DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Angela C. Kothe, OD, PhD
Associate Director, Regulatory Affairs
Alcon Research, Ltd.
6201 South Freeway R7-18
Fort Worth, TX 76134-2099

RE: NDA # 21-257
Travatan® (travoprost ophthalmic solution) 0.004%
MACMIS ID # 13257

Dear Dr. Kothe:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a flash card (TRV04512VS) for Travatan® (travoprost ophthalmic solution) submitted by Alcon Research, Ltd., (Alcon) under cover of Form FDA 2253. The flash card is false or misleading because it fails to reveal material facts, presents unsubstantiated superiority claims, broadens the indication, minimizes risks, and presents dosing claims that are unsubstantiated and inconsistent with the approved product labeling (PI) for Travatan. Thus, the flash card misbrands the drug in violation of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. 352(a) and 321(n). These violations are concerning from a public health perspective because they suggest that Travatan is safer or more effective than has been demonstrated, and they encourage use in circumstances other than those for which the drug has been shown to be safe and effective.

Background

According to the approved product labeling (PI):

> TRAVATAN® 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.

According to the PI, Travatan is associated with serious risks, including the following Warnings [emphasis in original]:

> **TRAVATAN® has 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.**
>
> TRAVATAN® 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 TRAVATAN®.
>
> TRAVATAN® Ophthalmic Solution 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 disparity between the eyes in length, thickness, and/or number of eyelashes.

Pertinent precautions in the PI include:

> …bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products….TRAVATAN® 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.

Additionally, "The most common ocular adverse event observed in controlled clinical studies was ocular hyperemia which was reported in 35 to 50% of patients. Approximately 3% of patients discontinued therapy due to conjunctival hyperemia."

Failure to Reveal Material Facts/Unsubstantiated Comparative and Superiority Claims

Promotional materials are misleading if they fail to reveal facts that are material in light of the representations they make. The flash card presents the claim "24 hours post dose, TRAVATAN® Solution mean IOP was **2.9 mm Hg lower** than XALATAN[1]" [emphasis in original]. This claim is misleading because it compares the efficacy of two products with dissimilar indications without revealing the differences in indication. Specifically, Travatan is indicated as second-line therapy due to safety concerns, whereas Xalatan is indicated as first-line therapy. When comparing first line therapies to second line therapies it is important to reveal this difference because without doing so, you misleadingly suggest that the second line therapy is superior to the first and should be used before the first line therapy. This difference in indication is not revealed in the flash card.

Furthermore, this claim is misleading because it is unsubstantiated. The study cited[1] (reference 1 below) in support of this claim is not considered substantial evidence or substantial clinical experience because it is an open-label trial. Trials with an open-label design are not appropriate for studying IOP changes because open-label trials do not include measures to minimize bias which affects both efficacy and safety data.

The flash card also presents the following superiority claims for Travatan in comparison to Lumigan:

- "TRAVATAN® Solution hyperemia is primarily the result of full FP receptor agonism, not the activation of EP_1 inflammatory pathways, as occurs with LUMIGAN[7,8]" (references 2 and 3 below)
- "EP_1 receptors are proven to play a direct role in inflammation and redness[9]" (reference 4 below)

These claims suggest that, because Travatan acts on FP receptors instead of EP_1 receptors like Lumigan, it is associated with comparatively less inflammation and redness (as related to hyperemia) than Lumigan. These claims thus imply that Travatan causes less discomfort in comparison to Lumigan, when this has not been demonstrated in adequate and well-controlled head-to-head clinical trials. Rather, these claims are based on animal and tissue culture data[2,3,4], and suggest that Travatan will have a clinical benefit in humans in terms of its side effects compared to Lumigan when the clinical significance of this animal and tissue culture data has not been established.

Broadening of Indication

The flash card presents the headline claim "TRAVATAN® provides 24-hour IOP control" followed by a bullet which states: "24-hr IOP control is essential for visual field protection[2-4]." (references 5, 6, and 7 below) These claims misleadingly broaden the indication for Travatan by suggesting that Travatan will protect the visual field. According to the PI, Travatan is indicated for the reduction of intraocular pressure. The three references cited[5,6,7] in support of this claim do not discuss or provide analysis with respect to the effect of specific IOP-lowering treatment on visual field loss. In addition, the Stewart[7] publication did not include Travatan in its review. Therefore, you have not cited substantial evidence or substantial clinical experience to support your claim that treatment with Travatan provides visual field protection.

