

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
022184Orig1s000

OTHER REVIEW(S)

MEMORANDUM

Date	August 30, 2010
To	Nam Kim, Esq. (Office of Regulatory Policy)
From	John Farley, M.D., M.P.H.
Subject	Proposed labeling for Lumigan 0.01% and 0.03% (bimatoprost ophthalmic solution)
NDA#	22-184
Applicant Name	Allergan, Inc.
Indication(s)	Lumigan (bimatoprost ophthalmic solution) 0.01% Reduction of elevated intraocular pressure in patients with open angle glaucoma or hypertension

This Memorandum also addresses issues related to: NDA 21-275 Lumigan (bimatoprost ophthalmic solution) 0.03%

Background

Lumigan (bimatoprost ophthalmic solution) 0.03% was approved March 16, 2001 (NDA 21-275). The applicant, Allergan Inc., has submitted NDA 22-184 for bimatoprost ophthalmic solution 0.01% with the proposed trade name, "Lumigan RC". In the course of the review of NDA 22-184, a consult was requested from the Office of Surveillance and Epidemiology regarding the proposed trade name. They recommended managing the proposed product (bimatoprost ophthalmic solution 0.01%) under the existing trade name, Lumigan, with an educational program to increase awareness among practitioners of the new strength. Thus, a common package insert is proposed for Lumigan 0.01% and 0.03%. Pfizer has submitted a citizen petition dated November 2, 2006 and supplement dated August 26, 2008 (Docket 2006-P-0072) requesting that the approval of Lumigan 0.03% (a 505(b)(2) application) be revoked and that FDA refuse to approve Lumigan 0.01% (a 505(b)(1) application). These issues have been addressed elsewhere. The purpose of this memorandum is to clarify that certain labeling statements concerning pigmentation and eyelash changes in the proposed labeling can be supported solely by studies submitted by Allergan or studies to which Allergan has a right of reference.

Relevant excerpts from the proposed labeling are included below:

5 WARNINGS AND PRECAUTIONS

5.1 Pigmentation

Bimatoprost ophthalmic solution has been reported to cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the iris, periorbital tissue (eyelid) and eyelashes. Pigmentation is expected to increase as long as bimatoprost is administered. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. After discontinuation of bimatoprost, pigmentation of the iris is likely to be permanent, while pigmentation of the periorbital tissue and eyelash changes have been reported to be reversible in some patients. Patients who receive treatment should be informed of the possibility of increased pigmentation. The long term effects of increased pigmentation are not known.

Iris color change may not be noticeable for several months to years. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire

iris or parts of the iris become more brownish. Neither nevi nor freckles of the iris appear to be affected by treatment...

5.2 Eyelash Changes

LUMIGAN® 0.01% and 0.03% may gradually change eyelashes and vellus hair in the treated eye. These changes include increased length, thickness, and number of lashes. Eyelash changes are usually reversible upon discontinuation of treatment.

17 PATIENT COUNSELING INFORMATION

17.1 Potential for Pigmentation

Patients should be advised about the potential for increased brown pigmentation of the iris, which may be permanent. Patients should also be informed about the possibility of eyelid skin darkening, which may be reversible after discontinuation of LUMIGAN® 0.01% and 0.03% (bimatoprost ophthalmic solution).

17.2 Potential for Eyelash Changes

Patients should also be informed of the possibility of eyelash and vellus hair changes in the treated eye during treatment with LUMIGAN® 0.01% and 0.03%. These changes may result in a disparity between eyes in length, thickness, pigmentation, number of eyelashes or vellus hairs, and/or direction of eyelash growth. Eyelash changes are usually reversible upon discontinuation of treatment.

Data Supporting Proposed Labeling Regarding Pigmentation and Eyelash Changes

As described on page 4 of the Division Director Review of NDA 22-184 and page 3 of the Deputy Office Director Memorandum regarding NDA 21-275, Allergan conducted primate studies of bimatoprost ophthalmic solution. Cynomolgus monkeys were topically treated with different concentrations of bimatoprost ophthalmic solution up to 0.1% once or twice a day for 1 year to determine the ocular and systemic toxicity of the drug. Clinical observations and ocular examinations showed increased iridal pigmentation and periocular changes characterized by a prominent upper and/or lower sulcus and/or widening of the palpebral fissure in the treated eyes. No functional or anatomic ocular abnormalities were noted. The periocular findings were completely reversed by the end of the recovery period, while the increased iridal pigmentation was not reversible. These findings were also observed in this study in monkeys treated with other PG analogues and the findings were considered to be related to this pharmacological class. Of note, histologic examinations of affected irides were similar regardless of which prostaglandin analog the animals had been exposed to, with increased melanin synthesis evident in stromal melanocytes, but no increase in the number of melanocytes. No systemic toxicity was observed at any dose.

