CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-369

OTHER REVIEW(S)

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Memorandum

*****Pre-Decisional Agency Information *****

Date: November 15, 2008

To: Mike Puglisi, Project Manager
Division of Anti-Infective and Ophthalmology Products

From: Beth Carr, Pharm.D.
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: Latisse (bimatoprost ophthalmic solution) 0.03%
NDA: 22-369

DDMAC has reviewed the proposed product labeling, including the package insert (PI), patient information sheet, applicator blister pack, applicator box, carton, tray, container labeling, and the business reply card for Latisse submitted by the applicant on June 26, 2008; and we offer the following comments. We have also taken into consideration the labeling for Lumigan (bimatoprost ophthalmic solution) 0.03%. Please feel free to contact me with any questions or clarifications.

Package Insert

General Comment

- We note that there are three tables (one adverse event table and two clinical trial efficacy data tables) in the draft label that are not numbered. We recommend that the tables be numbered.

HIGHLIGHTS OF PRESCRIBING INFORMATION

In addition to the comments for this section, please see the comments in the Full Prescribing Information section. Comments in the Full Prescribing Information section that apply to the highlights section will have the following disclaimer:

"Please apply these comments to the HIGHLIGHTS section."

9 Page(s) Withheld

X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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/s/

Beth M Carr
12/5/2008 11:04:54 AM
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: November 28, 2008

TO: Michael Puglisi, Regulatory Project Manager
Rhea Lloyd, Medical Officer
Division of Anti-Infective and Ophthalmic Products

FROM: Jean Mulinde
Good Clinical Practice Branch 2
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth
Branch Chief
Good Clinical Practice Branch 2
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

NDA or BLA: 22-369

APPLICANT: Allergan, Inc.

DRUG: Latisse (bimatoprost solution) 0.03%

NME: No

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: To improve the prominence of natural eyelashes as measured by increases in growth (length), fullness (thickness) and darkness (intensity).

CONSULTATION REQUEST DATE: July 28, 2008

DIVISION ACTION GOAL DATE: December 27, 2008

PDUFA DATE: December 27, 2008

I. BACKGROUND:

Bimatoprost is a synthetic prostamide, structurally related to prostaglandin F2a (PGF2a), which exerts its action by selectively mimicking the effects of naturally occurring prostaglandins. Increased eyelash growth has been reported as an adverse event following the use of all topical ophthalmic prostamides (latanoprost, travoprost, and bimatoprost).

Bimatoprost ophthalmic solution 0.03% (LUMIGAN®) was approved in the United States in 2001 as an ocular hypotensive agent for the treatment of ocular hypertension and primary open-angle glaucoma. During the clinical development program for glaucoma, eyelash growth was spontaneously reported as an adverse event in patients receiving bimatoprost 0.03% as a topical ophthalmic solution. In the 2 active-control phase 3 pivotal trials of similar design that evaluated bimatoprost in patients with glaucoma, "growth of eyelashes" was reported as an adverse event statistically significantly more frequently in the bimatoprost-treated groups compared with the active comparator (timolol) group. As a result of this clinical experience, additional investigator initiated research reported in the literature, and supportive postmarketing surveillance data, Allergan initiated a clinical program comprised of 2 clinical studies: one to test the reliability and reproducibility of a scale evaluating eyelash prominence, and one to assess the safety and efficacy of bimatoprost solution 0.03% applied topically to the upper eyelid margins for the enhancement of eyelash growth (Protocol #192024-032).

In NDA 22-369, the Applicant (Allergan, Inc.) has requested that bimatoprost ophthalmic solution 0.03% be approved "to improve the prominence of natural eyelashes as measured by increases in growth (length), fullness (thickness) and darkness (intensity)." To support approval, the Applicant has provided data from one pivotal clinical trial:

Protocol #192024-032: A Multicenter, Double-Masked, Randomized, Parallel Study Assessing the Safety and Efficacy of Once-Daily Application of Bimatoprost Solution Compared to Vehicle in Increasing Overall Eyelash Prominence

The primary efficacy endpoint of this study was the subject's overall eyelash prominence at Month 4 as measured by the Global Eyelash Assessment (GEA) score. [The GEA is a 4-point scale that is scored 1 through 4 based on comparison of subjects eyelash prominence to a photoguide provided with the protocol.] Secondary supportive endpoints included:

- The subject's upper eyelash length at Month 4 as measured by digital image analysis
- The subject's upper eyelash thickness at Month 4 as measured by digital image analysis
- The subject's upper eyelash darkness (intensity) at Month 4 as measured by digital image analysis
- Patient satisfaction with overall eyelash prominence as measured by the patient reported outcomes (PRO) questionnaires

Safety measurements included assessment of adverse events, vital signs, biomicroscopy, intraocular pressure, ophthalmoscopy (dilated), and visual acuity.

The sites requested for inspection are the domestic centers that were among the highest enrollers in the study.

II. RESULTS (by Site):

Name of CI/Sponsor Location	Protocol # Site # # of Subjects	Inspection Date	Final Classification
William P. Werschler, M.D. Premier Clinical Research 104 W. 5th Avenue, Suite 320 Spokane, WA 99204	Protocol #192024-032-00 Site #10014 18 Subjects	08/25/2008-08/29/2008	NAI
Stacy Smith, M.D. Therapeutics Clinical Research 9025 Balboa Avenue, Suite 105 San Diego, CA 92123	Protocol #192024-032-00 Site #10012 33 Subjects	09/17/2008-09/22/2008	NAI
Steven Yoelin, M.D. 355 Placentia, Suite 203 Newport Beach, CA 92663	Protocol #192024-032-00 Site #10011 24 Subjects	09/24/2008-10/03/2008	Pending (Interim Classification VAI)

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations.
Pending = Preliminary classification. Official letter has not issued.

