

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-275

CORRESPONDENCE

ALLERGAN

2525 Dupont Drive, P.O. Box 19534, Irvine, California, USA 92623-9534 Telephone: (714) 246-4500 Website: www.allergan.com



September 18, 2000

*WBS
New
10/11/00*

Food & Drug Administration
Center for Drug Evaluation and Research
Central Document Room
12229 Wilkins Avenue
Rockville, MD 20852



Re: Lumigan™ (bimatoprost ophthalmic solution) 0.03%
NDA 21-275
Original NDA
Request for Priority Review

Gentlemen:

Allergan hereby submits, under 21 CFR 314.50, an original NDA for AGN 192024 (bimatoprost ophthalmic solution) 0.03%, indicated for the reduction of elevated intraocular pressure (IOP) in patients with glaucoma or ocular hypertension with once-daily application.

Priority review

Allergan requests that this NDA be considered for priority review, based on the pharmacology of the active ingredient NCE, bimatoprost. Bimatoprost (AGN 192024) is pharmacologically unique and represents a new class of IOP-lowering compounds. Its novel pharmacology is conferred by replacement of the carboxylic acid group of PGF_{2α} with an electrochemically neutral substituent. Since the carboxylic acid group is critical for interaction with PGF_{2α}-sensitive FP receptors, bimatoprost exhibits no meaningful pharmacological activity at FP receptors showing that it is a unique synthetic analog of prostaglandin F_{2α} (PGF_{2α}). Moreover, extensive studies have demonstrated that bimatoprost has no meaningful, pharmacological activity at all other known prostaglandin receptors. Based on the lack of affinity for prostaglandin receptors, we called AGN 192024 an "ocular hypotensive lipid." Continued research into the mechanism of action of bimatoprost has revealed that its pharmacology appears to be related to that of PGF_{2α} 1-ethanolamide (prostanamide F_{2α}). This is a newly discovered, naturally occurring substance which is biosynthesized from anandamide by a pathway involving cyclooxygenase (COX)-2 but not COX-1. This new pathway, named the prostanamide pathway, leads to the synthesis of endogenous lipid amides that lower IOP. A comparison of the pharmacology of prostanamide F_{2α} and AGN 192024 suggests that AGN 192024 is a more potent and selective mimetic of prostanamide F_{2α}. In light of this more recent information, Allergan now refers to AGN 192024 as a prostanamide.

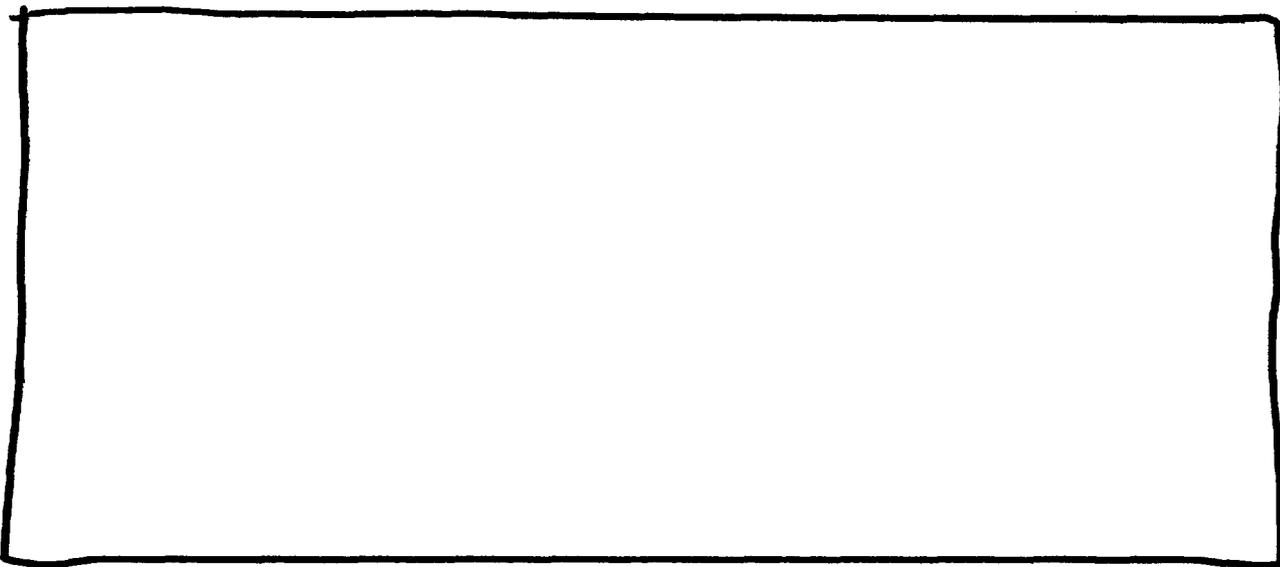
Two phase 3 clinical studies (192024-008 and 192024-009) were conducted in a total of 1198 subjects (both regimens of bimatoprost, and timolol), comparing bimatoprost ophthalmic solution dosed once- and twice-daily against timolol dosed twice daily, as first-line therapy in

DUPLICATE

001 005

the treatment of glaucoma and ocular hypertension. The results of these studies demonstrate that bimatoprost dosed once daily is superior in IOP-lowering activity to timolol dosed twice daily.

For these reasons – the unique pharmacologic activity of bimatoprost and its superior efficacy compared to standard topical treatment of glaucoma, in addition to its safety profile as supported in this submission – Allergan contends that a priority rating for review is appropriate as is a designation for first-line therapy.



Pediatric studies

No studies have been performed to date using bimatoprost ophthalmic solution 0.03% in pediatric populations; a statement to this effect appears in the summary section of the NDA, section 3.7.2.4, Areas of Special Interest.

The Agency agreed to granting a waiver for performing pediatric studies both in a

Based on the final rule "Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients" (Federal Register December 2, 1998; 63 (231): 66632-66672 at 66670), Allergan proposes that, since bimatoprost is a new chemical entity, pediatric studies should be delayed until additional safety and efficacy data have been collected in a larger number of adults subsequent to approval of the NDA. As soon as practical, Allergan will assess the appropriateness of either pursuing studies in pediatric populations, at which time a formal proposal will be submitted, or requesting a full or partial waiver based on the criteria set forth in the final rule.

Electronic submission

As agreed to at the April 12, 2000 Pre-NDA Meeting, sections 11 (Case Report Tabulations/Data Listings) and 12 (Case Report Forms) are being submitted either totally or partially in electronic format. Every effort was made to comply as closely as possible with the Guidance for Industry: Providing Regulatory Submissions in Electronic Format — NDAs, IT3, January 1999.

Section 11

The data listings from all phase 1 and 2 (non-pivotal) studies are being provided in hard copy only. The data sets from the two phase 3 pivotal trials, 192024-008 and 192024-009, are being provided as SAS transport files whose parameters will be searchable, and with accompanying documentation, annotated sample CRFs and hyperlinks.

Section 12

CRFs are organized by study and then by site (investigator), with an accompanying document with explanatory notes and hyperlinks. Both the archival and review copies are being provided in electronic format only.

As agreed to at the April 12, 2000 Pre-NDA Meeting, Allergan will provide copies of all ocular photographs from the two pivotal studies. The photos were copied onto CDs in PowerPoint format and are arranged by study, then by site, and finally by subject with baseline and 3 month results in one file, and the 6 month results in a separate file.

At the request of Randy Levin and then confirmed by Dr. Chambers during the week of August 21, 2000, Allergan is providing electronic copies of the text of the two phase 3 study reports. These are available in a "modular" format (each section as a separate document or documents), and wherever possible the text will be in Microsoft Word 97 format.

