

Pfizer Inc  
235 East 42<sup>nd</sup> Street 235/24/10A  
New York, NY 10017-5755  
Tel 212 733 5225 Fax 646 383 9498  
Email Jeffrey.b.chasnow@pfizer.com



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**Jeffrey B. Chasnow**  
Assistant General Counsel  
Legal Division

August 26, 2008

Division of Dockets Management  
Food and Drug Administration  
Department of Health and Human Services  
5630 Fishers Lane, Room 1061 (HFA-305)  
Rockville, MD 20852

**Re: Supplement to Citizen Petition  
FDA-2006-P-0072 (formerly 2006P-0450)**

Dear Madam or Sir:

Pfizer Inc. submits this Supplement to Pfizer's Citizen Petition, FDA-2006-P-0072 (formerly 2006P-0450) ("Pfizer Petition"), to address new information that was not available to Pfizer when the petition was submitted in November 2006.

The Pfizer Petition requests that FDA revoke or deny approval of sNDAs seeking first-line indications for Allergan's prostamide product Lumigan® and Alcon's prostaglandin product Travatan®, unless the sNDAs contain appropriate safety data. The petition contends that the sNDAs cannot properly be approved in reliance on Pfizer's NDA for Xalatan®; in the absence of adequate safety data specific to the Allergan and Alcon products; and inconsistently with requirements that FDA imposed on Pfizer for a similar sNDA.

This Supplement is being submitted in order to address new information pertaining to the Pfizer Petition, namely:

1. On or about July 8, 2008, Pfizer observed "Coming Soon" advertisements placed by Allergan in ophthalmology journals announcing the expected approval of a new formulation of Lumigan®—Lumigan® 0.01%. Pfizer wishes to clarify that all of the arguments set forth in the Pfizer Petition (as supplemented here) apply to all formulations of Lumigan®, including Lumigan® 0.01%.

FDA-2006-P-0072

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2. On July 5, 2006, a vendor acting on Pfizer's behalf submitted a Freedom of Information Act ("FOIA") request for documents relating to FDA's review and approval of Allergan's sNDA 21-257/S-013. On May 1, 2008, Pfizer received the documents that FDA released in response to the FOIA request. As described herein, these materials (collectively, "Lumigan® Review") provide information relevant to and supportive of the Pfizer Petition.<sup>1</sup>

## 1. Background

### a. FDA's Approval of Xalatan® for First-Line Use<sup>2</sup>

Xalatan® (latanoprost ophthalmic solution) 0.005% was approved in 1996 as a second-line agent for the treatment of elevated intraocular pressure ("IOP") in patients with open-angle glaucoma and/or ocular hypertension. The restriction to second-line use was primarily based on potential risks associated with increases in iris pigmentation and potential growth of ocular structures within the eye. On June 30, 1999, Pfizer submitted an sNDA seeking approval to indicate Xalatan® for first-line use. In October 1999, FDA ruled that the sNDA would not be approvable until Pfizer completed adequate and well-controlled studies addressing four issues of concern, including risks associated with ocular pigmentation changes.<sup>3</sup>

In October 2001, after Pfizer reported data from an ongoing five-year study evaluating iris pigmentation changes, FDA again declined to approve Xalatan® for first-line use, declaring Pfizer's sNDA deficient because "[p]otential safety issues related to increasing ocular pigmentation and growth of ocular structures have not been fully evaluated."<sup>4</sup> Although no association was seen between the pigmentation changes and IOP or other adverse events, FDA determined that "the full safety profile cannot be adequately assessed until the pigmentation changes and growth of ocular structures have ceased."<sup>5</sup>

On December 20, 2002, FDA approved Xalatan® for first-line use after reviewing the data from Pfizer's completed five-year study, as well as extensive additional clinical, histopathological, and post-marketing information Pfizer provided. *See* Pfizer Petition at 2-3. FDA noted: "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."<sup>6</sup> Finding that the investigational work Pfizer performed was essential to approval of Xalatan® for first-line use, FDA awarded Pfizer three years of market exclusivity.

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<sup>1</sup> Relevant excerpts of the Lumigan® Review are attached in Appendix A and referenced therein.

<sup>2</sup> Relevant excerpts of FDA's review of Pfizer's sNDA 20-597/S-010 for Xalatan® are attached in Appendix B and referenced therein.

<sup>3</sup> 1999 Xalatan® Not-Approvable Letter, App. B-1.

<sup>4</sup> 2001 Xalatan® Not-Approvable Letter, App. B-3.

<sup>5</sup> 2001 Xalatan® Medical Review at 3, App. B-8.

<sup>6</sup> 2002 Xalatan® Medical Review at 2, App. B-31.

Pfizer's sNDA contained no data specifically establishing the safety of other prostaglandin products, and FDA's reviews of the sNDA did not describe any such data. Nevertheless, FDA's 2002 Xalatan® Medical Review opined that the extensive data demonstrating the safety of Xalatan® might reflect a "class phenomenon," and thus that "[t]he conclusions related to latanoprost are relevant to all of the other prostaglandin like drug products."<sup>7</sup>

b. FDA's Rejection of Lumigan® for First-Line Use (2003)

In July 2003, Allergan submitted an sNDA (NDA 21-275/S-013) proposing that Lumigan® (bimatoprost ophthalmic solution) 0.03% be approved as first-line therapy for elevated IOP in patients with open-angle glaucoma or ocular hypertension. In November 2003, FDA notified Allergan that the sNDA was "not approvable" because, *inter alia*:

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.<sup>8</sup>

The accompanying Clinical Review stated:

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.<sup>9</sup>

The Clinical Review also stated that "[t]he applicant should commit to perform and complete a study to evaluate [redaction]."<sup>10</sup>

In its 2003 review of Allergan's sNDA, FDA expressly noted the opinion expressed in the 2002 Xalatan® Medical Review that "[t]he safety and efficacy effects seen with this product appear to be class effects."<sup>11</sup> FDA did not approve Lumigan® for first-line use on the basis of this purported class effect, however, but instead decided that Allergan's sNDA could not be approved in the absence of data specifically demonstrating the safety of Lumigan® for first-line use. In its review of Lumigan®, FDA noted that a first-line indication had been demonstrated to be appropriate for Xalatan® because "[t]he 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 . . .*"<sup>12</sup> By contrast, FDA found, Allergan's sNDA did not contain adequate data measuring changes in pigmentation. First, the quality of Allergan's

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<sup>7</sup> Id. at 3, App. B-32.

<sup>8</sup> 2003 Lumigan® Not-Approvable Letter, App. A-1.

<sup>9</sup> 2003 Lumigan® Clinical Review at 20, App. A-22.

<sup>10</sup> Id.

<sup>11</sup> 2003 Lumigan® Clinical Review at 8, App. A-10.

<sup>12</sup> Id. (emphasis supplied).

photographs was “not sufficient to detect change” in iris pigmentation.<sup>13</sup> Second, the studies Allergan performed were inadequate in terms of both size and duration:

Only 183 subjects completed the 36-month extension [trial]. With over 83% of the original [1088] subjects effectively removed from photographic analysis, it is clear that the potential safety issues related to increasing ocular pigmentation have not been fully evaluated.<sup>14</sup>

The record thus reflects that, notwithstanding the suggestions in the 2002 Xalatan® Medical Review that prostaglandin safety might be determined on a class basis, FDA determined upon reviewing Allergan’s sNDA that specific data were necessary to support a first-line indication for Lumigan®.

c. FDA’s Approval of Lumigan® for First-Line Use (2006)

Following FDA’s November 2003 “not approvable” determination, Allergan made several additional submissions in support of its sNDA.<sup>15</sup> In June 2006, FDA approved Allergan’s sNDA and granted a first-line indication to Lumigan®. The approval letter asserts that Allergan’s “submission of December 20, 2005, constituted a complete response” to the November 2003 “not approvable” letter.<sup>16</sup>

Pfizer has not seen the additional submissions Allergan made in support of its sNDA, but it is clear from the Lumigan® Review documents that Allergan did not submit any data of the kind that FDA’s 2003 “not approvable” letter and 2003 Clinical Review had said would be necessary for approval. The 2006 Lumigan® Clinical Review noted that, although FDA’s 2003 review had deemed Allergan’s sNDA deficient for failing to include data fully evaluating “[p]otential safety issues related to increasing ocular pigmentation and growth of ocular structures,” Allergan’s December 20, 2005, response did not provide the missing data but instead relied by reference on “information in the Xalatan (latanoprost ophthalmic solution) 0.005% application (NDA 20-597) . . .”<sup>17</sup>

FDA’s 2006 Lumigan® Clinical Review recommended approval of Allergan’s sNDA on the basis that Pfizer’s data for Xalatan® had demonstrated “a class phenomenon common to all prostaglandin analogs, and thus these conclusions are relevant to all of the other prostaglandin-like products including bimatoprost.”<sup>18</sup> This was a total reversal of FDA’s 2003 “not approvable” decision, which had held that the earlier-postulated class effect was not an adequate basis for approval and that Allergan therefore must submit data specifically demonstrating the safety of Lumigan® in order to receive approval for first-line use. There is no explanation in the Lumigan® Review

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<sup>13</sup> Id. at 18, App. A-20 .

<sup>14</sup> Id. at 19, App. A-21.

<sup>15</sup> 2006 Lumigan® Approval Letter, App. A-24.

<sup>16</sup> Id.

<sup>17</sup> 2006 Lumigan® Clinical Review at 5, App. A-32.

<sup>18</sup> Id.

documents for why the purported class effect was considered insufficient for approval in 2003, but then adequate for approval—without any new information—in 2006.

## 2. Discussion

### a. FDA’s Unexplained Reversal of Its “Not Approvable” Determination Regarding Allergan’s sNDA Was Improper And Should Be Corrected

As discussed above, in November 2003 FDA ruled that Allergan’s sNDA was “not approvable” for the express reason that the sNDA did not include data establishing the safety of Allergan’s product for first-line use. The record indicates that Allergan never provided to FDA the data that the agency said would be required for approval of Lumigan® for first-line use. Nevertheless, in June 2006 FDA approved Allergan’s sNDA. The administrative record of FDA’s action on Allergan’s sNDA does not explain why FDA abandoned its November 2003 judgment that data specific to Lumigan® would be required for approval.

FDA’s “unexplained reversal” of its regulatory judgment regarding Allergan’s sNDA requires correction.<sup>19</sup> In *Purepac*, FDA made two conflicting decisions regarding a patent submission that the agency had received from an NDA holder. On the one hand, FDA decided that the submission encompassed treatment for neurodegenerative diseases, and in light of that judgment assigned the patent an Orange Book “use code” corresponding to neurodegenerative diseases. On the other hand, FDA made a separate decision that the same submission claimed only treatment of epilepsy, and on that basis disallowed a generic company’s patent certification directed to neurogenerative diseases. The court of appeals ruled that the inherent contradiction in FDA’s judgments “represents the height of arbitrary and capricious decision making,” and thus must be disallowed.<sup>20</sup>

Here, similarly to the situation in *Purepac*, FDA has made two conflicting decisions based on identical information without explaining why different approaches were taken. First, FDA decided in 2003 that, notwithstanding an earlier opinion that the safety data for Xalatan® suggested “a class phenomenon,” Allergan’s sNDA could not be approved in the absence of safety data specific to Allergan’s product. Then, in 2006, FDA reversed course and approved Allergan’s sNDA in the absence of any such data. FDA provided no explanation for this total reversal of judgment. As in *Purepac*, therefore, FDA’s “unexplained reversal” must be set aside.<sup>21</sup>

Pfizer submits that FDA’s 2003 “not approvable” judgment regarding the Lumigan® sNDA was the correct one. The opinions expressed in the 2002 Xalatan®

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<sup>19</sup> *Purepac Pharmaceutical Co. v. Thompson*, 354 F.3d 877, 884 (D.C. Cir. 2004).

<sup>20</sup> *Id.*

<sup>21</sup> See also *Missouri Pub. Serv. Comm’n v. FERC*, 337 F.3d 1066, 1071-75 (D.C. Cir. 2003) (invalidating a regulator’s “unexplained reversal” when “[n]o new facts prompted the Commission’s change of heart . . . [n]or did the Commission suggest that its reversal was due to a reevaluation of any previously considered facts”).

Medical Review regarding possible class effects were premised solely on data regarding Xalatan®. The agency’s 2003 “not approvable” decision for Lumigan® confirms that, in 2002, FDA did not have adequate data regarding the relevant safety concerns for other, distinct prostaglandin or prostamide products, and thus had no basis for concluding that these products would function similarly to Xalatan® with respect to ocular pigmentation and the growth of ocular structures.

As explained in the Pfizer Petition, *see* Pfizer Petition at 3-6, although prostaglandin products may exhibit *qualitative* class effects, each product is chemically distinct and is uniquely formulated with varying product concentrations. These differences are likely responsible for each product’s clinically unique safety profile, with each product having *quantitatively* different rates and intensities of side effects. In the absence of data from adequate and well-controlled long-term clinical studies, it is unknown whether Lumigan® or Travatan® is appropriate for first-line use given their unique product differences (in chemical structure, concentrations, and clinical safety profile).

