DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

David E.I. Pyott
President and Chief Executive Officer
Allergan, Inc.
PO Box 19534
Irvine, CA 92623-9534

RE: NDA # 21-275
Lumigan® (bimatoprost ophthalmic solution) 0.03%
MACMIS ID # 13256

WARNING LETTER

Dear Mr. Pyott:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a sales aid (4942236) for Lumigan® (bimatoprost ophthalmic solution) submitted by Allergan, Inc. (Allergan) under cover of Form FDA 2253. The sales aid is false or misleading because it presents unsubstantiated superiority claims and thus misbrands the drug in violation of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 352 (a) and 321(n).

Moreover, DDMAC had previously objected, in an untitled letter dated March 26, 2001, to the dissemination of a "Dear Doctor" letter that contained unsubstantiated superiority claims for Lumigan. We are concerned that you are continuing to promote Lumigan in a violative manner.

Background

According to the approved product labeling (PI):

> LUMIGAN® (bimatoprost ophthalmic solution) 0.03% is indicated for the reduction of elevated intraocular pressure (IOP) 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, Lumigan is associated with several risks, including the following bolded Warning and other Warnings [original emphasis]:

> **LUMIGAN® (bimatoprost ophthalmic solution) 0.03% has been reported to cause changes to pigmented tissues. These reports include increased pigmentation and growth of eyelashes and increased pigmentation of the iris and periorbital tissue (eyelid). These changes may be permanent.**
>
> LUMIGAN® may gradually change eye color, increasing the amount of brown pigment 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 several months to years. Patients should be informed of the possibility of iris color change.
>
> Eyelid skin darkening has also been reported in association with the use of LUMIGAN®.
>
> LUMIGAN® may gradually change eyelashes; these changes include increased length, thickness, pigmentation, and 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 tissue, and eyelashes in the treated eye and thus, heterochromia between the eyes. They should also be advised of the potential for a disparity between the eyes in length, thickness, and/or number of eyelashes.

Pertinent precautions in the PI include the risk of "bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products." In addition, Lumigan should be used with caution in patients with active intraocular inflammation, aphakic patients, pseudophakic patients with a torn posterior lens capsule and in patients with known risk factors for macular edema.

Unsubstantiated Superiority Claims

The sales aid presents the following false or misleading claims regarding the superiority of Lumigan over competitor products:

- "Weight of evidence proves LUMIGAN® produces lowest mean IOP. For example…vs beta-blockers… vs travoprost… vs latanoprost… vs dual therapy[1-12]"
- "When 'good enough' isn't low enough, turn to the proven performance of LUMIGAN®"

As discussed in more detail below, these claims are misleading because they suggest Lumigan is superior in its effectiveness to other medications used for reducing IOP when this has not been demonstrated by substantial evidence or substantial clinical experience. Furthermore, the claim that Lumigan is superior to "dual therapy" is misleading because it implies that Lumigan is better than

combination ophthalmic therapy, such as a beta-blocker/prostaglandin combination, when this, too, has not been demonstrated by substantial evidence or substantial clinical experience.

The sales aid also contains the following claims which misleadingly imply that Lumigan is a superior choice because it is preferred by patients.

- "Vast majority of patients want lower IOP and will adhere to therapy to get it"
- "92% of patients prefer medication that lowers IOP the most[14]" [reference 1 below]

These claims contribute to the misleading impression created by the piece as a whole that Lumigan is superior to other medications that reduce elevated IOP. When considered in conjunction with the numerous superiority claims presented throughout the piece, the above claims imply that patients will adhere to and prefer Lumigan over other products because of its purported superior ability to lower IOP. Furthermore, these claims are misleading because they are not supported by substantial evidence. No references were cited to support the first claim. The reference cited[1] for the second claim is not considered substantial evidence; rather it is a survey (Glaucoma Research Foundation Patient Survey) that included one question regarding a hypothetical situation assuming that all treatment options for glaucoma have the same safety profile and dosing requirements, which is not the case in actual use. Patient preference encompasses multiple aspects of patient experiences and cannot be adequately measured by a single item in a survey; rather, patient preference claims require well-designed and controlled studies using validated and well-developed instruments that can evaluate patient preference.

Finally, the claim "LUMIGAN® patients refill their prescription at the same rate as patients on other lipid therapies[16]" [reference 2 below] is misleading because it suggests that Lumigan therapy results in equivalent patient adherence as "other lipid therapies" when this has not been demonstrated by substantial evidence. The reference cited[2] to support this claim is a medical and pharmacy database study poster presentation. The study protocol is inadequate to support an adherence claim because the protocol required that the patients stay on the same medication for 12 months, which essentially excludes patients who discontinued therapy for reasons such as lack of efficacy or side effects. There are many factors that affect patient adherence, including side effects, effectiveness, dosing schedule, dosage form, and cost. An adherence claim must be supported by substantial evidence taking into account these types of determinants of patient adherence. This refill database study does not support an adherence claim for Lumigan because it did not take these factors into account and does not reflect adherence rates that are experienced with actual real-world use.