Finally, NDA sections 1-3 (certifications, labeling and sectional summaries) will also be provided electronically, in Microsoft Word wherever possible, to facilitate the Agency's preparation of draft labeling and the reviewers' summaries.

We confirm that the electronic and hard copies of all files herewith submitted are identical.

Statistical data

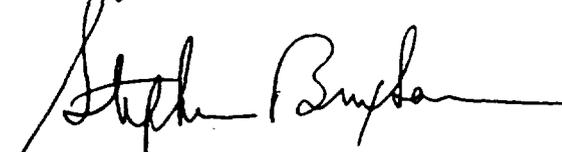
As agreed to at the Pre-NDA Meeting of April 12, 2000, section 10 of the NDA, statistical data, is an exact duplication (including item numbers) of section 8, clinical data.

Tradename

Allergan has included draft labeling in this submission with the tradename LUMIGAN. On February 23, 2000, Allergan was informed by Raphael Rodriguez, CSO, that the Office of Postmarketing Drug Risk Assessment (OPDRA) had tentatively approved the use of this tradename. We understand that final approval cannot be given until closer to the time of approval of this NDA. Allergan therefore requests that the Agency seek clearance for the tradename LUMIGAN at the appropriate time during the NDA review cycle.

Allergan concludes that all the available data from pharmacology, toxicology, pharmacokinetics and clinical studies demonstrate that LUMIGAN (bimatoprost ophthalmic solution) 0.03% dosed once daily is safe and effective for its intended use.

Sincerely,



Stephen Buxbaum
Director, Regulatory Affairs

**APPEARS THIS WAY
ON ORIGINAL**

OCT - 3 2000

NDA 21-275

Allergan
Attention: Stephen Buxbaum
Director, Regulatory Affairs
2525 Dupont Drive
P.O. Box 19534
Irvine, California 92623

Dear Mr. Buxbaum:

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

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

Review Priority Classification: Priority (P)

Date of Application: September 18, 2000

Date of Receipt: September 18, 2000

Our Reference Number: NDA 21-275

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on November 17, 2000, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be March 18, 2000.

Be advised that, as of April 1, 1999, 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 (63 FR 66632). We note that you have requested a waiver as discussed in your Pre-NDA meeting of April 12, 2000.

Under 21 CFR 314.102(c) of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone.

NDA 21-275

Page 2

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products, HFD-550
Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products, HFD-550
Division Document Room
9201 Corporate Blvd.
Rockville, Maryland 20850-3202

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

Sincerely,

/S/

Leslie Vaccari 10-3-00
Chief, Project Management Staff
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

**APPEARS THIS WAY
ON ORIGINAL**



October 10, 2000

NDA DRUG AMENDMENT



BC

Wiley Chambers, M.D.
Deputy Director
Division of Analgesic, Anti-Inflammatory
& Ophthalmologic Drug Products (HFD-550)
Food & Drug Administration
9201 Corporate Blvd., Building 2
Rockville, MD 20850

Re: Lumigan™ (bimatoprost ophthalmic solution) 0.03%
NDA 21-275
Responses to CMC Questions Received September 22 to October 2, 2000

Dear Dr. Chambers,

Questions about the CMC section of NDA 21-275 were posed by the chemistry reviewer, Dr. Su Tso, over a period spanning September 22 to October 2, 2000. Below are the answers to those questions or requests.

Request of September 22

1. CMC section in electronic format
Copies of the text/narrative portions of the CMC section in Word 8.0 format, specifically volume 2 of the NDA and the [] validation report, were sent to the attention of Michael Puglisi, Project Manager, on September 26, 2000. Included on the disk were PDF files representing the output from CoreDossier of the entire CMC section.
2. Facilities information
The continuation sheet to the 356h form was updated to include the facility responsible for [] sterilization of the container/closure components, and attached to the September 26, 2000, mailing. Another copy of that list is attached. (Appendix 1)

Allergan confirms that all facilities responsible for the manufacture, control and packaging of Lumigan™ ophthalmic solution are ready for inspection.
3. Revision of DMF authorization letters
A request was made to revise two of the DMF letters to include details of the filing chronology and location of information within the files. The authorization letter for DMF [] has been revised and is attached (Appendix 2); the letter for DMF [] is being revised and will be sent in as soon as it is available.

DUPLICATE

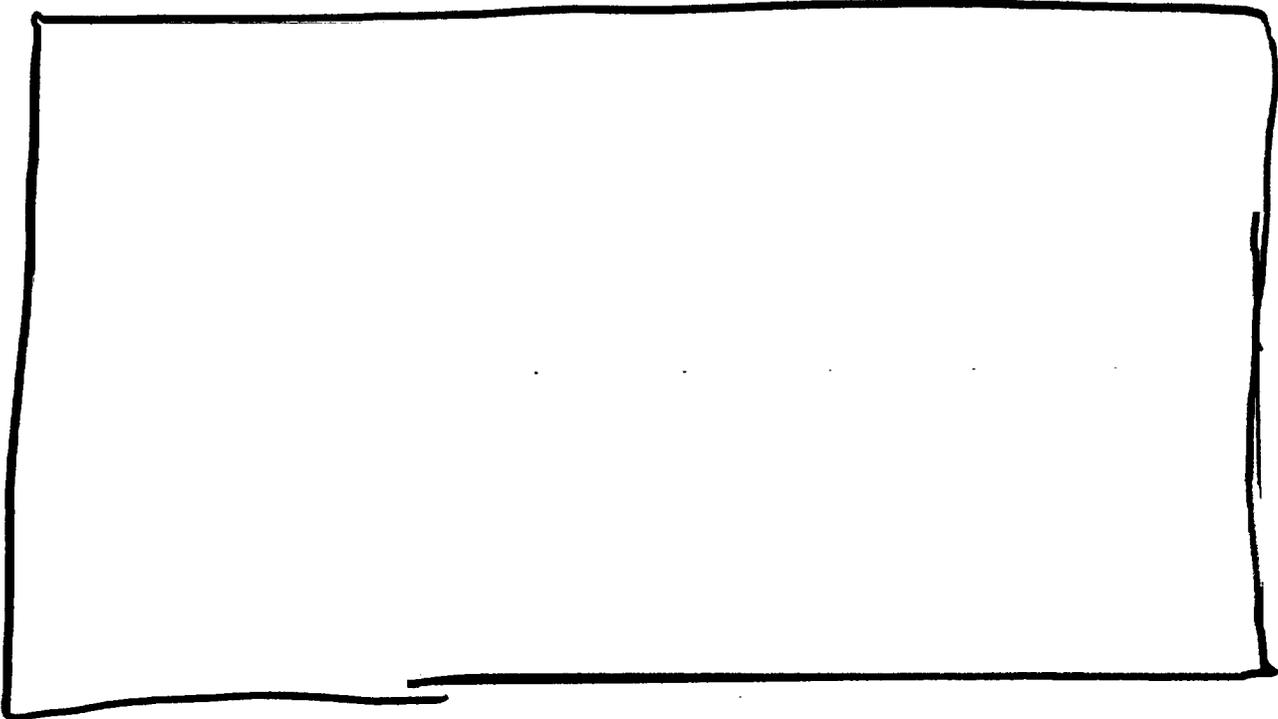


Table 2 Clinical Trial Formulae - Preserved Formulations

Formulation Number	9105X	9106X	9131X
Ingredients	Percentage Formulation (% w/v)		
<u>Active Ingredient</u>			
Bimatoprost			
<u>Other Ingredients</u>			
Sodium Phosphate [redacted]			
[redacted]			
Citric Acid [redacted]			
Sodium Chloride			
Benzalkonium Chloride			
Dilute Hydrochloric Acid and/or			
Dilute Sodium Hydroxide			
Purified Water			

September 27

1. Overall index for section 4

This NDA was produced using CoreDossier, which automatically creates tables of contents, with as much detail as the user defines. The NDA contains three types of indexes/tables of contents: the *master index* for the entire submission, a *section* table of contents which appears in the first volume of each section, and a *volume* table of contents. Without meaning to get too complicated, the items in the printed tables of contents are based on the outline of the submission in CoreDossier, which in turn is based on the nature of the documents comprising each volume.

