3	3/3	1/3	0/3	1/3	1/3	1/3	1/3	1/3	2/3	1/3	1/3
3	♂	mean	0.3	1.3	0.3	0.7	0	1.3	0.3	0.7	0	0	0	0.7
		incidence	1/3	3/3	1/3	1/3	0/3	3/3	1/3	2/3	0/3	0/3	0/3	2/3
4	♀	mean	0.7	1.3	0.3	0.7	0.7	1.7	0.7	0.7	0.7	0.7	0.3	1.0
		incidence	2/3	3/3	1/3	1/3	2/3	3/3	2/3	2/3	2/3	1/3	1/3	3/3
4	♂	mean	1.0	1.7	0.3	0	0.3	1.3	0	0.7	0	0.7	0.3	0.3
		incidence	3/3	3/3	1/3	0/3	1/3	2/3	0/3	2/3	0/3	1/3	1/3	1/3

Conjunctival swelling: Numerous instances of minimal (score = 1) conjunctival swelling were observed on Day 14 (see table below). Findings were distributed across all treatment and control groups in both eyes. Two instances of moderate (score = 2) conjunctival discharge were observed on Day 14 of the left eye of one Group 1 male and the right eye of one Group 2 female. The distribution of findings did not indicate any treatment-related association.

Summary of Conjunctival Swelling (mean score and incidence)

group	sex		Right (treated) eyes						Left eyes					
			Pretest	1 hr	24 hr	Day 4	Day 7	Day 14	Pretest	1 hr	24 hr	Day 4	Day 7	Day 14
1	♀	mean	0	0	0	0	0	0	0	0	0	0	0	0
		incidence	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
1	♂	mean	0	0	0	0	0	0.3	0	0	0	0	0	0.7
		incidence	0/3	0/3	0/3	0/3	0/3	1/3	0/3	0/3	0/3	0/3	0/3	1/3
2	♀	mean	0	0	0	0	0	1.3	0	0	0	0	0	0.7
		incidence	0/3	0/3	0/3	0/3	0/3	3/3	0/3	0/3	0/3	0/3	0/3	2/3
2	♂	mean	0	0	0	0	0	0	0	0	0	0	0	0.3
		incidence	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	1/3
3	♀	mean	0	0	0	0	0	0.3	0	0	0	0	0	0.3
		incidence	0/3	0/3	0/3	0/3	0/3	1/3	0/3	0/3	0/3	0/3	0/3	1/3
3	♂	mean	0	0	0	0	0	0.3	0	0	0	0	0	0.3
		incidence	0/3	0/3	0/3	0/3	0/3	1/3	0/3	0/3	0/3	0/3	0/3	1/3
4	♀	mean	0	0	0	0	0	0.7	0	0	0	0	0	0.7
		incidence	0/3	0/3	0/3	0/3	0/3	2/3	0/3	0/3	0/3	0/3	0/3	2/3
4	♂	mean	0	0	0	0	0	0	0	0	0	0	0	0
		incidence	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3

Conjunctival discharge: A single instance of minimal discharge (score = 1) in the left eye of Group 1 male animal was observed on Day 4. Numerous instances of minimal conjunctival discharge, observed on Day 14, were distributed across all treatment and control groups in both eyes. The distribution of findings did not indicate any treatment-related association.

Summary of Conjunctival Discharge on Day 14 (mean score and incidence)

group	sex		Right (treated) eyes	Left eyes
			Day 7	Day 14
1	♀	mean	0	0
		incidence	0/3	0/3
1	♂	mean	0.3	0.3
		incidence	1/3	1/3
2	♀	mean	1.3	0.7
		incidence	3/3	1/3
2	♂	mean	0	0.3
		incidence	0/3	1/3
3	♀	mean	0.3	0.3
		incidence	1/3	1/3
3	♂	mean	0.7	0.7
		incidence	2/3	2/3
4	♀	mean	0.7	0
		incidence	2/3	0/3
4	♂	mean	0	0
		incidence	0/3	0/3

The sponsor indicated that the numerous instances of conjunctival congestion, swelling and discharge on Day 14 were distributed relatively evenly across all treatment and control groups and were found in both eyes. The reasons might be that slit-lamp evaluations were performed after a weekend in which the cage pans were not changed. The urine vapor, which is slightly irritating, might cause the increase in these findings. Also, previous slit-lamp evaluations on Days 4 and 7 did not reveal any ocular adverse effects, suggesting the Day 14 findings were unrelated to treatment. The reviewer agrees that the Day 14 findings are not treatment-related.

