CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21-275 / S-013

Trade Name: **Lumigan**

Generic Name: **Bimatoprost ophthalmic solution**

Sponsor: **Allergan**

Approval Date: **June 22, 2006**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-275 / S-013

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-275 / S-013

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-275/S-013

Allergan, Inc.
Attention: Lewis Gryziewicz
Senior Director, Regulatory Affairs
2525 Dupont Drive
P.O. Box 19534
Irvine, California 92623-9534

Dear Mr. Gryziewicz:

Please refer to your supplemental new drug application dated July 1, 2003, received July 2, 2003, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Lumigan (bimatoprost ophthalmic solution) 0.03%.

We acknowledge receipt of your submissions dated November 20, 2003, December 20, 2005, and March 9, May 23, and June 20, 2006.

Your submission of December 20, 2005, constituted a complete response to our November 12, 2003, action letter.

This supplemental new drug application provides for the use of Lumigan (bimatoprost ophthalmic solution) 0.03% for the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

Please submit the content of the labeling [21 CFR 314.50(1)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical to the enclosed draft labeling submitted June 20, 2006. Upon receipt and verification, we will transmit that version to the National Library of Medicine for posting on the DailyMed website.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for this application.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
WO 22, Room 4447
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Michael Puglisi, Project Manager, at (301) 796-0791.

Sincerely,

{See appended electronic signature page}

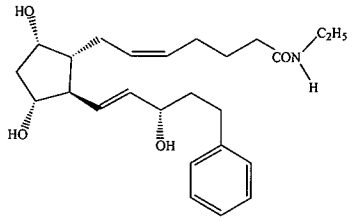
Janice M. Soreth, M.D.
Director
Division of Anti-Infective and
Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure

LUMIGAN®
(bimatoprost ophthalmic solution) 0.03%

DESCRIPTION

LUMIGAN® (bimatoprost ophthalmic solution) 0.03% is a synthetic prostamide analog with ocular hypotensive activity. Its chemical name is (Z)-7-[(1R,2R,3R,5S)-3,5-Dihydroxy-2-[1E,3S)-3-hydroxy-5-phenyl-1-pentenyl]cyclopentyl]-5-N-ethylheptenamide, and its molecular weight is 415.58. Its molecular formula is $C_{25}H_{37}NO_4$. Its chemical structure is:



Bimatoprost is a powder, which is very soluble in ethyl alcohol and methyl alcohol and slightly soluble in water. **LUMIGAN®** is a clear, isotonic, colorless, sterile ophthalmic solution with an osmolality of approximately 290 mOsmol/kg.

Contains: Active: bimatoprost 0.3 mg/mL; **Preservative:** Benzalkonium chloride 0.05 mg/mL; **Inactives:** Sodium chloride; sodium phosphate, dibasic; citric acid; and purified water. Sodium hydroxide and/or hydrochloric acid may be added to adjust pH. The pH during its shelf life ranges from 6.8-7.8.

CLINICAL PHARMACOLOGY

Mechanism of Action

Bimatoprost is a prostamide, a synthetic structural analog of prostaglandin with ocular hypotensive activity. It selectively mimics the effects of naturally occurring substances, prostamides. Bimatoprost is believed to lower intraocular pressure (IOP) in humans by increasing outflow of aqueous humor through both the trabecular meshwork and uveoscleral routes. 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.

Pharmacokinetics

Absorption:
After one drop of bimatoprost ophthalmic solution 0.03% was administered once daily to both eyes of 15 healthy subjects for two weeks, blood concentrations peaked within 10 minutes after dosing and were below the lower limit of detection (0.025 ng/mL) in most subjects within 1.5 hours after dosing. Mean C_{max} and $AUC_{0\text{-}24hr}$ values were similar on days 7 and 14 at approximately 0.08 ng/mL and 0.09 ng•hr/mL, respectively, indicating that steady state was reached during the first week of ocular dosing. There was no significant systemic drug accumulation over time.

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/s/

Janice Soreth
6/22/2006 03:50:49 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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LABELING

Distribution
Bimatoprost is moderately distributed into body tissues with a steady-state volume of distribution of 0.67 L/kg. In human blood, bimatoprost resides mainly in the plasma. Approximately 12% of bimatoprost remains unbound in human plasma.

Metabolism
Bimatoprost is the major circulating species in the blood once it reaches the systemic circulation following ocular dosing. Bimatoprost then undergoes oxidation, N-deethylation and glucuronidation to form a diverse variety of metabolites.

Elimination
Following an intravenous dose of radiolabeled bimatoprost (3.12 µg/kg) to six healthy subjects, the maximum blood concentration of unchanged drug was 12.2 ng/mL and decreased rapidly with an elimination half-life of approximately 45 minutes. The total blood clearance of bimatoprost was 1.5 L/hr/kg. Up to 67% of the administered dose was excreted in the urine while 25% of the dose was recovered in the feces.

Clinical Studies:
In clinical studies of patients with open angle glaucoma or ocular hypertension with a mean baseline IOP of 26 mmHg, the IOP-lowering effect of **LUMIGAN®** (bimatoprost ophthalmic solution) 0.03% once daily (in the evening) was 7-8 mmHg.

Results of dosing for up to five years with products in this drug class showed that the onset of noticeable increased iris pigmentation occurred within the first year of treatment for the majority of the patients who developed noticeable increased iris pigmentation. Patients continued to show signs of increasing iris pigmentation throughout the five years of the study. Observation of increased iris pigmentation did not affect the incidence, nature or severity of adverse events (other than increased iris pigmentation) recorded in the study. IOP reduction was similar regardless of the development of increased iris pigmentation during the study.

In patients with a history of liver disease or abnormal ALT, AST and/or bilirubin at baseline, **LUMIGAN®** had no adverse effect on liver function over 48 months.

INDICATIONS AND USAGE

LUMIGAN® (bimatoprost ophthalmic solution) 0.03% is indicated for the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension.

CONTRAINDICATIONS

LUMIGAN® (bimatoprost ophthalmic solution) 0.03% is contraindicated in patients with hypersensitivity to bimatoprost or any other ingredient in this product.

WARNINGS

LUMIGAN® (bimatoprost ophthalmic solution) 0.03% 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, and growth of eyelashes. Pigmentation is expected to increase as long as LUMIGAN is administered. After discontinuation of LUMIGAN 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 effects of increased pigmentation beyond 5 years are not known.

PRECAUTIONS

General: LUMIGAN (bimatoprost ophthalmic solution) 0.03% may gradually increase the pigmentation of the iris. The eye color change is due to increased melanin content in the stromal melanocytes of the iris rather than to an increase in the number of melanocytes. This change may not be noticeable for several months to years (see **WARNINGS**). 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. While treatment with LUMIGAN can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly.

During clinical trials, the increase in brown iris pigment has not been shown to progress further upon discontinuation of treatment, but the resultant color change may be permanent.

Eyelid skin darkening, which may be reversible upon discontinuation of the treatment has been reported in association with the use of **LUMIGAN®**.

LUMIGAN® 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.

LUMIGAN® (bimatoprost ophthalmic solution) 0.03% should be used with caution in patients with active intraocular inflammation (e.g., uveitis).

Macular edema, including cystoid macular edema, has been reported during treatment with bimatoprost ophthalmic solution. **LUMIGAN®** should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

LUMIGAN® has not been evaluated for the treatment of angle closure, inflammatory or neovascular glaucoma.

There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface (see **PRECAUTIONS**, Information for Patients).

Contact lenses should be removed prior to instillation of **LUMIGAN®** and may be reinserted 15 minutes following its administration (see **PRECAUTIONS**, Information for Patients).

Information for Patients: (see **WARNINGS** and **PRECAUTIONS**): 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.

Patients should also be informed of the possibility of eyelash and vellus hair changes in the treated eye during treatment with LUMIGAN. 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.

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye, surrounding structures, fingers, or any other surface in order to avoid contamination of the solution by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

Patients should also be advised that if they develop an intercurrent ocular condition (e.g., trauma or infection) or have ocular surgery, they should immediately seek their physician's advice concerning the continued use of the multidose container.

Patients should be advised that if they develop any ocular reactions, particularly conjunctivitis and eyelid reactions, they should immediately seek their physician's advice.

Patients should be advised that LUMIGAN® contains benzalkonium chloride, which may be absorbed by soft contact lenses. Contact lenses should be removed prior to instillation of LUMIGAN® and may be reinserted 15 minutes following its administration.

If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes between applications.

Carcinogenesis, Mutagenesis, Impairment of fertility: Bimatoprost was not carcinogenic in either mice or rats when administered by oral gavage at doses of up to 2 mg/kg/day and 1mg/kg/day respectively (approximately 192 times and 291 times the recommended human exposure based on blood AUC levels respectively) for 104 weeks

Bimatoprost was not mutagenic or clastogenic in the Ames test, in the mouse lymphoma test, or in the *in vivo* mouse micronucleus tests.

Bimatoprost did not impair fertility in male or female rats up to doses of 0.6 mg/kg/day (approximately 103 times the recommended human exposure based on blood AUC levels).

Pregnancy: Teratogenic effects: *Pregnancy Category C.* In embryo/fetal developmental studies in pregnant mice and rats, abortion was observed at oral doses of bimatoprost which achieved at least 33 or 97 times, respectively, the intended human exposure based on blood AUC levels.

At doses 41 times the intended human exposure based on blood AUC levels, the gestation length was reduced in the dams, the incidence of dead fetuses, late resorptions, peri- and postnatal pup mortality was increased, and pup body weights were reduced.

There are no adequate and well-controlled studies of **LUMIGAN®** administration in pregnant women. Because animal reproductive studies are not always predictive of human response, **LUMIGAN®** should be administered during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing mothers: It is not known whether **LUMIGAN®** is excreted in human milk, although in animal studies, bimatoprost has been shown to be excreted in breast milk. Because many drugs are excreted in human milk, caution should be exercised when **LUMIGAN®** is administered to a nursing woman.

Pediatric use: Safety and effectiveness in pediatric patients have not been established.

Geriatric Use: No overall clinical differences in safety or effectiveness have been observed between elderly and other adult patients.