We were aware that the contents of some volumes did not appear in the master index. An example would be a clinical study report, which because of its size spanned three volumes; only the first volume would have been listed. We did this to keep the size of the master index reasonable. However, the reviewer requested greater detail, and a more detailed table of contents for the chemistry section was generated and e-mailed to Dr. Tso on September 27, 2000.

With this in mind, we generated the master index for the entire submission with greater detail; that master index is attached. (Appendix 3)

October 2

Question 1:

There should be a section which discusses all the formulations used for pre-clinical and clinical studies. If the formulation is the same all the way from beginning of the IND to the NDA submission, please state so. However, if there are actually different formulations used, you must discuss the formulation change history and include a column "formulation" in the correlation table on pg. 85, vol. 3. In addition, please indicate the phase # (phase II or Phase III) under the column "clinical studies #".

Response:

There were minor changes made to the composition of the formulation as the project progressed from the IND to the NDA submission. Early probe formulations of bimatoprost were non-preserved. This permitted a rapid formulation development and screening of several concentrations of bimatoprost. These concentrations were evaluated in Phase 1/Phase 2 clinical studies to support the claim of lowering intraocular pressure in patients with glaucoma or ocular hypertension.

1 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

Table 3 Toxicology Formulae – Gavage Formulation

Formulation Number	9121X	9124X
Ingredients	Percentage Formulation (%w/v)	Percentage Formulation (%w/v)
<u>Active Ingredient</u> Bimatoprost		
<u>Other Ingredients</u> Sodium Phosphate [redacted]		
Citric Acid, [redacted]		
Sodium Chloride		
Dilute Hydrochloric Acid and/or Dilute Sodium Hydroxide		
Purified Water		

Table 4 Toxicology Formulae – Intravenous Formulation

Formulation Number	9122X	9123X
Ingredients	Percentage Formulation (%w/v)	Percentage Formulation (%w/v)
<u>Active Ingredient</u> Bimatoprost		
<u>Other Ingredients</u> Sodium Phosphate [redacted]		
Citric Acid, [redacted]		
Sodium Chloride		
Dilute Hydrochloric Acid and/or Dilute Sodium Hydroxide		
Water for Injection		

Table 5 Clinical Trial Formulae – Radioisotope-labeled Formulation

Formulation Number	9176X
Ingredients	Percentage Formulation (%w/v)
<u>Active Ingredient</u>	
Bimatoprost	
<u>Other Ingredients</u>	
[Redacted]	
Sodium Phosphate [Redacted]	
Citric Acid [Redacted]	
Sodium Chloride	
1N Hydrochloric Acid and/or 1N Sodium Hydroxide	
[Redacted]	
[Redacted]	

- a Includes a mixture of radiolabelled and non-radiolabelled drug substance
- b Tritium labelled Bimatoprost in 100% ethanol. Each mL contains 0.028 mg of Bimatoprost with a radiolabelled activity [Redacted]

Question 2:

Are all the stability data obtained in the final container/closure configuration with or without final label on the bottle.

Response:

The labels utilized for the primary registration stability studies are representative of the final label. The adhesive, ink colors and ink coverage utilized on the labels will be utilized for marketed product. The following stability lots and sublots were packaged in the proposed container/closure configuration containing the proposed label.

1 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

Question 3:

When will you have the 24 month stability data available?

Response:

A complete data set including the 24 month stability data would be available by March 15, 2001 (which includes a 28-day period for microbiology testing). The [redacted] 24-month timepoint for registration lots 11442, 11443 and 11444 is scheduled to occur according to the following dates:

Lot Number	Age of Study (months)	Scheduled Date for 24-Month Timepoint
11442	24	03-Dec-00
11443	24	10-Dec-00
11444	24	07-Jan-01

Question 4:

We recommended in the pre-NDA meeting that you included the complete testing results of the last time point for the stability of the drug product. But there is not sterility or preservative effectiveness testing data [redacted]

[redacted]

[redacted]



Question 5:

Please confirm the production batch size of the API.

Response:

The expected batch size in kilograms for bimatoprost step 5, the final step leading to the active ingredient, is [redacted] which can be calculated from information provided in summary table 4A.2.3.2 (volume/page 002 025).

Bimatoprost step 5 was validated by the procedure provided on volume/pages 002 080 to 002 085. The quantity of step 4 intermediate (starting material) used in step 5 can range from [redacted] which is established by the size of the batch which can be manufactured in the qualified equipment. The expected yield range of step 5 is [redacted] based on yields obtained from approximately ten pilot scale development batches, four full scale demonstration batches, and the three validation batches. As additional experience is gained with full scale production, the % yield range may be tightened.

The validation data for step 5 is provided in the following table:

Validation Batch	Starting Material (Kg)	Yield		
		Expected (%)	Actual (Kg)	Actual (%)
AA02743	[redacted]			
AA02781				
AA02782				

Sincerely,

Stephen Buxbaum
Director, Regulatory Affairs

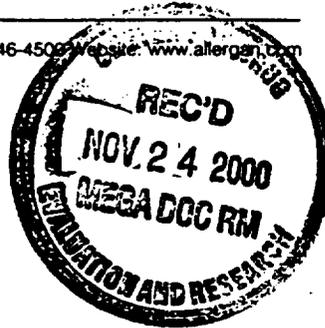
ALLERGAN

2525 Dupont Drive, P.O. Box 19534, Irvine, California, USA 92623-9534 Telephone: (714) 246-4500 Website: www.allergan.com

NDA ORIG AMENDMENT



October 26, 2000



BC

Su Tso, Ph.D.
Chemist
Division of Analgesic, Anti-Inflammatory
& Ophthalmologic Drug Products (HFD-550)
Food and Drug Administration
9201 Corporate Blvd., Building 2
Rockville, MD 20850

Re: Lumigan™ (bimatoprost ophthalmic solution) 0.03%
NDA 21-275
Response to CMC Questions Received October 24, 2000

Dear Dr. Tso,

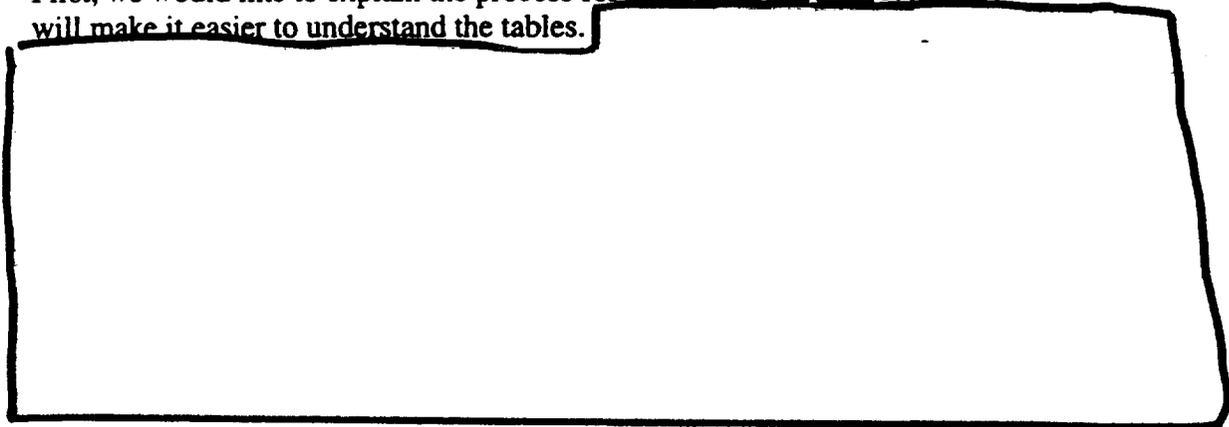
This letter is in response to the questions you asked on October 24, 2000, regarding the CMC section of NDA 21-275. The questions and answers are listed below.