1. **William P. Werschler, M.D.**
   Premier Clinical Research
   104 W. 5th Avenue, Suite 320
   Spokane, WA 99204
   Site #10014

   a. **What was inspected:**
   This inspection was conducted in accordance with Compliance Program 7348.811 between 08/25/2008-08/29/2008. A total of 24 subjects were screened, 18 subjects were enrolled and 15 completed the study. Records for 18 enrolled subjects were reviewed to verify primary efficacy data, adverse event data, and informed consent. Individual Patient Reported Outcomes were verified for 4 enrolled subjects. In addition, drug accountability records, IRB approval and dates, and sponsor monitoring records were reviewed. There were no limitations to the inspection.

b. **General observations/commentary**:
The inspection of Dr. Werschler's site did not reveal regulatory violations. A Form FDA 483, Inspectional Observations, was not issued.

c. **Assessment of data integrity**:
Based on the provided Establishment Inspection Report (EIR) for this site and Dr. Werschler's comments to investigator observations made during the inspection and documented in the EIR, data derived from Dr. Werschler's site are considered acceptable.

2. **Stacy R. Smith, M.D.**
9025 Balboa Ave, Ste 105
San Diego, CA 921123
Site #10012

a. **What was inspected**:
This inspection was conducted in accordance with Compliance Program 7348.811 between 09/17/2008-09/22/2008. A total of 43 subjects were screened, 33 subjects were enrolled and 32 completed the study. Records for 17 enrolled subjects were reviewed in depth for assessment of primary efficacy endpoints, adverse event reporting, intraocular pressure measurements, protocol deviations, subject randomization, and concomitant medication use. Complete review of the Patient Reported Outcome (PRO) log for 1 subject was completed and review of PRO logs from 2 visits per subject was completed for the balance of enrolled subjects. All enrolled subject records were reviewed for informed consent documentation. In addition, drug accountability records, IRB approval and dates, and sponsor monitoring records were reviewed. There were no limitations to the inspection.

b. **General observations/commentary**:
The inspection of Dr. Smith's site did not reveal regulatory violations. A Form FDA 483, Inspectional Observations, was not issued.

c. **Assessment of data integrity:**
Based on the provided Establishment Inspection Report (EIR) for this site and Dr. Smith's comments to investigator observations made during the inspection and documented in the EIR, data derived from Dr. Smith's site are considered acceptable.

3. **Steven G. Yoelin, M.D.**
355 Placentia Ave., Ste. 203
Newport Beach, CA 92663
Site #10011

a. **What was inspected**:

This inspection was conducted in accordance with Compliance Program 7348.811 between 09/24/2008-10/03/2008. A total of 42 subjects were screened, 24 subjects were enrolled and 23 completed the study. Records for 14 enrolled subjects were reviewed in depth for assessment of primary efficacy endpoints, adverse event reporting, intraocular pressure measurements, subject randomization, and concomitant medication use. Complete review of the Patient Reported Outcome (PRO) log for 1 subject was completed and review of random portions of PRO logs for other enrolled subjects was completed. All enrolled subject records were reviewed for informed consent documentation. In addition, drug accountability records, IRB approval and dates, and sponsor monitoring records were reviewed. There were no limitations to the inspection.

b. **General observations/commentary:**
The inspection of Dr. Yoelin's site revealed regulatory violations. A Form FDA 483, Inspectional Observations, was issued to this investigator, mainly for:

i. Failure to conduct the study according to the signed investigator statement and the investigational plan [21 CFR 312.60]. Specifically, for:

- Failing to utilize updated source documents specifically provided by the Sponsor that had been revised to include sections for recordation of vitreous exams. This resulted in suboptimal documentation in source records for completion of these examinations and specific exam findings.
- Failing to report intraocular pressure assessments that were not completed within the specified +/- 2 hour visit time frame (specified in newsletters to the sites) to the sponsor for 3 subjects.
- Failing to report all out-of-window visits to the sponsor as protocol deviations.

c. **Assessment of data integrity:**
Although a number of regulatory violations were noted, it is unlikely that they significantly affect overall data reliability from the site as subject data related to these observations appears to have been accurately captured in the NDA database. Based on the provided Establishment Inspection Report (EIR) for this site and Dr. Yoelin's written response to the Form FDA 483 observations, dated November 7, 2008, data derived from Dr. Yoelin's site are considered acceptable.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Three clinical investigator inspections have been completed for this NDA. Based on the results of these inspections, the study appears to have been conducted adequately and the data in support of the NDA appear reliable. No regulatory violations were noted for Dr. Werschler or Dr. Smith. Although regulatory violations were noted and Form FDA 483 was issued to Dr. Yoelin, the nature of the violations makes it unlikely that they significantly affect overall reliability of safety and efficacy data from this site.

{See appended electronic signature page}

Jean M. Mulinde, M.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

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

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/s/

Jean Mulinde
11/28/2008 10:47:51 AM
MEDICAL OFFICER

Tejashri Purohit-Sheth
11/28/2008 01:26:04 PM
MEDICAL OFFICER