ADVERSE REACTIONS

In clinical trials, the most frequent events associated with the use of **LUMIGAN®** (bimatoprost ophthalmic solution) 0.03% occurring in approximately 15% to 45% of patients, in descending order of incidence, included conjunctival hyperemia, growth of eyelashes, and ocular pruritus. Approximately 3% of patients discontinued therapy due to conjunctival hyperemia.

Ocular adverse events occurring in approximately 3 to 10% of patients, in descending order of incidence, included ocular dryness, visual disturbance, ocular burning, foreign body sensation, eye pain, pigmentation of the periocular skin, blepharitis, cataract, superficial punctate keratitis, eyelid erythema, ocular irritation, and eyelash darkening. The following ocular adverse events reported in approximately 1 to 3% of patients, in descending order of incidence, included: eye discharge, tearing, photophobia, allergic conjunctivitis, asthenopia, increases in iris pigmentation, and conjunctival edema. In less than 1% of patients, intraocular inflammation was reported as iritis.

Systemic adverse events reported in approximately 10% of patients were infections (primarily colds and upper respiratory tract infections). The following systemic adverse events reported in approximately 1 to 5% of patients, in descending order of incidence, included headaches, abnormal liver function tests, asthenia and hirsutism.

OVERDOSAGE

No information is available on overdosage in humans. If overdose with **LUMIGAN®** (bimatoprost ophthalmic solution) 0.03% occurs, treatment should be symptomatic.

In oral (by gavage) mouse and rat studies, doses up to 100 mg/kg/day did not produce any toxicity. This dose expressed as mg/m^2 is at least 70 times higher than the accidental dose of one bottle of LUMIGAN® for a 10 kg child.

DOSAGE AND ADMINISTRATION

The recommended dosage is one drop in the affected eye(s) once daily in the evening. The dosage of **LUMIGAN®** (bimatoprost ophthalmic solution) 0.03% should not exceed once daily since it has been shown that more frequent administration may decrease the intraocular pressure lowering effect.

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

LUMIGAN® may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

HOW SUPPLIED

LUMIGAN® (bimatoprost ophthalmic solution) 0.03% is supplied sterile in opaque white low density polyethylene ophthalmic dispenser bottles and tips with turquoise polystyrene caps in the following sizes:

2.5 mL fill in 5 mL container - NDC 0023-9187-03
5 mL fill in 10 mL container - NDC 0023-9187-05
7.5 mL fill in 10 mL container - NDC 0023-9187-07

Storage: LUMIGAN® should be stored in the original container at 2° to 25°C (36° to 77°F).

Rx only
Revised June 2006

Irvine, CA 92612

US Pat. No. 5,688,819 and 6,403,649.

9106X

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-275/S-013

Allergan, Inc.
Attention: Stephen Buxbaum
Director, Regulatory Affairs
2525 Dupont Drive
P.O. Box 19534
Irvine, CA 92623-9534

Dear Mr. Buxbaum:

Please refer to your supplemental new drug application dated July 1, 2003, received July 2, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for for Lumigan (bimatoprost ophthalmic solution) 0.03%.

We acknowledge receipt of your submissions dated July 9 and 17, 2003.

This supplemental new drug application proposes the use of Lumigan (bimatoprost ophthalmic solution) 0.03% for first-line therapy for the reduction of intraocular pressure in patients with open angle glaucoma or ocular hypertension.

We completed our review and find the information presented is inadequate, and the supplemental application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies are summarized as follows:

1. Potential safety issues related to increasing ocular pigmentation and growth of ocular structures have not been fully evaluated. Data demonstrating a plateau in these ocular changes and data demonstrating safety at the time of the plateau should be provided prior to changing the indication to first-line therapy.

2. Patent information has not been included in the application. This information should be provided.

3. Financial certification or disclosure has not been included in the application. This information should be provided.

4. Debarment certification has not been included in the application. This certification should be provided.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. If you do not follow one of these options, we will consider your lack of response a request to

withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with this division to discuss what steps need to be taken before the application may be approved.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change before approval of this supplemental application.

If you have any questions, call Michael Puglisi, Regulatory Project Manager, at (301) 827-2090.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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

/s/

Wiley Chambers
11/12/03 01:33:39 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-275 / S-013

MEDICAL REVIEW(S)

CLINICAL REVIEW of NDA 21-275/SE1-013

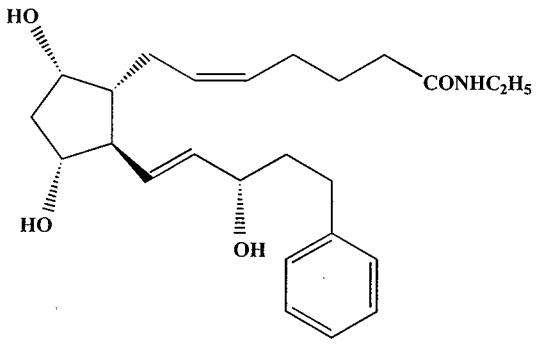
Efficacy Supplement

Submitted:	July 1, 2003
Received:	July 2, 2003
Review completed:	October 30, 2003
Reviewer:	William M. Boyd, M.D.

Tradename: Lumigan 0.03%

Generic Name: bimatoprost ophthalmic solution

Chemical Name:



Bimatoprost $C_{25}H_{37}NO_4$

(Z)-7-[(1R,2R,3R,5S)-3,5-Dihydroxy-2-[(1E,3S)-3-hydroxy-5-phenyl-1-pentenyl]cyclopentyl]-5-N-ethylheptenamide

Sponsor: Allergan
2525 Dupont Drive
P.O. Box 19534
Irvine, California 92623-9534

Pharmacologic Category: synthetic analogue of prostaglandin $F_{2\alpha}$ (PG $F_{2\alpha}$)

Proposed Indication: Reduction of elevated intraocular pressure in patients with glaucoma or ocular hypertension

Reviewer's Comments:

The italicized text within this review is intended to represent the comments and conclusions of this reviewer.

Table of Contents

Executive Summary

I. Recommendations

A. Recommendation on Approvability

Supplemental NDA 21-275/SE1-013 is not recommended for approval for the reduction of elevated intraocular pressure in patients with glaucoma or ocular hypertension.

The potential safety issues related to increasing ocular pigmentation have not been fully evaluated.

[ ]

[ ]

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

Bimatoprost should remain a "second line" therapy for lowering intraocular pressure in patients with glaucoma or ocular hypertension who are intolerant of other IOP-lowering medications or insufficiently responsive to another IOP-lowering medication.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Bimatoprost was approved on March 16, 2001, for lowering intraocular pressure in patients with glaucoma or ocular hypertension who are intolerant of other IOP-lowering medications or insufficiently responsive to another IOP-lowering medication. This designation as a "second line" therapy was based in the potential risks associated with uncontrolled increases in pigmentation and the potential growth of other structures within the eye.

In response to the Agency's request for commitment dated February 28, 2001, Allergan committed to perform long term post-marketing studies to further evaluate the potential pigmentary safety issues.

Allergan submitted this efficacy supplement dated July 31, 2003, to effect a change in the indication for bimatoprost to allow its use as a "first line" therapy for the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension.

B. Efficacy

The efficacy of bimatoprost in reducing intraocular pressure was adequately evaluated in the original NDA submission.

C. Safety

The potential safety issues related to increasing ocular pigmentation and growth of ocular structures have not been fully evaluated.

The increase in eyelash growth continues through the 36-month extension although it decreases in frequency with time.

Conjunctival hyperemia remains the most frequently noted adverse event (13%) in the 36-month extension.

D. Dosing

No change to the current dosing regimen is proposed in this submission.

E. Special Populations

There are no known differences with respect to age, gender, race, or hepatic impairment.

- A study to evaluate pigmentation in the trabecular meshwork after patients have been treated with bimatoprost ophthalmic solution 0.03% for over two years.

Allergan submitted this efficacy supplement dated July 31, 2003, to effect a change in the indication for bimatoprost to allow its use as a "first line" therapy for the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension.

D. Other Relevant Information N/A

E. Important Issues with Pharmacologically Related Agents

The safety and efficacy effects seen with this product appear to be class effects.

Xalatan (latanoprost ophthalmic solution) 0.005% was the first prostaglandin derived product approved for the reduction of elevated intraocular pressure. It was approved as a "second line" therapy because of the unknown long term effects related to the potential risks associated with uncontrolled increases in pigmentation and the potential growth of other structures within the eye.

In December 2002, a Xalatan NDA supplement was approved granting a "first line" indication for the reduction of elevated intraocular pressure in patients with glaucoma or ocular hypertension. The iris pigmentary effect had been studied for at least five years, and while it continued to progress, it did not appear to have serious consequences within that period of time for this particular product (five years was considered a considerable period of time in the expected lifespan of many individuals with glaucoma).

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

All relevant issues have been discussed in pervious reviews for this drug product.

III. Human Pharmacokinetics and Pharmacodynamics

All relevant issues have been discussed in previous reviews for this drug product.

IV. Description of Clinical Data and Sources

A. Overall Data

The overall data reviewed consisted of clinical study reports, clinical protocols, and literature reports.

B. Tables Listing the Clinical Trials

Table 1 – Clinical Trials

Protocol Number	192024-014		192024-029
Study Design	Multicenter, Double-Masked, Randomized, Parallel, (Extension)		Masked Histological Examination (Proposed)
Treatment Duration	36 months		2 year (proposed)
Treatment Groups	Bimatoprost vs. Timolol		Bimatoprost vs. Other topical Ophthalmic IOP-lowering Drugs
No. Sites	23 (24 months) 15 (36 months)		20
No. Subjects	379 enrolled subjects 284 completed 24 months 183 completed 36 months		20 specimens (10 per group)
Status	Completed		Proposed

Reviewer's Comments:

Study 192024-014 is submitted as two separate reports with 24-month and 36-month safety and efficacy data. This extension study followed subjects from sites utilized in the original Phase 3, 12-month comparisons of bimatoprost versus timolol. The 36-month extension report served as the basis for the decision-making process regarding the approvability for this supplement.

Study 192024-029 was not utilized in the decision-making process regarding the approvability for this supplement. There is no reviewable data submitted.

C. Postmarketing Experience

The product has been marketed in the United States for approximately two years.

D. Literature Review

There was no significant new information found in the published literature.