Misleading Superiority to Beta-Blockers

The sales aid contains the following claims and presentations comparing Lumigan to beta-blockers:

- "LUMIGAN® produces lowest mean IOP…vs beta-blockers[1-4]" [references 3-5, and 9 below]

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[1] Glaucoma Research Foundation. Glaucoma Patient Survey. August 2003.

[2] Kline S, Walt J, Carlson A, Trygstad G. Patients' persistence and adherence with glaucoma therapy; a longitudinal retrospective database analysis of ophthalmic lipids. Poster presented at: the Annual Meeting of the Association of Research in Vision and Ophthalmology; April 25-29, 2004; Fort Lauderdale, Fla.

- Graph titled "Effects of LUMIGAN® replacement of beta-blocker therapy on mean IOP[3]," depicting that Lumigan provides a "4.4 mm Hg additional mean reduction" at month 2. [reference 5 below]

These claims are misleading because they imply Lumigan is superior to beta-blockers when this has not been demonstrated by substantial evidence or substantial clinical experience. The studies cited, Higginbotham et al.,[3] Cohen et al.,[4] and Walters et al.,[9] demonstrated changes in IOP that are not considered clinically significant. Differences of 2-3 mm Hg are not considered clinically significant because such differences are commonly seen in clinical trials without a change in therapy. Further, the applanation tonometer is calibrated in 2 mm Hg increments. Since 2 mm Hg is the smallest change the instrument can detect, physicians are unlikely to alter patient therapy based on a 2 mm Hg change in IOP.

Further, the study cited[5] in support of the graph depicting a "4.4 mm Hg additional mean reduction" is not considered a well-controlled study because it is an open-label, single-arm, non-concurrently controlled study in which Lumigan was substituted for timolol. This design is sometimes referred to as a "baseline controlled" study, but, in actuality, it is uncontrolled because there is no comparison with a control group except insofar as one believes the IOP would have remained the same once patients entered the study. There is, however, no way to know whether the IOP would have remained the same. Compliance could be different (better) in the test drug (Lumigan) phase of the study because of different patient or investigator expectations or biased observations. The proper design for such a trial is randomization to Lumigan or timolol drops in a blinded study. Open-label studies are not appropriate for studying IOP changes because they do not include measures to minimize bias. IOP readings themselves may be biased and should be carried out without knowledge of treatment assignment. Therefore, the study cited does not constitute substantial evidence to support your claim because it was not adequate and well-controlled.

In addition, promotional materials are misleading if they fail to reveal facts that are material in light of the claims made in the piece. For comparative claims, it is misleading to compare the efficacy of two products with dissimilar indications without revealing the differences in indication. Lumigan is indicated as second-line therapy due to safety concerns, whereas timolol, the beta-blocker the sales aid compares Lumigan to, 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 is not revealed in the sales aid.

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[3] Higginbotham EJ, Schuman JS, Goldberg I, et al., for the Bimatoprost Study Groups 1 and 2. One-year, randomized study comparing bimatoprost and timolol in glaucoma and ocular hypertension. *Arch Ophthalmol*. 2002;120(10):1286-1293.

[4] Cohen JS, Gross RL, Cheetham JK, VanDenburgh AM, Bernstein P, Whitcup, SM. Two-year double-masked comparison of bimatorprost with timolol in patients with glaucoma or ocular hypertension. *Surv Ophthalmol*. 2004;49(2 suppl 1):S45-S52.

[5] Lee D, Gross R, Mundorf T, Severin T, for the Lumigan® Early Experience Study. Efficacy and safety of bimatoprost 0.03% (Lumigan) in a large-scale, open-label clinical trial. Poster presented at: the annual Meeting of the Association for Research in Vision and Ophthalmology; May 5-10, 2002; Fort Lauderdale, Fla.