Lens: One Group 4 female animal was identified to have an early focal opacity at the axial junction of the nucleus and anterior cortex in the left eye. A second female

animal in the same group had a faint ring-shaped opacity on the posterior capsule in both eyes. These findings were not considered treatment-related.

Necropsy: No treatment-related abnormal findings were noted.

Histopathology: No microscopic lesions considered related to administration of the vehicle or test article formulations were noted in eyes or ocular adnexa of male or female rabbits. The few changes including mononuclear cell infiltration, Harderian gland atrophy, eyelid epidermal hyperplasia, retinal fold formation were seen in both eyes of control and treated groups with similar incidence and severity, and were all considered incidental and unrelated to treatment.

In summary, New Zealand White rabbits were topically treated with vehicle, two Travatan[®] BAC-free ophthalmic formulations 10 times a day for one day and observed for 14 days. Conjunctival congestion was seen in all groups but a slightly high incidence and greater mean score was noted in drug-treated groups. The sponsor indicated that travoprost was known to cause hyperemia clinically and the increased incidence at one hr after dosing was not an unexpected finding. Conjunctival congestion, swelling and discharge were also observed in other examination times with similar distribution and severity, and were not considered as drug-related. No other toxicologically findings were noted. In conclusion, Travatan[®] BAC-free ophthalmic formulations showed a low ocular irritation potential in the treated eye. No significant ocular toxicity was seen.

2.6.6.3 Repeat-dose toxicity

TDOC-0003456: Three month topical ocular irritation and toxicity study of Travatan[®] BAC-free in New Zealand White rabbits

Key study findings: Travatan[®] BAC-free ophthalmic solution exhibited a very low ocular irritation potential in this three month rabbit study.

Document #: TDOC-0003456

Protocol #: N-46-167

Study Aim: To evaluate the ocular irritation and systemic toxicity potential of Travatan[®] BAC-free ophthalmic solution, 0.004%, following topical ocular administration, three times daily, to New Zealand White rabbits for three months

Compound/Vehicle: Travatan[®] vehicle, Travatan[®] BAC-free vehicle, Travatan[®], 0.004%, Travatan[®] BAC-free, 0.004%, or Travatan[®] BAC-free vehicle plus 5X ZnCl₂. Travatan[®] BAC-free, 0.004% is the same as the proposed clinical drug formulation.

**Appears This Way
On Original**

Ingredient (% w/v)	Travatan® (marketed product)	Travatan® BAC-free	Travatan® BAC-free vehicle plus 5x ZnCl ₂
FID #	92860	107047	107884
Lot #	03-500565-1	04-38249-1	04-38236-1
AL-6221	0.004	0.004	
Polyoxyl 40 hydrogenated castor oil			
Tromethamine			
Boric Acid, NF			
Sorbitol, NF			
Propylene glycol, USP			
Mannitol			
EDTA			
Benzalkonium Chloride, NF			
Zinc chloride, USP			
NaOH, NF and/or HCl, NF			
Purified H ₂ O			

Dose & Route: Two drops (25 µl each)/eye, right eyes, three times daily x 3 months (91 days for males and 92 days for females)

Animals: New Zealand White rabbits, 3-4 months old, weighing 2.9-3.3 kg, 5/sex/group

Study Location: Alcon Laboratory, Inc., 6201 South Freeway, Fort Worth, TX 76134

Compliance with GLP/QAU: Yes

Study Initiation: 12/9/2004

Group	n/sex
1 Travatan vehicle	5
2 Travatan BAC-free vehicle	5
3 Travatan (marketed product)	5
4 Travatan BAC-free	5
5 Travatan BAC-free vehicle plus 5x ZnCl ₂	5

Observations and times:

Daily observations: Twice daily

Body weights: Weekly

Ophthalmic biomicroscopic examinations: Pretest, Weeks 1, 3, 5, 9 and 13

Pachymetry, IOP and indirect ophthalmoscopic examinations: Pretest and Week 13

Clinical pathology: Week 13

Necropsy: All animals

Histopathology: All animals. See Histopathology Inventory Table

Results:

Clinical observations: No drug-related abnormal findings were noted. Detailed health examinations showed pustules or reddened areas in urogenital regions in several vehicle treated animals (3 in Group 1 and 2 in Group 5) and in one Group 3 (Travatan®) animal. One male rabbit in Group 5 (Travatan® BAC-free vehicle plus 5X ZnCl₂) exhibited a swollen eye (OD) on Day 52, which was diagnosed as subpalpebral conjunctival edema. Normal dosing was suspended while the eye was treated with Bion Tears®. Normal dosing resumed on Day 55. This ocular finding was resolved by Day 59. One Group 5 female exhibited a reddened iris (OS) and was later found to have a granuloma in its left iris. None of these findings were considered drug-related.