V. Clinical Review Methods

A. How the Review was Conducted

All submitted clinical study reports, clinical protocols, and literature reports were reviewed. A CD-ROM with iris color photographs for Study 192024-014 was reviewed.

B. Overview of Materials Consulted in Review

The majority of the application was submitted in paper format. Proposed draft labeling, Sections 16.3 and 16.4 (Case Report Forms and Individual Patient Data Listings), and iris color photographs for Study 192024-014 were provided electronically.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

Photographic data was reviewed and compared to the submitted data. The data was reviewed for consistency with other applications in this class.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

The trials were conducted in accordance with accepted ethical standards.

E. Evaluation of Financial Disclosure

Study 192024-014 is an extension study which followed subjects from sites utilized in the original Phase 3, 12-month comparisons of bimatoprost versus timolol. The original NDA submission identifies only a single investigator, [redacted] M.D., with a financial interest in the drug product that is the subject of this supplemental application.

If this Investigator is excluded, there is no change in the results of Study 192024-014

VI. Integrated Review of Efficacy

Brief Statement of Conclusions

The efficacy of the drug product was well established during the original NDA approval. No information has been submitted which would alter those conclusions.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

The potential safety issues related to increasing ocular pigmentation have not been fully evaluated.

Bimatoprost should remain a "second line" therapy for lowering intraocular pressure in patients with glaucoma or ocular hypertension who are intolerant of other IOP-lowering medications or insufficiently responsive to another IOP-lowering medication.

B. Description of Patient Exposure

Study 192024-014 contains 24-month and 36-month safety data. This extension study followed subjects from sites utilized in the original Phase 3, 12-month comparisons of bimatoprost versus timolol.

C. Methods and Specific Findings of Safety Review

All submitted clinical study reports, clinical protocols, and literature reports were reviewed. A CD-ROM with iris color photographs for Study 192024-014 was reviewed.

Individual Study Review

Study 192024-014

Study 192024-014 is submitted as two separate reports with 24-month and 36-month safety and efficacy data. This extension study followed subjects from sites utilized in the original Phase 3, 12-month comparisons of bimatoprost versus timolol.

Reviewers' Comments:

Both study reports have been reviewed. The 24-month extension report is inadequate to serve as the basis for approvability of this supplement. No photographs were submitted for the 101 subjects who completed the 24-month extension but did not enroll in the 36-month extension.

Because the 36-month extension report provides the most information regarding the potential safety issues related to increasing ocular pigmentation with bimatoprost, this **Individual Study Review** *will focus on the 36-month extension.*

Title: A Multicenter, Double-masked, Randomized, Parallel, Extension Study Evaluating the Safety and Efficacy of Bimatoprost 0.03% Ophthalmic Solution, Compared with Timolol 0.5% Ophthalmic Solution, in Patients with Glaucoma or Occur Hypertension

Objective: The overall objective of the 192024-014 study is to evaluate the long term safety and efficacy of bimatoprost 0.03% compared with timolol 0.5% in patients at selected sites who had completed the Month 12 visit in either of the Phase 3 studies (-008 and -009).

Study Design:

This was a multicenter, double-masked, randomized, active-controlled, parallel group study with 4 scheduled visits during the post-24 to month 36 period (months 27, 30, 33, and 36). Approximately 1200 patients were enrolled in the -008 and -009 studies at 61 sites. These patients had been diagnosed with ocular hypertension, chronic open-angle glaucoma, chronic angle-closure glaucoma with a patent iridotomy, pseudoexfoliative glaucoma, or pigmentary glaucoma. The extension study protocol allowed for up to 600 patients to enroll. A total of 379 patients participated at 23 sites in the month 12 to 24 period of the extension study. A total of 15 of the 23 sites participated in this post-month 24 to month 36 period of the extension study. Of the 284 patients who completed the 24 month visit, 183 patients enrolled into this post-month 24 to month 36 period of the extension study, based on the site's willingness to participate in the extension as well as the patient's eligibility and willingness to continue.

Patients were initially randomized in the -008 or -009 studies to bimatoprost 0.03% QD, bimatoprost 0.03% BID, or timolol 0.5% BID. This randomization scheme was maintained through the month 24 visit of the extension study. At the month 24 visit, patients in the bimatoprost BID group were switched, in a masked manner, to bimatoprost QD therapy (hereafter referred to as the BID/QD group). Patients in the bimatoprost QD and timolol groups remained on their same therapies. Investigators and patients continued to be masked to study treatment for the duration of this study.

Inclusion Criteria:

The following were key requirements for patient entry into this post-Month 24 to 36 period of the extension study:

- Patient completed the month 24 visit
- Informed consent was obtained for this period of participation at month 24
- Ability to follow study instructions and likely to complete all required visit; willingness to continue masked therapy
- Ability to fast (i.e., not have ingested any foods or liquids, other than water) for 8 to
- 10 hours prior to blood sample collection on the morning of the month 36 visit.

Exclusion Criteria:

The following were key criteria for patient exclusion from participating in this period of the extension study:

- Uncontrolled systemic disease (e.g., hypertension, diabetes)
- Females who were pregnant, nursing, or planning a pregnancy, or females of childbearing potential who were not using a reliable means of contraception. A female was considered of childbearing potential unless she was post-menopausal or without a uterus and/or both ovaries. Females with a bilateral tubal ligation were eligible for enrollment
- Clinically relevant low or high pulse rate or blood pressure for age or contraindications to beta-blocker therapy such as chronic obstructive pulmonary disease, bronchial asthma, heart block more severe than first degree, uncontrolled congestive heart failure
- Corneal abnormalities that could have precluded accurate IOP readings with an applanation tonometer
- Any other active ocular disease other than glaucoma or ocular hypertension (e.g., uveitis, ocular infections, or severe dry eye); however, patients with chronic mild blepharitis, cataract, age-related macular degeneration, or a background diabetic retinopathy could have been enrolled at the discretion of the investigator
- Required chronic use of other ocular medications during the study other than the study medications. Intermittent use of artificial tear products or topical decongestant antihistamine was allowed. Use of these within 24 hours of a scheduled visit was prohibited
- Functionally significant visual field loss or evidence of progressive visual field loss within the last year
- Contraindications to pupil dilation
- A condition or situation which, in investigator's opinion may have put the patient at significant risk, may have confounded the study results, or may have interfered significantly with the patient's participation in the study.

Subject Demographics and Disposition for 36-month Extension:

Table 2 – Demographics for ITT Population

Variable		BIM QD (n=90)	BIM BID/QD (n=50)	TIM (n-43)	Total (n=183)	p-value
Age (years)	N	90	50	43	183	0.807
	Mean	61.3	60.0	61.2	60.9	
	SD	11.99	12.02	9.84	11.48	
	Median	63.5	61.5	61.0	62.0	
	Min	34.0	33.0	38.0	33.0	
	Max	91.0	82.0	79.0	91.0	
Sex	N	90	50	43	183	0.981
	Male	40 (44%)	23 (46%)	19 (44%)	82 (45%)	
	Female	50 (56%)	27 (54%)	24 (56%)	101 (55%)	
Race	N	90	50	43	183	0.627
	Black	14 (16%)	5 (10%)	7 (16%)	26 (14%)	
	Non-black	76 (84%)	45 (90%)	36 (84%)	157 (86%)	
Iris Color	N	90	50	43	183	0.294
	Light	48 (53%)	29 (58%)	18 (42%)	95 (52%)	
	Dark	42 (46%)	21 (42%)	25 (58%)	88 (48%)	

Reviewers Comments:

There are no significant differences in any of the study demographics.

Of the 284 patients who completed month 24 at 23 sites, a total of 183 patients at 15 sites were eligible and consented to enroll into this extension period (post month 24 to month 36) with 90 patients in the bimatoprost QD group, 50 patients in the bimatoprost BID/QD group, and 43 patients in the timolol group.

Overall, in the ITT population, 88.5% (162/183) of patients completed the month 36 visit. A total of 7.8% (7/90) of patients in the bimatoprost QD group, 16.0% (8/50) of patients in the bimatoprost BID/QD group, and 14.0% (6/43) of patients in the timolol group discontinued the study after month 24 and at or prior to month 36.

Patients who discontinued prematurely are listed in the following table.

Table 3 – Discontinued Subjects

Treatment Group	Patient	No. of Days on Treatment [1]	Reason for Discontinuance
Bimatoprost QD	1584-2705	1091	Lack of Efficacy
	1584-2727	927	Personal Reasons (moved out of state)
	1634-2917	1046	CVA/Heart Attack/Death
	2232-1318	819	Diplopia
	2232-1329	744	Personal Reasons (no comments on CRF)
	2429-1132	1097	Cataract (NOS)
	2942-1921	1096	Concomitant Therapy
Bimatoprost BID/QD	1584-2707	747	Other (inconsistent IOPs OS and VF changes)
	1584-2714	911	Personal Reasons (time constraints – wanted to travel)
	2117-2210	1016	Lack of Efficacy
	2710-3011	907	Relocated
	2821-1462	1007	Lack of Efficacy
	2942-1902	1091	Concomitant Therapy
	2942-1919	1002	Concomitant Therapy
	2953-2007	792	Lack of Efficacy
Timolol BID	2037-1618	812	Lost to Follow-up
	2037-1624	1036	Other (study drug bottles mislabeled with wrong subject No.)
	2710-3013	1030	Personal Reasons (could not get off work for Exit Visit)
	2953-2001	986	Non-compliance
	2956-3332	955	Personal Reasons (stopped study med; refused Exit Visit)
	2961-1560	853	Other (off study meds > 2 wks; hospitalized for cardiac cath)

[1]Number of days of treatment in addition to 24 month extension.

Reviewer's Comments:

Comments in parentheses in the "Reason for Discontinuance" column were added by this medical reviewer after review of the CRFs.

Subject 2037-1624 was discontinued after study drug bottles were mislabeled with the wrong subject number per the CRF. This protocol deviation is not noted in Section 10.2 of the study report. This subject was excluded from the Per-Protocol analysis because of scheduled visits outside the permissible Per-Protocol visit window.