While iris histology studies are generally only feasible in animals, Allergan submitted to NDA 21-275 the report of a masked histologic evaluation of trabecular meshwork specimens collected from patients who had been treated with Lumigan 0.03% for at least 2 years which found no deposition of pigment in the trabecular meshwork.

Data regarding the characterization/clinical presentation of the adverse effects of pigmentation and eyelash changes were included in the clinical studies originally submitted to NDA 21-275. Allergan also submitted data to NDA 21-275 detailing the

follow-up of subjects who experienced adverse effects in the Lumigan 0.03% clinical trials. In addition, Allergan submitted to NDA 21-275 the 48-month report for the Lumigan 0.03% long-term follow-up study as well as ocular photographic assessment of subjects enrolled in this Lumigan 0.03% long-term follow-up study. These data provided information regarding the clinical characterization of iris color change and eyelash changes included in the labeling. These data also provide a basis for concluding that the eyelash changes were usually reversible after discontinuation of Lumigan, but increased iris pigmentation was likely to be permanent.

Conclusion

The proposed labeling regarding pigmentation and eyelash changes is based upon studies conducted by Allergan, Inc.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- NDA-22184	----- ORIG-1	----- ALLERGAN INC	----- Lumigan (bimatoprost ophthalmic solution) 0.01%

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/s/

JOHN J FARLEY
08/31/2010

Medical Officer's Review NDA 22-184
Labeling Review #2

NDA 22-184

Submission Date: April 25, 2008

Review Date: May 1, 2008

Sponsor:

Allergan
2525 Dupont Drive
Irvine, California 92612

Drug:

Lumigan (bimatoprost ophthalmic solution)
0.01%

Pharmacologic Category:

Prostaglandin Analog

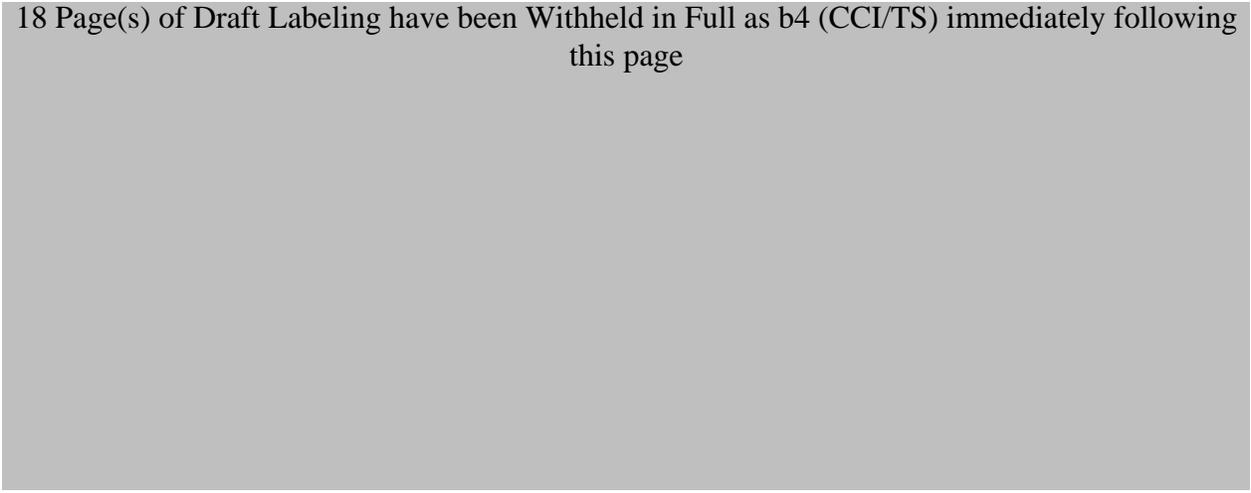
Submitted:

The applicant has submitted an amended package insert and carton/container labels. The current amendment is in response to the draft proposed label provided to the applicant on April 24, 2008.

Reviewer's Comments:

Following is the labeling submitted by the applicant. Applicant deletions are in the margin and additions are highlighted in color.

18 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page



Recommendations:

The proposed labeling is acceptable and approval is recommended.