Body weights: Body weight gain data are summarized in the table below. Although body weight gain in the drug-treated groups (Groups 3 and 4) was lower than in vehicle-treated groups, the final body weights were similar. The differences in body weight gain were not considered as toxicologically significant.

Body weight data (kg ± SD)

Group	Male	1	2	3	4	5
Pretreatment		3.08± 0.08	3.18± 0.04	3.12± 0.15	3.14 ±0.09	3.06± 0.11
Week 13		3.60± 0.07	3.68± 0.20	3.52± 0.26	3.48± 0.13	3.46± 0.27
% Group 1 BW at W13		100	100	97.8	96.7	96.1
Body weight gain		0.52	0.50	0.40	0.34	0.40
% Group 1 BW gain		100	96.2	76.9	65.4	76.9
	Female					
Pretreatment		3.14± 0.09	3.06± 0.05	3.12± 0.13	3.12± 0.08	3.12± 0.08
Week 13		3.64± 0.18	3.48± 0.11	3.52± 0.18	3.56± 0.13	3.66± 0.15
% Group 1 BW at W13		100	95.6	96.7	97.8	100
Body weight gain		0.50	0.42	0.40	0.44	0.54
% Group 1 BW gain		100	84	80	88	100

Ophthalmic examinations:

Biomicroscopic examinations: Minimal conjunctival congestion (score = 1) was seen in all groups in both eyes during all observation time-points with similar incidence. Moderate conjunctival congestion (score = 2) was seen in one Group 1 animal (Week 9, left eye), one Group 3 animal (Week 13, both eyes), and one Group 4 animal (Week 9, right eye with moderate conjunctival discharge). One Group 5 female was found to have a granuloma present in the iris stroma in the untreated eye during Week 13. This abnormality elicited moderate conjunctival congestion (grade of 2), conjunctival swelling (grade of 2), conjunctival discharge (grade of 1), aqueous flare (grade of 2) and iritis (grade of 4). Marked swelling and congestion was observed in the iris as well as a shallow peripheral anterior chamber. None of the findings were considered as drug-related.

Indirect ophthalmoscopic examinations: No remarkable indirect ophthalmoscopy findings were noted at the Week 13 examination.

Pachymetry: No remarkable findings were noted in pachymetric examinations.

IOP: IOP data are summarized in the table below. No toxicologically significant findings were noted. The sponsor indicated that at the one month interval, the IOP measured in female Group 5 rabbits (Travatan® BAC-free vehicle plus 5X ZnCl₂) was statistically significantly lower in the treated eye (OD, -15.3%) and untreated eye (OS, -18.6%) respectively, than was measured in Travatan® vehicle-treated female rabbits. However, the IOP values for this group were lower than the other groups before treatment. Therefore, this finding is not biologically relevant.

IOP data (mmHg, mean \pm SD)