Mean Intraocular Pressure

Table 4 – Mean IOP (mmHg) with Bimatoprost or Timolol (ITT-LOCF)

Time-point	Visit	Bimatoprost QD (N = 90)	Bimatoprost BID/QD (N = 50)	Timolol (N = 43)
Hour 0	Baseline	25.8	25.9	25.4
	Month 27	17.6[a]	18.1[b]	19.1
	Month 30	17.9[a]	18.8[b]	19.7
	Month 33	18.1[a]	19.1[b]	19.5
	Month 36	18.3	19.2[b]	19.2
Hour 2	Baseline	24.5	24.0	23.6
	Month 27	16.6[a,c]	18.0[b]	18.5
	Month 30	17.1[a,c]	18.1[b]	18.7
	Month 33	17.3[a]	18.1[b]	18.7
	Month 36	17.3[a]	18.0[b]	18.4

N = number of patients at baseline
a bimatoprost QD statistically superior to timolol ($p \leq 0.021$)
b bimatoprost BID/QD statistically non-inferior to timolol based on 1.5 mmHg criterion
c bimatoprost QD statistically non-inferior to bimatoprost BID/QD ($p \leq 0.028$)

Reviewer's Comments:

The efficacy of bimatoprost was adequately evaluated in the original NDA submission. No information has been submitted which would alter those conclusions.

Adverse Events

Table 4 – Number (%) of Subjects with Adverse Events, Regardless of Causality, Reported by ≥ 3.0% in any Treatment Group

BODY SYSTEM Preferred Term	Bimatoprost QD (N = 90)	Bimatoprost BID/QD (N = 50)	Timolol (N = 43)	Among-group P-value[a]
OVERALL	73 (81.1%)	42 (84.0%)	32 (74.4%)	0.512
BODY AS A WHOLE				
infection	6 (6.7%)	4 (8.0%)	4 (9.3%)	0.822
accidental injury	5 (5.6%)	3 (6.0%)	2 (4.7%)	>0.999
back pain	5 (5.6%)	2 (4.0%)	1 (2.3%)	0.894
flu syndrome	4 (4.4%)	0 (0.0%)	1 (2.3%)	0.434
allergic reaction	3 (3.3%)	1 (2.0%)	2 (4.7%)	0.757
abdominal pain	1 (1.1%)	2 (4.0%)	0 (0.0%)	0.320
asthenia	0 (0.0%)	1 (2.0%)	2 (4.7%)	0.077
CARDIOVASCULAR				
hypertension	8 (8.9%)	6 (12.0%)	1 (2.3%)	0.199
METABOLIC AND NUTRITIONAL DISORDERS				
hypercholesteremia	5 (5.6%)	2 (4.0%)	2 (4.7%)	>0.999
diabetes mellitus	1 (1.1%)	2 (4.0%)	2 (4.7%)	0.301
hyperglycemia	0 (0.0%)	2 (4.0%)	0 (0.0%)	0.128
MUSCULO-SKELETAL				
arthritis	5 (5.6%)	2 (4.0%)	1 (2.3%)	0.894
arthralgia	3 (3.3%)	1(2.0%)	1 (2.3%)	>0.999
NERVOUS SYSTEM				
anxiety	5 (5.6%)	0 (0.0%)	1 (2.3%)	0.225
RESPIRATORY SYSTEM				
sinusitis	3 (3.3%)	0 (0.0%)	1 (2.3%)	0.680
bronchitis	1 (1.1%)	0 (0.0%)	2 (4.7%)	0.210
dyspnea	0 (0.0%)	3 (6.0%)	0 (0.0%)	0.032
SPECIAL SENSES (OCULAR)				
conjunctival hyperemia	12 (13.3%)	9 (18.0%)	0 (0.0%)	0.006
cataract (NOS)	9 (10.0%)	2 (4.0%)	5 (11.6%)	0.360
eye dryness	5 (5.6%)	3 (6.0%)	1 (2.3%)	0.745
blepharitis	3 (3.3%)	3 (6.0%)	1 (2.3%)	0.687
visual acuity worsened	3 (3.3%)	2 (4.0%)	2 (4.7%)	0.889
visual field defect	3 (3.3%)	1 (2.0%)	1 (2.3%)	>0.999
foreign body sensation	3 (3.3%)	1 (2.0%)	0 (0.0%)	0.810
superficial punctate keratitis	2 (2.2%)	3 (6.0%)	1 (2.3%)	0.554
visual disturbance	2 (2.2%)	2 (4.0%)	2 (4.7%)	0.646
growth of eyelashes	2 (2.2%)	2 (4.0%)	0 (0.0%)	0.568
eye pain	1 (1.1%)	3 (6.0%)	0 (0.0%)	0.128
eye pruritus	0 (0.0%)	3 (6.0%)	2 (4.7%)	0.039
corneal erosion	0 (0.0%)	2 (4.0%)	0 (0.0%)	0.128
UROGENITAL SYSTEM				
cystitis	4 (4.4%)	0 (0.0%)	0 (0.0%)	0.185

Reviewer's Comments:

Conjunctival hyperemia remains the most frequently noted adverse event (13%) with administration of bimatoprost QD as noted in the 36-month extension.

Approximately 2% of subjects on bimatoprost QD experienced notable eyelash growth during the 36-month extension. Per the 24-month extension of Study 192024-014, approximately 7% of subjects of subjects on bimatoprost QD experienced notable eyelash growth.

Iris Photographs

Each patient's eye was photographed under standardized conditions with a Polaroid Macro 5 SLR camera prior to fluorescein instillation at months 15, 18, 21, 24, 27, 30, 33, and 36. Any changes in iris color were to be recorded on the adverse event CRF. Follow-up photographs were to be compared by the investigator with those from Day 0 (in the original -008 and -009 studies) to assess changes in iris color pigmentation. Per Allergan, due to the length of this study and the quality of Polaroid film, the evaluation was limited.

No changes in iris color were noted by the investigators in any treatment group in either the 24-month or 36-month extension.

Reviewer's Comments:

All submitted iris color photographs were reviewed by this medical reviewer. The quality of the photographs varied by investigator.

No change in iris color in any treatment group in any subject over 48 total months could be determined based on the submitted iris photographs. The methodology was sufficient to detect changes in pigmentation, but the quality of the resultant photographs was not sufficient to detect change.

See additional comments regarding the total number of subjects with photographs and partial photographic records in **Adequacy of Safety Testing.**

D. Adequacy of Safety Testing

No information was submitted in this supplement regarding pigmentation in the trabecular meshwork after treatment with bimatoprost ophthalmic solution 0.03%.

It is not clear that Study 192024-014 was of adequate duration to assess all the potential safety issues related to increasing ocular pigmentation. The evaluation methods were appropriate for the drug product and the indication.

Allergan stated in Study 192024-014 36-month extension that iris color photograph evaluation was limited. Allergan cited the length of the study and the quality of the resultant photographs.

Reviewers' Comments:

1088 subjects completed the original Phase 3, 3-month comparisons of bimatoprost versus timolol (192024-008 and -009) which included the assessment of iris photographs taken at Baseline (Day 0), Weeks 2 and 6, and Month 3. Only 183 subjects completed the 36-month extension. With over 83% of the original subjects effectively removed from photographic analysis, it is clear that the potential safety issues related to increasing ocular pigmentation have not been fully evaluated.

Of the 183 subjects enrolled in the 36-month extension of Study 192024-014, iris color photographs are submitted for 178 subjects. No photographs are submitted for 5 subjects who discontinued the 36-month extension early, and only partial photographic records are submitted for an additional 17 subjects.

No photographs were submitted for the 101 subjects who completed the 24-month extension but did not enroll in the 36-month extension.

E. Summary of Critical Safety Findings and Limitations of Data

The potential safety issues related to increasing ocular pigmentation have not been fully evaluated.

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The increase in eyelash growth continues through the 36-month extension although it decreases with time.

Conjunctival hyperemia remains the most frequently noted adverse event (13%) in the 36-month extension.

VIII. Dosing, Regimen, and Administration Issues

No change to the current dosing regimen is proposed in this submission.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

Comparison of safety and efficacy was evaluated in all studies with respect to gender in the original NDA submission. There were no significant differences

with respect to gender for safety or efficacy.

No information has been submitted which would alter those conclusions.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

Comparison of safety and efficacy was evaluated with respect to age, race, ethnicity and iris color. There were no significant differences with respect to age, race, ethnicity or iris color for safety or efficacy in the original NDA submission. There were no significant differences with respect to gender for safety or efficacy.

No information has been submitted which would alter those conclusions.

C. Evaluation of Pediatric Program

Bimatoprost is not indicated in pediatric patients based in the potential risks associated with uncontrolled increases in pigmentation and the potential growth of other structures within the eye.

D. Comments on Data Available or Needed in Other Populations

There are no known differences with respect to hepatic impairment.

X. Conclusions and Recommendations

A. Conclusions

Supplemental NDA 21-275/SE1-013 is not recommended for approval for the reduction of elevated intraocular pressure in patients with glaucoma or ocular hypertension.

The potential safety issues related to increasing ocular pigmentation and growth of ocular structures have not been fully evaluated.

B. Recommendations

Bimatoprost should remain a "second line" therapy for lowering intraocular pressure in patients with glaucoma or ocular hypertension who are intolerant of other IOP-lowering medications or insufficiently responsive to another IOP-lowering medication.

The applicant should commit to perform and complete a study to adequately address concerns raised by the report of increased iris pigmentation and the potential for changes in eyelash length and density over time.

The applicant should commit to perform and complete a study to evaluate

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

/s/

William Boyd
11/7/03 09:51:04 AM
MEDICAL OFFICER

Wiley Chambers
11/7/03 01:53:06 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	21-275
Submission Number	SE1
Submission Code	013 AZ
Letter Date	December 20, 2005
Stamp Date	December 22, 2005
PDUFA Goal Date	June 22, 2006
Reviewer Name	William M. Boyd, M.D.
Review Completion Date	June 16, 2006
Established Name	bimatoprost ophthalmic solution
(Proposed) Trade Name	Lumigan 0.03%
Therapeutic Class	prostaglandin analog
Applicant	Allergan
Priority Designation	S
Formulation	active ingredient: bimatoprost
Dosing Regimen	one drop once daily in the evening
Indication	reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension
Intended Population	patients with open angle glaucoma or elevated intraocular pressure

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Supplemental NDA 21-275/SE1-013 is recommended for approval for the reduction of elevated intraocular pressure in patients with glaucoma or ocular hypertension with revision of the labeling submitted on December 20, 2005.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

No additional studies are considered necessary. If further epidemiological studies are undertaken, these studies should compare patients treated with beta-blockers and include rates of death, hypertension, and stroke.

