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**
DIVISION DIRECTOR:	**Janice Soreth, MD**
PROJECT MANAGER:	**Mike Puglisi**

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 angel 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 (PGF2α receptor) with a Ki of 52 nM and a functional potency (EC_{50}) 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

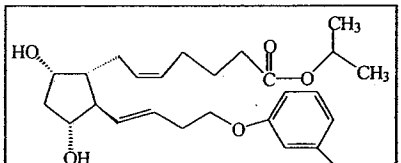
2.6.1 INTRODUCTION AND DRUG HISTORY

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: $C_{26}H_{35}F_3O_6$; MW=500.55
Structure:



Travoprost (AL-6221)

Relevant INDs/NDAs/DMFs: DMFs [redacted], IND 51,000; NDA 21-257

Drug class: $PGF_{2\alpha}$ analogue

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