Group	Male	1	2	3	4	5
Pretreatment	Right	17.8 \pm 5.44	21.0 \pm 2.18	19.5 \pm 4.24	21.4 \pm 1.52	17.8 \pm 2.36
Month 1		22.4 \pm 1.95	20.8 \pm 3.01	20.6 \pm 4.32	23.9 \pm 0.96	18.1 \pm 4.25
Month 3		21.7 \pm 4.25	22.6 \pm 3.09	25.4 \pm 2.07	23.0 \pm 1.58	17.6 \pm 1.64
Pretreatment	Left	18.0 \pm 2.70	20.2 \pm 1.20	20.2 \pm 2.61	21.1 \pm 0.96	18.7 \pm 2.22
Month 1		23.3 \pm 1.99	22.3 \pm 2.73	19.6 \pm 4.62	20.9 \pm 3.27	18.6 \pm 3.21
Month 3		19.2 \pm 3.21	22.0 \pm 2.81	20.0 \pm 3.04	18.2 \pm 2.28	16.8 \pm 2.25
	Female					
Pretreatment	Right	17.2 \pm 2.93	19.1 \pm 2.77	19.4 \pm 2.77	19.1 \pm 3.11	19.4 \pm 3.47
Month 1		22.9 \pm 1.43	22.6 \pm 1.34	24.0 \pm 1.90	23.5 \pm 0.71	19.4 \pm 2.92
Month 3		22.3 \pm 2.86	23.0 \pm 1.66	24.5 \pm 2.00	25.6 \pm 2.51	18.5 \pm 2.37
Pretreatment	Left	18.3 \pm 3.75	19.0 \pm 2.42	19.9 \pm 1.34	21.5 \pm 1.41	16.8 \pm 3.33
Month 1		23.6 \pm 1.24	22.5 \pm 1.90	22.8 \pm 2.91	21.4 \pm 2.33	19.2 \pm 3.70
Month 3		20.0 \pm 1.58	22.3 \pm 3.27	20.9 \pm 1.78	21.0 \pm 4.18	17.6 \pm 3.09

Clinical pathology:

Serum chemistry: A statistically significant increase in the activity of creatinine phosphokinase (CK) were detected in both Group 3 male and female rabbits treated with Travatan[®] as compared with serum values for the same parameters in rabbits treated with Travatan[®] vehicle. The toxicological significance of this finding was not clear since there were no muscle, heart or other tissue injuries. No other biologically relevant findings were noted.

Summary of serum creatinine phosphokinase levels (U/l, mean \pm SD)

Group	1	2	3	4	5
Males	302.4 \pm 69.64	298.2 \pm 64.08	529.6 \pm 68.69	453.8 \pm 202.53	288.8 \pm 72.75
Females	338.0 \pm 142.6	429.0 \pm 145.25	815.0 \pm 752.29	472.4 \pm 235.83	523.8 \pm 424.88

Hematology and coagulation parameters: There were no toxicologically significant findings in hematology or coagulation examinations.

Organ weights: No toxicologically significant findings were noted. The sponsor indicated that the relative liver weights of male rabbits treated with Travatan[®] BAC-free vehicle (Group 2) was significantly (15.3%) greater than that measured for male rabbits treated with Travatan[®] vehicle (see table below). However, the Travatan[®] BAC-free treated animals showed no increase in liver weights. The reviewer believes that this finding is not toxicologically significant.

Summary of liver weights (g, mean \pm SD)

Group	1	2	3	4	5
Males	84.66 \pm 7.45	99.42 \pm 12.43	86.94 \pm 7.40	79.86 \pm 7.14	82.70 \pm 9.95
Relative wt %	2.38 \pm 0.17	2.74 \pm 0.25	2.41 \pm 0.19	2.28 \pm 0.17	2.44 \pm 0.26
Females	74.64 \pm 4.35	74.32 \pm 7.54	81.40 \pm 8.43	77.88 \pm 1.91	82.86 \pm 8.51
Relative wt %	2.04 \pm 0.15	2.14 \pm 0.28	2.33 \pm 0.29	2.16 \pm 0.13	2.33 \pm 0.35

Necropsy: Macroscopic observations were confined to the bilateral ovarian cysts in one Group 1 and one Group 4 rabbit, bilaterally pitted kidneys in two Group 2 and one Group 5 rabbits, and the granuloma seen in the iris (left eye) of a Group 5 female rabbit. There were no macroscopic findings that were considered drug-related.

Histopathology: Histopathological examinations were performed on the eyes and adnexa as well as selective major tissues from all treatment groups. There were no drug-related microscopic lesions observed in the ocular tissues from rabbits in any treatment group. Similarly, no drug-related or treatment-related lesions were observed in any of the selected non-ocular tissues from rabbits in any treatment group.

In summary, NZW rabbits were topically treated with Travatan® vehicle, Travatan® BAC-free vehicle, Travatan®, Travatan® BAC-free, or Travatan® BAC-free vehicle plus 5X ZnCl₂ three times daily for 3 months. No drug-related abnormal findings were noted in clinical observations, body weight changes, ophthalmic examinations, hematology examinations, and post-mortem examinations. Clinical chemistry showed an increase in serum CK activity in drug-treated groups. The toxicological significance is not known since no other findings were noted. One Group 5 (Travatan® BAC-free vehicle plus 5X ZnCl₂) rabbit exhibited subpalpebral conjunctival edema on Day 52. This Group 5 rabbit was temporarily withdrawn from normal dosing and was treated instead with Bion Tears® for three days. The swelling and redness was resolved by Day 59 and did not reappear. Granuloma was noted in one Group 5 female in the untreated eye on Day 91. These findings were neither drug nor treatment related. Based on the results of this study in New Zealand White rabbits, Travatan® BAC-free ophthalmic solution exhibited a very low ocular irritation potential in this 3-month study.