1.2.2 Required Phase 4 Commitments

No additional studies are considered necessary.

1.2.3 Other Phase 4 Requests

Not applicable. No additional studies are considered necessary.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Bimatoprost was approved on March 16, 2001, for lowering intraocular pressure in patients with glaucoma or ocular hypertension who are intolerant of other IOP-lowering medications or insufficiently responsive to another IOP-lowering medication. This designation as a "second line" therapy was based in the potential risks associated with uncontrolled increases in pigmentation and the potential growth of other structures within the eye.

In response to the Agency's request for commitment dated February 28, 2001, Allergan committed to perform long term post-marketing studies to further evaluate the potential pigmentary safety issues.

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Name:	Lumigan (bimatoprost ophthalmic solution) 0.03%
Pharmacologic Category:	synthetic analogue of prostaglandin $F_{2\alpha}$ (PG $F_{2\alpha}$)
Proposed Indication:	reduction of elevated intraocular pressure in patients with glaucoma or ocular hypertension
Dose Regimen:	one drop in the affected eye(s) once daily in the evening

B. State of Armamentarium for Indication(s)

The following classes of products are approved for the reduction of intraocular pressure. This list includes "first line" therapies, "second line" therapies, and adjunctive therapies:

- Miotics (i.e. pilocarpine)
- Sympathomimetics (i.e. dipivefrin HCl)
- β-adrenergic Blocking Agents (i.e. betaxolol HCl, carteolol HCl, levobunolol HCl, metipranolol, timolol hemihydrate, timolol maleate)
- Hyperosmotics (i.e. mannitol, urea)
- Carbonic Anhydrase inhibitors (i.e. acetazolamide, brinzolamide, dorzolamide HCl, methzolamide)
- α_2 Selective Agonists (i.e. apraclonidine, brimonidine)
- Prostaglandin Analogues (i.e. latanoprost, travoprost, unoprostone).

C. Important Milestones in Product Development

Bimatoprost was approved on March 16, 2001, for lowering intraocular pressure in patients with glaucoma or ocular hypertension who are intolerant of other IOP-lowering medications or insufficiently responsive to another IOP-lowering medication. This designation as a "second line" therapy was based in the potential risks associate with uncontrolled increases in pigmentation and the potential growth of other structures within the eye

In response to the Agency's request for commitment dated February 28, 2001, Allergan committed to perform post-marketing studies as detailed below:

- A post-marketing study or the continuation of current studies to adequately address concerns raised by the report of increased iris pigmentation and the potential for changes in eyelash length and density over time

Allergan submitted this efficacy supplement dated July 31, 2003, to effect a change in the indication for bimatoprost to allow its use as a "first line" therapy for the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension.

Allergan received a not approvable letter dated November 12, 2003, with the following deficiencies:

1. Potential safety issues related to increasing ocular pigmentation and growth of ocular structures have not been fully evaluated. Data demonstrating a plateau in these ocular changes and data demonstrating safety at the time of the plateau should be provided prior to changing the indication to first-line therapy.
2. Patent information has not been included in the application. This information should be provided.
3. Financial certification or disclosure has not been included in the application. This information should be provided.
4. Debarment certification has not been included in the application. This certification should be provided.

Reviewer's Comments:

For Allergan's response to Item #1, see Section 7 of this review. Allergan has requested that this supplemental application be amended to a 505(b)(2) application.

Items #2, 3, and 4 are provided in the December 20th submission.

Allergan submitted a complete response to this letter on December 20, 2005. Reference was made to the approved indication for Xalatan (latanoprost ophthalmic solution) 0.005%; Allergan requested approval for the same indication since the marketing exclusivity for Xalatan expired on December 20, 2005.

Since the supplemental application refers to information in the Xalatan (latanoprost ophthalmic solution) 0.005% application (NDA 20-597), a request to amend the supplemental new drug application to a 505(b)(2) application was submitted on March 9, 2006.

Reviewer's Comments:

In the Medical Officer's review of Supplemental application 010 for NDA 20-597 for Xalatan (latanoprost ophthalmic solution) 0.005% dated December 20, 2002, it was concluded that the effect of latanoprost on iris pigmentation, eyelash changes, and skin pigmentation was a class phenomenon common to all prostaglandin analogs, and thus these conclusions are relevant to all of the other prostaglandin-like products including bimatoprost.

1.3.2 Efficacy

The efficacy of the drug product was well established during the original approval. No information has been submitted to alter those conclusions.

1.3.3 Safety

The Agency has concluded that the following conclusions are relevant to all of the other prostaglandin-like products, including bimatoprost, per the Medical Officer's review of Supplemental application 010 for NDA 20-597 for Xalatan (latanoprost ophthalmic solution) 0.005% dated December 20, 2002:

- The increase in pigment color of the iris appears to be related to increases in melanin. There does not appear to be an increase in melanocytes, and the atypia seen in the melanocytes appears to be related cellular activity. The mechanism appears to be related to tyrosinase activity in the melanocytes and is a class phenomenon not just related to latanoprost. The location of the melanocytes also appears to affect the degree of increased melanin, with anterior cells demonstrating more of a change.

- The iris pigmentary effect does not appear to stop as long as a prostaglandin related drug product is administered. It does not appear to reverse even if administration of the drug product is stopped. It appears to occur in almost all individuals; however, due to the location of the melanocytes, there is variability in the observable iris color and iris pigmentation pattern.

- The iris pigmentary effect has been studied for at least five years and does not appear to have serious consequences within this period of time. Elevations in intraocular pressure tend to be problematic in older patients. Five years of time is a considerable period of time in the expected lifespan of many individuals with glaucoma. The study information therefore constitutes a sufficient safety data base to permit this class of drug products to be administered as a first line therapy.

- Increased growth of eyelashes and skin pigmentation also appear to be a class effect but appear to be reversible if the drug product is discontinued. There is no evidence of neoplastic growth.

- In patients with a risk factor for CME, such as cataract surgery, bimatoprost, like other prostaglandin analogues may be the trigger which leads to CME. It is clearly an independent risk factor. While bimatoprost may be unlikely to cause CME in patients without other risk factors, it clearly increases the incidence of CME in patients with risk factors.

- Bimatoprost, like the other prostaglandin related products, has an effect on the blood-aqueous and blood-retinal barriers.

- The Warnings/Precautions sections of the labeling reflect the need for caution in patients with active inflammation and that the product should be used with caution in patients with a history of uveitis.

- All of the effects, with respect to safety and efficacy, appear to be due to the same mechanisms of action of all of the prostaglandin-like products. While small differences in the rate of these reactions have been reported, this appears to be related to the observational techniques and the size of the particular study, not the mechanism or type of effect.

1.3.4 Dosing Regimen and Administration

No change in dosing is proposed or recommended.

1.3.5 Drug-Drug Interactions

There were no drug-drug interactions noted in the original approval. No information has been submitted to alter those conclusions.

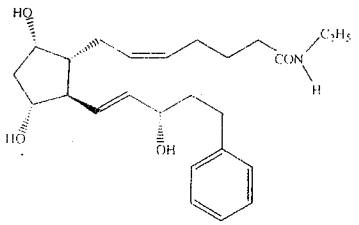
1.3.6 Special Populations

There were no known differences with respect to age, gender, or race noted in the original approval. No information has been submitted to alter those conclusions.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Name:	Lumigan (bimatoprost ophthalmic solution) 0.03%
Pharmacologic Category:	synthetic analogue of prostaglandin F2α (PG F2α)
Proposed Indication:	reduction of elevated intraocular pressure in patients with glaucoma or ocular hypertension
Dose Regimen:	one drop in the affected eye(s) once daily in the evening



2.2 Currently Available Treatment for Indications

The following classes of products are approved for the reduction of intraocular pressure. This list includes "first line" therapies, "second line" therapies, and adjunctive therapies:

- Miotics (i.e. pilocarpine)
- Sympathomimetics (i.e. dipivefrin HCl)
- β-adrenergic Blocking Agents (i.e. betaxolol HCl, carteolol HCl, levobunolol HCl, metipranolol, timolol hemihydrate, timolol maleate)
- Hyperosmotics (i.e. mannitol, urea)
- Carbonic Anhydrase inhibitors (i.e. acetazolamide, brinzolamide, dorzolamide HCl, methzolamide)
- α_2 Selective Agonists (i.e. apraclonidine, brimonidine)
- Prostaglandin Analogues (i.e. latanoprost, travoprost, unoprostone).

2.3 Availability of Proposed Active Ingredient in the United States

Bimatoprost was approved on March 16, 2001, for lowering intraocular pressure in patients with glaucoma or ocular hypertension who are intolerant of other IOP-lowering medications or insufficiently responsive to another IOP-lowering medication. This designation as a "second line" therapy was based in the potential risks associate with uncontrolled increases in pigmentation and the potential growth of other structures within the eye

In response to the Agency's request for commitment dated February 28, 2001, Allergan committed to perform post-marketing studies as detailed below:

- A post-marketing study or the continuation of current studies to adequately address concerns raised by the report of increased iris pigmentation and the potential for changes in eyelash length and density over time

- A study to evaluate pigmentation in the trabecular meshwork after patients have been treated with bimatoprost ophthalmic solution 0.03% for over two years.

Allergan submitted this efficacy supplement dated July 31, 2003, to effect a change in the indication for bimatoprost to allow its use as a "first line" therapy for the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension.

2.4 Important Issues with Pharmacologically Related Products

The safety and efficacy effects seen with this product are class effects.

Xalatan (latanoprost ophthalmic solution) 0.005% was the first prostaglandin derived product approved for the reduction of elevated intraocular pressure. It was approved as a "second line"

therapy because of the unknown long term effects related to the potential risks associated with uncontrolled increases in pigmentation and the potential growth of other structures within the eye.