Misleading Superiority to Travoprost

The sales aid contains the following claims and presentations comparing Lumigan to travoprost:

- "LUMIGAN® produces lowest mean IOP…vs travoprost[5-7]" [references 6-8 below]
  - "16% to 29% greater mean IOP reduction[5]" [reference 6 below]
- "In a randomized, investigator-masked, 6-month clinical trial, LUMIGAN® (n = 14) provided greater mean IOP reduction than travoprost (n = 12)[5]" [reference 6 below]
- Graph titled "LUMIGAN® vs travoprost: diurnal mean IOP at month 3" depicting a "lower mean IOP all day long[7]" [reference 8 below]

These claims are misleading because they imply Lumigan is superior to travoprost when this has not been demonstrated by substantial evidence or substantial clinical experience. The references cited in the sales aid are not sufficient to support these claims. First, Cantor et al.,[6] the 6-month study comparing Lumigan and travoprost, showed no statistically significant difference in mean IOP lowering. While the sales aid does contain the statement "Differences not statistically significant due to small sample size"; this statement is false (the reason for lack of statistical significance cannot possibly be known) and, in any case, does not correct the overwhelmingly misleading impression that Lumigan is superior to travoprost. Second, Mundorf et al.,[7] is a poster presentation and contains inadequate information regarding investigative methods, masking procedure, patient populations, washout periods, applanation tonometry protocol, and statistical analysis. If you have additional information, please submit it to FDA for review. Lastly, Parrish et al.,[8] showed that Lumigan and travoprost were not statistically different in their ability to reduce IOP.

Misleading Superiority to Latanoprost

The sales aid contains the following claims and presentations comparing Lumigan to latanoprost:

- "LUMIGAN® produces lowest mean IOP…vs latanoprost[4,7-11]" [references 8-13 below]
  - "27% to 42% greater mean IOP reduction[8]" [reference 11 below]
- "In a randomized, investigator-masked, 6-month clinical trial, LUMGIAN® (n=133) provided statistically significantly greater mean IOP reduction than latanoprost (n=136) at every time point, every study visit[8]" [reference 11 below]
- Graph titled "Effects of LUMIGAN® replacement of latanoprost therapy on mean IOP" demonstrating a "3.6 mm Hg additional mean reduction[9]" [reference 12 below]

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[6] Cantor LB, WuDunn D, Cortes A, et al. Ocular hypotensive efficacy of bimatoprost 0.03% versus travoprost 0.004% in patients with glaucoma or ocular hypertension. *Surv Ophthalmol*. 2004;49(2 supp 1):S12-S18.

[7] Mundorf T, Noecker R, Dirks M, Earl ML. A multicenter, randomized, investigator-masked comparison of the efficacy of bimatoprost 0.03% versus travoprost 0.004% in African Americans with glaucoma or ocular hypertension. Poster presented at: the Annual Meeting of the American Glaucoma Society; March 4-7, 2004: Sarasota, Fla.

[8] Parrish RK, Palmberg P, Sheu W-P, for the XLT Study Group. A comparison of latanoprost, bimatoprost, and travoprost in patients with elevated intraocular pressure: a 12-week, randomized, masked-evaluator, multicenter study. *Am J Ophthalmol.* 2003;135(5):688-703.

These claims are misleading because they imply Lumigan is superior to latanoprost when this has not been demonstrated by substantial evidence or substantial clinical experience. The references cited in the sales aid are not sufficient to support these claims. The studies cited, Parrish et al.,[8] Walters et al.,[9] and Dubiner et al.,[10] demonstrated no statistically significant difference between Lumigan and latanoprost in their ability lower IOP. Furthermore, the other studies cited, Noecker et al.,[11] Bournias et al,[12] and Gandolfi et al.,[13] are not considered substantial evidence. The study by Noecker et al.[11] did not take adequate measures to control for bias. For example, the statistical analysis did not adjust for multiple comparisons. If multiple comparisons were accounted for, the IOP reduction would not have been statistically significant at "every time point, every study visit." Bournias et al.[12] is an open-label, replacement trial in which Lumigan was used alone or in combination with other glaucoma medications at the physician's discretion. As mentioned previously, such a design is sometimes referred to as a "baseline controlled" study, but, in actuality is uncontrolled because there is no comparison with a control group except insofar as one believes the IOP would have remained the same once patients entered the study. There is, however no way to know whether that would have been the case. Compliance could be different (better) in the test drug (Lumigan) phase of the study because of different patient or investigator expectations or biased observations. The proper design for such a trial is randomization to Lumigan or latanoprost drops in a blinded study. Open-label studies are not appropriate for studying IOP changes because they do not include measures to minimize bias. IOP readings themselves may be biased and should be carried out without knowledge of treatment assignment. Finally, the study by Gandolfi et al.[13] is not considered substantial evidence because it utilizes an unacceptable primary efficacy variable. Measuring IOP at only one time point (8 AM) at all study visits is not considered an acceptable primary efficacy variable because it does not capture the variations of IOP throughout the day.

In addition, as stated above, promotional materials are misleading if they fail to reveal facts that are material in light of the claims made in the piece. It is misleading to compare the effectiveness of two products with dissimilar indications without revealing the differences in indication. Latanoprost is indicated as first-line therapy, while Lumigan is indicated as second-line therapy due to safety concerns, a fact that is not revealed. 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.