Histopathology Inventory

Study	TDOC-0003456
Species	NZW rabbits
Adrenals	X*
Aorta	
Bone Marrow smear	X
Bone (femur)	X
Brain	X*
Cecum	
Cervix	X
Colon	
Duodenum	
Epididymis	X
Esophagus	
Eye	X
Fallopian tube	
Gall bladder	
Gross lesions	X
Harderian gland	
Heart	X*
Ileum	
Injection site	
Jejunum	
Kidneys	X*
Lachrymal gland	X
Larynx	X
Liver	X*
□Lungs	X

Lymph nodes, cervical	
Lymph nodes mandibular	
Lymph nodes, mesenteric	
Mammary Gland	
Nasal cavity	X
Optic nerves	X
Ovaries	X
Pancreas	
Parathyroid	
Peripheral nerve	
Pharynx	
Pituitary	X*
Prostate	X
Rectum	
Salivary gland	
Sciatic nerve	
Seminal vesicles	X
Skeletal muscle	
Skin	
Spinal cord	
Spleen	X*
Sternum	
Stomach	
Testes	X
Thymus	
Thyroid	
Tongue	
Trachea	
Urinary bladder	
Uterus	X
Vagina	X
Zymbals gland	

X, histopathology performed

*, organ weight obtained

2.6.6.4 Genetic toxicology

Genotoxicity studies were submitted under NDA 21-257. AL-6221 was negative in Ames test, in the in vivo micronucleus cytogenetic assay in mice, and in an in vivo chromosomal aberration assay in rats. Two in vitro mouse lymphoma TK assays were performed. One was negative. The other assay showed equivocal effects with the activation of S9. For detailed reviews for these genotoxicity studies, please see Review and Evaluation of Pharmacology and Toxicology Data for NDA 21-257 (October 2000).

2.6.6.5 Carcinogenicity

Two-year carcinogenicity studies were submitted by the sponsor on June 27, 2002 under NDA 21-257. The studies showed no carcinogenic potential in rats or mice. The

following is the Executive CAC meeting minutes. For detailed review, please see Review and Evaluation of Pharmacology and Toxicology Data for NDA 21-257 (October 2002).

Executive CAC

Date of Meeting: November 26, 2002

Committee: Joseph Contrera, Ph.D., HFD-901, Acting Chair
Jeri El Hage, Ph.D., HFD-510, Alternate Member
Tim McGovern, Ph.D., HFD-170, Alternate Member
Josie Yang, Ph.D., HFD-550, Team Leader
Zhou Chen, Ph.D., HFD-550, Presenting Reviewer

Author of Draft: Zhou Chen

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

NDA #: 21-257

Drug Name: Travatan[®] (Travoprost Ophthalmic Solution, 0.004%)

Sponsor: Alcon Laboratories, Inc.

Background: Travatan[®] (travoprost, AL-6221) is a PGF₂ α analog. The drug was approved in March 2001 for the indication of elevated IOP in patients with open-angle glaucoma or ocular hypertension.

2.6.6.6 Reproductive and developmental toxicology

All reproductive studies were submitted with NDA 21-257 package in 2000. These studies are summarized in the table below. For detailed review information, please see Review and Evaluation of Pharmacology and Toxicology Data for NDA 21-257 (October 2000).