In December 2002, a Xalatan NDA supplement was approved granting a "first line" indication for the reduction of elevated intraocular pressure in patients with glaucoma or ocular hypertension. The iris pigmentary effect had been studied for at least five years, and while it continued to progress, it did not appear to have serious consequences within that period of time for this particular product (five years was considered a considerable period of time in the expected lifespan of many individuals with glaucoma).

2.5 Presubmission Regulatory Activity

See Section 1.3.1.

2.6 Other Relevant Background Information

Not applicable.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Not applicable. There is no proposed change to the chemistry or manufacturing process for the drug product.

3.2 Animal Pharmacology/Toxicology

Allergan proposes the following change to the labeling regarding carcinogenicity:

[ ]

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

A previous, in-depth clinical review of this supplement was completed on November 7, 2003. This review concluded that the potential safety issues related to increasing ocular pigmentation and growth of ocular structures had not been fully evaluated.

The December 20, 2005, complete response was submitted electronically. All study reports were reviewed. All submitted photographs were reviewed.

The medical officer reviews of Supplemental application 010 for NDA 20-597 for Xalatan (latanoprost ophthalmic solution) 0.005% were reviewed in depth. These reviews formed the basis for a "first line" indication for Xalatan for the reduction of elevated intraocular pressure in patients with glaucoma or ocular hypertension. The Agency has concluded that those conclusions are relevant to all of the other prostaglandin-like products, including bimatoprost.

4.2 Tables of Clinical Studies

Table 1 – Clinical Trials

Protocol Number	**192024-014**	**MM-HTL-001**	**192024-029**
Study Design	Multicenter, Double-Masked, Randomized, Parallel, (Extension)	Multicenter Open-label (Extension)	Masked Histological Examination (Proposed)
Treatment Duration	48 months	5 years	2 year
Treatment Groups	Bimatoprost vs. Timolol	Bimatoprost QD or BID vs. Timolol (years 1-4) Bimatoprost (year 5)	Bimatoprost vs. Other topical Ophthalmic IOP-lowering Drugs
No. Subjects	379 enrolled subjects 284 completed 24 months 162 completed 36 months 141 completed 48 months	[Tx group in years 1-4] 16 subjects HTLQD 4 subjects HTL BID/QD 7 Timolol	12 specimens (6 per group)
Status	Completed	Completed	Preliminary Report Provided

4.3 Review Strategy

The December 20, 2005, complete response was submitted electronically. All study reports were reviewed. All submitted photographs were reviewed.

A literature search conducted by this reviewer failed to identify any literature references which were contrary to the information provided or referenced by Allergan in this application for this indication.

The medical officer reviews of Supplemental application 010 for NDA 20-597 for Xalatan (latanoprost ophthalmic solution) 0.005% were reviewed in depth. These reviews formed the basis for a "first line" indication for Xalatan for the reduction of elevated intraocular pressure in patients with glaucoma or ocular hypertension.

4.4 Data Quality and Integrity

There is no evidence that these studies were not conducted in accordance with acceptable clinical ethical standards.

Original photographic data was reviewed and compared to the submitted data. Any differences observed were relatively minor and did not significantly alter the conclusions of this reviewer.

4.5 Compliance with Good Clinical Practices

All studies were conducted in accordance with accepted clinical and ethical standards.

4.6 Financial Disclosures

Financial Disclosure forms were reviewed. There were no investigators with proprietary interest or with any significant equity interest in the drug product.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

All relevant issues have been discussed in previous clinical reviews.

5.2 Pharmacodynamics

All relevant issues have been discussed in previous clinical reviews.

5.3 Exposure-Response Relationships

All relevant issues have been discussed in previous clinical reviews.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

Indication sought: reduction of elevated intraocular pressure in patients with glaucoma or ocular hypertension

6.1.1 Methods

A previous, in-depth clinical review of this supplement was completed on November 7, 2003. This review concluded that the potential safety issues related to increasing ocular pigmentation and growth of ocular structures had not been fully evaluated.

The December 20, 2005, complete response was submitted electronically. All study reports were reviewed. All submitted photographs were reviewed.

The medical officer reviews of Supplemental application 010 for NDA 20-597 for Xalatan (latanoprost ophthalmic solution) 0.005% were reviewed in depth. These reviews formed the basis for a "first line" indication for Xalatan for the reduction of elevated intraocular pressure in patients with glaucoma or ocular hypertension.

Reviewer's Comments:

In the Medical Officer's review of Supplemental application 010 for NDA 20-597 for Xalatan (latanoprost ophthalmic solution) 0.005% dated December 20, 2002, it was concluded that the effect of latanoprost on iris pigmentation, eyelash changes, and skin pigmentation was a class phenomenon common to all prostaglandin analogs, and thus these conclusions are relevant to all of the other prostaglandin-like products including bimatoprost.

The clinical study reports provided by Allergan in previous submissions and in this submission support this conclusion. These reports, although reviewed in depth by this reviewer, comprise only a small portion of the available data on this class of drug. Their synopsis in this review is meant to be cursory.

6.1.2 General Discussion of Endpoints

The efficacy of the drug product was well established during the original approval.

Potential safety issues related to increasing ocular pigmentation and growth of ocular structures were to be fully evaluated. Data demonstrating a plateau in these ocular changes and data demonstrating safety at the time of the plateau was to be provided prior to a change in the indication to first-line therapy. See Section 7.

6.1.3 Study Design

192024-014: A Multicenter, Double-masked, Randomized, Parallel, Extension Study Evaluating the Safety and Efficacy of Bimatoprost 0.03% Ophthalmic Solution, Compared with Timolol 0.5% Ophthalmic Solution in Patients with Glaucoma or Ocular Hypertension – 48 month report

The objective of the 192024-014 extension study was to continue to evaluate (through Month 48) the long term safety and efficacy of bimatoprost 0.03% compared with timolol 0.5% in patients who completed the month 12 visit of 1 of 2 phase 3 studies (192024-008 or 192024–009).

In Studies 192024-008 and 192024-009 patients were randomized in a ratio of 2:2:1 to receive bimatoprost QD, bimatoprost BID, or timolol BID using a block size of 5. Patients continued to receive their randomized study medication through Month 24 of the extension study. At the Month 24 visit, patients in the bimatoprost BID group were switched, in a masked manner, to bimatoprost QD and are referred to as the bimatoprost BID/QD group. Patients in the bimatoprost QD and timolol groups remained on their same therapies for the remainder of their participation in the study (i.e., through Month 48).

MM-HTL-001: A fifth year iris photograph assessment for a clinical evaluation of Lumigan 0.03% in patients with glaucoma or ocular hypertension.

This was a Phase 4, multicenter, open-label, non-comparative clinical evaluation.
Phase 3 studies 192024-008 and 192024-009, were multicenter, randomized, double-masked studies evaluating the safety and efficacy of bimatoprost 0.03% administered once (QD) or twice (BID) daily compared with timolol 0.05% administered BID for up to 12 months (Months 0 to 12) in patients with glaucoma or ocular hypertension. Patients completing studies 192024-008 and 192024-009 could enter the Phase 3b extension study 192024-014 for up to an additional 36 months (total treatment period of up to 48 months). Patients randomized to bimatoprost QD or timolol in the Phase 3 studies received the same treatment regimen up to the Month 48 visit. Patients randomized to bimatoprost BID in the Phase 3 studies remained on bimatoprost BID through the Month 24 visit at which they were switched, in a masked fashion, to receive bimatoprost QD through Month 48. Any patient completing the fourth year (Month 48) of study 192024-014 could be enrolled in this open-label 5th year assessment study (Months 48 to 60) by the participating investigator. All patients received bimatoprost 0.03% QD in this study.

192024-029 (Preliminary Analysis): A Masked Histological Evaluation of Trabecular Meshwork Specimens Collected From Trabeculectomy Patients With Primary Open-Angle Glaucoma Treated With Bimatoprost 0.03% Ophthalmic Solution Once-Daily (QD) for at Least Two Years Compared With Primary Open-Angle Glaucoma Patients Treated With Other Topical Ophthalmic IOP-Lowering Drugs

For this preliminary report, 17 patients from 10 sites met the study eligibility criteria, of whom 12 patients from 8 sites had evaluable specimens.

Histological evaluation of trabecular meshwork specimens was the primary assessment for this study. At the time that the patients were undergoing trabeculectomy surgery, the specimens were collected, fixed in formalin solution, and sent to Allergan Pathology Laboratory for routine processing and slide preparation.

The fixed stained and unstained slides were numbered sequentially and sent to an external pathology laboratory for reading. The evaluator, an ophthalmic pathologist, did not know which slides were those from bimatoprost patients and which slides were from patients on other therapies. Pigmentation was graded using the following scale: absent, marginal, moderate, and marked.

6.1.4 Efficacy Findings

The efficacy of the drug product was well established during the original approval. No information has been submitted to alter those conclusions.

6.1.5 Clinical Microbiology

Not applicable.

6.1.6 Efficacy Conclusions

The efficacy of the drug product was well established during the original approval. No information has been submitted to alter those conclusions.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The December 20, 2005, complete response was submitted electronically. All study reports were reviewed. All submitted photographs were reviewed.

Regarding Allergan's submitted studies:

- **Allergan's Conclusions for 192024-014:**
  Bimatoprost 0.03% ophthalmic solution administered once-daily was effective and well tolerated over 48 months of treatment in patients with open angle glaucoma or ocular hypertension.

- **Allergan's Conclusions for MM-HTL-001**:
  19 patients out of a total of 964 patients experienced increases in iris pigmentation during treatment with bimatoprost 0.03% for up to 5 years. Thus, the overall incidence of increased iris pigmentation was 1.97% (19/964), which is well within the incidence listed (1% to 3%) in the currently approved product labeling (Lumigan Package Insert).

- **Allergan's Conclusions for 192024-029 (Preliminary Analysis)**
  The pigmentation evaluation of the trabecular specimens from patients treated with bimatoprost for at least 2 years (without exposure to ocular prostaglandins or with exposure of no more than 6 weeks) was essentially the same as that obtained from patients treated with other topical, ophthalmic IOP-lowering therapies (without exposure to ocular prostaglandins or with exposure of no more than 6 weeks).

Reviewer's Comments:

The results from 192024-029 (histological evaluation of trabecular meshwork specimens) are limited by the preliminary nature of the study report. The study planned to evaluate 20 specimens but only evaluated 12.