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[1] Dubiner HB, Sircy MD, Landry T, et al. Comparison of the diurnal ocular hypotensive efficacy of travoprost and latanoprost over a 44-hour period in patients with elevated intraocular pressure. *Clin Ther*. 2004;26:84-91.
[2] Hellberg MR, Sallee VL, McLaughlin MA, et al. Preclinical efficacy of travoprost, a potent and selective FP prostaglandin receptor agonist. *J Ocul Pharmacol Ther*. 2001;17:421-432.
[3] Sharif NA, Kelly CR, Crider JY, Williams GW, Xu SX. Ocular hypotensive FP prostaglandin (PG) analogs: PG receptor subtype binding affinities and selectivities, and agonist potencies at FP and other PG receptors in cultured cells. *J Ocul Pharmacol Ther*. 2003;19:501-515.
[4] Stock JL, Shinjo K, Burkhardt J, et al. The prostaglandin $E_2$$EP_1$ receptor mediates pain perception and regulates blood pressure. *J Clin Invest*. 2001;107:325-331.
[5] Asrani S, Zeimer R, Wilensky J, Gieser D, Vitale S, Lindenmuth K. Large diurnal fluctuations in intraocular pressure are an independent risk factor in patients with glaucoma. *J Glaucoma*. 2000;9:134-142.
[6] Zeimer RC, Wilensky JT, Gieser DK, Viana MA. Association between intraocular pressure peaks and progression of visual field loss. *Ophthalmology*. 1991;98:64-69.
[7] Stewart WC. Diurnal curves truly measure efficacy. *Rev Ophthalmol*. 2001;8(11):128-132.

Minimization of Risk

The flash card presents several claims that minimize the risks of hyperemia associated with Travatan. For example, the following claims are presented under the prominent header, "TRAVATAN® Solution tolerability is easy to endure":

- "Moderate or higher hyperemia with TRAVATAN® Solution regresses over 3 months[6]" along with graphic presentation (reference 8 below)
- "Hyperemia with TRAVATAN® Solution regresses over 3 months[6]" (reference 8 below)
- "Hyperemia with TRAVATAN® Solution is mild and diminishes over time"

These claims suggest that hyperemia associated with Travatan regresses or diminishes over time and can be classified as "mild." FDA is not aware of evidence to support these suggestions. The reference cited[8] in support of these claims is not a complete study report and therefore cannot be evaluated. If you have additional information about the study, please provide it to the Agency. Moreover, the Phase 3 trials that were the basis for approval of Travatan do not support the claims that hyperemia associated with Travatan regresses or diminishes over time or can be classified as "mild." Although a statement with regard to the incidence of hyperemia is presented at the bottom of the flash card, it does not correct the overwhelmingly misleading impression created by the above prominent claims that this risk is mild and regresses or diminishes over time.

Misleading Dosing Claims

The flash card presents several prominent dosing claims in large, bolded font that are inconsistent with the PI and misleadingly imply that Travatan does not need to be dosed once a day. For example:

- "Endurance with TRAVATAN® Solution – It goes on and on"
- "TRAVATAN® Solution controls IOP throughout the day and beyond. [1]" (reference 1 above)
- "TRAVATAN® Solution offers IOP lowering for up to 84 hours"
- "Even when your patients forget, TRAVATAN® doesn't…TRAVATAN® Solution **maintains 90% of its IOP-lowering effect** for at least 36 hours after the last dose[1]" [emphasis in original] (reference 1 above)

The Dosage and Administration section of the PI states, however, that "The recommended dosage is one drop in the affected eye(s) once-daily in the evening." Moreover, the reference cited[1] in the flash card in support of the above claims was an open-label trial, which is subject to investigator bias that affects both the safety and efficacy data and is not appropriate for studying the effect of a drug on IOP-lowering. Thus, the reference does not constitute substantial evidence or substantial clinical experience to support the use of alternative dosing regimens beyond once a day. Furthermore, this reference did not demonstrate that Travatan provided adequate IOP control beyond 24 hours. Although the statement "The recommended dosage is one drop in the affected eye(s) once daily in the evening" appears in non-bolded font near the bottom of the flash card, this statement is not adequate to

[8] Netland P, Landry T, Sullivan EK, et al. Travoprost compared with latanoprost and timolol in patients with open-angle glaucoma or ocular hypertension. *Am J Ophthalmol.* 2001;132:472-484.

overcome the overwhelmingly misleading impression created by the above claims that Travatan can be dosed less frequently than once a day.

Conclusion and Requested Action

For the reasons discussed above, the flash card fails to reveal material facts, presents unsubstantiated superiority claims, broadens the indication, minimizes risks, and presents dosing claims that are unsubstantiated and inconsistent with the PI for Travatan. Accordingly, the flash card misbrands Travatan in violation of the Federal Food, Drug, and Cosmetic Act (Act). See 21 U.S.C. 352 (a) and 321(n).

DDMAC requests that Alcon immediately cease the dissemination of violative promotional materials for Travatan such as those described above. Please submit a written response to this letter on or before October 6, 2005, stating whether you intend to comply with this request, listing all violative promotional materials for Travatan such as those described above, and explaining your plan for discontinuing use of such materials. Please direct your response to me at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705-1266, facsimile at 301.796.9877 or 301.796.9878. In all future correspondence regarding this matter, please refer to MACMIS ID # 13257 in addition to the NDA number. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Travatan comply with each applicable requirement of the Act and FDA implementing regulations.

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

Suzanne Berkman, PharmD
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

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

/s/

Suzanne Berkman
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