Species/strain	N/sex/group	Dose level	Regimen	Duration	Findings
Rat/Sprague Dawley	26	0, 1, 3 and 10 µg/kg/day	sc, qd	%: 4 wks prior to and through gestation, & 2 wks prior to mating through gestation	No effects on fertility in rats. 10 µg/kg: ↑ early resorptions. NOAEL = 3 µg/kg
Rat/Sprague Dawley	26♀	0, 1, 3 and 10 µg/kg/day	iv, qd	Gestation Days 6-17	10 µg/kg: dams: ↓body weight gain and food consumption, ↓number of viable fetuses/dam, ↑ post-implantation loss. Fetuses: ↓body weights, ↑incidence of malformations and variation NOAEL = 3 µg/kg for dams and fetuses
Mice/CD-1(ICR)BR	30♀	0, 0.1, 0.3 and 1.0 µg/kg	qd, sc	Gestation Days 6-16	1.0 µg/kg: dams: ↑early deliveries, abortions and total litter resorptions, ↓number of viable fetuses/dam, ↑ post-implantation loss. Fetuses: No teratogenic effects NOAEL = 0.3 µg/kg for dams and fetuses
Rat/Sprague Dawley	26♀	0, 0.12, 0.36 and 0.72 µg/kg/day	sc, qd	Gestation Day 7-lactation Day 21	F ₀ : All doses: ↓food consumption during gestation, ↓gestation length, ↑litters with stillborn pups. 0.72 µg/kg: prolapsed uterus (1 dam), ↑abortions, ↓litters with viable fetuses, ↓number of pups/litter F ₁ : All doses: ↓ pup survival during Days 1-4 of lactation, ↓body weights, ↓physical development and motor activity F ₂ : not affected
Rat/Sprague Dawley	26♀	0, 0.01, 0.03 and 0.1 µg/kg/day	sc, qd	Gestation Day 7-lactation Day 21	No significant toxicity effects on maternal parameters and pup development. ↓implantation sites and number of pups/litter at 0.01 and 0.1 µg/kg, which might not be drug-related. NOAEL = 0.1 µg/kg for both dams and pups.

2.6.6.7 Local tolerance

No studies were performed.

2.6.6.8 Special toxicology studies

012-30-0101: Two week topical ocular irritation toxicity evaluation of _____ ophthalmic solution in New Zealand White rabbits

Key study findings: At the concentration of 0.00010% administered topically, _____ presented no toxic potential to NZW rabbits.

Report #: 012-30-0101

Protocol #: N-00-328

Study Aim: To evaluate the ocular irritation and toxicity potential of _____, a degradation impurity, following topical ocular administration, three times daily, to New Zealand White rabbits for two weeks

Compound/Vehicle: Vehicle, 0.00003% _____ ophthalmic solution, 0.00010% _____ ophthalmic solution, and 0.00003% _____ plus 0.004% AL-6221 ophthalmic solution

Ingredient (% w/v)	Vehicle	0.00003%	0.00010%	AL-6221
Lot #	00-27987-2	00-20993-2	00-20994-2	00-20997-7
AL-6221	0	0	0	0.004
Polyoxyl 40 hydrogenated castor oil				
Tromethamine				
Boric Acid, NF				
Mannitol				
EDTA				
Benzalkonium Chloride, NF				
NaOH, NF and/or HCl, NF				
Purified H ₂ O				

Dose & Route: One drop (30 µl)/eye, right eyes, three times daily for two weeks
 Animals: New Zealand White rabbits, 6-8 months old, weighing 3.1-4.2 kg, 3/sex/group
 Study Location: Alcon Laboratory, Inc., 6201 South Freeway, Fort Worth, TX 76134
 Compliance with GLP/QAU: Yes
 Study Initiation: 12/2/2000
 Study Design: Drug or vehicle was applied to the right eye of each rabbit three times daily for two weeks. The left eye served as the untreated control. The day of dosing was designated as Day 1.

Group	Lot number	Dose (µg/day)	n/sex
1 Vehicle	00-27987-2		3
2 0.00003%	00-27993-2	0.027	3
3 0.00010%	00-27994-2	0.9	3
4 0.00003%/AL-6221 0.004%	00-27992-2	0.027/3.6	3

Observations and times:

Daily observations: Twice daily

Body weights: Days 0, 3, 6 and before necropsy

Ophthalmic biomicroscopic examinations: Pretest and weekly

Necropsy: All animals

Organ weights: The following organs from all animals were weighed: adrenal, liver, kidneys, heart, brain, gonads, and spleen.

Histopathology: The eye and adnexa from all animals.

Results:

Daily observations: No drug-related clinical abnormal findings were noted.

Body weights: No toxicologically significant findings in body weight examination were noted.

Biomicroscopic evaluation: No abnormal findings were seen in the cornea, aqueous chamber, iris, lens, and light reflex evaluations. Conjunctival congestion (score = 1) was seen in most animals in all groups in both eyes, and was considered as a spontaneous finding and not toxicologically significant. Conjunctival discharge (score = 1) was seen in one Group 2 female (right eye), one Group 3 female (left eye), and one Group 4 female (right eye) at the final examination interval. Because of the low incidence in both eyes, this finding was not considered as biologically relevant.