A literature search conducted by this reviewer failed to identify any literature references which were contrary to the information provided or referenced by Allergan in this application for this indication.

The medical officer reviews of Supplemental application 010 for NDA 20-597 for Xalatan (latanoprost ophthalmic solution) 0.005% were reviewed in depth. These reviews formed the basis for a "first line" indication for Xalatan for the reduction of elevated intraocular pressure in patients with glaucoma or ocular hypertension.

The Agency has concluded that the following conclusions are relevant to all of the other prostaglandin-like products, including bimatoprost, per the Medical Officer's review of Supplemental application 010 for NDA 20-597 for Xalatan (latanoprost ophthalmic solution) 0.005% dated December 20, 2002:

- The increase in pigment color of the iris appears to be related to increases in melanin. There does not appear to be an increase in melanocytes, and the atypia seen in the melanocytes appears to be related cellular activity. The mechanism appears to be related to tyrosinase activity in the melanocytes and is a class phenomenon not just related to latanoprost. The location of the melanocytes also appears to affect the degree of increased melanin, with anterior cells demonstrating more of a change.

- The iris pigmentary effect does not appear to stop as long as a prostaglandin related drug product is administered. It does not appear to reverse even if administration of the drug product is stopped. It appears to occur in almost all individuals; however, due to the location of the melanocytes, there is variability in the observable iris color and iris pigmentation pattern.

- The iris pigmentary effect has been studied for at least five years and does not appear to have serious consequences within this period of time. Elevations in intraocular pressure tend to be problematic in older patients. Five years of time is a considerable period of time in the expected lifespan of many individuals with glaucoma. The study information

therefore constitutes a sufficient safety data base to permit this class of drug products to be administered as a first line therapy.

- Increased growth of eyelashes and skin pigmentation also appear to be a class effect but appear to be reversible if the drug product is discontinued. There is no evidence of neoplastic growth.

- In patients with a risk factor for CME, such as cataract surgery, bimatoprost may be the trigger which leads to CME. It is clearly an independent risk factor. While bimatoprost may be unlikely to cause CME in patients without other risk factors, it clearly increases the incidence of CME in patients with risk factors.

- Bimatoprost, like the other prostaglandin related products, has an effect on the blood-aqueous and blood-retinal barriers.

- The Warnings/Precautions sections of the labeling reflect the need for caution in patients with active inflammation and that the product should be used with caution in patients with a history of uveitis.

- All of the effects, with respect to safety and efficacy, appear to be due to the same mechanisms of action of all of the prostaglandin-like products. While small differences in the rate of these reactions have been reported, this appears to be related to the observational techniques and the size of the particular study, not the mechanism or type of effect.

7.2 Adequacy of Patient Exposure and Safety Assessments

Potential safety issues related to increasing ocular pigmentation and growth of ocular structures have been studied for at least five years and do not appear to have serious consequences within this period of time. Elevations in intraocular pressure tend to be problematic in older patients. Five years of time is a considerable period of time in the expected lifespan of many individuals with glaucoma.

A sufficient safety data base exists to permit this class of drug products, i.e. prostaglandin analogs, to be administered as a first line therapy.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

There is no information, either from Allergan's submitted trials or from the Agency's conclusions regarding the class phenomenon common to all prostaglandin analogs, which alters the current adverse event profile for this drug product. It is recommended that the Adverse Event section of the Lumigan labeling remain unchanged:

In clinical trials, the most frequent events associated with the use of LUMIGAN® (bimatoprost ophthalmic solution) 0.03% occurring in approximately 15% to 45% of patients, in descending order of incidence, included conjunctival hyperemia, growth of eyelashes, and ocular pruritus. Approximately 3% of patients discontinued therapy due to conjunctival hyperemia.

Ocular adverse events occurring in approximately 3 to 10% of patients, in descending order of incidence, included ocular dryness, visual disturbance, ocular burning, foreign body sensation, eye pain, pigmentation of the periocular skin, blepharitis, cataract, superficial punctate keratitis, eyelid erythema, ocular irritation, and eyelash darkening. The following ocular adverse events reported in approximately 1 to 3% of patients, in descending order of incidence, included: eye discharge, tearing, photophobia, allergic conjunctivitis, asthenopia, increases in iris pigmentation, and conjunctival edema. In less than 1% of patients, intraocular inflammation was reported as iritis.

Systemic adverse events reported in approximately 10% of patients were infections (primarily colds and upper respiratory tract infections). The following systemic adverse events reported in approximately 1 to 5% of patients, in descending order of incidence, included headaches, abnormal liver function tests, asthenia and hirsutism.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

No change in dosing is proposed or recommended.

8.2 Drug-Drug Interactions

There were no drug-drug interactions noted in the original approval. No information has been submitted to alter those conclusions.

8.3 Special Populations

There were no known differences with respect to age, gender, or race noted in the original approval, although there are suggestions that all of the prostaglandin analogs may be more effective in patients with dark colored irides. No information has been submitted to alter those conclusions.

8.4 Pediatrics

Safety and effectiveness in pediatric patients have not been established in pediatric patients; potential safety issues related to increasing ocular pigmentation and growth of ocular structures

have not been evaluated. While five year safety data is known and considered sufficient for the elderly population in which elevated intraocular pressure is more commonly seen, it is not sufficient for a pediatric population. A long term study in pediatric patients would require at least 20 years of follow-up.

8.5 Advisory Committee Meeting

Not applicable.

8.6 Literature Review

A literature search conducted by this reviewer failed to identify any literature references which were contrary to the information provided or referenced by Allergan in this application for this indication.

8.7 Postmarketing Risk Management Plan

No additional studies are considered necessary. If further epidemiological studies are undertaken, these studies should compare patients treated with beta-blockers and include rates of death, hypertension, and stroke.

8.8 Other Relevant Materials

Not applicable.

9 OVERALL ASSESSMENT

9.1 Conclusions

The submitted studies support the first line indication for this class of products.

The efficacy of the drug product was well established during the original approval. No information has been submitted to alter those conclusions.

The Agency has concluded that the following safety issues are relevant to all of the other prostaglandin-like products including bimatoprost:

The increase in pigment color of the iris appears to be related to increases in melanin. There does not appear to be an increase in melanocytes, and the atypia seen in the melanocytes appears to be related cellular activity. The mechanism appears to be related to tyrosinase activity in the melanocytes and is a class phenomenon not just related to latanoprost. The location of the melanocytes also appears to affect the degree of increased melanin, with anterior cells demonstrating more of a change.

The iris pigmentary effect does not appear to stop as long as a prostaglandin related drug product is administered. It does not appear to reverse even if administration of the drug product is stopped. It appears to occur in almost all individuals; however, due to the location of the melanocytes, there is variability in the observable iris color and iris pigmentation pattern.

The iris pigmentary effect has been studied for at least five years and does not appear to have serious consequences within this period of time. Elevations in intraocular pressure tend to be problematic in older patients. Five years of time is a considerable period of time in the expected lifespan of many individuals with glaucoma. The study information therefore constitutes a sufficient safety data base to permit this class of drug products to be administered as a first line therapy.

Increased growth of eyelashes and skin pigmentation also appear to be a class effect but appear to be reversible if the drug product is discontinued. There is no evidence of neoplastic growth.

In patients with a risk factor for CME, such as cataract surgery, bimatoprost may be the trigger which leads to CME. It is clearly an independent risk factor. While bimatoprost may be unlikely to cause CME in patients without other risk factors, it clearly increases the incidence of CME in patients with risk factors.

Bimatoprost, like the other prostaglandin related products, has an effect on the blood-aqueous and blood-retinal barriers.

The Warnings/Precautions sections of the labeling reflect the need for caution in patients with active inflammation and that the product should be used with caution in patients with a history of uveitis.

All of the effects, with respect to safety and efficacy, appear to be due to the same mechanisms of action of all of the prostaglandin-like products. While small differences in the rate of these reactions have been reported, this appears to be related to the observational techniques and the size of the particular study, not the mechanism or type of effect.

9.2 Recommendation on Regulatory Action

Supplemental NDA 21-275/SE1-013 is recommended for approval for the reduction of elevated intraocular pressure in patients with glaucoma or ocular hypertension with the labeling submitted on December 20, 2005.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

No additional studies are considered necessary.

9.3.2 Required Phase 4 Commitments

No additional studies are considered necessary.

9.3.3 Other Phase 4 Requests

No additional studies are considered necessary.

9.4 Labeling Review

See Section 10.2.

9.5 Comments to Applicant

Allergan should make the revisions noted in the line-by-line labeling review of the Package Insert.

9 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Medical- 1a

REFERENCES

Not applicable.

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/s/

William Boyd
6/21/2006 11:41:06 AM
MEDICAL OFFICER

Wiley Chambers
6/21/2006 04:51:44 PM
MEDICAL OFFICER

Janice Soreth
6/22/2006 03:24:47 PM
MEDICAL OFFICER

Labeling Review
(Medical Officer's Review #2)

Application	21-257
Submission	SE1-13 AZ
Primary Reviewer	William M. Boyd, M.D.
Date of Labeling Submission	June 20, 2006
Date of Labeling Review	June 20, 2006
Established Name	bimatoprost ophthalmic solution
Trademark	Lumigan 0.03%
Therapeutic Class	Vascular endothelial growth factor (VEGF) inhibitor
Applicant	Allergan 2525 Dupont Drive P.O. Box 19534 Irvine, CA 92623

Submitted

Submitted is revised labeling based on previous review and discussion between the applicant, the Deputy Division Director, the medical officer, and the project manager on June 20, 2006.

In this submission, the sponsor has accepted all requested changes to the package insert.

6 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Medical- 2a

Recommendations

Supplemental NDA 21-275/SE1-013 is recommended for approval for the reduction of elevated intraocular pressure in patients with glaucoma or ocular hypertension with the labeling submitted on June 20, 2006.