It was therefore appropriate for FDA, as it did in 2003, to require Allergan to demonstrate the safety of Lumigan® with data specific to that drug product. Indeed, requiring specific safety data was consistent with FDA’s traditional view that inferences about class effects do not provide a proper basis for approving or expanding drug indications. *See* Pfizer Petition at 9-10.

For these reasons, FDA should vacate its approval of Allergan’s sNDA and should deny approval for similar sNDAs—including Allergan’s sNDA for Lumigan® 0.01% and Alcon’s sNDA for Travatan®—that are not supported by appropriate data establishing the safety of the applicant’s drug product.

b. FDA Should Investigate Whether It Relied Improperly On Pfizer’s NDA Data to Approve the Allergan sNDA

The Lumigan® Review also indicates another potentially serious defect in FDA’s approval of Allergan’s sNDA: that FDA may have relied improperly on confidential data contained in Pfizer’s NDA for Xalatan®.

As noted above, FDA’s approval of Allergan’s sNDA was premised entirely on the agency’s view that the extensive data Pfizer submitted to support a first-line indication for Xalatan® established “a class phenomenon.” The Pfizer Petition contends that such reliance is unauthorized and thus improper. *See* Pfizer Petition at 7. In response to earlier petitions, FDA has asserted that it may permissibly rely on “findings” from NDA data to approve applications under section 505(b)(2). The agency has acknowledged, however, that its reviewers may not reference NDA data directly. Applying that dichotomous approach,<sup>22</sup> in 2004 FDA suspended the approval under

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<sup>22</sup> Pfizer disputes FDA’s position that there is any meaningful distinction between relying on “findings” from data versus relying on the data themselves. *See* Pfizer Petition at 7, and Pfizer’s Reply to Comments

section 505(b)(2) of an amlodipine maleate product<sup>23</sup> after the agency “became aware that a first line reviewer made reference to certain studies of Pfizer’s in the documentation of his review of [the 505(b)(2) application].”<sup>24</sup>

In this case, it appears that agency reviewers may have crossed the boundary FDA identified in the amlodipine maleate situation by looking behind the “findings” that supported approval of the Xalatan® sNDA and referencing specific data in Pfizer’s NDA. The repeated, specific, and extensive references to Pfizer’s NDA data in the 2006 Lumigan® Clinical Review, in and of themselves, raise the question whether FDA’s reviewers relied only on “findings” derived from those data or on the data themselves. Even more troubling, however, are these statements in the Lumigan® Review suggesting that FDA relied directly on Pfizer’s data:

- The 2006 Lumigan® Clinical Review asserts that Allergan’s sNDA “refers to information in the Xalatan (latanoprost ophthalmic solution) 0.005% application (NDA 20-597) . . . ”<sup>25</sup>
- FDA’s Exclusivity Summary for Allergan’s sNDA similarly asserts that “clinical investigation . . . necessary to support approval” of the sNDA “is available in NDA 20-597 for Xalatan (latanoprost ophthalmic solution).”<sup>26</sup>

These statements in the Lumigan® Review suggest that FDA may have relied directly on Pfizer’s confidential Xalatan® data to approve Allergan’s sNDA, an approach that would clearly violate Pfizer’s trade secret rights. See Pfizer Petition at 7-8. We ask that FDA investigate this point further and take appropriate remedial action consistent with the approach taken in connection with amlodipine maleate.

c. FDA Cannot Validly Apply A Lower Data Requirement for Allergan or Alcon Than Was Imposed on Pfizer

As discussed above and in the Pfizer Petition, Xalatan®, Lumigan® and Travatan® were all initially approved by FDA for second-line treatment. In supplements, each of the sponsors has requested approval for first-line use. Thus, the three sponsors are similarly situated.

In order to gain first line indication, Pfizer submitted extensive additional studies in response to FDA requests. These studies included:

- A five-year long-term safety study of 344 patients;

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of Dr. Reddy’s Laboratories, No. 02P-0447, at 15-20 (April 28, 2003), *available at* <http://www.fda.gov/ohrms/dockets/dailys/03/Apr03/043003/02p-0447-rc00001-v01.pdf>

<sup>23</sup> App. C-1.

<sup>24</sup> App. C-4.

<sup>25</sup> 2006 Lumigan® Clinical Review at 5, App. A-32.

<sup>26</sup> Lumigan® Exclusivity Summary at 4-5, App. A-57-A-58.

- A five-year, comprehensive post-marketing surveillance study involving 5000 patients;
- Morphological examinations of trabeculectomy specimens taken from patients treated with latanoprost for up to 41 months;
- A study of melanin in the trabecular meshwork of latanoprost patients; and
- Five years of post marketing experience during which time approximately 17 million patients were treated with latanoprost.

Pfizer is unaware of a similar complement of robust studies or safety data by either Allergan or Alcon in support of their sNDAs seeking first-line approval. In fact, FDA decided in its 2003 “not approvable” letter for Lumigan® that further safety data were needed. Approval of either Lumigan® or Travatan® without the extensive safety data FDA itself deemed necessary and that FDA required Pfizer to provide for Xalatan® would be arbitrary and capricious action that treats similarly situated parties differently. *See generally* Pfizer Petition at 10-11.

### **3. Conclusion**

For the reasons stated in the Pfizer Petition, in Pfizer’s April 2007 Reply to comments by Alcon, and in this Supplement, Pfizer respectfully requests that FDA withdraw approval of Allergan’s sNDA 21-257/S-013 and deny approval of any other NDAs or sNDAs (including Allergan’s pending application for Lumigan® 0.01%) that do not contain an adequate package of safety data specific to the products for which first-line use is requested, as was required for Xalatan®.

### **4. Verification**

Pursuant to 21 USC § 355(q)(1)(I), I certify that, to my best knowledge and belief: (a) I have not intentionally delayed submission of this document or its contents; and (b) the information upon which I have based the action requested herein first became known to Pfizer on May 1, 2008 (when Pfizer received the Lumigan® Review) and on or about July 8, 2008 (when Pfizer first saw “Coming Soon” announcements for Lumigan® 0.01%). If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: Pfizer Inc. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Respectfully submitted,

*Jeffrey Chasnow*

Jeffrey B. Chasnow  
Assistant General Counsel

Alessandra Ravetti  
Senior Corporate Counsel  
Pfizer Inc.  
235 East 42<sup>nd</sup> Street  
New York, NY 10017  
(212) 733-2323

Cc: Wiley A. Chambers, MD  
Division of Anti-Infective and Ophthalmology Products

Elizabeth Dickinson  
Office of Chief Counsel

Jane A. Axelrad  
Nancy Boocker  
Office of Regulatory Policy

**Appendix A**



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

NDA 21-275/S-013

Page 2

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/

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Wiley Chambers  
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**CHEMICAL REVIEW of NDA 21-275/SET 01**

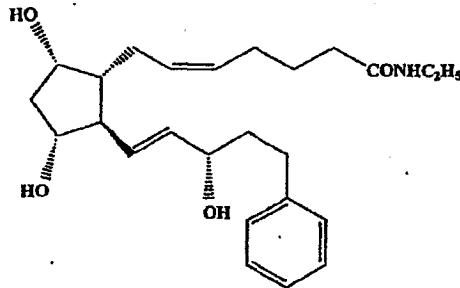
**Efficacy Supplement**

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<sub>25</sub>H<sub>37</sub>NO<sub>4</sub>  
(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<sub>2α</sub> (PG F<sub>2α</sub>)

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.*

**CENTRAL REVIEW of NDA 21-275 SERIES**

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**CLINICAL REVIEW of NDA 21-275/SE1-013**

Executive Summary Section

**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.

CLINICAL REVIEW of NDA 21-215 SECTION

Executive Summary Section

**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.

**CLINICAL REVIEW of NDA 21-275/SE**

**Clinical Review Section**

- 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 previous reviews for this drug product.

**III. Human Pharmacokinetics and Pharmacodynamics**

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

**Clinical Review of NDA 21-275/Sup 01**

**Clinical Review Section**

**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
Study Design	Multicenter, Double-Masked, Randomized, Parallel, (Extension)
Treatment Duration	36 months
Treatment Groups	Bimatoprost vs. Timolol
No. Sites	23 (24 months) 15 (36 months)
No. Subjects	379 enrolled subjects 284 completed 24 months 183 completed 36 months
Status	Completed

Protocol Number	192024-029
Masked Histological Examination (Proposed)	
2 year (proposed)	
Bimatoprost vs. Other topical Ophthalmic IOP-lowering Drugs	
20	
20 specimens (10 per group)	
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.

**Clinical Review of NDA 21-275/SEI-014**

**Clinical Review Section**

**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, \_\_\_\_\_ 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.

**CLINICAL REVIEW of NDA 21-275/SIBENICIK**

Clinical Review Section

**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.*

**CLINICAL REVIEW of NDA 21-275 SECTION 1**

Clinical Review Section

**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 Ocular 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.

## CLINICAL REVIEW of NDA 21-275/SIG

### Clinical Review Section

#### 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.

**Clinical Review of NDA 21-275 (SELLOIS)**

**Clinical Review Section**

**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
<b>Age (years)</b>	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	
<b>Sex</b>	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%)	
<b>Race</b>	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%)	
<b>Iris Color</b>	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.

## CLINICAL REVIEW of NDA 21-275/SET 003

## Clinical Review Section

Table 3 – Discontinued Subjects

Treatment Group	Patient	No. of Days on Treatment <sup>1</sup>	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
Timolol BID	2953-2007	792	Lack of Efficacy
	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)

<sup>1</sup>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.

**CLINICAL REVIEW of NDA 21-275 (SEI)**

Clinical Review Section

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 <sup>a</sup>	18.1 <sup>b</sup>	19.1
	Month 30	17.9 <sup>a</sup>	18.8 <sup>b</sup>	19.7
	Month 33	18.1 <sup>a</sup>	19.1 <sup>b</sup>	19.5
	Month 36	18.3	19.2 <sup>b</sup>	19.2
Hour 2	Baseline	24.5	24.0	23.6
	Month 27	16.8 <sup>a,c</sup>	18.0 <sup>b</sup>	18.5
	Month 30	17.1 <sup>a,c</sup>	18.1 <sup>b</sup>	18.7
	Month 33	17.3 <sup>a</sup>	18.1 <sup>b</sup>	18.7
	Month 36	17.3 <sup>a</sup>	18.0 <sup>b</sup>	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.*

**Clinical Review of NDA 21-275/SEI-01**

Clinical Review Section

**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*
<b>OVERALL</b>	73 (81.1%)	42 (84.0%)	32 (74.4%)	0.512
<b>BODY AS A WHOLE</b>				
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
asthma	0 (0.0%)	1 (2.0%)	2 (4.7%)	0.077
<b>CARDIOVASCULAR</b>				
hypertension	8 (8.9%)	6 (12.0%)	1 (2.3%)	0.199
<b>METABOLIC AND NUTRITIONAL DISORDERS</b>				
hypercholesterolemia	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
<b>MUSCULO-SKELETAL</b>				
arthritis	5 (5.6%)	2 (4.0%)	1 (2.3%)	0.894
arthralgia	3 (3.3%)	1 (2.0%)	1 (2.3%)	>0.999
<b>NERVOUS SYSTEM</b>				
anxiety	5 (5.6%)	0 (0.0%)	1 (2.3%)	0.225
<b>RESPIRATORY SYSTEM</b>				
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
<b>SPECIAL SENSES (OCULAR)</b>				
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 pruritis	0 (0.0%)	3 (6.0%)	2 (4.7%)	0.039
corneal erosion	0 (0.0%)	2 (4.0%)	0 (0.0%)	0.128
<b>UROGENITAL SYSTEM</b>				
cystitis	4 (4.4%)	0 (0.0%)	0 (0.0%)	0.185

**Clinical Review of NDA 21-2531 (b) (4)**

**Clinical Review Section**

**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 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.

## CLINICAL REVIEW of NDA 21-2511

### Clinical Review Section

#### 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.

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

**Clinical Review of NDA 21-275/SE1-013**

Clinical Review Section

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

**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**



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.

NDA 21-275/S-013

Page 2

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

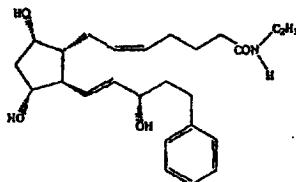
A000025

**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<sub>25</sub>H<sub>37</sub>NO<sub>4</sub>. 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<sub>max</sub> and AUC<sub>0-24hr</sub> 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/

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

## **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

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## **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.

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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 20<sup>th</sup> 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.*

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### 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.

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- 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:

Pharmacologic Category:

Proposed Indication:

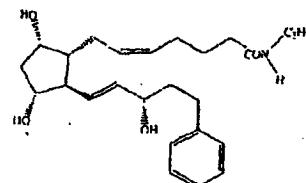
Dose Regimen:

Lumigan (bimatoprost ophthalmic solution) 0.03%

synthetic analogue of prostaglandin F<sub>2α</sub> (PG F<sub>2α</sub>)

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

one drop in the affected eye(s) once daily in the evening



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## 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)
- $\beta$ -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)
- $\alpha_2$  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"

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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:

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## 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.

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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.

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## 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.

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### 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.