Necropsy: No treatment-related abnormal findings were noted.

Organ weights: No treatment-related effects in organ weights were noted.

Histopathology: There were no ocular pathological findings related to treatment with _____ alone or in combination with AL-6221.

In summary, NZW rabbits were topically treated with _____, three times daily for 14 days. No treatment-related abnormal findings were noted in clinical observations, body weights, biomicroscopic and post-mortem examinations.

The patient exposure at the recommended dosage would be 0.012 µg/day, or 0.00024 µg/kg/day. The sponsor indicated that at _____ would present no hazard to the user. Based on the study results, the reviewer concurs. In conclusion, at the concentrations up to _____ presented no toxicity potential when administered topically to the eye of NZW rabbits.

051-30-0601: One month topical ocular irritation and systemic toxicity evaluation of AL-6221 (travoprost) epoxide impurity using New Zealand rabbits

Key study findings: 0.12% AL-6221 with _____ of active label caused neither ocular irritation nor systemic toxicity in New Zealand F1 cross rabbits.

Report #: 051-30-0601

Protocol #: N-01-050

Study Aim: To evaluate the ocular irritation and systemic toxicity potential of AL-6221 with _____ following topical ocular administration, three times daily to New Zealand F1 cross rabbits for one month

Compound/Vehicle: Vehicle, 0.04% travoprost with _____ solution, 0.012 travoprost with _____ solution

Ingredient (% w/v)	Vehicle	AL-6221 0.004%	AL-6221 0.012%
Lot #	01-28882-1	01-28880-1	01-28881-1
AL-6221	0	0.004	0.012
Polyoxyl 40 hydrogenated castor oil			
Tromethamine			
Boric Acid, NF			
Mannitol			
EDTA			
Benzalkonium Chloride, NF			
NaOH, NF and/or HCl, NF			
Purified H ₂ O			

Dose & Route: One drop (30 µl)/eye, right eyes, three times daily for one month

Animals: New Zealand F1 cross rabbits, weighing 2.3-2.8 kg; 4/sex/group.

Study Location: Alcon Laboratory, Inc., 6201 South Freeway, Fort Worth, TX 76134

Compliance with GLP/QAU: Yes

Study Initiation: 5/7/2001

Study Design: Drug or vehicle was applied to the right eye of each rabbit three times daily for one month. The left eye served as the untreated control. The day of dosing was designated as Day 1.

Group	Lot number	n/sex
1 Vehicle	01-28882-1	4
2 AL-6221 0.004% with _____	01-28880-1	4
3 AL-6221 0.012% with _____	01-28881-1	4

Observations and times:

Daily observations: Twice daily

Body weights: Days 0, 3, 6 and before necropsy

Ophthalmic biomicroscopic examinations: Pretest, Weeks 1, 2 and prior to necropsy

Pachymetry: Prior to necropsy on Day 35

Clinical pathology: Last week on all animals

Necropsy: All animals on Day 36

Organ weights: The following organs from all animals were weighed: adrenal, liver, kidneys, heart, brain, gonads, and spleen.

Histopathology: The eye and adnexa from all animals. [Reviewer's comments: The study has some deficiencies. Tissues from one Group 3 female and three Group 3 males were not processed and evaluated. No reason was given.]

Results:

Daily observations: No treatment-related abnormal clinical findings were noted.

Body weights: No toxicologically significant findings in body weights were noted.

Biomicroscopic evaluation: No conjunctival swelling, discharge, iritis, neovascularization, flare or abnormal light reflexes were reported. Slight conjunctival congestion (score = 1) was seen in many animals in all groups in both eyes at all examination intervals with similar incidence and severity, which was considered as a spontaneous finding. One Group 1 male showed mild conjunctival congestion (score = 2) in the right eye on Day 7. Corneal cloudiness (score = 1) was seen in one Group 1 male in the right eye on Day 35. Fluorescein staining (score = 1) was seen in one Group 1 female (right eye, Day 35; left eye, Day 7) and one Group 2 female (right eye, Day 35). One Group 1 female on Day 35 showed early cataract (both eyes). None of these findings were considered treatment-related.

Pachymetry evaluation: No toxicologically significant changes were noted.