1. Where are the BAK titration-to-failure studies which are to in volume 3, page 32, located in the NDA?

The BAK titration studies (17423, 17424, and 18064/65) although referenced in volume 3, do not actually appear there, but rather in the Microbiology Section 7, volume 50, pages 324-347. For your convenience, I have attached copies of these pages.

2. Please explain the residual tables in volume 5, and identify where the

First, we would like to explain the process for extracting the residuals, which will make it easier to understand the tables.



ORIGINAL

Therefore, the first (left) column of the tables in volume 5, pages 249-250, represents the number of days following [REDACTED]

The columns titled TS-015D and TS-015D (Day 5) represent the [REDACTED] which are 4 and 5 days, respectively.

The [REDACTED] conditions are located in Volume 5, page 253.

If I can be of further assistance, please let me know.

Sincerely,



Stephen Buxbaum
Director, Regulatory Affairs

**APPEARS THIS WAY
ON ORIGINAL**



November 1, 2000

NDA ORIG AMENDMENT

Wiley Chambers, M.D.
Deputy Director
Division of Analgesic, Anti-Inflammatory
& Ophthalmic Drug Products (HFD-550)
Food & Drug Administration
9201 Corporate Blvd., Building 2
Rockville, MD 20850

BB



Re: Lumigan™ (bimatoprost ophthalmic solution) 0.03%
NDA 21-275
Responses to PK Questions Received October 27, 2000

Dear Dr. Chambers,

On October 27, 2000, questions were faxed to Allergan regarding the Human Pharmacokinetics section of the above referenced NDA. As requested, we are providing the following information in response.

1. Question

The assay validation report summary has been provided by the sponsor, but I would like to see the complete assay validation report with the actual raw data for the QC sample [redacted] rather than mean % CVs reported with the current submission.

Response

A copy of the assay validation report, PK-00-004, has been included in the NDA and contains the raw data you seek. It is located in volume 45 on page 258.

ORIGINAL

11/1/00

Page 2 of 2

2. **Question**

**It appears that the long term stability (12 months) of the human plasma samples
I would like to know how long were the human plasma samples
stored before they were analyzed for the end metabolite content.**

Response

The long-term stability study of AGN 192024 (bimatoprost) in human blood after storage at [redacted] The 12-month stability samples [redacted]
[redacted] The last point tested was [redacted] and the results showed that AGN 192024 remained stable in human blood. Copies of the stability protocol and [redacted] of stability data are attached.

3. **Question**

The PK studies and in vitro studies are also provided as individual study summaries. Only study summaries are not acceptable without individual subject data. The sponsor should provide detailed reports rather than just reporting mean values. Similarly all values should be reported from the therapeutic drug monitoring of the Phase III studies rather than reporting mean values at Day 0 and Month 3.

Response

The Tabular Summary of Individual Final Clinical Study Reports table, section 6.6-1, includes the summary of data and also provides the study report numbers. The study reports contain the individual subject data. The study reports and cross-references location within the NDA are listed in section 6.9, volume 48, starting on page 38.

Sincerely,



Stephen Buxbaum
Director, Regulatory Affairs

ALLERGAN

525 Dupont Drive, P.O. Box 19534, Irvine, California, USA 92623-9534 Telephone: (714) 246-4500 Website: www.allergan.com



December 21, 2000

Wiley Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic
& Ophthalmologic Drug Products (HFD-550)
Food & Drug Administration
9201 Corporate Blvd., Building 2
Rockville, MD 20850



Re: Lumigan™ (bimatoprost ophthalmic solution) 0.03%
NDA 21-275
Detail of Inactive Ingredients in Developmental Formulations

NDA 21-275 AMENDMENT

BP

Dear Dr. Chambers,

On December 20, 2000, we received a request from the pharmacology reviewer through Michael Puglisi, Project Manager, to provide details of the inactive ingredients used in several of the developmental formulations used in the pre-clinical studies which were submitted in support of our NDA for Lumigan™. In addition, the pharmacology reviewer noted that page 8 of study report 1012C-3137-5 was omitted from the NDA (note: the study begins on pg. 152 of Vol. 29).

A brief history of the formulations used in the development of this product follows immediately below.

Formulation Development History

Early probe formulations of bimatoprost were [redacted] This permitted a rapid formulation development and screening of several concentrations of bimatoprost. These early probe formulations contained concentrations of bimatoprost at [redacted] [redacted] These formulations were similar in composition to bimatoprost 0.03% formulation (9106X) except for the presence of a [redacted] (benzalkonium chloride).

The pH of the bimatoprost 0.03% formulation (9106X) was stable. This allowed for the reduction in total buffer capacity, [redacted]

[redacted] Based on clinical dose response studies of these early formulations, a concentration of 0.03% (w/v) bimatoprost was

ORIGINAL

selected for the final product (9106X). This concentration, in conjunction with data from

Benzalkonium chloride 0.005% (w/v) was added to the formulation as the preservative to meet preservative effectiveness criteria for ophthalmic multiple-dose solutions.