Jennifer D. Harris, MD
Medical Officer

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/s/

Jennifer Harris
5/1/2008 02:45:27 PM
MEDICAL OFFICER

William Boyd
5/1/2008 02:48:21 PM
MEDICAL OFFICER



Internal Consult

Pre-decisional Agency Information

To: Mike Puglisi
Project Manager
Division of Anti-Infective and Ophthalmology Products (DAIOP)

From: Lynn Panholzer, PharmD
Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Date: April 24, 2008

Re: NDA 22-184, Bimatoprost ophthalmic solution, 0.01%
Labeling Review

Thank you for forwarding this consult request, dated July 17, 2007, to DDMAC. We have reviewed the draft package insert sent to DDMAC from DAIOP via e-mail on April 24, 2008, and the draft bottle and carton labeling submitted by the applicant dated July 2, 2007, and have the following comments:

PACKAGE INSERT

ADVERSE REACTIONS

- We note inconsistency between the incidences of conjunctival hyperemia and ocular pruritis reported in HIGHLIGHTS versus the incidences reported in the FULL PRESCRIBING INFORMATION (FPL). Specifically, the incidence of these most common adverse reactions is reported as (b)(4) in HIGHLIGHTS. However, the FPL reports the incidence of conjunctival hyperemia as “range 25%-45%” and the incidence of ocular pruritis as “>10%.” Promotionally, Allergan could cherry-pick which incidences to use to promote this drug in its best light, potentially making it look safer than was demonstrated in clinical trials. In the case of conjunctival hyperemia, use of the incidence reported in HIGHLIGHTS would under-represent the actual incidence of this adverse reaction in the clinical trials, whereas the FPL under-represents the incidence of ocular pruritis. We recommend that the incidences of the most common adverse reactions be reported consistently between HIGHLIGHTS and FPL, and that the incidences most accurately represent the actual incidences in the clinical trials.

DOSAGE AND ADMINISTRATION

- “Reduction of the intraocular pressure starts approximately 4 hours after the first administration with maximum effect reached within approximately 8 to 12 hours.”

This statement implies that the full 7-8 mmHg drop in IOP will be realized within 8 to 12 hours of the first drop of bimatoprost. Is this accurate?

CLINICAL PHARMACOLOGY

- **12.1 Mechanism of Action**

“Elevated IOP presents a major risk factor for glaucomatous field loss. The higher the level of IOP, the greater the likelihood of optic nerve damage and visual field loss.”

These “disease awareness” claims address the disease, glaucoma, rather than the drug, bimatoprost. Their presence in the bimatoprost label strongly implies that bimatoprost will reduce ocular damage and visual field loss caused by elevated IOP, and they would allow Allergan to promote the drug as having these effects. However, the clinical studies section of the draft label only presents data for reduction of IOP. It does not report data showing a beneficial effect on optic nerve damage or visual field loss. Is there substantial evidence that demonstrates that bimatoprost ophthalmic solution reduces ocular damage and visual field loss caused by elevated IOP, or, has the FDA concluded that any drug that lowers IOP will have these effects and therefore their labels can say so? If not, then we recommend that these claims be deleted.

CLINICAL STUDIES

- The draft label states that the IOP-lowering effect of Lumigan 0.01% once daily in the evening was “up to 7 mmHg.” It is unclear from this statement what the typical reduction seen in clinical trials was, but it gives the impression that a 7 mmHg reduction is a typical response. Is this accurate? If not, can the efficacy be reported to more accurately represent the typical efficacy in clinical trials?

BOTTLE and CARTON LABELING

- We note that dosing appears on the bottle and carton labels. Is this standard for the ophthalmic drugs? DDMAC views dosing as a representation about the use of the drug which necessitates presentation of risk information and full indication. If this has been allowed for other ophthalmic drugs, including Lumigan 0.03%, then we do not object. If not, we recommend that the dosing be deleted from the bottle and carton labeling.

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/s/

Lynn Panholzer
4/24/2008 03:14:54 PM
DDMAC REVIEWER

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: February 13, 2008

TO: Michael Puglisi, Regulatory Project Manager
Jennifer Harris, M.D., Clinical Reviewer
Division of Division Of Anti-Infective And Ophthalmology Products, HFD-550

THROUGH: Tejashri Purohit-Sheth, M.D.
Acting Branch Chief
Good Clinical Practice Branch 2, HFD-47
Division of Scientific Investigations

FROM: Dianne D. Tesch, Consumer Safety Officer

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-184

NME: No

APPLICANT: Allergan

DRUG: bimatoprost 0.01%

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: (b) (4) or prophylaxis of primary open angle glaucoma

CONSULTATION REQUEST DATE: July 24, 2007

DIVISION ACTION GOAL DATE: February 1, 2008

PDUFA DATE: May 3, 2008

I. BACKGROUND:

Glaucoma refers to a group of eye diseases characterized by an increase in the intraocular pressure (IOP) which causes pathological changes in the optic disc and defects in the field of vision. It affects one person in 200 over the age of 40. It is the leading cause of irreversible blindness in the United States. Glaucoma causes a progressive loss of retinal nerve fibers, resulting in vision loss. The various types of glaucoma are distinguished by the causative physiological defect.