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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).

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- 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

Clinical Review  
William M. Boyd, M.D.  
21-275 SE1 AZ  
Lumigan (bimatoprost ophthalmic solution) 0.3%

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:

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Lumigan (bimatoprost ophthalmic solution) 0.3%

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

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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.

**Clinical Review**

William M. Boyd, M.D.

21-275 SE1 AZ

Lumigan (bimatoprost ophthalmic solution) 0.3%

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.

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**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.

Clinical Review  
William M. Boyd, M.D.  
21-275 SE1 AZ

Lumigan (bimatoprost ophthalmic solution) 0.3%

## REFERENCES

Not applicable.

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this page is the manifestation of the electronic signature.**

*/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



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.

NDA 21-275/S-013

Page 2

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

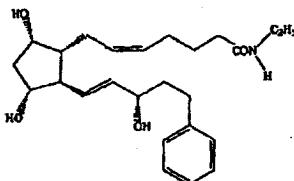
Enclosure

**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-[(1*R*,2*R*,3*R*,5*S*)-3,5-Dihydroxy-2-[1*E*,3*S*]-3-hydroxy-5-phenyl-1-pentenyl]cyclopentyl]-5-N-ethylheptenamide, and its molecular weight is 415.58. Its molecular formula is C<sub>25</sub>H<sub>37</sub>NO<sub>4</sub>. 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<sub>max</sub> and AUC<sub>0-24hr</sub> 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

## **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 (latanoprost 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

Explain:

NO

Explain:

Investigation #2

YES

Explain:

NO

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/

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

## **Appendix B**



## DEPARTMENT OF HEALTH &amp; HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville MD 20857

NDA 20-597/S-010

OCT 20 1999

Pharmacia & Upjohn Company  
Attention: Mark A. Mannebach, Ph.D., R.Ph.  
Regulatory Associate Director, U.S. Regulatory Affairs  
7000 Portage Road  
Kalamazoo, MI 49001

Dear Dr. Mannebach:

Please refer to your supplemental new drug application dated June 30, 1999, received July 1, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xalatan (latanoprost ophthalmic solution), 0.005% Sterile Ophthalmic Solution.

We acknowledge receipt of your submissions dated July 27 and August 19, 1999.

This supplement proposes to expand the indication for first line treatment of open-angle glaucoma and ocular hypertension and to support labeling of a \_\_\_\_\_

We have completed our review and find the information presented is inadequate, and the supplemental application is not approvable at this time. Under section 505(d) of the Act and 21 CFR 314.125(b)(4) of the FDA implementing regulations, there is insufficient information about the drug to determine whether the product is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling. Specifically, insufficient information has been submitted to support the safety of latanoprost ophthalmic solution if it were to be administered as a first line therapy. The potential risks associated with uncontrolled increases in iris pigmentation and the potential growth of other ocular structures has not been adequately assessed to establish the safety of the drug product when used as suggested in the proposed labeling. The \_\_\_\_\_ associated with these risks is not consistent with the labeling regulations under 21 CFR 201.57(e). In addition, the potential risks of using latanoprost as a first line therapy in pseudophakic patients and patients with inflammation or a history of inflammation has not been adequately evaluated.

Under section 505(d) of the Act and 21 CFR 314.125(b)(5) of the FDA implementing regulations, there is a lack of substantial evidence consisting of adequate and well controlled investigations, as defined in §314.126, that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling. Specifically, the suggested claim that \_\_\_\_\_ is not supported in the application

by adequate and well-controlled studies where the products are compared in an unbiased manner. In addition, the comparisons are potentially misleading because they fail to include appropriate consideration of the individual products' known pharmacological effects and their associated safety profiles.

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 the other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. 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) of the new drug regulations, you may request an informal meeting or telephone conference with this Division to discuss what further 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 these changes prior to approval of this supplemental application.

If you have any questions, contact Raphael R. Rodriguez, Project Manager, at (301) 827-2090.

Sincerely,



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



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville MD 20857

NDA 20-597/S-010

Pharmacia Corporation  
Attention: Mark A. Mannebach, Ph.D.  
Associate Director, Global Regulatory Affairs  
7000 Portage Road  
Kalamazoo, Michigan 49001

Dear Dr. Mannebach:

Please refer to your supplemental new drug application dated June 30, 1999, received July 1, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xalatan (latanoprost ophthalmic solution) 0.005%.

We acknowledge receipt of your submissions dated January 22, February 26, April 13, May 14, and May 24, 2001. Your submission of April 13, 2001, constituted a complete response to our October 20, 1999, action letter.

This supplemental new drug application proposes for the use of Xalatan (latanoprost ophthalmic solution) 0.005% for first line therapy in patients with open-angle glaucoma or ocular hypertension.

We have 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 may be summarized as follows:

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.

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. In the absence of any such action FDA may proceed to withdraw the application. 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) of the new drug regulations, you may request an informal meeting or telephone conference with this division to discuss what further steps need to be taken before the application may be approved.

NDA 20-597/S-010  
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This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change prior to approval of this supplemental application.

If you have any questions, call Michael Puglisi, 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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**Medical Officer's Review of NDA 20-597/S-010**  
Amendment 1

**Tradename:** Xalatan (latanoprost ophthalmic solution)

**Sponsor:** Pharmacia & Upjohn  
7000 Portage road  
Kalamazoo, MI 49001-0199

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

**Date of Submission:** April 16, 2001  
**Date of Review:** July 9, 2001

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## Executive Summary

### I. Recommendations

- A. It is recommended that supplemental NDA 20-587/S-010 not be approved. The application fails to support a first line indication because the potential safety issue related to increasing ocular pigmentation has not been fully evaluated.
- B. Xalatan should remain a second line therapy for increased intraocular pressure associated with glaucoma or ocular hypertension until an adequate safety database can be established.

### II. Summary of Clinical Findings

#### A. Overview of clinical program

The review is for an efficacy supplement for Xalatan (latanoprost ophthalmic solution) which is prostaglandin F2 $\alpha$  currently approved for the treatment of elevated intraocular pressure in patients with glaucoma or ocular hypertension who are intolerant or insufficiently responsive to other IOP lowering medications. The restriction to a second line therapy was based primarily on the potential risks associated with uncontrolled increases in pigmentation and the potential growth of other structures within the eye.

The sponsor committed to long term studies to further evaluate the potential safety issue with respect to uncontrolled increases in iris pigmentation and eyelash length. These studies included a 5-year trial to evaluate the long-term safety of latanoprost.

#### B. Efficacy

The efficacy of this product is not in question for this product since its efficacy was evaluated in the original NDA submission.

#### C. Safety

The 5-year study is not complete. The safety report submitted based on 4-year data shows that the uncontrolled increase in iris pigmentation and eyelash growth related to Xalatan is a continuing process that occurs throughout the study period. These changes occur in all color irides and there does not appear to be any identifiable risk factor related to their development. To date there has been no association between the presence of pigmentation changes and intraocular pressure or other adverse events. However, since these processes are ongoing, the full safety profile cannot be adequately assessed until the pigmentation changes and growth of ocular structures have ceased.

#### D. Dosing – N/A

#### E. Special Populations – N/A

## Clinical Review

### I.

**Tradename:** Xalatan (latanoprost ophthalmic solution)

**Sponsor:** Pharmacia & Upjohn  
7000 Portage Road  
Kalamazoo, MI 49001-0199

**Pharmacologic Category:** Prostaglandin F<sub>2</sub>α

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

**Dosage Form and Route of Administration:** Ophthalmic solution for topical ocular administration

NDA 20-597 was approved in June 1996, for the reduction of intraocular pressure in patients with open angle glaucoma or ocular hypertension who are intolerant or insufficiently responsive to other IOP lowering medications. The restriction to a second line therapy was based primarily on the potential risks associated with uncontrolled increases in pigmentation and the potential growth of other structures within the eye. The increased pigmentation has been associated with an increase in the number of melanosomes within the melanocytes.

The sponsor committed to long term studies to further evaluate the potential safety issue. These studies included a 5-year trial to evaluate the long-term safety of latanoprost. The applicant reported the results of the 2-year data in supplemental NDA 20-597/S-010 dated June 1999. This supplemental application was not approved based on the fact that it failed to support a first line indication because there continued to be a potential safety issue related to increasing ocular pigmentation which had not been fully evaluated. As discussed with the sponsor since the Advisory Committee meeting in the spring of 1996, consideration of Xalatan as a

first line therapy would not be given until there was an adequate demonstration of a plateau effect of the pigmentation.

- II. Clinically Relevant Findings from Chemistry, Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews - N/A**
- III. Human Pharmacokinetics and Pharmacodynamics - N/A**

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NDA 20-597/S-010 Amendment I Xalatan (latanoprost ophthalmic solution)

#### IV. Description of Clinical Data Sources

Table 1 – Clinical Data Sources

Protocol Type	Study Design	Treatment Duration	Patient Population	Treatment Groups	Dosing	No. Patients Enrolled/ Completed
<b>Phase IV Studies</b>						
Safety CTN9400PG034	5 year Open-label	Ongoing – 48 months	subjects with glaucoma or ocular hypertension	latanoprost	Latanoprost PM	sex M: 52.6% (200/380) F: 47.4% (180/380) race C: 97.8% (372/380) B: 0.5% (2/380) A: 0.3% (1/380)
Safety	Follow-up/observational	Not Applicable	Patients withdrawn from the phase 3 studies with IIP	Not Applicable	Not Applicable	Sex M:62% (49/79) F:38% (30/79)

**V. Clinical Review Methods**

The overall approach to the review of this supplement was to determine the long-term safety profile of Xalatan with respect to the increased in iris pigmentation and growth of eyelashes associated with use of this product. The efficacy of this product is not in question for this product since its efficacy was evaluated in the original NDA submission. While it is known that the increase in pigmentation of the iris has been associated with an increase in the number of melanosomes within the melanocytes, the pathogenesis of increase in eye lash length and the potential sequelae related to both of these phenomena are unknown. This review is focused on determining if these two uncontrolled, undefined events cease and if there are any adverse events related to their presence.

**VI. Integrated Review of Efficacy – N/A****VII. Integrated Review of Safety****A. Conclusions:**

These studies show that the risk associated with increased iris pigmentation continues for at least 4 years. Additionally, increases in iris pigmentation are permanent. Although there does not appear to be any increased risk of adverse events associated with developing this increase in pigmentation, the full safety profile cannot be adequately evaluated until a point of cessation is reached.

**B. Individual Study Review****Study 1**

**Protocol CTN: 9400PG034 (Interim Report after 4 years of the study)**

**Title:** A long-term open study of safety of latanoprost as adjunctive therapy in glaucoma patients with uncontrolled intraocular pressure. A multicenter study in Sweden, Great Britain, The Netherlands, Belgium and Australia-Extension Phase

**Objective:** To follow specified safety variables during long-term treatment with latanoprost as adjunctive therapy.

**Study Design:** This study was designed as a 3-year open, prospective, multicenter, multinational study with a 2-year extension phase to evaluate the safety and the IOP-reducing effect of latanoprost when given as adjunctive therapy. The primary objective was to evaluate the

long-term safety of latanoprost as an adjunctive therapy with regard to increased iris pigmentation (IIP). The secondary objective was to evaluate the IOP-reducing effect of latanoprost when used as an adjunctive therapy to other ocular hypotensive drugs. The study was performed in patients with uni- or bilateral primary open-angle or exfoliation glaucoma. Eligible patients were judged uncontrolled with mono IOP reducing therapy. Patients on dual therapy were eligible after wash-out of one of the medications.

All patients were treated with latanoprost 50ug/ml once daily as adjunctive therapy to one of the following medications:  $\beta$ -adrenergic antagonists, adrenergic agonists, cholinergic agonists, or carbonic anhydrase inhibitors. One or more pressure-reducing therapies, including argon laser trabeculoplasty (ALT) could be added if the IOP was still not controlled.

**Test Drug Schedule:** One drop administered in each study eye daily.

#### **Study Population – Inclusion and Exclusion Criteria**

##### **Inclusion Criteria**

The following were requirements for entry into the study:

1. Minimum of 18 years
2. Primary open-angle glaucoma or exfoliation glaucoma
3. Unilateral or bilateral uncontrolled, treated glaucoma (definition of uncontrolled: investigator intended to add another therapy)
4. Mono IOP therapy with one of the following medications:
  - $\beta$ -adrenergic antagonist
  - adrenergic agonist
  - cholinergic agonist
  - carbonic anhydrase inhibitor
5. Patients on dual therapy were eligible after a wash-out period of one of the medications prior to the baseline of at least:
  - 3 weeks for  $\beta$ -adrenergic antagonists
  - 2 weeks for adrenergic agonists
  - 5 days for cholinergic agonists
  - 5 days for carbonic anhydrase inhibitors
6. Informed consent obtained

**Exclusion Criteria**

The following were criteria for exclusion from participating in this study:

**Ocular conditions:**

1. History of acute angle closure
2. Pigmentary glaucoma
3. Advanced or rapidly advancing glaucoma likely to require surgery within 3 years
4. Any condition preventing reliable applanation tonometry
5. Closed or barely open anterior chamber angle
6. Intraocular surgery within 6 months prior to study start
7. Ocular inflammation or infection occurring within 3 months prior to study start
8. Other abnormal ocular conditions or symptoms preventing the patient from entering the study according to the investigator's judgement

**Therapy:**

9. Prior treatment with latanoprost at any time
10. Any systemic disease, active or chronic, judged by the investigator to be a reason for non-inclusion

**Women:**

11. Pregnancy
12. Woman of childbearing potential who were not using adequate contraceptive methods
13. Nursing mother

**General:**

14. Inability to adhere to treatment/visit plan
15. Had participated in a clinical trial with an investigational drug within 3 months prior to study start

**Study Medications**

Xalatan® eye drops (latanoprost 50ug/ml) contains latanoprost 50ug, benzalkonium chloride 0.2mg, sodium dihydrogen phosphate monohydrate — disodium hydrogen phosphate anhydrous — sodium chloride — and water for injection 1mL.