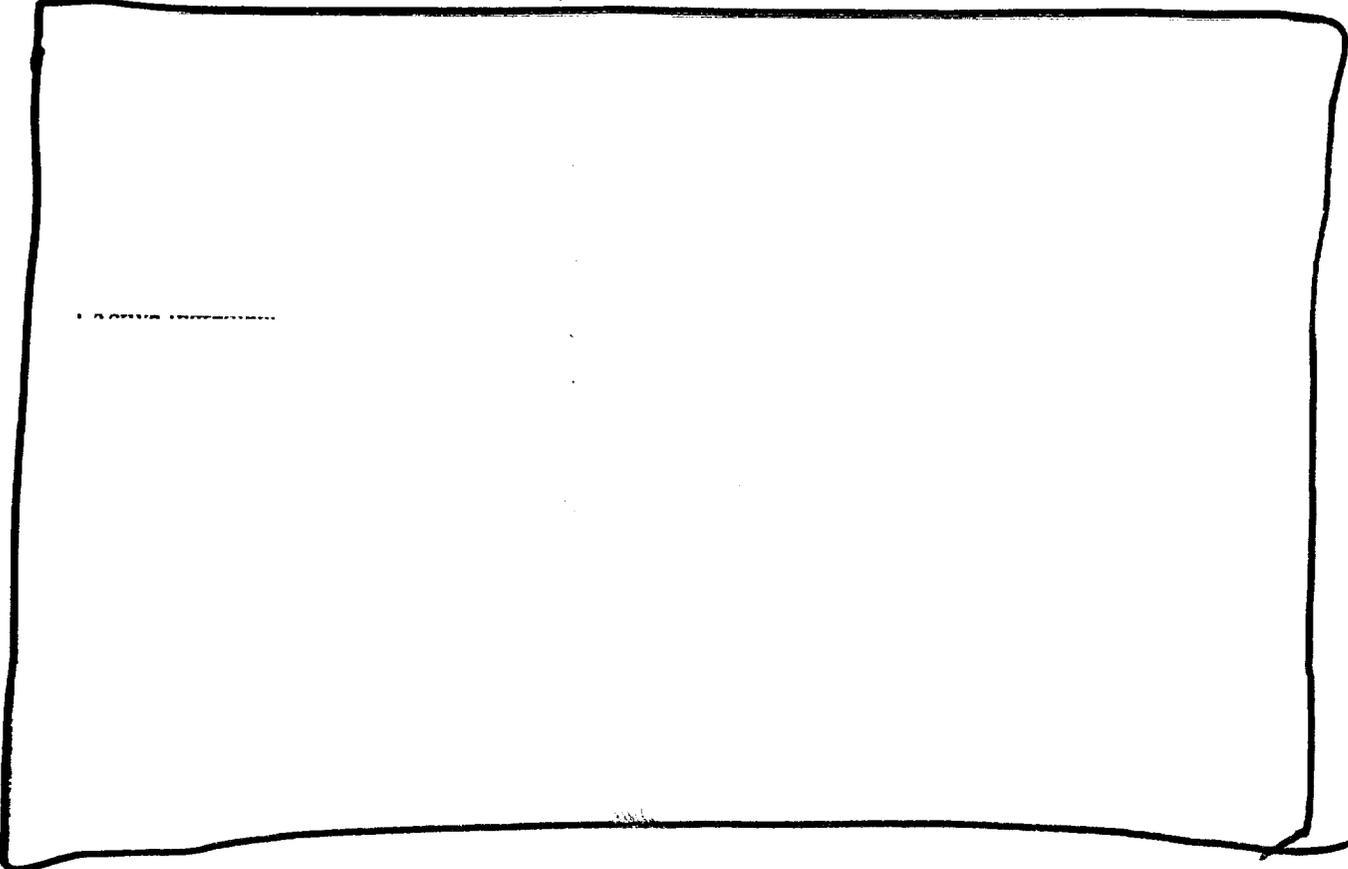
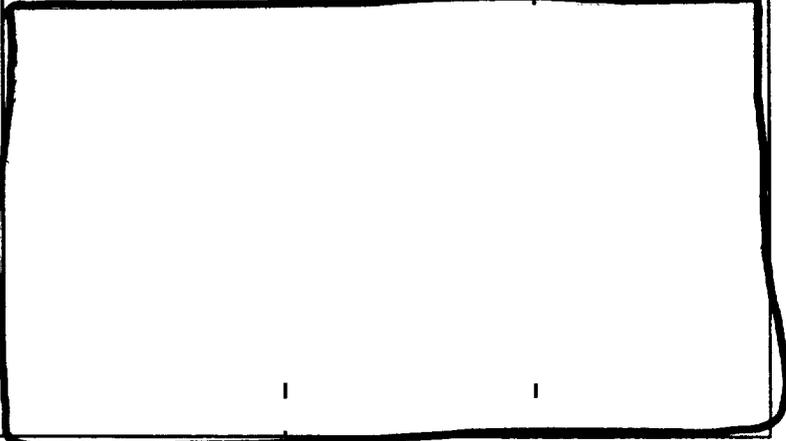
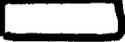
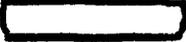


Table 1.1-2 Preserved Formulations of AGN 192024 Ophthalmic Solution

Formulation Number	9105X	9106X	9131X
Ingredients	Concentration (% w/v)		
<u>Active Ingredient</u>			
Bimatoprost (AGN 192024)			
<u>Other Ingredients</u>			
Sodium Phosphate [redacted]			
[redacted]			
Citric Acid, [redacted]			
Sodium Chloride			
Benzalkonium Chloride			
Dilute Hydrochloric Acid and/or			
Dilute Sodium Hydroxide			
Purified Water			

Table 1.1-2 Preserved Formulations of AGN 192024 Ophthalmic Solution

Formulation Number	9105X	9106X	9131X
Ingredients	Concentration (% w/v)		
<u>Active Ingredient</u>			
Bimatoprost (AGN 192024)			
<u>Other Ingredients</u>			
Sodium Phosphate 			
			
Citric Acid 			
Sodium Chloride			
Benzalkonium Chloride			
Dilute Hydrochloric Acid and/or Dilute Sodium Hydroxide			
Purified Water			

I hope you find our response acceptable for your review.

Sincerely,



Stephen Buxbaum
Director, Regulatory Affairs

Enclosure

cc: Michael Puglisi, Project Manager, Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products (HFD-550)

ALLERGAN

525 Dupont Drive, P.O. Box 19534, Irvine, California, USA 92623-9534 Telephone: (714) 246-4500 Website: www.allergan.com



December 22, 2000

Wiley Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic
& Ophthalmologic Drug Products (HFD-550)
Food & Drug Administration
9201 Corporate Blvd., Building 2
Rockville, MD 20850



Re: Lumigan™ (bimatoprost ophthalmic solution) 0.03%
NDA 21-275
Response to Clinical Question of December 22, 2000

B m

Dear Dr. Chambers,

On December 22, 2000, we received by fax through Michael Puglisi, Project Manager, the following question from the Medical Officer:

Regarding Protocol 192024-002:

In the Appendices, Section E1, Mean IOP at Each Timepoint [paper NDA volume 58, page 381], the values for the 4PM timepoints on Days 14, 21 and 28 are missing.

Can you provide the location of these mean IOPs or direct me to their location in the NDA? Thanks.

In response, our statistician regenerated Appendix E1 and included the 4PM timepoint for the days that were lacking.

I hope you find our response acceptable for your review.

Sincerely,

Stephen Buxbaum
Director, Regulatory Affairs

cc: Michael Puglisi, Project Manager

ALLERGAN

2525 Dupont Drive, P.O. Box 19534, Irvine, California, USA 92623-9534 Telephone: (714) 246-4500 Website: www.allergan.com



December 28, 2000

Wiley Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic
& Ophthalmologic Drug Products (HFD-550)
Food & Drug Administration
9201 Corporate Blvd., Building 2
Rockville, MD 20850



Re: Lumigan™ (bimatoprost ophthalmic solution) 0.03%
NDA 21-275
Response to Clinical Question of December 27, 2000

Handwritten scribble

Bm

Dear Dr. Chambers,

On December 27, 2000, we received by fax through Michael Puglisi, Project Manager, the following question from the Medical Officer:

Regarding Protocol 192024-003, Volume 59:

I am unable to locate the mean IOPs (not mean changes from baseline) for the timepoints measured on Days 1, 14, 28 and 29.

Can you provide these mean IOPs or direct me to their location in the NDA? Thanks.

In response, our statistician generated new tables to provide the data that were lacking. These tables of mean IOPs parallel the tables of IOP changes from baseline that are in the clinical study report.

I hope you find our response acceptable for your review.