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[9] Walters TR, DuBiner HB, Carpenter SP, Khan B, VanDenburgh AM, for the Bimatoprost Circadian IOP Study Group. 24-hour IOP control with once-daily bimatoprost, timolol gel-forming solution, or latanoprost: a 1-month, randomized, comparative clinical trial. *Surv Ophthalmol*. 2004; 49(2 suppl 1):S26-S35.

[10] Dubiner H, Cooke D, Dirks M, Stewart WC, VanDenburgh AM, Felix C. Efficacy and safety of bimatoprost in patients with elevated intraocular pressure: a 30-day comparison with latanoprost. *Surv Ophthalmol.* 2001;45(suppl 4):S353-S360.

[11] Noecker RS, Dirks MS, Choplin NT, et al. A six-month randomized clinical trial comparing the intraocular pressure-lowering efficacy of bimatoprost and latanoprost in patients with ocular hypertension or glaucoma. *Am J Ophthalmol.* 2003;135(1):55-63.

[12] Bournias T, Lee D, Gross R, Mattox C. Ocular hypotensive efficacy of bimatoprost when used as a replacement for latanoprost in the treatment of glaucoma and ocular hypertension. *J Ocul Pharmacol Ther.* 2003;19(3):193-203.

[13] Gandolfi S, Simmons ST, Sturm R, et al. Three-month comparison of bimatoprost and latanoprost in patients with glaucoma and ocular hypertension. *Adv Ther*. 2001;18(3):110-121.

Misleading Superiority to Dual Therapy

The sales aid contains the following claims and presentations comparing Lumigan to dual therapy:

- "LUMIGAN® produces lowest mean IOP….vs dual therapy[9, 12]" [reference 12, 14 below]
  - "14% to 27% great mean IOP reduction than *Cosopt*®[12]" [reference 14 below)
- "In a randomized, investigator-masked, 3-month clinical trial, LUMIGAN® (n=90) provided statistically significantly greater mean IOP reduction than *Cosopt*® (n=87) at 3 out of the 4 measured time points[12]" [reference 14 below]
- Graph titled "Effects of LUMIGAN® replacement of dual therapy on mean IOP" for "**any** dual therapy to LUMIGAN® monotherapy" [emphasis added] depicting a "3.5 mm Hg additional mean reduction[13]" [reference 15 below]

These claims are misleading because they imply Lumigan is superior to any dual therapy, including Cosopt, when this has not been demonstrated by substantial evidence or substantial clinical experience. The references cited in the sales aid are not sufficient to support these claims. The study by Bournias et al.[12] is an open-label, replacement trial in which Lumigan was used alone or in combination with other glaucoma medications at the physician's discretion. As explained above, such a design is sometimes referred to as a "baseline controlled" study, but, in actuality it is uncontrolled because there is no comparison with a control group except insofar as one believes the IOP would have remained the same once patients entered the study. The proper design for such a trial is randomization to Lumigan or dual therapy in a blinded study. Furthermore, while the study by Coleman et al.[14] indicates that Lumigan produces lower IOP than timolol/dorzolamide (Cosopt), these differences are not considered clinically significant. Differences of 2-3 mm Hg are not considered clinically significant because such differences are commonly seen in clinical trials without a change in therapy. Further, the applanation tonometer is calibrated in 2 mm Hg increments. Since 2 mm Hg is the smallest change the instrument can detect, physicians are unlikely to alter patient therapy based on a 2 mm Hg change in IOP. Finally, the data on file[15] referenced contain insufficient information regarding the study design and methodology to be considered substantial evidence.

Conclusion and Requested Action

For the reasons discussed above, the sales aid presents unsubstantiated superiority claims for Lumigan. Accordingly, the sales aid misbrands Lumigan in violation of the Act. See 21 U.S.C. 352 (a) and 321 (n).

DDMAC requests that Allergan immediately cease the dissemination of violative promotional materials for Lumigan such as those described above. Please submit a written response to this letter on or before September 20, 2005, stating whether you intend to comply with this request, listing all violative promotional materials for Lumigan such as those described above, and explaining your plan

[14] Coleman AL, Lerner SF, Bernstein P, Whitcup SM, for the Lumigan/Cosopt Study Group. A 3-month randomized controlled trial of bimatoprost (LUMIGAN) versus combined timolol and dorzolamide (Cosopt) in patients with glaucoma or ocular hypertension. *Ophthalmology*. 2003;110(12):2362-2368.
[15] Data on file, Allergan, Inc. EPIC results.

for discontinuing use of such materials. Because the violations described above are serious, we request, further, that your submission include a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional 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 301-796-9878. In all future correspondence regarding this matter, please refer to MACMIS ID # 13256 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 Lumigan® 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}

Thomas W. Abrams, RPh, MBA
Director
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/

Thomas Abrams

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