Clinical pathology: No treatment-related abnormal findings were noted.

Necropsy: All tissues and organs examined for all animals in all groups were within normal limits. No treatment-related abnormal findings were noted.

Organ weights: The brain weight in the Group 3 females was lower than that of the control animals, and the liver weight of Groups 2 and 3 females were higher than that of

control animals. Similar changes were not seen in males, in other studies with AL-6221, and no corresponding findings (e.g., increases in ALT) were noted. These changes were considered incidental.

Histopathology: There are a few lesions in treated and untreated eyes and adenxa from various groups. These lesions included mononuclear cell infiltrates in the corneal limbus, eyelids, nictitating membrane, Harderian gland, and lacrimal gland, lacrimal gland atrophy, and epidermal hyperplasia. The degrees of the lesions were all minimal, and the types of the lesions were commonly seen spontaneously in rabbits of this strain. In some cases, the same lesions were present in both eyes. None of these lesions were considered as treatment-related.

In summary, New Zealand F1 cross rabbits were topically treated with AL-6221 (0.004% or 0.012%) with _____ of active labeling) three times daily for one month. No treatment-related abnormal findings were noted in clinical observations, body weights, ophthalmic or post-mortem examinations. In conclusion, topical ocular treatment with 0.004% travoprost with _____ and 0.012% travoprost with _____ was well tolerated and caused no sign of ocular irritation or toxicity in rabbits.

2.6.6.9 Discussion and Conclusions

The new formulation, Travatan[®] Z, showed a similar toxicity profile as compared to the marketed formulation, Travatan[®]. The drug showed a low irritation potential when administered topically to the rabbit eye. Studies with impurities including _____ and _____ showed no biologically relevant toxicity.

2.6.7 TOXICOLOGY TABULATED SUMMARY

Not applicable

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Travoprost (AL-6221) is a highly selective and potent agonist at the FP prostanoid receptor. Pharmacological studies indicated that travoprost was effective in reducing intraocular pressure in animal models. Travoprost is approved as Travatan[®] in 2001 for the reduction of IOP in patients with open angle glaucoma or ocular hypertension. In the current NDA application, the sponsor proposed a new benzalkonium chloride-free formulation. The sponsor indicated that benzalkonium chloride in IOP-lowering medications had been implicated in exerting a deleterious effect on the conjunctiva that resulted in altered postoperative wound healing.

Many nonclinical studies were reviewed under NDA 21-257 in 2000. Topical ocular administration of travoprost in monkeys resulted in an increase in palpebral fissure, noted clinically as "big eye", and iris pigmentation. In a 6-month rat study with repeated subcutaneous administration, treatment-related mortalities were noted at 100

$\mu\text{g}/\text{kg}$ ($600 \mu\text{g}/\text{m}^2$). Microscopic bone changes (endosteal fibrosis and hyperostosis) were noted at the doses $> 30 \mu\text{g}/\text{kg}$ ($180 \mu\text{g}/\text{m}^2$). These doses were at least 121-fold above the possibly highest human daily dose ($1.48 \mu\text{g}/\text{m}^2$). Therefore, travoprost was generally considered as safe and systemically well tolerated.

One PK and three ocular toxicity studies were conducted with the new formulation. The new formulation showed a slightly lower ocular exposure to the drug following topical ocular administration to NZW rabbits. The BAC-free formulation provided similar IOP-lowering effects to Travatan[®] in human patients since clinical trials showed that travoprost 0.002% and 0.004% had the same IOP-lowering effect. No unexpected, toxicologically significant findings were noted in the supportive toxicity studies. The new formulation exhibited essentially the same pharmacology/toxicology profile.

This NDA application is approvable from a nonclinical perspective.

Conclusions: The NDA is approvable from the nonclinical safety point of view.

Unresolved toxicology issues (if any): There are no unresolved toxicology issues.

Recommendations: An "approval" is recommended.

Suggested labeling: The new drug, Travatan[®] Z, shares the same pharmacology/toxicology profiles with the approved drug, Travatan[®]. The pharmacology/toxicology-related parts of the labeling proposed by the sponsor are the same as those proposed for Travatan[®]. The reviewing pharmacologist has no objection.

Signatures:

Reviewer Signature _____

Supervisor Signature _____ Concurrence Yes ___ No ___

APPENDIX/ATTACHMENTS

Not applicable

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/s/

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