In the normal eye, active secretion accounts for approximately 80% of the aqueous production. It is secreted by the non-pigmented ciliary epithelium. The remaining 20% of the aqueous production is passive via processes such as ultra filtration and diffusion. These processes are dependent on the level of blood pressure in the ciliary capillaries, the plasma oncotic pressure and the level of intraocular pressure.

Aqueous outflow is primarily through the trabecular meshwork, a series of channels in the uveal and corneoscleral layers of the epithelium.

Normal intra-ocular pressure varies between 10 and 21 mm Hg. The rate of aqueous secretion, resistance in the outflow channels, and the level of episcleral venous pressure determine intra-ocular pressure. Intra-ocular pressure follows a diurnal pattern. It is higher in the morning than in the evening. Individuals with glaucoma have a greater diurnal variation than normal individuals. Blood pressure, pulse and respiration also affect IOP.

Primary open angle glaucoma (POAG) is a slowly progressive disease. It is usually bilateral, but progression can be asymmetric. The symptoms are insidious, and there is usually some degree of visual field loss before a diagnosis is made. In POAG, the primary abnormality is over-production of aqueous.

The diagnosis of glaucoma is made based on repeated elevations of IOP >21 mm Hg, changes in the appearance of the optic disc, and characteristic changes in the visual field. Generally, POAG is asymptomatic. Most diagnoses are made at the time of a routine ophthalmologic exam.

Treatment of glaucoma consists of both medical and surgical interventions. The treatments are designed to decrease the intra-ocular pressure by decreasing aqueous secretion, or increasing aqueous outflow. Bimatoprost is a synthetic prostamide analog with ocular hypotensive activity. Bimatoprost is believed to lower intraocular pressure (IOP) in humans by increasing outflow of aqueous humor through both the trabecular meshwork and uveoscleral routes.

Preclinical studies have demonstrated that changing the original formulation of LUMIGAN® by increasing the concentration of benzalkonium chloride (BAK) from 50 parts per million (ppm) to 200 ppm will increase the amount of bimatoprost (the active ingredient) reaching the target sites in the eye. The increase in ocular exposure of the active ingredient will allow the concentration of bimatoprost to be reduced in an effort to maintain efficacy with the aim of improving the safety profile in clinical use.

This inspection audited one study, Study #192024-031-00. The study took place over eight visits: prestudy (day -50 to -2), baseline (day 0), week 2, week 6, and months 3, 6, 9, and 12. All visits except the prestudy and month 9 visits will consist of 3 diurnal time points [hour 0 (07:00 – 09:00), hour 4, and hour 8]. The prestudy visit had one time point (at any time during the day) and the month 9 visit had hour 0 and hour 4 time points only.

IOP was the key efficacy variable for this protocol. The IOP change from baseline was the primary endpoint for efficacy assessment. The average of the IOP changes from both eyes were used in the analysis. The primary analysis was performed using data collected up to and including the month 3 visit although the study had a masked, 9 month extension for a total of 12 months of treatment.

II. RESULTS (by protocol/site):

Name of CI and site #	City, State	Protocol #	Insp. Date	EIR Received Date	Final Classification
Monte S. Dirks, M.D. site 2078	Rapid City, South Dakota	192024- 031-00	10/15/07- 10-18-07	12/28/07	NAI
Jason Bacharach, M.D.	Petaluma, California	192024- 031-00	11/19/07- 12/14/07	1/14/08	VAI

Key to Classifications

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.

VAI-Response Requested = Deviation(s) form regulations. See specific comments below for data acceptability

OAI = Significant deviations for regulations. Data unreliable.