**Study Masking**

Treatment was open-label, both to the investigator and the patient.

**Efficacy Variable**

IOP was to be measured with a Goldmann applanation tonometer at each visit.

**Safety Variable**

Color photos (slides) of the irides and "en face" photos were taken at each visit.

**Table 2 – Examination Schedule**

Examinations	Visit1	Visit2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15	Follow-up
	Baseline	Month 1	Month 4	Month 8	Month 12	Month 16	Month 20	Month 24	Month 28	Month 32	Month 36	Month 42	Month 48	Month 54	Month 60	+2-4 weeks
Signed Informed Consent	X										X*					
Demographics	X															
Medical and ocular history	X															
Concurrent medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Iris photography	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
IOP	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse event reported by patient and/or investigator		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study drug dispensed(D) returned (C)	D	D/R	D/R	D/R	D/R	D/R	D/R	D/R	D/R	D/R	D/R	D/R	D/R	D/R	R	

\* Informed consent for the 2 year extension

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### Subject Disposition and Demographics

Out of 519 patients enrolled into the study, 435 completed 3 years. These 435 patients were eligible for participation in the extension phase of the study. One center was closed, as the investigator did not submit the application to the Ethics Committee in time. Consequently, thirteen patients were not allowed to participate. Additionally, 42 patients denied participation in the extension phase. Thus, 380 patients at 25 centers were included in the extended part of the study.

**Table 3 - Patients who did not give informed consent to participation in the extension of study PG034.  
Information given in the CRFs.**

Pat No	Reason for not participating	Center	IIP	IIP-Grade
118	no info	1	yes	weak
316	no info	3	no	
406	Increase in cupping of right optic disc, therefore Patient did not wish to continue study extension	4	yes	weak
409	Patient did not wish to continue extension period for personal reasons	4	no	
414	Patient first said ok to extension but due to later ill-health further attendance was not possible	4	no	
513	Patient refused consent to follow up study due to poor general health - angina + ? (ischemic heart disease CABG, indigestion)	5	no	
516	Patient not keen to continue on study as his glaucoma is well controlled now	5	yes	weak
520	Patient withdrawn, stopped drops prior to 36-m	5	yes	moderate
703	Non suitable for study extension (non-compliant with visits)	7	no	
822	Patient did not wish to continue study	8	yes	weak
1007	Patient concluded study satisfactory, has moved interstate and thus cannot extend for two years	10	no	
1203	no info	12	yes	marked
1208	no info	12	yes	weak
1217	no info	12	no	
1309	no info	13	no	
1317	Patient chose not to continue in study extension	13	no	
1515	To old to do the follow-up study	15	no	
1518	no info	15	no	
1520	Latanoprost OD ceased	15	no	
1521	no info	15	no	
1722	no info	17	yes	weak
1905	no info	19	yes	weak
1906	phaco/trabeculectomy advised	19	no	
1909	no info	19	no	
1913	Patient dropped out due to COPD and exacerbation	19	no	
1916	no info	19	no	
1919	no info	19	no	
1920	no info	19	no	
2009	Not keen to participate in the trial extension	20	no	
2103	no info	21	no	
2208	Patient gave no reason for not continuing with study. He is happy to continue using latanoprost and is going to do so	22	no	
2210	Patient will continue on latanoprost. Follow-up in glaucoma clinic	22	no	

Pat No	Reason for not participating	Center	IIP	IIP-Grade
2302	Patient's commitments made things difficult to complete follow-up visits, some appointments for fields missed. Did not wish to continue with 2 year extension.	23	yes	marked
2501	no info (patient refused a lot of examinations, ever asked?)	25	no	
2504	Timolol without preservative was prescribed. Allergic reaction probably due to benzalkonium chloride	25	yes	moderate
2505	no info	25	no	
2507	no info	25	yes	moderate
2508	Will not continue in the extension part	25	yes	moderate
2510	no info (bad compliance earlier in study)	25	no	
2511	no info	25	no	
2519	no info	25	yes	moderate
2520	no info (but conjunctival hyperemia reported last visit)	25	no	

Table 4 – Discontinued Patients and Reason

Patient Number	Increased Iris pigmentation	Study eye(s)	Reason
213	Yes	Both	Adverse event – increased macular degeneration
508	No	Both	Adverse event – death (myeloma)
606	No	Right	Other – non compliance 2° to a cardiovascular accident
613	No	Both	Other
615	No	Both	Other – non compliance
620	No	Right	Consent withdrawn
708	No	Both	Adverse event – increased IOP
721	Yes	Both	Adverse event – increased IOP, sclerotomy, headache
812	Yes	Both	Death (dyspnea)
816	Yes	Right	Adverse event - trabeculectomy
917	No	Both	Adverse event – allergic reaction
1310	No	Left	Adverse event – death (ischemic heart disease)
1311	No	Both	Adverse event – worsening visual field
1315	No	Both	Adverse event – headache, iritis
1512	No	Both	Adverse event - trabeculectomy
1723	Yes	Left	Other - death
1911	No	Both	Other
1914	No	Both	Other – Intestinal CA with liver metastasis
2011	Yes	Both	Adverse event – death (hospitalized for sigmoid colectomy/laparotomy)
2113	No	Right	Adverse event – death (pulmonary embolism)
2207	Yes	Both	Adverse event – death (renal vasculitis)

**Reviewer's Comments:** Information of reasons for discontinuation of patients 613 and 1911 not provided in NDA. The sponsor stated in further correspondence that both patients were discontinued because of non-compliance.

Table 5 – Baseline Demographics (All Subjects)

Demographic Variable	Classification	Number (%) of Patients					
		NIIP N= 263		IIIP N= 117		All N= 380	
		N	%	N	%	n	%
Sex	Male	135	(51.3)	65	(55.6)	200	(52.6)
	Female	128	(48.7)	52	(44.4)	180	(47.4)
Age (years)	Mean	65		67		66	
	Min - Max	31 - 87		34 - 83		31 - 87	
	< 60	74	(28.1)	23	(19.7)	97	(25.5)
	60 - < 70	90	(34.2)	40	(34.1)	130	(34.2)
	≥ 70	99	(37.7)	54	(46.2)	153	(40.3)
Race	Caucasian	256	(97.3)	116	(99.1)	372	(97.8)
	Black	2	(0.8)	-	-	2	(0.5)
	Asian	1	(0.4)	-	-	1	(0.3)
	Oriental	2	(0.8)	1	(0.9)	3	(0.9)
	American Indian	1	(0.4)	-	-	1	(0.3)
	Other	1	(0.4)	-	-	1	(0.3)
Eye color (Study Eye) †	Blue, gray, green	163	(62.0)	19	(16.2)	182	(47.9)
	Homogeneously brown	19	(7.2)	39	(33.3)	58	(15.3)
	Blue/gray/green with yellow-brown pigment	74	(28.1)	45	(38.5)	119	(31.3)
	Yellow-brown	7	(2.7)	14	(12.0)	21	(5.5)
Family history of glaucoma	No	161	(61.2)	67	(57.3)	228	(60.0)
	Yes	102	(38.8)	49	(41.9)	151	(39.7)
Diagnosis	POAG (total)	242	(92)	109	(93)	351	(92)
	Right eye	9	(3.4)	7	(6)	16	(4.2)
	Left eye	13	(4.9)	1	(0.9)	14	(3.7)
	Both eyes	220	(83.6)	101	(86.3)	321	(86.5)
	Exfoliation glaucoma (total)	22	(8)	7	(6)	29	(8)
	Right eye	7	(2.7)	1	(0.9)	8	(2.1)
	Left eye	6	(2.3)	1	(0.9)	7	(1.8)
	Both eyes	9	(3.4)	5	(4.2)	14	(3.7)
Treated eye at Month 1 visit	Right eye	37	(14.1)	17	(14.5)	54	(14.2)
	Left eye	32	(12.2)	15	(12.8)	47	(12.4)
	Both eyes	194	(73.8)	85	(72.6)	279	(73.4)

† The iris color displayed in the demographic tables was determined by the investigator at the baseline visit. The iris color used in the analysis of increased iris pigmentation was determined by Pharmacia based on the iris photographs, and may not match the investigator-determined iris color for all patients.

Abbreviations: NIIP= No Increase in Iris Pigmentation, IIIP= Increase in Iris Pigmentation

## Results – Protocol CTN9400PG034

### Increased Iris Pigmentation (IIP)

Increased iris pigmentation compared to baseline was documented in 30.8% (117/380) of patients. The patients most likely to develop increased iris pigmentation had mixed color irides: green/brown, yellow/brown or blue/gray with brown.

**Table 6: Number of Patients Developing Increased Iris Pigmentation by Eye Color at Baseline at the Start of the Original Study**

Iris color at baseline	NIIP N=263		IIP N=117		All patients N=380
	n	%*	N	%*	N
<b>Blue/gray</b>					
Blue/gray	27	100	0	0	27
Blue/gray with slightly brown	166	92.7	13	7.3	179
<b>Mixed colors</b>					
Blue/gray with brown iris	36	56.3	28	43.7	64
Green-brown	19	24.7	58	75.3	77
Yellow-brown	3	15	17	85	20
<b>Brown</b>					
Brown (Caucasian)	6	85.7	1	14.3	7
Brown (Black*)	4	100	0	0	4
Brown (Asian)	2	100	0	0	2
<b>Total</b>	<b>263</b>	<b>69.2</b>	<b>117</b>	<b>30.8</b>	<b>380</b>

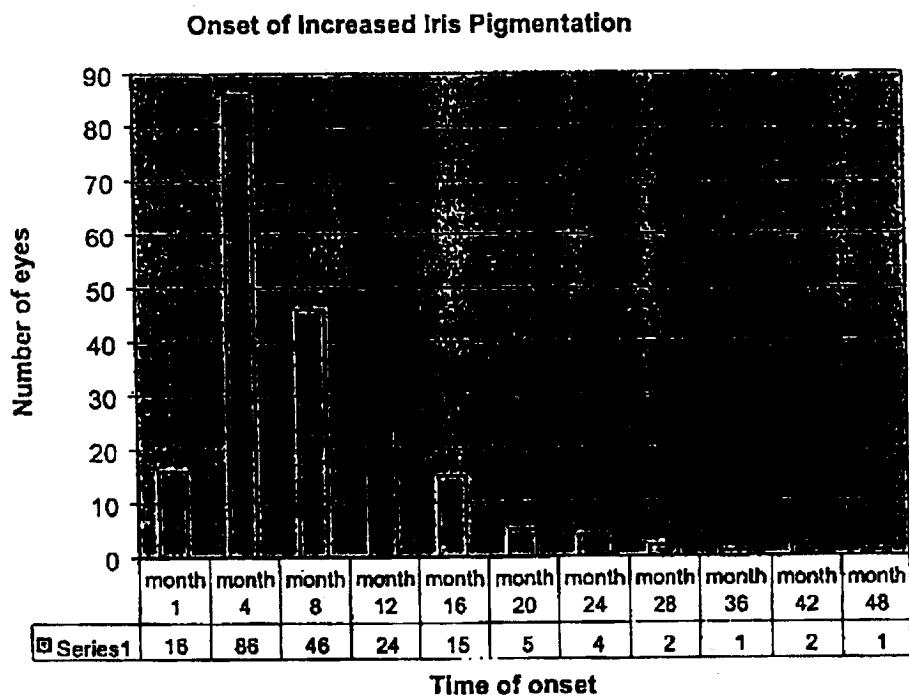
\* Row percent

\* Includes Indian

Abbreviations: NIIP=No increase in Iris Pigmentation, IIP=Increase in Iris Pigmentation

#### Reviewer's Comments:

*Increases in iris pigmentation occur in all types of irides, however, it does appear to be more prevalent (or more noticeable) in mixed color irides.*

**Fig. 1 The onset of Increased Iris Pigmentation in Patients by Visit**

The progression of the magnitude of the IIP was evaluated in the subgroup of the 380 patients continuing in the extension phase of study PG034. These patients have the longest time of exposure to latanoprost. During the 4-year treatment period, 202 eyes in 117 patients developed IIP, whereof 73% (148/202) had onset within the first 8 months of treatment. Few eyes had onset after 16 months of treatment. Follow-up data for more than three years after onset of the IIP are available for 124 out of these 202 eyes.