Sincerely,

Stephen Buxbaum
Director, Regulatory Affairs

cc: Michael Puglisi, Project Manager

ALLERGAN

5500 Central Expressway, P.O. Box 19534, Irvine, California, USA 92623-9534 Telephone: (714) 246-4500 Website: www.allergan.com
December 29, 2000



Wiley Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic
& Ophthalmologic Drug Products (HFD-550)
Food & Drug Administration
9201 Corporate Blvd., Building 2
Rockville, MD 20850

NDA 0118 AMENDMENT

BC

Re: Lumigan™ (bimatoprost ophthalmic solution) 0.03%, NDA 21-275
Additional Responses to CMC Questions Received November 28, 2000

Dear Dr. Chambers,

On December 8, 2000, an amendment to NDA 21-275 was submitted in response to questions about the CMC section posed by Dr. Tso (Chemistry Reviewer, FDA) in a facsimile dated November 28, 2000. This amendment provided responses to a majority of the comments, but specifically stated that final responses to questions 8, 13, 22 and 25 would be provided in a subsequent amendment.

On December 18, 2000, in a telephone conversation with Tania Hoffman (Sr. Regulatory Affairs Analyst, Allergan), Dr. Tso provided additional comments regarding our responses to some of her original questions (i.e., 2, 5, 23 and 24).

Below are the remaining answers to those questions or requests, and further clarification or revisions to some of the responses provided on December 8, 2000.

DRUG SUBSTANCE

2. Question: (Additional Comments)

On December 18, 2000, Dr. Tso requested that specifications be established for the following and that Table 2-2 provided in the December 8, 2000 be revised to include these specifications:

- Add acceptance criteria for:
 - Optical Rotation
 - Residual Solvents

- Add test and acceptance criteria for:



ALLERGAN

Upont Drive, P.O. Box 19534, Irvine, California, USA 92623-9534 Telephone: (714) 246-4500 Website: www.allergan.com



January 4, 2001

Wiley Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic
& Ophthalmologic Drug Products (HFD-550)
Food & Drug Administration
9201 Corporate Blvd., Building 2
Rockville, MD 20850



Re: Lumigan™ (bimatoprost ophthalmic solution) 0.03%
NDA 21-275
Amendment to Pharmacology Study 1012C-3137-5

NDA 21-275 AMENDMENT

BP

Dear Dr. Chambers,

On December 20, 2000, we received a comment from the pharmacology reviewer through Michael Puglisi, Project Manager, that page 8 of study report 1012C-3137-5 was omitted from our NDA for Lumigan™ (note: the study begins on pg. 152 of Vol. 29). Our investigation into this oversight revealed that this page was inadvertently misplaced prior to archiving the final report at Allergan. Therefore, enclosed is a copy of the amendment to the final report containing the missing page.

I hope you find our response acceptable for your review.

Sincerely,

Stephen Buxbaum
Director, Regulatory Affairs

Enclosure

cc: Michael Puglisi, Project Manager, DAAODP

s,
this

luct

04/01

number
534

cc

n

ALLERGAN

2525 Dupont Drive, P.O. Box 19534, Irvine, California, USA 92623-9534 Telephone: (714) 246-4500 Website: www.allergan.com



January 23, 2001

Wiley Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic
& Ophthalmologic Drug Products (HFD-550)
Food & Drug Administration
9201 Corporate Blvd., Building 2
Rockville, MD 20850



Re: Lumigan™ (bimatoprost ophthalmic solution) 0.03%
NDA 21-275
120-Day Safety Update

AMENDMENT
SU

Dear Dr. Chambers,

Allergan hereby submits, under 21 CFR 314.50, the 120-day safety update to NDA 21-275 Lumigan™ (bimatoprost ophthalmic solution) 0.03%, indicated for the reduction of elevated intraocular pressure (IOP) in patients with glaucoma or ocular hypertension with once-daily application.

Please note that since Section 12 of the NDA was submitted in electronic format, the additional Case Report Forms submitted herein are provided in like fashion (as required in the Guidance for Industry: Providing Regulatory Submissions in Electronic Format – NDAs, IT3, January 1999).

As part of this amendment, we have included proposed labeling changes to the package insert. These changes represent the update to the safety profile based upon the additional clinical study data.

Allergan concludes that the updated safety data from the clinical studies continues to demonstrate that Lumigan™ (bimatoprost ophthalmic solution) 0.03% dosed once daily is safe and effective for its intended use.

Sincerely,

Stephen Buxbaum
Director, Regulatory Affairs

Enclosure

cc: Michael Puglisi, Project Manager, DAAODP

ALLERGAN

2525 Dupont Drive, P.O. Box 19534, Irvine, California, USA 92623-9534 Telephone: (714) 246-4500 Website: www.allergan.com

February 1, 2001

Wiley Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic
& Ophthalmologic Drug Products (HFD-550)
Food & Drug Administration
9201 Corporate Blvd., Building 2
Rockville, MD 20850



Re: Lumigan™ (bimatoprost ophthalmic solution) 0.03%
NDA 21-275
Response to Pharmacology/Toxicology Question of January 31, 2001

NDA CHG AMENDMENT

BP

Dear Dr. Chambers,

On January 31, 2001, I received a request from Zhou Chen, Pharmacologist, that we provide clarification and some additional information related to our response submitted January 16, 2001.

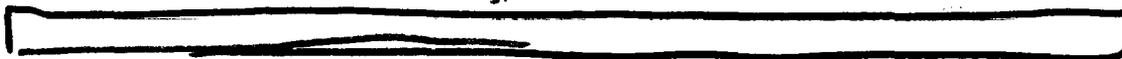
He asked that we confirm if the data reported for the rabbit species is correct or if the species should be rat. Also, we reported that the AUC exposure data was measured in plasma yet our labeling indicates blood. Finally, he asked that we explain the basis of the ratio 103 reported in the PRECAUTIONS: *Carcinogenesis, Mutagenesis, Impairment of Fertility* section of the package insert.

On the following page please find a revision to the table submitted on January 16, 2001. The species which was previously listed incorrectly as rabbit has been updated to list rat. The revised table also includes references to the specific study and calculations which are the basis of the unbound AUC ratio of 103 (see row #3 of table on the next page).

The reported pharmacokinetic (PK) results for AGN 192024 in the NDA and in the proposed label are based entirely on blood concentrations. Plasma protein binding results were utilized in order to estimate free drug concentration in the blood, which approximates drug exposure at the sites of action. Consequently, animal/human PK parameter ratios were calculated based on free drug concentration. The calculation was based on the following algebraic expression:



Since AGN 192024 does not bind appreciably to red blood cell (NDA 21-275 Section 5.6.1.2), the unbound fraction in red blood cell equals to one and the previous mathematical expression is simplified to the following one:



1 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

ALLERGAN

ORIG AMENDMENT

BP

2525 Dupont Drive, P.O. Box 19534, Irvine, California, USA 92623-9534 Telephone: (714) 246-4500 Website: www.allergan.com



February 2, 2001

Wiley Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic
& Ophthalmologic Drug Products (HFD-550)
Food & Drug Administration
9201 Corporate Blvd., Building 2
Rockville, MD 20850



Re: Lumigan™ (bimatoprost ophthalmic solution) 0.03%
NDA 21-275
Response to Pharmacology/Toxicology Request of February 2, 2001

Dear Dr. Chambers,

On February 2, 2001, Zhou Chen informed me that he was unable to locate the pharmacokinetics study report PK-00-102 referenced in the original NDA (Section 5.6, Vol. 11, pages 268 and 280) and the recent amendments dated January 16, 2001 and February 1, 2001 (footnote "e").

After reviewing the information provided in these submissions and examining report PK-00-102, we determined that this was not the relevant report to have been referenced. The proper reference should be pharmacokinetics study report PK-00-112. A copy of this report is enclosed.

We hope you find this response satisfactory for your review.