William M. Boyd, M.D.
Clinical Team Leader

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/s/

William Boyd
6/21/2006 01:56:05 PM
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6/21/2006 04:53:37 PM
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Janice Soreth
6/22/2006 03:33:02 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-275 / S-013

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW # 1	1. ORGANIZATION HFD-550 DAAODP	2. NDA NUMBER 21-275
3. NAME AND ADDRESS OF APPLICANT *(City and State)* Allergan 2525 Dupont Drive, P.O. Box 19534, Irvine, CA		4. AF NUMBER 5. SUPPLEMENT(S) NUMBER(S) DATES(S) SE1-013 7/1/2003
6. NAME OF DRUG: Lumigan® (bimatoprost ophthalmic solution) 0.03%.	7. NONPROPRIETARY NAME: Bimatoprost	
8. SUPPLEMENT PROVIDES FOR: Change of indication as "first line therapy for the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension." PA supplement		9. AMENDMENT(S), REPORT(S), ETC. NUMBER(S) DATE(S) SE1-013 BC 7/17/03
10. PHARMACOLOGICAL CATEGORY	11. HOW DISPENSED RX X OTC	12. RELATED IND/NDA/DMF
13. DOSAGE FORM(S) Solution	14. POTENCY 0.03%	
15. CHEMICAL NAME AND STRUCTURE		16. RECORDS AND REPORTS CURRENT YES__NO REVIEWED YES__NO

17. COMMENTS:

a. Allergan has claimed a categorical exclusion from the environmental assessment with accordance to 21CFR25.31(b).
b. According to the applicant, the estimated concentration of the drug substance at the point of entry onto the aquatic environment will be below 1 part per billion.
c. Some labeling change has been occured in the clinical section of the package insert, however, no labeling change of the CMC interest has been implemented in the package insert or the immediate container for this product.

18. RRECOMMENDATION:

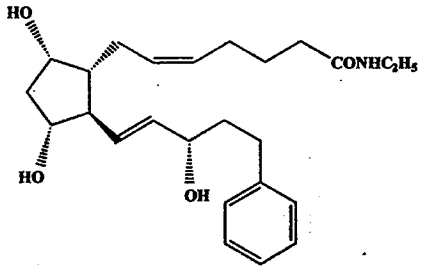
a. From CMC standpoint, this supplement is approved.

cc:
Orig. NDA 21-275/SE1-013
HFD-550/div. File
HFD-550/HKhorshidi
HFD-550/LNg
HFD-550/WChambers
HFD-550/MPuglisi
R/D Init. by:_LNg_

F/T by: HKhorshidi
doc # N:\NDA\21-275\SE1-013\Chem\2003. 11. 07. REV

19. REVIEWER NAME: Hossein S. Khorshidi	SIGNATURE	DATE COMPLETED November 7, 2003

Review Note



Lumigan®(bimatoprost ophthalmic solution) 0.03%

* The current PA supplement provides for change of indication as [redacted] or the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension."

* Allergan has claimed a categorical exclusion from the environmental assessment with accordance to 21CFR25.31(b).

* According to the applicant, the proposed action, approval of this supplement will increase the use of the active moiety, but the estimated concentration of the drug substance at the point of entry onto the aquatic environment will be below 1 part per billion.

* Some labeling change has been occurred in the clinical section of the package insert (refer to the clinical review), however, no labeling change of the CMC interest has been implemented in the package insert or the immediate container for this product.

Conclusion:

From CMC standpoint, this supplement may be approved.

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/s/

Hossein Khorshidih
11/10/03 09:45:31 AM
CHEMIST

Linda Ng
11/10/03 05:00:59 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-275 / S-013

PHARMACOLOGY REVIEW(S)

Division of Anti-Infective and Ophthalmology Products

Memorandum for NDA 21-275
Date: March 3, 2006
From: Zhou Chen, MD, PhD
To: Mike Puglisi
Through: Terry Peters, DVM

Sponsor: Allergan, 2525 Dupont Drive, P.O. Box 19534, Irvine, CA 92623-9534
Drug: Lumigan® (bimatoprost, AGN 192024)
Drug Class: Prostaglandin $F_{2\alpha}$ analogue
Related IND/NDA/BB-IND/BLA: IND
Indication: Reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension

Route of Administration: Ocular, Topical

Background: Lumigan® was approved in 2001 for the treatment of glaucoma. In 2002, the sponsor submitted carcinogenicity studies for this drug in mice and rats under IND . On December 20, 2005, the sponsor submitted a supplement for NDA 21-275, requesting the labeling changes in the "Carcinogenesis, Mutagenesis, Impairment of Fertility" section.

Review: Carcinogenicity studies conducted in rats and mice were submitted under IND . Below is a summary of pharmacology/toxicology review for these studies.

In rat study, groups of 60 rats/sex were orally dosed by gavage with AGN 192024 at doses of 0.1, 0.3, and 1.0 mg/kg/day for 104 weeks. Two control groups were treated with vehicle only. The selection of these doses, previously concurred by the Exec. CAC, was based on the AUC that is over 90-times the human exposure. Mortality rate was high in both treated and control groups and was not considered as drug-related. No toxicologically significant findings in clinical signs, body weight changes, food consumption, and gross and histopathological examinations were noted. No drug-related increases in the tumor incidence were demonstrated in this study. There were no statistically significant tumor findings in either male or female animals. The incidence of interstitial cell tumors of the testis was increased in MD and HD males. However, considering that this tumor was a common tumor, the incidence was not statistically significant and was within historical control range provided by the sponsor, and no other drug-related changes were noted in the testis; the reviewer believes that the interstitial cell tumor of the testis may be classified as non-drug-related.

In mouse study, groups of 65 mice/sex were orally dosed by gavage with AGN 192024 at doses of 0.3, 1.0, and 2.0 mg/kg/day for 104 weeks. Two control groups were treated with vehicle only. The selection of these doses was based on the AUC that is over 80-times the human exposure. Mortality rate was high in both treated and control groups and was not considered as drug-related. No toxicologically significant findings in clinical

signs, body weight changes, food consumption, and gross and histopathological examinations were noted. No statistically significant, drug-related increases in the tumor incidence were demonstrated in this study.

On February 17, 2004, the Executive CAC concluded that both rat and mouse carcinogenicity studies were adequate and there were no treatment-related increases in tumor findings (see Attachment 1).

The following are changes of the labeling regarding carcinogenicity proposed by the sponsor.

The reviewing pharmacologist has communicated with the sponsor regarding the values and calculation used in the labeling, and the reviewer is satisfied with the sponsor's explanation (see Attachment 2). Based on the carcinogenicity study results, the reviewer considers the labeling changes proposed by the sponsor are acceptable.

Recommendation:

The reviewer concurs with the labeling changes proposed by the sponsor.

Signatures:

Reviewer Signature _____

Supervisor Signature_____ Concurrence Yes ___ No ___

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/s/

Zhou Chen
3/3/2006 09:39:17 AM
PHARMACOLOGIST

Terry Peters
3/6/2006 07:50:54 AM
PHARMACOLOGIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-275 / S-013

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 21-275 SUPPL # 013 HFD # 520

Trade Name Lumigan

Generic Name bimatoprost ophthalmic solution

Applicant Name Allergan, Inc.

Approval Date, If Known June 22, 2006

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2), SE1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☐ NO ☒

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 21-275 Lumigan (bimatoprost ophthalmic solution)

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☒ NO ☐

If yes, explain:

The information is available in NDA 20-597 for Xalatan (latonoprost ophthalmic solution).

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES ☒	NO ☐
Investigation #2	YES ☐	NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA 20-597, Xalatan (latanoprost ophthalmic solution)

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES ☐	NO ☐
Investigation #2	YES ☐	NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND #	YES ☐	! NO ☐
		! Explain:
Investigation #2		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Michael Puglisi
Title: Consumer Safety Officer
Date: June 20, 2006

Name of Office/Division Director signing form: Wiley Chambers, M.D.
Title: Deputy Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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/s/

Janice Soreth
7/24/2006 04:42:46 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA # : 21-275 Supplement Type (e.g. SE5): SE1 Supplement Number: 013

Stamp Date: July 1, 2003 Action Date: June 22, 2006

HFD- 520 Trade and generic names/dosage form: Lumigan (bimatoprost ophthalmic solution) 0.03%

Applicant: Allergan, Inc.

Indication previously approved: 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 other intraocular pressure lowering medications.

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: **For the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension**

Is there a full waiver for this indication (check one)?

- ☐ √ **Yes: Please proceed to Section A.**
- ☐ No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ √ **There are safety concerns**
- ☐ Other:_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**

- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

[See appended electronic signature page]

_____
Regulatory Project Manager

cc: NDA 21-275/S-013
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

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/s/

Janice Soreth
7/14/2006 02:13:13 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-275/S-013

Allergan, Inc.
Attention: Stephen Buxbaum
Director, Regulatory Affairs
2525 Dupont Drive
P.O. Box 19534
Irvine, CA 92623-9534

Dear Mr. Buxbaum:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Lumigan (bimatoprost ophthalmic solution) 0.03%.

NDA Number: 21-275

Supplement number: S-013

Review Priority Classification: Standard (S)

Date of supplement: July 1, 2003

Date of receipt: July 2, 2003

This supplemental application proposes a first line therapy indication for the drug product.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 31, 2003, in accordance with 21 CFR 314.101(a).

Please cite the application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application

should be addressed as follows:

U.S. Postal Service:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products, HFD-550
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products, HFD-550
9201 Corporate Boulevard
Rockville, Maryland 20850-3202

If you have any questions, call Michael Puglisi, Project Manager, at (301) 827-2090.

Sincerely,

{See appended electronic signature page}

Carmen DeBellas, R.Ph.
Chief, Project Management Staff
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

Michael Puglisi
7/15/03 09:15:15 AM
for Carmen DeBellas

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING ISSUES IDENTIFIED

NDA 21-275/S-013

Allergan, Inc.
Attention: Stephen Buxbaum
Director, Regulatory Affairs
2525 Dupont Drive
P.O. Box 19534
Irvine, CA 92623-9534

Dear Mr. Buxbaum:

Please refer to your July 1, 2003, supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lumigan (bimatoprost ophthalmic solution) 0.03%.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on August 31, 2003, in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issue:

> The submission lacks an expected study report. Protocol 192024-029 is submitted as a draft protocol synopsis without an accompanying complete study report.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

A response to this letter is not expected and any such response may not be reviewed during the current review cycle.

If you have any questions, call Michael Puglisi, Regulatory Project Manager, at (301) 827-2090.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

Wiley Chambers
9/12/03 03:25:14 PM