**Reviewer's Comments:**

*There is a higher risk of developing increased iris pigmentation associated with Xalatan within the first 2 years of use, however, this risk is present for at least 4 years. Additionally, there are no clearly definable risk factors associated with "late" onset of iris pigmentation.*

**Table 7: Number of eyes graded as Weak, Moderate or Marked According to Time from Onset of IIP**

Time Since Onset (Days)	Maximal grade of iris pigmentation						Total	
	Weak		Moderate		Marked			
	N	%	N	%	N	%		
0 - 365	75	60.5	41	33.1	8	6.5	124	
366- 730	46	37.1	54	43.6	22	17.7	124#	
731- 1095	43	35.3	51	41.8	28	22.9	122*	
> 1095	43	34.7	51	41.1	30	24.2	124	

%Percentage of row, #2 eyes graded "NIIP", \*missing photos for 2 patients

This data suggest that the rate of progression decreases with increasing time after onset. This hypothesis was further addressed by an analysis of the individual patient regression coefficients for the regression of photo rank, against chronological order. This analysis was performed for each patient and period for all eyes with increased iris pigmentation.

Assuming that all eyes with a regression coefficient < 0 have had no change in iris pigmentation, then by reason of symmetry, the same proportion of false increases can be predicted. If the proportion of eyes with a regression coefficient < 0 (reflecting a decrease in iris pigmentation), the difference may estimate the proportion of eyes with an increase in iris pigmentation (so-called symmetry adjusted estimate).

**Table 8: Proportion of Eyes (%) with an estimated Increase in Pigmentation,  
Estimated by the Regression Coefficients for the Rate of Progression**

Time from onset (days)	Regression Coefficient			Symmetry-adjusted estimate of increase in Pigmentation, %
	< 0	= 0	> 0	
0 – 365	7.1	26.3	66.7	59.6
366 – 730	8.7	55.2	36.1	27.4
731 – 1095	11.0	62.3	26.7	15.7
> 1095	10.7	76.8	12.5	1.8

These results show that the progression of iris pigmentation slowed with time. By the third year and fourth year after onset, only 15.75 % and 1.8% of eyes respectively had a definite progression.

**Reviewers Comments:**

*The agency agrees that the progression of iris pigmentation slows with time, however, the data also shows that the progression is an ongoing process and has failed to cease by 4 years.*

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**Table 9: Intraocular pressure (mmHg) per visit. Population: all patients with observed values**

		IOP study eye(s)													
		Visit													
		baseline	Month 1	Month 4	Month 8	Month 12	Month 16	Month 20	Month 24	Month 28	Month 32	Month 36	Month 42	Month 48	
Increased iris pigmentation															
No	Mean	23.7	17.1	17.1	17.2	17.8	17.4	17.7	17.5	17.6	17.6	17.6	18.0	18.2	
	Std	4.7	3.8	3.4	3.3	3.9	3.6	3.7	3.7	3.6	3.8	3.8	3.8	4.4	
Yes	Mean	23.9	17.4	17.5	17.1	17.4	17.3	17.5	17.6	17.8	17.6	17.2	17.3	17.3	
	Std	3.9	3.7	3.3	3.5	3.3	2.8	3.0	3.2	3.3	3.5	3.5	3.6	3.6	
Total	Mean	23.8	17.2	17.2	17.2	17.7	17.4	17.6	17.5	17.7	17.6	17.5	17.8	17.9	
	Std	4.4	3.7	3.4	3.4	3.7	3.4	3.5	3.6	3.5	3.7	3.7	3.8	4.2	

**Reviewer's Comments:** Increase in iris pigmentation did not appear to have an effect on intraocular pressure during the course of this study.

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**Table 10: Ocular Adverse Events that Occurred in more than 1% of patients from baseline to 48 months of latanoprost treatment. All Patients.**

Body System	Preferred term	NIIIP N= 263		IIP N= 117		All patients N= 380	
		n	%	n	%	n	%
Skin & Appendages	Dermatitis	5	1.9	2	1.7	7	1.8
	Hypertrichosis	31	11.8	15	12.8	46	12.1
	Rash erythematous	3	1.1	3	2.6	6	1.6
	Skin disorder	12	4.6	2	1.7	14	3.7
Central & Peripheral Nervous System	Headache	3	1.1	1	0.9	4	1.1
	Optic atrophy	46	17.5	24	20.5	70	18.4
	Ptosis	6	2.3	2	1.7	8	2.1
	Visual field defect	95	36.1	45	38.5	140	36.8
Vision	Blepharitis	36	13.7	10	8.5	46	12.1
	Blindness temporary	3	1.1	1	0.9	4	1.1
	Cataract	67	25.5	39	33.3	106	27.9
	Chalazion	2	0.8	2	1.7	4	1.1
	Conjunctival disorder	23	8.7	7	6.0	30	7.9
	Conjunctival haemorrhage	11	4.2	3	2.6	14	3.7
	Conjunctivitis	26	9.9	11	9.4	37	9.7
	Corneal disorder	61	23.2	30	25.6	91	23.9
	Diplopia	4	1.5	2	1.7	6	1.6
	Epiphora	9	3.4	5	4.3	14	3.7
	Errors of refraction	17	6.5	12	10.3	29	7.6
	Eye abnormality	81	30.8	38	32.5	119	31.3
	Eye hyperaemia	69	26.2	35	29.9	104	27.4
	Eye pain	23	8.7	13	11.1	36	9.5
	Increased intraocular pressure	51	19.4	22	18.8	73	19.2
	Iris pigmentation increased	18	6.8	60	51.3	78	20.5
	Irritation eye	83	31.6	38	32.5	121	31.8
	Keratitis	4	1.5	1	0.9	5	1.3
	Lacrimation abnormal	12	4.6	14	12.0	26	6.8
	Macula lutea degeneration	6	2.3	3	2.6	9	2.4
	Melbomianitis	3	1.1	5	4.3	8	2.1
	Photophobia	9	3.4	5	4.3	14	3.7
	Retinal deposits	9	3.4	4	3.4	13	3.4
	Retinal disorder	11	4.2	3	2.6	14	3.7
	Retinal haemorrhage	7	2.7	-	-	7	1.8
	Vision abnormal	57	21.7	26	22.2	83	21.8
	Vitreous detachment	16	6.1	2	1.7	18	4.7
General	Allergic reaction	4	1.5	6	5.1	10	2.6
	Surgical intervention	17	14.5	43	31.3	26	9.9

In general, the pattern of adverse events was independent of the presence of IIP, although a slighter higher incidence of abnormal lacrimation, allergic reactions and cataract was reported in patients who developed IIP with those who did not. Blepharitis was reported slightly more in patients who did not develop IIP than in those who did.

**Reviewer's comments:**

*This interim 4-year report does not reveal any new clinically significant safety concerns associated with increased iris pigmentation, however, the full safety profile cannot be assessed until this uncontrolled process abates.*

**Study 2**

**Protocol number:** Not applicable

**Title:** A long-term safety follow-up of patients who developed increased iris pigmentation during the phase III trials of latanoprost in patients with Primary Open Angle Glaucoma or Ocular Hypertension after cessation of latanoprost treatment.

**Objective:** The aim of the follow-up program was to evaluate the long-term development of the increased iris pigmentation and related ocular tissues after cessation of latanoprost.

**Study Design:** Patients withdrawn from the phase 3 studies that had exhibited or were suspected to have exhibited increased iris pigmentation entered a follow-up program. The follow-up period was originally planned to be 2 years but was extended to 5 years.

**Study Population – Inclusion and Exclusion Criteria**

**Patient Selection:**

Patients who exhibited increased or were suspected to have exhibited increased iris pigmentation and were withdrawn from the phase 3 clinical studies in the US, Scandinavia and the UK were asked to participate in the follow-up program.

**Study Schedule**

The patients were seen approximately every six months. Examinations were photography of the irides, en face photographs and standard ocular examinations: gonioscopy, tonometry and slit lamp.

#### **Subject Disposition and Demographics**

A total of 79 patients were included in the follow-up program. Additional two patients were not included in the analyses since very few photos were taken and no CRF's were completed.

**Table 11: Duration of follow-up after cessation of latanoprost treatment**

Months	0 - <12	≥12<24	≥24<36	≥36<48	≥48<60	≥60
Number of patients	4	8	11	12	26	18

**Table 12: Demographic and other baseline characteristics before latanoprost treatment in the phase III studies**

<b>Sex</b>		
Male	N	49
Female	N	30
<b>Age</b>		
Mean		67.6
SD		10.7
Min		40.4
Max		87.2
<b>Eye color study eye(s)</b>		
Blue-gray	N	1
Blue-gray with slight brown	N	3
Blue-gray with brown	N	15
Green-brown	N	51
Yellow-brown	N	6
Brown	N	3
<b>Latanoprost treated eye</b>		
Unilateral	N	21
Bilateral	N	58

#### **Results**

##### **Increased Iris Pigmentation (IIP)**

During the follow-up period, no change in pigmentation grade in the irides could be verified from the photos, except in one patient, where a slight decrease was assessed. Thus the increased iris pigmentation is stable, for at least 5 years.

**Table 13: Grade of increased iris pigmentation at the time of withdrawal from latanoprost treatment compared with before start of treatment, number of patients (%)**

Maximum grade	N	%
None	12	15.2
Weak	28	35.4
Moderate	33	41.8
Marked	4	5.1
No information	2	2.5

#### Eyelashes

"Weak" or "moderate" changes of eyelashes were reported in 54.4% of the patients at time of withdrawal from the phase 3 studies compared with before start of treatment with latanoprost.

The changes of the eyelashes developed during the latanoprost treatment had disappeared in all patients at the first assessable photograph during the follow-up program with the exception of one patient. This patient was assessed to have "weak" changes of the eyelashes up to 20 months after cessation of latanoprost. At the following visit, at 25 months, no changes of the eyelashes could be observed.

**Table 14: Grade of changes of eyelashes at the time of withdrawal from latanoprost treatment compared with before start of treatment, number of patients (%)**

Maximum grade	N	%
None	31	39.3
Weak	28	35.4
Moderate	15	19.0
Marked	0	0
No information	5	6.3

**Reviewer's comments:** *Increased iris pigmentation associated with the use of latanoprost is irreversible for at least 5 years after cessation of drug. Changes (darkening/lengthening/thickening) in eyelashes associated with latanoprost appear to be reversible, however, the time required to return to baseline varies.*

**VIII. Dosing, Regiment, and Administration Issues - N/A****IX. Use in Special Populations - N/A****X. Conclusions and Recommendations****A. Conclusions**

This submission fails to support a 1<sup>st</sup> line indication for Xalatan.

**B. Recommendation:**

Xalatan should remain a second line therapy for increased intraocular pressure associated with glaucoma or ocular hypertension until an adequate safety database can be established.

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Medical Officer's Review of NDA 20-597  
Supplement 10

NDA #20-597/S-010  
M.O. Review #3

Submissions: 6/19/02, 12/6/02, 12/16/02  
Review completed: 12/19/02

**Drug name:** Xalatan (latanoprost ophthalmic solution) 0.005%

**Applicant:** Pharmacia & Upjohn  
7000 Portage Road  
Kalamazoo, MI 49001-0199  
(616) 833-4000

**Pharmacologic Category:** Prostaglandin F2<sub>a</sub> analogue

**Proposed Indication(s):** For the reduction of elevated intraocular pressure in patients with open-angle glaucoma and ocular hypertension.

**Related Reviews:** Medical Officer's Review dated 2/16/96  
Medical Officer's Review dated 10/20/99

**Submitted:** Supplement proposing  
1. Expanded indication for first line treatment  
2. Revised labeling

**Background:**

NDA 20-597 was approved in June 1996, for the reduction of intraocular pressure in patients with open angle glaucoma or ocular hypertension who are intolerant or insufficiently responsive to other IOP lowering medications. The restriction to a second line therapy was based primarily on the potential risks associated with uncontrolled increases in pigmentation and the potential growth of other structures within the eye. Prior to approval, the applicant committed to long term studies to further evaluate the potential safety issue.

The increased pigmentation has been associated with an increase in the number of melanosomes within the melanocytes. To date, continued administration has resulted in continued increases in pigmentation and melanin production. The advice given to the sponsor from the time of the original NDA approval was that a request for Xalatan to be a first line therapy should include an adequate demonstration of a plateau effect of the pigmentation.

## **Executive Summary**

### **I. Recommendations**

#### **A. Recommendation on Approvability**

It is recommended that supplemental NDA 20-597/S-010 be approved with the revised labeling submitted on December 16, 2002.

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

No additional studies are considered necessary.

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### **II. Summary of Clinical Findings**

#### **A. Brief Overview of Clinical Program**

This product was the first prostaglandin-derived product approved for the reduction in elevated intraocular pressure. It was approved as a second line therapy because of the unknown long term effects related to increasing iris pigmentation. This supplement addresses issues raised by the FDA as important prior to changing the indication to a first line indication.

#### **B. Efficacy**

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

#### **C. Safety**

1. 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.

2. 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.
3. In patients with a risk factor for CME, such as cataract surgery, latanoprost may be the trigger which leads to CME. It is clearly an independent risk factor. While latanoprost may be unlikely to cause CME in patients without other risk factors, it clearly increases the incidence of CME in patients with risk factors.
4. Latanoprost, like the other prostaglandin related products, has an effect on the blood-aqueous and blood-retinal barriers.
5. The ~~—~~ Precautions sections of the labeling need to be strengthened to recommend that the product not be used in patients with active inflammation and that the product be used with caution in patients with a history of uveitis.
6. 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 has 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. The conclusions related to latanoprost are relevant to all of the other prostaglandin like drug products.

D. Dosing

No change in dosing is proposed or recommended.

E. Special Populations

There are no known differences with respect to age, gender, renal or hepatic impairment. Efficacy data in the original application is suggestive of an increased efficacy in patients with dark colored irides.

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**I. Introduction and Background**

This product was the first prostaglandin derived product approved for the reduction in elevated intraocular pressure. It was approved as a second line therapy because of the unknown long term effects related to increasing iris pigmentation. This supplement addresses issues raised by the FDA as important prior to changing the indication to a first line indication.

**A. Drug Established and Proposed Trade Name:**

Xalatan (latanoprost ophthalmic solution) 0.005%

**Sponsor's Proposed Indication:**

Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension

**C. Important Milestones in Product Development**

Prior to the approval of the original application and during the first couple of months following the approval of the original application, the information necessary to support a first line indication was discussed with the sponsor. The current supplement (Supplement 10) was originally received by the FDA on July 1, 1999. The supplement did not address the concerns which had led to the product's second line indication as discussed with the sponsor in 1996. A study [034] designed to address several of the concerns had been started but not completed. A "Not Approvable" letter was issued on October 20, 1999. A response to the FDA's action was received on April 13, 2001. The principal study [034] had still not been completed. A second "Not Approval" letter was issued by the agency. The present submission includes the final results of study 034.

**E. Important Issues with Pharmacologically Related Agents**

The effects seen with respect to both safety and efficacy are class effects for this product.

**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 previous clinical reviews.

**III. Human Pharmacokinetics and Pharmacodynamics**

All relevant issues have been discussed in previous clinical reviews.

**IV. Description of Clinical Data and Sources****A. Overall Data**

Clinical study reports and literature reports.

**B. Tables Listing the Clinical Trials and Reports**

Clinical Study 034  
Pharmacia Report c0027616 2/2/2001  
Pharmacia Report c0040478 6/14/2002  
Pharmacia Report c0027276 3/30/2000  
Pharmacia Report c0026636 5/22/2000  
Pharmacia Report c0031838 10/17/2000  
Pharmacia Report c0013595  
Pharmacia Report c0013532 11/5/1999  
Pharmacia Report KP9400243  
Pharmacia Report KP9400369  
Pharmacia Report KP9400215  
Pharmacia Report 9600213 -1996  
Pharmacia Report 9710623 -1997  
Pharmacia Report 9710622 -1997  
Pharmacia Report 9400611, 9400612 -1994  
Pharmacia Report 9600011, 9600012 -1996

**C. Postmarketing Experience**

The product has been marketed in the United States and multiple other countries for over 5 years.

**D. Literature Review**

All relevant literature was submitted or referenced. In addition, as part of this review, a Medline literature search was conducted and the relevant articles were reviewed.

**V. Clinical Review Methods****A. How the Review was Conducted**

All study report and literature reports were reviewed.

**B. Overview of Materials Consulted in Review**

IND and NDA Paper and electronic information were reviewed including copies of the photographic data.

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

Original photographic data was reviewed and compared to the submitted data. Differences observed were relatively minor and do not significantly alter the conclusions.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

All studies were conducted in accordance with accepted ethical standards.

E. Evaluation of Financial Disclosure

Financial Disclosure forms were reviewed. There is no significance difference in the study results when the data from investigators with potential conflicts of interest are removed.

VI. Integrated Review of Efficacy

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

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

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

B. Description of Patient Exposure

5 year post marketing data  
5 year clinical study

C. Methods and Specific Findings of Safety Review

Review of all relevant studies

D. Adequacy of Safety Testing

Safety testing considered adequate.

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#### E. Summary of Critical Safety Findings and Limitations of Data

Four issues of concern were identified by the Division in its not approvable letter. Pharmacia has addressed each of the concerns as follows:

**Reviewer's Comments:** *The text listed below is from the sponsor's submission and does not necessarily represent the reviewer's conclusions unless listed in the Reviewer's Comments.*

1. Uncontrolled increases in melanosomes that may result in continuing increases in iris pigmentation and in increases in IOP as a result of interference in the trabecular meshwork.

**Applicant's Response:**

Iris color is associated with the number of melanocytes of the anterior border layer of the iris stroma and not with the number of melanocytes per unit iridal surface. The number of iridal melanocytes is similar in persons with blue or with brown irides; however, the melanocytes in brown irides contain larger melanosomes. Ocular melanocytes are generally regarded as stable since they do not leak or donate melanin to other cells. A potential consequence of accumulation of melanin within the melanosomes is pigmentary glaucoma with a subsequent risk for increased IOP due to obstruction of the trabecular meshwork. The melanin involved in the pathogenesis of pigmentary glaucoma is the result of the rubbing of the lens zonules against the epithelium and does not originate from the iris stroma. Nevertheless, there is no clear relationship between the amount of melanin entering the outflow system and IOP elevation in pigmentary glaucoma. Pigmentary glaucoma was not reported in any of the patients in study 034. Further, no other adverse events were reported as a consequence of increased iris pigmentation. Importantly, IOP was well maintained, independent of the degree of increased pigmentation observed; mean IOP and long-term IOP control was similar between patients who developed increased iris pigmentation and those who did not.

A change in pigmentation of the trabecular meshwork was not revealed from histopathological results. Further, no evidence was found for a latanoprost-induced increase in melanin within the iris epithelial cells or for a latanoprost-induced promotion of the release of melanin granules from this epithelium. These data argue strongly that latanoprost treatment does not lead to melanin release from melanocytes. This finding is consistent with the lack of active synthesis of melanin in the iridal epithelium or in any other intraocular-pigmented cells in monkeys with latanoprost-induced increased iris pigmentation.

In study 034, 33% of all patients experienced a darkening of iris color that was presumably due to increases in the melanin content of the melanosomes of the melanocytes in the iris. The majority of patients (80%) with mixed color irides (e.g., green-brown or yellow-brown) experienced a darkening of iris color. For some patients, iris pigmentation increased during the first 2 years of therapy, but the rate of progression decreased over time and was negligible after 3 years (based on reported severity). The physiological variation in pigmentation is the result of differences in melanogenesis

rather than in melanocyte number. Latanoprost has been shown to change the relative amounts of eumelanin (black/brown melanin) and pheomelanin (red/yellow melanin) produced, favoring the production of the more photoprotective eumelanin over pheomelanin in monkeys.

Nonclinical data together with the results from the morphological examinations of human iris specimens convincingly demonstrated that the latanoprost-induced pigmentation change was not associated with any proliferative, degenerative or inflammatory changes, or with other histopathological alterations in the iris. A morphologic study that includes quantitative morphometric analyses of iris specimens from 17 patients with iris darkening following up to 41 months of latanoprost therapy is in progress.

Latanoprost increased transcription of tyrosinase in iridial melanocytes, both *in vivo* in monkeys and in cultured human iris melanocytes. In addition, *in vitro* data suggest that the variability of iris darkening following latanoprost treatment in patients may reflect the natural variability in the basal transcription of tyrosinase. However, iris color changes resulting from increased melanogenesis may be questioned after evaluation of the results of a recent ultrastructural study, which included quantitative evaluation and computerized image analysis of iridectomy specimens from 2 patients with latanoprost-induced increased iris pigmentation. An increase in maturing melanin granules (melanosomes types 2 and 3) was not observed, nor was an increase in mature melanin granules in the melanocytes in the anterior border layer or in the stroma. The only change was a minor increase in the size of the melanin granule in the melanocytes at the anterior border layer, which was in line with the mild modification in melanosome size that was noted in monkeys. These data did not provide compelling evidence of increased melanogenesis, but instead, indicated a process of melanin granule maturation, making the possible risk of excessive pigmentation accumulation even more unlikely. This conclusion was further supported by the subtle alterations in the melanosomal system associated with pigmentation change (i.e., very small increases in granule size may lead to relatively dramatic changes in iris pigmentation that are observed clinically) and by the lack of evidence of melanin release from melanocytes and of proliferative or degenerative changes in the iris, either in humans or in monkeys, even after long-term treatment with latanoprost.

In summary, there is no evidence of increased pigmentation of the trabecular meshwork, of free pigment in the anterior chamber, or of increased IOP in patients with increased iris pigmentation following treatment with latanoprost.

Histopathological studies showed the increase in pigmentation to be limited to a minor increase in the size of melanin granules in the iris stroma.

#### **Reviewer's Comments:**

*As reported in a number of the references, the number of iris or trabecular specimens used to make these conclusions is small. Further study is clearly needed. It does appear that the increase in pigment color of the iris is 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 to cellular activity.*

*The mechanism of increased iris pigmentation 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 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 [Arch Ophthalmol 1996, 114: 437-447].*

2. Uncontrolled growth of eyelashes or any other ocular structure. There is no in vitro or in vivo evidence that latanoprost has a mitogenic effect on any ocular cells or tissues, or on human melanoma cell lines. The number of melanocytes and other cells in the iris is similar between latanoprost-treated patients and control patients.

A change in eyelashes during latanoprost treatment is a well-known, but apparently harmless, side effect of all IOP-lowering prostaglandin analogues. After discontinuation of latanoprost, this change is reversible within the normal eyelash growth cycle. As detailed in the 3-year clinical study report for study 034, 47.6% (247/519) of the patients experienced an apparent change (i.e., thickening, lengthening, darkening, or increase in the number) of eyelashes. The majority of eyelash changes occurred within the first year of treatment. The incidence of newly reported changes slowed after 4 months and leveled off after 12 months of latanoprost treatment, which was within the normal growth cycle of eyelashes. No relationship was found between changes in eyelashes and increases in iris pigmentation. Similar percentages of patients both with and without a change in iris pigmentation had changes in eyelashes.

In animal models, latanoprost induced anagen phase hair growth and produced significant increases in both the length and the thickness of hair. Latanoprost likely produces a similar effect on human eyelashes, which is an amplification of the growth of existing follicles and does not imply the formation of new follicles since the number of eyelash follicles is genetic and unchanged after birth. The darkening of eyelashes that has been noted with latanoprost use is likely related to its effect on melanogenesis, which may be the same as for hypertrichosis.

Tumors of the iris and ocular structures were not observed in either nonclinical or clinical studies following treatment with latanoprost. Further, since the introduction of latanoprost worldwide in 1996, the incidence of all such tumors reported through pharmacovigilance was not higher than expected for this population independent of treatment. A suspected iridal tumor was reported in only 1 latanoprost-treated patient, which is consistent with the calculated incidence of 0.9 cases in the general population and 3.6 cases in an older population.

Uncontrolled growth of other ocular structures was not observed. In an ongoing investigation, the histological features of irides from patients undergoing filtering surgery, and who may or may not have previously received treatment with latanoprost, were compared. Three hundred fourteen latanoprost-treated specimens and 118 control specimens

were evaluated. Four hundred specimens were analyzed by eye color. All comparisons were made after adjusting for sex and iris color. Latanoprost-treated eyes had a statistically significantly higher number of stromal cells. Based on these observations, an immunohistochemical staining study of 114 of the above-mentioned specimens (brown-eyed female specimens) has been conducted. Similar percentages of melanocytes were noted in the irides of both the latanoprost-treated patients and the control patients.

In summary, increases in eyelash length, thickness, and darkness seem to be the result of synchronous induction of the anagen phase of hair growth; there is no evidence of an increase in the number of hair follicles. Finally, these increases appear to be reversible and are neither associated with nor correlated with any other adverse event, including iris pigmentation.

**Reviewer's Comments:**

*This effect also appears to be a class effect which is reversible if the drug product is discontinued. There is no evidence of neoplastic growth.*

3. Cystoid macular edema (CME) has been reported among patients treated with latanoprost, with the major proportion of reports in patients with existing CME risk factors. The main risk factor was a previous history of cataract surgery, regardless of when this surgery was performed. However, in most of these case reports, there was a recent temporal relation between latanoprost initiation and the occurrence of CME (range, 1 day to 11 months; mean, 9.5 weeks). A few of the patients with CME continued latanoprost treatment and the event resolved despite continued treatment, but the overwhelming majority discontinued treatment with latanoprost and the event resolved. All of the patients with CME recovered from this adverse event, with or without treatment with an anti-inflammatory drug. The appearance and/or disappearance of CME do not appear to have a relationship to latanoprost treatment.

**Reviewer's Comments:** *Strongly disagree. There is a clear temporal relationship between the use of latanoprost and development of CME, and there have been cases of challenge, de-challenge, re-challenge exhibiting CME.*

The main risk factor (i.e., cataract surgery) for CME was removed as a consideration in 5 pivotal studies with latanoprost. Patients who underwent any intraocular surgery, including cataract surgery less than 3 months prior to entry in 2 of the clinical studies or less than 6 months prior to entry in the other 3 studies, were excluded from study participation. Upon routine clinical examinations, CME was not evident in any of the patients ( $n = 1683$ ) treated with latanoprost in any of these studies, thereby providing additional evidence that latanoprost use is not a risk factor for CME.

**Reviewer's Comments:** *Disagree. These patients had not had cataract surgery.*

A 4-week study was designed to assess CME in the pseudophakic eyes with intact posterior capsules of patients (16 treated with latanoprost and 8 with placebo) who underwent cataract surgery at least 6 months prior to study start. None of the 16 latanoprost-treated patients had any clinical evidence of CME whereas 1 of the 8 placebo-treated patients did.

**Reviewer's Comments:** *The methodology used in this study was seriously flawed.*

NDA 20-597/S-010 Xalatan (latanoprost ophthalmic solution)

*Patients with intact posterior capsules are not the high risk group. The number of patients is low and the duration evaluated was short. This contributes to a low power to detect a change. Twenty-five percent of the patients did not complete the study. The placebo patient demonstrating leakage did not exhibit classical CME leakage and had no change in visual acuity (20/20).*

In another study, 145 patients were all treated with latanoprost before, during, and after cataract surgery. There were statistically significantly more cases of angiographic, but not clinical, CME in the latanoprost-treated group. However, nonsteroidal anti-inflammatory drugs abolished the difference between groups, indicating that any effect was indirect. The same effect was noted (angiographically but not clinically) following timolol treatment as was noted above following latanoprost treatment. This observation suggests that latanoprost poses no specific risk for CME.

**Reviewer's Comments:** *Contrary to the applicant's summary above, this study demonstrates a positive relationship between latanoprost and CME.*

Of the 5849 patients enrolled in study 071, 3934 were randomized to treatment with latanoprost and 1915 to treatment with the so-called usual care group (i.e., receiving any nonprostaglandin IOP-lowering medication that the patients might normally be prescribed). At least 1 CME risk factor was identified in 81.8% (3218/3934) of the patients in the latanoprost group and in 62.5% (1197/1915) of the patients in the usual care group. During the first year of the study, CME was reported in 0.6% (22/3934) of the patients in the latanoprost group and in 0.4% (8/1915) of the patients in the usual care group. Of the 30 patients with reported CME, 23 had at least 1 risk factor at baseline. Two patients (1 in each treatment group) had a history of CME and 1 patient in the usual care group had CME at baseline. A complete recovery from CME was reported in 54.5% (12/22) of those in the latanoprost group and in 37.5% (3/8) of those in the usual care group. Patients who develop CME are being evaluated for all risk factors relating to lens status (e.g., aphakia, pseudophakia, phakia, and presence or absence of intact or ruptured lens capsule).

During the first 3 years of the 5-year study 034, CME was reported in 5 of the 519 patients treated with latanoprost as an adjunctive IOP-reducing therapy. Existing retinal vascular disease had been reported in each of these 5 patients at baseline; therefore, a direct cause and effect between CME and latanoprost use in these patients was unclear.

The current label contains adequate warnings and precautions related to CME. Nevertheless, caution is recommended when using latanoprost in aphakic patients, in pseudophakic patients with torn posterior lens capsule, in patients with anterior chamber lenses, or in patients with known risk factors for CME (e.g., cataract surgery). Thus, there is no evidence that latanoprost is an independent risk factor for CME, the incidence of which is extremely rare and is nearly always associated with at least 1 known risk factor.

**Reviewer's Comments:** *The preceding paragraph is misleading. In patients with a risk factor for CME, such as cataract surgery, latanoprost may be the trigger which leads to CME. It is clearly an independent risk factor. While latanoprost may be unlikely to cause CME in patients without other risk factors, it clearly increases the incidence of CME in patients with risk factors.*

4. Iritis/Uveitis. Prostaglandins are believed to play a role as inflammatory mediators and are known to cause a breakdown of the blood-aqueous barrier. Warnings on this topic are included in the current label.

Unlike other prostaglandins, both nonclinical and clinical studies suggest that latanoprost does not have an effect on the blood-aqueous barrier. Data from study 034 and from pharmacovigilance showed that the majority of the latanoprost-treated patients who developed iritis/uveitis had other known predisposing risk factors.

**Reviewer's Comments:** *Strongly disagree. Latanoprost, like the other prostaglandin related products has an effect on the blood-aqueous and blood-retinal barriers.*

The 12-month interim data from the 5-year postmarketing surveillance study 071 on patients with open-angle glaucoma or ocular hypertension showed similarly high percentages of patients in each treatment group with risk factors for iritis/uveitis at baseline (e.g., history of diabetes mellitus, history of iritis/uveitis, previous ocular surgical procedures, argon laser trabeculoplasty, trabeculectomy, aphakia, pseudophakia, yttrium-aluminum-garnet capsulotomy, anterior vitrectomy, and retinal surgery). A new event of iritis/uveitis between baseline and month 12 was reported in 0.9% (34/3934) of the patients in the latanoprost group and in 0.7% (13/1915) of the patients in the usual care. At least 1 risk factor for iritis/uveitis was noted in 61.8% (21/34) of the patients in the latanoprost group and in 76.9% (10/13) of the patients in the usual care group. The incidence of reported iritis/uveitis adverse events was very low and was similar between treatment groups. The risk for iritis/uveitis after 1 year of treatment was the same for patients treated with latanoprost as for patients treated with the usual care.

**Reviewer's Comments:** *The methodology of this study is seriously flawed. The percentages are based on a mixed population base and unlike events are counted together.*

Adverse events coded as iritis, uveitis, and iridocyclitis were tabulated from the pharmacovigilance database for the period from 5 June 1996 through 28 February 2002. During this period, 96 cases of uveitis were reported, 25 of which were classified as serious; 11 cases of iridocyclitis were reported, 5 of which were classified as serious; and 84 cases of iritis were reported, 18 of which were reported as serious. Since more than 13 million patients worldwide have received latanoprost over the same period, the incidence of such events is quite low. The diagnosis of iritis/uveitis was, in some reported cases, based only on findings of trace cells in the anterior chamber. In many of these cases, the patients were receiving other ophthalmic medications concomitantly. The majority of the patients recovered, regardless of whether or not an anti-inflammatory treatment was administered.

Previous incisional ocular surgery or history of uveitis were the primary predisposing factors for iritis/uveitis. The best-estimated background incidence of 17/100,000 cases of iritis/uveitis is above that of 4/100,000 reported to be associated with latanoprost use. Risk factors for iritis/uveitis were identified for the majority of patients.

These combined data indicate that latanoprost does not cause an inflammatory response, despite its being a prostaglandin analogue. Furthermore, since the condition is both reversible and treatable, it does not seem sufficient to contraindicate the use of latanoprost.

**Reviewer's Comments:** *Strongly disagree. The \_\_\_\_\_ /Precautions sections of the labeling need to be strengthened to recommend that the product not be used in patients with active inflammation and that the product be used with caution in patients with a history of uveitis.*

#### Other Prostaglandins

Data from the estimated \_\_\_\_\_ person years of total patient exposure to latanoprost confirmed the side effect profile of latanoprost that had been identified at the time of its registration in 1996. Pharmacia conducted two 5-year postmarketing studies 034 and 071 using latanoprost, from which data on long-term exposure were obtained. Other IOP-lowering prostaglandin analogues have been available for a shorter time than latanoprost; therefore, information about the total human exposure to them is more limited. Further, the clinical studies conducted with these other prostaglandins have been of relatively short duration, and so perhaps have not provided a sufficient period of time for long-term side effects to fully manifest themselves.

Latanoprost exerts its IOP-lowering effect through its interaction with prostaglandin receptors, including the FP receptor. The IOP-lowering mechanism of action is presumed to be the same for latanoprost as for the other prostaglandin analogues. The side effects observed after administration of latanoprost, including iris pigmentation and eyelash changes, are thought to be related to the interaction with prostaglandin receptors since similar effects are noted following administration of all of the IOP-lowering prostaglandin analogues. For example, travoprost is known to produce initial increases in iris pigmentation at approximately the same rate as latanoprost and to produce a higher rate of eyelash change than latanoprost. Whether the rate of increased iris pigmentation for the other prostaglandins such as travoprost will plateau after time as it does for latanoprost is unknown.

Safety information pertaining to other prostaglandins is not applicable to the safety information about latanoprost because the published studies with other prostaglandin analogues are all of much shorter duration than those of latanoprost and the total human exposure to these medications is more limited. Despite similar chemical structures, modes of action, and degrees of IOP-lowering effect, latanoprost and the other prostaglandin analogues display remarkably different levels of patient tolerability. In comparative trials, both travoprost and bimatoprost produced rates and severity of hyperemia from 2 to 3 times higher than those of latanoprost, demonstrating that similar modes of action cannot be generalized to similar safety and side effect profiles until long-term comparative studies have been completed.

**Reviewer's Comments:** *The statements above are not supported by the references. 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. Small differences in the rate of these reactions have been reported, but this appears to be related to the observation techniques and the size of the particular study, not the mechanism or type of effect. The conclusions related to latanoprost are relevant to all of the other prostaglandin-like drug products.*

### Benefit/Risk

The overall benefit/risk ratio for patients using latanoprost as a first-line agent for the reduction of IOP is highly positive. As the patient population ages, the rates of trabeculectomy might be expected to increase accordingly, even if the incidence of glaucoma remained the same. However, the rates of trabeculectomy have decreased since the introduction of latanoprost, although it is not clear that latanoprost is solely responsible for this phenomenon. The overall incidence of reported treatment emergent adverse events was lower following latanoprost use than following the use of other IOP-lowering prostaglandins such as travoprost, bimatoprost, and unoprostone. Other benefits of using latanoprost as a first-line agent are the reduction in patient exposure to agents with defined risks such as timolol and an improvement in patient compliance resulting from the once-daily dosing regimen.

A risk model was created to evaluate the potential safety impacts to patients of changing from beta-blockers (primarily timolol) to latanoprost as first-line therapy for the treatment of elevated IOP in patients with glaucoma. The model predicted the occurrence of 3 serious systemic adverse events (i.e., newly developed asthma, exacerbated asthma in patients with a history of asthma and/or chronic obstructive pulmonary disease [COPD], and either nonfatal or fatal cardiac failure) in 5 hypothetical cohorts, each containing 10,000 patients with glaucoma whose medical history was followed for 5 years. In accordance with the results from postmarketing studies, it was assumed that the rates of these events for latanoprost users would be the same as the general population, and changes in risk associated with timolol exposure were obtained from literature and pharmacovigilance systems. Apart from beta-blockers exposure, the prevalence of asthma and COPD in the cohorts, obtained from literature, was considered an important outcome modifier.

During the simulated 5-year follow-up, deaths were estimated to increase from 988 in the latanoprost/general population group to 1014 with exposure to timolol. This increase in estimated deaths was attributed to an increase in heart failure, from 267 patients to 352. New cases of asthma were projected to increase only from 94 to 96 patients, whereas exacerbation of asthma and COPD varied from 12% (402 exacerbations) for the latanoprost (general population) cohort to 9% (410 exacerbations) for the timolol (pharmacovigilance) cohort, for which 547 exacerbations would have been projected if timolol users had the same characteristics as latanoprost users. Overall, the estimated death rate in the timolol group increased between 2% and 3% over that in the latanoprost (general population)-group. The numbers of projected events were considered to have been underestimated based on limitations of the model, which included omission of prevalent cases of heart failure, and deaths due to asthma and COPD, as well as inclusion of the effect of timolol labeling on estimates of relative risks. If adherence to timolol labeling were absolute, the risk would be diminished; however, patient screening for such warnings is often ineffective. The model also assumes the same benefit to patients from therapy using either timolol or latanoprost, which is not necessarily true. Therefore, the 5 hypothetical cohorts were the following: 1) Latanoprost / general population. The risk to latanoprost-treated patients for each of the adverse events was considered the same as for the general population. Of this group, 12% had asthma. 2) Timolol, most probable. Despite being contraindicated in patients with asthma and/or COPD, 9% of patients treated with timolol had asthma. 3) Timolol, no label. This scenario presumed that contraindications for timolol use were completely ignored. The prevalence of asthma was, therefore, the same as for the general population (i.e., 12%). 4) Timolol, pharmacovigilance cohort. This cohort simulated the actual conditions under which timolol was used. Data were from spontaneous reports to

pharmacovigilance units. The prevalence of asthma was assumed to be 9%. 5) Timolol, pharmacovigilance cohort, no label. This cohort was the same as that above except that it presumed no labeling restrictions. The prevalence of asthma was assumed to be 12% patients may have a greater net gain in switching from timolol to latanoprost than is estimated from the model in the reduction of only serious systemic adverse events.

Clinical studies and postmarketing studies of the duration and size of study 034 efficiently provide safety data about adverse events with rates of greater than 1 in 1000 and with an induction period of not longer than 5 years. Hence, these studies cannot exclude the potential of rare adverse events that require longer periods to manifest themselves. Pharmacia is committed to the postmarketing surveillance of its products using common pharmacovigilance approaches such as adverse event monitoring and pharmacoepidemiological studies.