Sincerely,

A handwritten signature in black ink that reads 'Stephen Buxbaum'.

Stephen Buxbaum
Director, Regulatory Affairs

cc: Michael Puglisi, Project Manager

ORIGINAL

ALLERGAN

DuPont Drive, P.O. Box 19534, Irvine, California, USA 92623-9534 Telephone: (714) 246-4500 Website: www.allergan.com



February 12, 2001

Wiley Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic
& Ophthalmologic Drug Products (HFD-550)
Food & Drug Administration
9201 Corporate Blvd., Building 2
Rockville, MD 20850



NDA ORIG AMENDMENT
BC

Re: Lumigan™ (bimatoprost ophthalmic solution) 0.03%
NDA 21-275
Response to CMC Request of January 26, 2001 for Revised Methods

Dear Dr. Chambers,

On January 26, 2001, we received by fax through Michael Puglisi, Project Manager, questions from the Chemistry Reviewer.

As part of our response dated February 1, 2001, we committed to provide copies by February 13, 2001 of the revised [redacted] used to monitor extractables listed below:

[redacted]

Allergan has updated these methods to detail the monitoring of extractables.

We hope that you find our response to this CMC issue satisfactory for your review and approval.

Sincerely,

Stephen Buxbaum
Director, Regulatory Affairs

cc: Michael Puglisi, Project Manager

101

as. tion of



February 23, 2001

Wiley Chambers, M.D.
Deputy Director
Division of Analgesic, Anti-Inflammatory
& Ophthalmologic Drug Products (HFD-550)
Food & Drug Administration
9201 Corporate Blvd., Building 2
Rockville, MD 20850



Re: Lumigan™ (bimatoprost ophthalmic solution) 0.03%
NDA 21-275
Suggested Revisions to the Proposed Package Insert

NDA 21-275

BC

Dear Dr. Chambers,

On February 16, 2001, Allergan received from Dr. William Boyd a copy of the Agency's proposal for the package insert for Lumigan™ (bimatoprost ophthalmic solution) 0.03%. We have reviewed this version carefully and thoroughly and have found several areas that we feel need further revision. To this end, we are enclosing a copy of your draft with our changes indicated. The format of the insert is dual column, with your proposed text on the left with or without any changes by us, and comments and explanations on the right.

There are two points we bring to your attention concerning the Clinical Studies and Indications sections.

In the section on Clinical Studies we have reworded one sentence to state that the IOP-reduction of Lumigan was superior to that seen with timolol. This is strongly supported by the clinical data from each of the phase III studies. Since the data show that the IOP lowering with Lumigan was both clinically and statistically greater at all timepoints for all study visits, we believe that a superiority claim for IOP-lowering efficacy is justified.

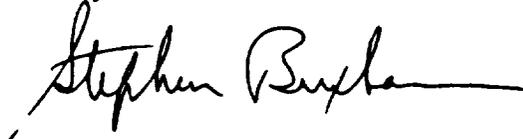
We have resubmitted wording stating that Lumigan is indicated for the reduction of elevated intraocular pressure in patients with glaucoma or ocular hypertension. Our request for first line therapy is based on the efficacy and safety of this medication. In our two pivotal studies, bimatoprost demonstrates IOP lowering that is both clinically and statistically superior to timolol at all timepoints for all visits. Given recent data from the NIH-sponsored Advanced Glaucoma Intervention Study (AGIS) that visual field progression can return to age-adjusted rates at low target pressures, we believe the effective IOP lowering of bimatoprost will benefit patients. Bimatoprost was safe and well tolerated after 12 months of treatment. Only 1.5% (7/474) of patients treated with bimatoprost QD had reported iris

Letter to W. Chambers, M.D.
Lumigan™ NDA 21-275
February 23, 2001
Page 2 of 2

pigmentation changes. We believe that the actual rate may be far less than this. Notably, out of this small number of patients with iris pigmentation, 43% (3/7) were in African Americans and 57% (4/7) were from a single site. Only 4/474 (0.8%) cases of iris pigmentation in the Lumigan™ QD-treated group were noted on our masked reading of the photographs (patients 2666-T01, 2942-L23, 2963-A55, and 2964-Z10). In phase III trials iritis (0.4%; 2/474)/uveitis (0.2%; 1/474) was rarely reported. Conjunctival hyperemia was the most commonly reported adverse event, but was predominantly mild, not associated with intraocular inflammation, did not increase over time, and lead to discontinuation in only about 3% of patients. From these data, we feel that the risk benefit ratio of this medication clearly supports first line therapy.

We will be calling Mike Puglisi to arrange a teleconference to discuss finalizing the insert. If it is convenient to your schedule, we would like this telecon to be held during the week of February 26.

Sincerely,

A handwritten signature in black ink, appearing to read "Stephen Buxbaum". The signature is fluid and cursive, with a long horizontal stroke at the end.

Stephen Buxbaum
Director, Regulatory Affairs



February 26, 2001

Wiley Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic
& Ophthalmologic Drug Products (HFD-550)
Food & Drug Administration
9201 Corporate Blvd., Building 2
Rockville, MD 20850

Re: Lumigan™ (bimatoprost ophthalmic solution) 0.03%
NDA 21-275
Removal of Liver Function Test Statement from Draft Package Insert

Dear Dr. Chambers,

In preparation for the scheduled teleconference on February 28, 2001, to discuss our proposed package insert, Allergan is submitting the attached in justification of removing reference to "abnormal liver function tests" from the Adverse Reactions section. This internal Ophthalmology Clinical Research memo discusses individual patient data and contains "scattergram" plots of five laboratory variables. Based on a review of the data, we conclude that the results do not suggest that the use of Lumigan™ is associated with liver dysfunction.

Sincerely,

Stephen Buxbaum
Director, Regulatory Affairs

cc: Michael Puglisi, Project Manager

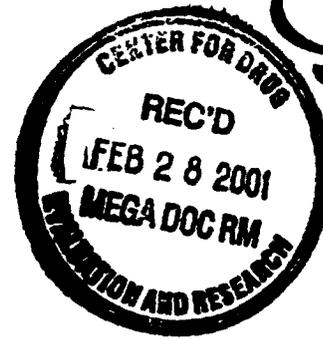
ALLERGAN

2525 Dupont Drive, P.O. Box 19534, Irvine, California, USA 92623-9534 Telephone: (714) 246-4500 Website: www.allergan.com



February 26, 2001

Wiley Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic
& Ophthalmologic Drug Products (HFD-550)
Food & Drug Administration
9201 Corporate Blvd., Building 2
Rockville, MD 20850



Re: Lumigan™ (bimatoprost ophthalmic solution) 0.03%
NDA 21-275
Response to CMC Question of February 26, 2001 Regarding 2.5 mL Labeling Change
Transmission of Lumigan Extractables Table and Explanation

Dear Dr. Chambers,

On February 26, 2001, an impromptu teleconference between FDA and Allergan was conducted to discuss the Lumigan™ labeling change from a 3.0 mL fill size to a 2.5 mL fill size. Drs. Linda Ng and Hossein Khorshidi represented the FDA and Stephen Buxbaum and Susan Martin represented Allergan Regulatory Affairs.

Dr. Ng asked about the intended target fill size for the 2.5 mL size, and if Allergan had stability data to support the change.

Allergan explained that Marketing had requested a change in the labeling for the 3 mL product configuration to list 2.5 mL as the fill size because of pricing and reimbursement issues. The 2.5 mL label would be placed on a 3 mL fill size unit. There will be no changes to the target fill size and its controls and limits, nor will there be changes to the manufacturing/filling procedures or the bottle size (8 mL). Allergan is only changing the fill volume notation on the labeling for this product configuration.