Protocol # 192024-031-00

1. Monte S. Dirks, M.D., Rapid City, South Dakota:

- a. Thirty-two subjects were screened, thirty subjects were randomized, and twenty-seven subjects completed the study. One subject withdrew after experiencing an allergic reaction, and one withdrew after experiencing hyperemia. The third subject withdrew for non-study related reasons. All thirty-two records were reviewed as part of the inspection.
- b. There were no limitations to the inspection.
- c. There were no regulatory deficiencies at this site.
- d. The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

2. Jason Bacharach, M.D., Petaluma, California:

- a. Forty-two subjects were screened, thirty-nine subjects were randomized, and thirty-six subjects completed the study. Two subjects withdrew due to red eyes. The third subject was discontinued due to high intraocular pressure. Thirty-nine of the records were reviewed for primary efficacy endpoint, and twenty-five records were reviewed in depth.
- b. There were no limitations to the inspection.
- c. The Clinical Investigator failed to report nine occurrences in five subjects of subject-reported redness of the eye. The CI also failed to report an occurrence of subject-reported periorbital darkening as an adverse event for two subjects, and self-reported eyelash growth for two subjects. The subjects with under-reporting of adverse events on one or more occasions were 30008, 300012, 300013, 300016, and 300020. Specifically,

Subject 30008 completed a study questionnaire on 2/1/07, Month 12, documenting that she had experienced “redness of one or both eyes” since she had started the investigational drug. This was not reported as an adverse event. Similar events were reported by subjects 30012, 30013, and 30020, and were not reported to the sponsor.

Subjects 30016 reported peri-orbital darkening on 7/24/06 and 2/9/07. Neither occurrence was reported to the sponsor. The same subject reported eyelash growth which was not reported to the sponsor.

Subject 30012 reported eyelash growth on two occasions. Neither was reported to the sponsor as an adverse event.

- d. Adverse event data for the five subjects noted was incomplete and inadequate. Adverse event reporting from this site is considered unreliable.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

This inspection audited two domestic sites, those of Dr. Dirks and Dr. Bacharach. The data from Dr. Dirks’ site are considered acceptable in support of the respective indication. However, the safety data at Dr. Bacharach’s site are considered incomplete. At Dr. Bacharach’s site, the major finding was related to under-reporting of adverse events in 5 subjects as outlined above. Therefore, the adverse event data from Dr. Bacharach’s site are considered unreliable. DSI recommends that the division take this into account

when evaluating the safety data from the affected subjects. The data in support of efficacy do, however, appear acceptable.

Dr. Bacharach's site should be chosen for inspection for the next available application to determine if he has made changes to his practice to reflect the recommendations made by the FDA field investigator.

{ See appended electronic signature page }

Dianne D. Tesch
Consumer Safety Officer

CONCURRENCE:

Supervisory comments

{ See appended electronic signature page }

Tejashri Purohit-Sheth, M.D.
Acting Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

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/s/

Dianne Tesch
2/15/2008 08:43:21 AM
CSO

Tejashri Purohit-Sheth
2/15/2008 09:13:25 AM
MEDICAL OFFICER

DSI CONSULT: Request for Clinical Inspections

Date: July 24, 2007

To: Mathew Thomas, HFD-45
Leslie K. Ball, M.D., Branch Chief, GCP2, HFD-47

Through: Gary Della'Zanna, D.O., Director
Division of Scientific Investigations, HFD-45

From: Michael Puglisi, Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products, HFD-520

Subject: **Request for Clinical Site Inspections**
Application: NDA 22-184
Sponsor: Allergan, Inc.
Drug: bimatoprost ophthalmic solution, 0.01%

Protocol/Site Identification:

Routine inspections of the clinical sites involved in this NDA are requested.

This NDA provides data for the following: approval of a lower strength formulation of the marketed product Lumigan (bimatoprost ophth.solution, 0.03% - NDA 21-275). The indication is the same as Lumigan - reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

This drug is not a New Molecular Entity (NME)

Site # (Name,Address, Phone number)	Protocol #	Number of Subjects	Indication
DSI Choice	192024-031		Reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension

Domestic Inspections:

We have requested inspections because (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify): Routine Inspections

International Inspections:

We have requested inspections because (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify):

Goal Date for Completion:

We request that the inspections be performed and the Inspection Summary Results be provided by (inspection summary goal date) **February 1, 2008**. We intend to issue an action letter on this application by (division action goal date) **March 1, 2008**. The PDUFA due date for this application is **May 3, 2008**.

Other Information:

The clinical portion of this application has been reviewed and no issues have been identified to date to suggest a problem with data integrity.

This NDA is an entirely electronic submission (Gateway submission). It can be found in the EDR.
There are no jackets to distribute.

Should you require any additional information, please contact Michael Puglisi, Project Manager at Ph: 301-796-0791

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

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/s/

Michael Puglisi
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