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**Reviewer's Comments:** *The preceding analysis is seriously flawed. It fails to account for potential benefits with respect to hypertension and stroke from taking beta-blockers. The reference "Topical glaucoma medications and cardiovascular risk in the elderly," [Clin Pharmacol Ther 1994;55:76-83] shows a trend toward decreased congestive heart failure with the use of ophthalmic beta-blockers. If further epidemiological studies are undertaken, they should include rates of death, hypertension and stroke.*

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On Original

NDA 20-597/S-010 Xalatan (latanoprost ophthalmic solution)

**WITHHOLD 24 PAGE(S)**

Draft Labeling

**VIII. Dosing, Regimen, and Administration Issues**  
No changes in the dosing or administration.

**IX. Use in Special Populations**

- A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation  
There are no known differences with respect to age, gender, renal or hepatic impairment.
- B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy  
There are no known differences with respect to age, gender, renal or hepatic impairment. Efficacy data in the original application is suggestive of an increased efficacy in patients with dark colored irides.
- C. Evaluation of Pediatric Program  
This product is not indicated for pediatric patients because of the continued increases in pigmentation.
- D. Comments on Data Available or Needed in Other Populations  
None.

**X. Conclusions and Recommendations**

A. Conclusions

- 1. 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 to 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 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 effects 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. 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.

- 2. 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.

3. In patients with a risk factor for CME, such as cataract surgery, latanoprost may be the trigger which leads to CME. It is clearly an independent risk factor. While latanoprost may be unlikely to cause CME in patients without other risk factors, it clearly increases the incidence of CME in patients with risk factors.
4. Latanoprost, like the other prostaglandin-related products has an effect on the blood-aqueous and blood-retinal barriers.
5. The Warnings/ \_\_\_\_\_ section of the labeling need to be strengthened to recommend that the product not be used in patients with active inflammation and that the product be used with caution in patients with a history of uveitis.
6. 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 has 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. The conclusions related to latanoprost are relevant to all of the other prostaglandin like drug products.
7. \_\_\_\_\_

B. Recommendations:

It is recommended that supplemental NDA 20-597/S-010 be approved with the revised labeling submitted on December 16, 2002.

XI. Appendix  
None.

Wiley A. Chambers, M.D.  
Medical Officer, Ophthalmology

NDA 20-597/S-010 Xalatan (latanoprost ophthalmic solution)

**This is a representation of an electronic record that was signed electronically and  
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**/s/**

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Wiley Chambers  
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**Wiley Chambers  
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## **Appendix C**

Feb-06-04

09:25am From-OCC/FDA

301-827-0873

T-896 P.002/002 F-144



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville MD 20857

February 4, 2004

RE: NDA 21-435

ADMINISTRATIVE STAY OF ACTION

In light of questions raised about the source of the data the Food and Drug Administration (FDA) relied on in approving Dr. Reddy Laboratories Ltd's New Drug Application for Amvaz, amlodipine maleate (NDA 21-435), FDA believes that it is in the public interest to stay the effective date of the approval of that NDA pending FDA's reevaluation of the basis for that approval. Accordingly, the effective date of the approval of NDA 21-435, is hereby stayed until FDA has reevaluated the application and determined that the drug has been shown to be safe and effective under the conditions of use described in the labeling based on data from appropriate sources. Marketing under NDA 21-435 is prohibited during the pendency of the stay.

  
William K. Hubbard  
Associate Commissioner for Policy and Planning

C000001

**UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF COLUMBIA**

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PFIZER, INC.,	)	
	)	
	)	
Plaintiff,	)	
	)	
v.	)	Case No. 03-02346 (RCL)
	)	
FOOD AND DRUG ADMINISTRATION,	)	
MARK B. McCLELLAN, M.D., Ph.D.,	)	
Commissioner, Food and Drug Administration,	)	
and TOMMY G. THOMPSON, Secretary	)	
of Health and Human Services,	)	
	)	
Defendants,	)	
	)	
and	)	
	)	
DR. REDDY'S LABORATORIES, INC., et al.	)	
	)	
Proposed Intervenor-Defendants.	)	
	)	

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**FEDERAL DEFENDANTS' MOTION FOR STAY OF PROCEEDINGS**

Federal defendants, U. S. Food and Drug Administration (FDA), Mark B. McClellan, Commissioner, FDA, and Tommy G. Thompson, Secretary, U.S. Department of Health and Human Services (HHS), through their undersigned attorneys, move to stay the proceedings in this case. In this action, plaintiff Pfizer, Inc. (Pfizer) challenges FDA's approval of a new drug application (NDA) submitted by Dr. Reddy's Laboratories Ltd. (Reddy) for amlodipine maleate tablets (NDA 21-435) under section 505(b)(2) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 355(b)(2) (a 505(b)(2) application). In its request for relief, Pfizer seeks a declaration that FDA's approval of NDA 21-435 was unlawful and an order vacating its approval. See Complaint, Docket Item (D.I.) 1, at 15. On February 5, 2004, FDA stayed the effective date of

the approval of NDA 21-435 to conduct a reevaluation of the basis for that approval to ensure that any approval is based on appropriate data. Once the reevaluation of the data is completed, FDA will determine whether the approval should be maintained.

Federal defendants request that the Court stay proceedings in this case to promote the efficient resolution of this case and avoid the issuance of an advisory opinion. If FDA ultimately determines that the approval of NDA 21-435 was in error and should be withdrawn, this case will be moot. If FDA reaffirms its initial approval of the NDA, it will then be able to complete the administrative record in this case and promptly proceed with litigation. As discussed below, until FDA has made such a determination and completed the administrative record, the administrative decision in this case is not yet ripe for review.

#### BACKGROUND

Prior to the initial approval of Reddy's product, Pfizer (and others) submitted citizen petitions to FDA challenging FDA's policies regarding section 505(b)(2) applications in general and consideration of Reddy's 505(b)(2) application for amlodipine maleate specifically. 2001P-0323/CP1 submitted by Morgan, Lewis & Bockius, LLP, on behalf of Pfizer Inc. and Pharmacia Corporation (2001 Pfizer petition) (attached as Exhibit A); 2002P-0447/CP1 submitted by Morgan, Lewis & Bockius, LLP on behalf of Pfizer Inc. (2002 Pfizer petition) (attached as Exhibit B). On October 14, 2003, FDA issued a partial response to Pfizer's citizen petitions, as well as citizen petitions filed by other parties, addressing the legal bases and policy reasons for its interpretation and application of section 505(b)(2) (October 2003 Petition Response) (attached as Exhibit C). In the October 2003 Petition Response, FDA reserved its response to the specific scientific arguments raised by certain of the petitions, including Pfizer's challenge to NDA 21-

435. See October 2003 Petition Response, Exhibit C, at 1 n.1 ("Because this application is not approved, FDA cannot comment on the scientific issues raised in this petition. (See 21 CFR 314.430.)").

On October 31, 2003, FDA approved NDA 21-435. On November 13, 2003, Pfizer filed its Complaint. See D.I. 1. Reddy moved to intervene, see D.I. 4, and the federal defendants have filed their Answer, see D.I. 5. The parties have discussed filing cross-motions for summary judgment after FDA's submission of the administrative record. At this point in the litigation, however, the record has not been filed and no party has filed a motion on the merits of the case.

During the course of preparing its Citizen Petition response to Pfizer's scientific challenge to NDA 21-435 and collecting the administrative record for the response, FDA became aware that a first line reviewer made reference to certain studies of Pfizer's in the documentation of his review of NDA 21-435. In light of this discovery, FDA determined that it should reevaluate whether the approval of NDA 21-435 was based upon data from appropriate sources. Thus, on February 5, 2004, FDA issued an Administrative Stay of Approval (attached as Exhibit D) pending its reevaluation of the source of the data FDA relied on in approving NDA 21-435. If FDA determines upon reevaluation that the approval of NDA 21-435 is appropriate, FDA will promptly complete its Citizen Petition response to Pfizer's scientific challenge to FDA's approval of NDA 21-435 and will lift the Administrative Stay.

Both Pfizer, the plaintiff, and Reddy, the proposed intervenor, have asked FDA to provide a deadline by which the reevaluation process will be complete. FDA has informed the parties it intends to conduct the process expeditiously, but cannot provide a definitive time for its completion. However, at this time, FDA anticipates that the process will be completed within

approximately two months. Pfizer had informed the federal defendants that it could not take a position on the motion to stay without a commitment by the federal defendants regarding the length of the stay. Reddy opposes a stay as proposed by the federal defendants and is not prepared at this time to agree to a stay of any set duration.

#### DISCUSSION

A stay of proceedings will promote judicial efficiency, avoid the potential for an advisory opinion, and serve the interests of justice. As noted above, if FDA determines that NDA 21-435 should not have been approved and proceeds to withdraw the approval, this case will be moot. If FDA reaffirms its initial approval of the NDA, it will then be able to complete its Citizen Petition response to Pfizer's challenge to FDA's approval of NDA 21-435 and the administrative record for that response. That, in turn, will allow FDA to complete and file the administrative record for this case. Once the administrative record is submitted, this case will be ready for summary judgment briefing. By contrast, any briefing now would be conducted on an incomplete record.

Proceeding with the case prior to the completion of the administrative record would be contrary to the ripeness doctrine. "A claim is not ripe for adjudication if it rests upon contingent future events that may not occur as anticipated, or indeed may not occur at all." Pfizer v. Shalala, 182 F.3d 975, 978 (D.C. Cir. 1999) (citations omitted). Thus, the ripeness requirement serves "to prevent the courts, through avoidance of premature adjudication, from entangling themselves in abstract disagreements over administrative policies, and also to protect the agencies from judicial interference until an administrative decision has been formalized and its effects felt in a concrete way by the challenging parties." Id. (citations omitted). Those requirements will not be

met for the purposes of this litigation until FDA completes its reevaluation of the basis for approval of Reddy's NDA.

Under controlling law, where FDA's determination on an approval decision is not certain, a claim by one of the applicant's competitors that FDA violated the law during the approval process is not yet ripe. See, e.g., id. at 978-79 (Pfizer's challenge of FDA's acceptance of a drug application for processing is not ripe for review until approval decision is made). This legal conclusion is based on several grounds. First, FDA's future actions could make judicial review unnecessary. See id. at 979. Second, premature judicial review could deprive the agency of the opportunity to apply its expertise and correct any mistakes it may have made. See id. Third, a competitor cannot claim economic injury required to sustain the action until FDA has made a final determination on the approval decision. See id. All of these grounds apply to the instant case.

CONCLUSION

For the foregoing reasons, the Court should grant a stay of this case until FDA has completed its reevaluation of the data in the application at issue and lifted the Administrative Stay of Approval.

Respectfully submitted,

PETER D. KEISLER  
Assistant Attorney General

EUGENE M. THIROLF  
Office of Consumer Litigation

/s/

By: DOUGLAS W. STEARN (DCBN 440735)  
Attorney  
Office of Consumer Litigation  
U.S. Department of Justice  
P.O. Box 386  
Washington, D.C. 20044  
(202) 307-0061

Of Counsel:

ALEX M. AZAR II  
General Counsel  
Dept. of Health & Human Services

DANIEL E. TROY  
Chief Counsel

KAREN E. SCHIFTER  
Associate Chief Counsel  
U.S. Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857  
(301) 827-1152

Dated: February 18, 2004

**CERTIFICATE OF SERVICE**

I hereby certify that I caused the foregoing Federal Defendants' Motion for Stay of Proceedings to be served by electronic mail and via the District Court's Electronic Filing System (ECF) upon:

Anthony Herman  
COVINGTON & BURLING  
1201 Pennsylvania Avenue NW  
Washington, DC 20004  
(202) 662-5280  
Fax : (202) 778-5280  
Email: [aherman@cov.com](mailto:aherman@cov.com)  
*Counsel for Pfizer, Inc.*

David G. Adams  
VENABLE, LLP  
Terrell Place  
575 Seventh Street, NW  
Washington, DC 20004-1601  
(202) 344-8014  
Fax : 202-344-8300  
Email: [dgadams@venable.com](mailto:dgadams@venable.com)  
*Counsel for Dr. Reddy's Laboratories, Inc. and Dr. Reddy's Laboratories, Ltd.*

Meredith Manning, Esq.  
Hogan & Hartson L.L.P.  
555 13th Street, N.W.  
Washington, DC 20004-1109  
Email: [mmanning@hhlaw.com](mailto:mmanning@hhlaw.com)  
*Counsel for Biotechnology Industry Organization*

this 18th day of February, 2004.

/s/  
Douglas W. Stearn

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PFIZER INC.  
685 3RD AVE.

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SYSTEM #749002 / CAFE2356  
ACTUAL WGT: 9.3 LBS SCALE

NEW YORK, NY 10017

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SEE LABEL  
SEE LABEL  
ROCKVILLE, MD 20852

7389 0626 9909 FedEx.

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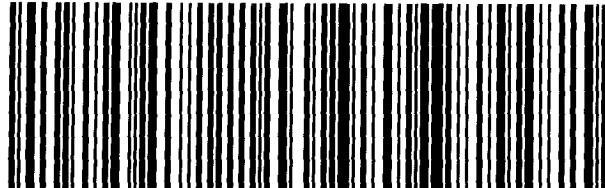
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