In addition, in a telephone message from Mike Puglisi on this date, we were asked to submit formally the table of bottle/label extractables which was faxed to the Agency on February 13, 2001 for our teleconference. That table is attached. Later in the day on February 13, Dr. Khorshidi had telephoned to ask for more details on how the "Fraction of Allowed TDI (per ICH Q3B Guidance)" was calculated. That explanation with the revised table are also attached.

ORIGINAL

Letter to W. Chambers, M.D.
NDA 21-275
February 26, 2001
Page 2 of 2

We trust that we have satisfactorily answered all outstanding questions on the calculation of safety multiples for the extractables and on the label change from 3.0 mL to 2.5 mL.

Sincerely,

A handwritten signature in black ink, appearing to read "Stephen Buxbaum", with a long horizontal flourish extending to the right.

Stephen Buxbaum
Director, Regulatory Affairs

cc: Michael Puglisi, Project Manager

ALLERGAN

2525 Dupont Drive, P.O. Box 19534, Irvine, California, USA 92623-9534 Telephone: (714) 246-4500 Website: www.allergan.com

ORIG. APPROVAL
BL



March 1, 2001

Wiley Chambers, M.D.
Deputy Director
Division of Analgesic, Anti-Inflammatory
& Ophthalmologic Drug Products (HFD-550)
Food & Drug Administration
9201 Corporate Blvd., Building 2
Rockville, MD 20850



Re: Lumigan™ (bimatoprost ophthalmic solution) 0.03%
NDA 21-275
Final Version of the Package Insert

Dear Dr. Chambers,

Subsequent to our teleconference on February 28, 2001, Allergan has implemented the changes to the package insert as mutually agreed upon. A copy of the draft revised insert is attached. As before, it is presented as dual column with the revised text on the left and comments on the right. In addition, a "clean" copy (strikethrough and underlines removed) is being provided.

In addition, we are in receipt of your February 28, 2001, fax asking for a commitment to perform post-marketing studies to evaluate increased iris pigmentation and the potential for changes in eyelash length and density over time, and pigmentation in the trabecular meshwork in patients treated with bimatoprost ophthalmic solution 0.03% for over two years. Allergan makes this commitment and will consult with the Agency at the appropriate time to agree on details of the study design and execution.

Sincerely,

Stephen Buxbaum
Director, Regulatory Affairs

DUPLICATE

ALLERGAN

2525 Dupont Drive, P.O. Box 19534, Irvine, California, USA 92623-9534 Telephone: (714) 246-4500 Website: www.allergan.com

OFFICE



March 2, 2001

Wiley Chambers, M.D.
Deputy Director
Division of Analgesic, Anti-Inflammatory
& Ophthalmologic Drug Products (HFD-550)
Food & Drug Administration
9201 Corporate Blvd., Building 2
Rockville, MD 20850



Re: Lumigan™ (bimatoprost ophthalmic solution) 0.03%
NDA 21-275
Revised Final Draft Version of the Package Insert Dated March 2, 2001

Dear Dr. Chambers,

In response to a telephone call today with Bill Boyd and Mike Puglisi, several addition minor changes have been made to the draft package insert. This version, dated March 2, 2001, is attached.

Sincerely,

Stephen Buxbaum
Director, Regulatory Affairs

DUPLICATE

ALLERGAN

2525 Dupont Drive, P.O. Box 19534, Irvine, California, USA 92623-9534 Telephone: (714) 246-4500 Website: www.allergan.com



March 14, 2001

Wiley Chambers, M.D.
Deputy Director
Division of Analgesic, Anti-Inflammatory
& Ophthalmologic Drug Products (HFD-550)
Food & Drug Administration
9201 Corporate Blvd., Building 2
Rockville, MD 20850

Re: Lumigan™ (bimatoprost ophthalmic solution) 0.03%
NDA 21-275
Final Revised Version of the Package Insert

Dear Dr. Chambers,

Subsequent to the Office-level review of the package insert and our telephone conference of March 14, 2001, we have implemented the changes to two sections of the package insert as recommended. A "clean" copy is herewith attached. You had indicated that we could use the previously-agreed to version of the insert if we so choose at product launch. That decision is being discussed, but in any event the next printing will contain the changes.

Please note that in the "Indications and Usage" section, we have added the letter "s" to the word "measurement" to read properly "...target IOP determined after multiple measurements over time ..."

Sincerely,

A handwritten signature in black ink that reads 'Stephen Buxbaum'.

Stephen Buxbaum
Director, Regulatory Affairs



TRANSMITTED BY FACSIMILE

Dave Garbe
Allergan, Inc.
2525 Dupont Drive
PO Box 19534
Irvine, CA 92623-9534

RE: **NDA 21-275 Lumigan (bimatoprost ophthalmic solution) 0.03%
MACMIS # 9815**

Dear Mr. Garbe:

This letter responds to Allergan, Inc.'s (Allergan) request for comments, dated March 8, 2001, on proposed launch promotional materials for Lumigan. You submitted a draft press release, a professional visual aid, and a journal advertisement. You requested that we give the draft press release a priority review. The Division of Drug Marketing, Advertising, and Communications (DDMAC), in consultation with the Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products, has reviewed your proposed press release and offers the following comments. Our comments on the proposed press release should be applied to all current and future promotional materials for Lumigan with the same or similar claims and representations.

Misleading Safety Information

Promotional materials are misleading if contain a representation that a drug is safer than has been demonstrated by substantial evidence or substantial clinical experience. In the proposed press release, you claim that Lumigan has "an excellent safety profile and was well tolerated by patients." This claim is misleading because it minimizes the risks associated with the drug and is inconsistent with the approved product labeling. For example, the drug has the potential to cause permanent changes to pigmented tissues. Thus, we recommend deleting the "excellent safety profile" claim.

New Class

Promotional materials are false or misleading if they contain claims that are not substantiated. In the proposed press release you claim that Lumigan is first in a new class of drugs. However, Lumigan's draft product labeling describes the drug as an analog of prostaglandin. As you know, the marketed drug latanoprost is also a prostaglandin analog. Thus your claim is misleading. We recommend deleting this claim.

Misleading Superiority Claims

In the draft press release you claim that Lumigan was superior to timolol 0.5% dosed bid in clinical trials. This claim is misleading because you compare the effectiveness of two products that have dissimilar indications. Timolol is indicated as a first line therapy whereas Lumigan is indicated as a second-line therapy. Further, the two drugs have very different adverse events, warnings, and contraindications. Thus, this comparison implies that Lumigan is indicated as a first line therapy, which is an unapproved indication.

In the draft press release you claim that "Lumigan achieves lower target intraocular pressures in more patients." This claim is misleading because it implies that the drug is more effective than other IOP lowering drugs without adequate evidence.

In the draft press release you claim that Lumigan is "an extremely effective drug that helps more patients reach lower target pressures...." As stated above, this claim is misleading because it implies that the drug is more effective than other IOP lowering drugs without adequate evidence. We recommend deleting the words "extremely" and "more patients" from the claim.

If you have any questions, please contact me by facsimile at (301) 594-6771, or by written communication at the Division of Drug Marketing, Advertising, and Communications, HFD-42; Room 17B-20; 5600 Fishers Lane; Rockville, MD 20857. DDMAC reminds Allergan that only written communications are considered official.

In all future correspondence regarding this matter, please refer to MACMIS # 9815 and NDA 21-275.

Sincerely,

{See appended electronic signature page}

Warren Rumble
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications