CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-262

CORRESPONDENCE

ALLERGAN

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

50 years GROWTH & INNOVATION

March 13, 2001

Wiley Chambers, MD
Deputy Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration HFD-550
Attention: Document Room
Building 2
9201 Corporate Blvd.
Rockville, MD 20850

RE Brimonidine-Purite™ Ophthalmic Solution 0.15%
New Drug Application 21-262
Response to FDA Questions on CMC

Reference is made to our original New Drug Application 21-262 submitted on June 29, 2000. Reference is made to a March 13, 2001 telephone conversation between Drs. Linda Ng and Libaniel Rodriguez of the Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products and myself. During the teleconference it was requested that Allergan establish finished product and stability specifications for extractables in Brimonidine-Purite™ Ophthalmic Solution 0.15%.

Allergan agrees to test finished product and stability samples for the following extractables:

[redacted]

At this time we will set the release and shelf specifications as Record Only. We commit to setting final specifications by September 30, 2001.

We hope the enclosed is satisfactory for your review and approval. If you have any questions, please call me at 714-246-6088.

Sincerely,

Lewis Gryziewicz
Director
Regulatory Affairs

Desk Copy: Libaniel Rodriguez, Ph.D., Review Chemist, DAAOP

LLERGAN

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

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MAR 9 2001

Wiley Chambers, MD
Deputy Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration HFD-550
Attention: Document Room
Building 2
9201 Corporate Blvd.
Rockville, MD 20850

CENTER FOR DRUG EVALUATION AND RESEARCH RECD MAR 12 2001 MEGA

NDA

BC

RE Brimonidine-Purite™ Ophthalmic Solution 0.15%
New Drug Application 21-262
[redacted]

Reference is made to our original New Drug Application 21-262 submitted on June 29, 2000. This NDA lists two suppliers of the Active Pharmaceutical Ingredient; [redacted]

At this time, we wish to withdraw [redacted] from NDA 21-262 as a supplier of the Active Pharmaceutical Ingredient (API). It is understood that this withdrawal does not prejudice any future filing of [redacted] to the application.

In accordance with 21CFR 314.71(b), Allergan is providing a field copy of this letter to the Dallas and the Los Angeles District offices.

Should you have any questions, please call me at 714-246-6088.

Sincerely,

Lewis Gryziewicz
Director
Regulatory Affairs

LG/JI

CC: Ms Lori Gorski, Project Manager, DAAOP

ORIGINAL

ALLERGAN

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

50 years GROWTH & INNOVATION

December 21, 2000

Wiley Chambers, MD
Deputy Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration HFD-550
Attention: Document Room
Building 2
9201 Corporate Blvd.
Rockville, MD 20850

Re: Brimonidine-Purite™ Ophthalmic Solution 0.15%
New Drug Application 21-262
Proposed Labeling

Reference is made to our original New Drug Application 21-262 submitted on June 29, 2000. Reference is also made to the FDA labeling for ALPHAGAN® P dated December 19, 2000 and to a teleconference between representatives of the Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products and Allergan earlier today.

Based on our teleconference, Allergan has made the following changes to the labeling for ALPHAGAN® P:

Under **Clinical Evaluations,** we reworded the section to read "Those results indicated that ALPHAGAN® P (brimonidine tartrate ophthalmic solution) 0.15% is comparable in IOP lowering effect to ALPHAGAN® (brimonidine tartrate ophthalmic solution) 0.2%, and effectively lowers IOP in patients with open-angle glaucoma or ocular hypertension by approximately 2 – 5 mm Hg".

Under **Geriatric Use**, we updated the section to read "No overall differences in safety or effectiveness have been observed between elderly and other adult patients".

We deleted **asthma** from the **Adverse Reactions** section. All of the patients that reported asthma as an adverse reaction reported asthma as a pre-existing condition in their medical history, Appendix 2. There was one patient who reported hay fever and dyspnea as pre-existing conditions. The investigator later noted on the Case Report Form that the patient did have a history of asthma.

Enclosed are four (4) copies of our draft labeling. A copy of our proposed labeling is included along with one that indicates the changes using underline and strikeout, Appendix 1. Additionally, an electronic version of the labeling is included in the desk copy provided to Ms. Gorski.

DUPLICATE

We hope the enclosed is satisfactory for your review and approval. If you have any questions, please call me at 714-246-6088.

Sincerely,

Lewis Gryziewicz
Director
Regulatory Affairs

LG/JI

Desk Copy: Lori Gorski, Project Manager DAAOP

ALLERGAN

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50 years GROWTH & INNOVATION

December 20, 2000

Wiley Chambers, MD
Deputy Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration HFD-550
Attention: Document Room
Building 2
9201 Corporate Blvd.
Rockville, MD 20850

RE Brimonidine-Purite™ Ophthalmic Solution 0.15%
New Drug Application 21-262
Response to FDA Request - CMC – Methods Validation Package

Reference is made to our original New Drug Application 21-262 submitted on June 29, 2000. Reference is also made to the fax received from Dr. Libaniel Rodriguez on November 29, 2000 requesting three copies of the Methods Validation Package.

Enclosed are three (3) copies of the Methods Validation Package. The information in this submission is from the initial NDA 21-262 as indicated on the page numbers. The specifications and analytical methods AP-L292 and AP-Z003 have been updated as agreed with the FDA during the NDA review.

Please note that the sequential page numbers on the lower right hand corner are the submission numbers.

We hope the enclosed is satisfactory for your review and approval. If you have any questions, please call me at 714-246-6088.

Sincerely,

Lewis Gryziewicz
Director
Regulatory Affairs

LG/JI

Desk Copy: Libaniel Rodriguez, Ph.D., Review Chemist, DAAOP

ORIGINAL

ALLERGAN

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

50 years GROWTH & INNOVATION

December 19, 2000

Wiley Chambers, MD
Deputy Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration HFD-550
Attention: Document Room
Building 2
9201 Corporate Blvd.
Rockville, MD 20850

NDA
NC

RE Brimonidine-Purite™ Ophthalmic Solution 0.15%
New Drug Application 21-262

Reference is made to our original New Drug Application 21-262 submitted on June 29, 2000 and to a December 19, 2000 telephone message from Lori Gorski, Project Manager, Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products.

In response to Ms. Gorski's question, Allergan does not intend to use the P in ALPHAGAN® P for anything other than Purite™.

Should you have additional questions, please contact me at 714-246-6088.

Sincerely,

Lewis Gryziewicz
Director
Regulatory Affairs

LG/JI

DUPLICATE

ALLERGAN

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

50 years GROWTH & INNOVATION

December 13, 2000

Wiley Chambers, MD
Deputy Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration HFD-550
Attention: Document Room
Building 2
9201 Corporate Blvd.
Rockville, MD 20850

Re: Brimonidine-Purite™ Ophthalmic Solution 0.15%
New Drug Application 21-262
Comments on Proposed Labeling

Reference is made to our original New Drug Application 21-262 submitted on June 29, 2000. Reference is also made to the fax received from Lori Gorski, FDA Project Manager on December 4, 2000 regarding the Division's proposed labeling, copy attached. We have reviewed the Agency's comments and proposals. While we agree generally with the Agency's proposal, we have proposed several changes to the insert.

Enclosed are four (4) copies of our draft labeling in response to the Agency's proposed labeling. Additionally, an electronic version of the labeling is included in the desk copy provided to Ms. Gorski. Appendix 1 contains the revised labeling and a version of the labeling comparing the Allergan draft label to that proposed by FDA.

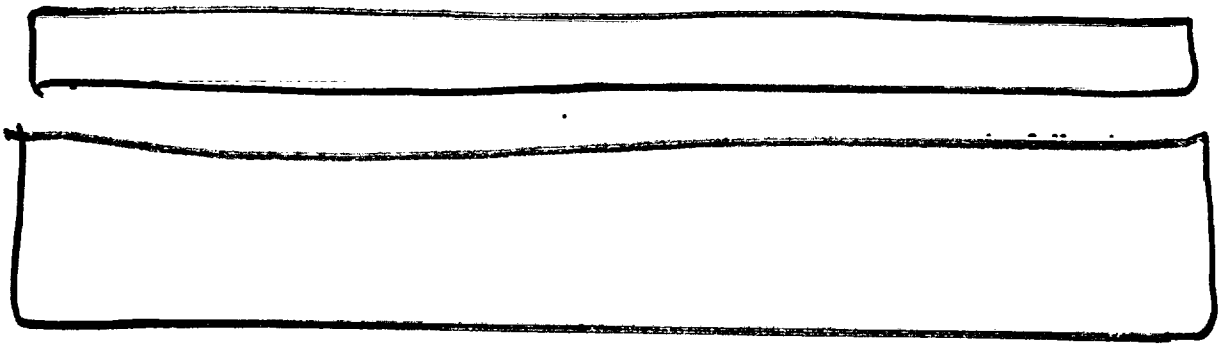
Below are the changes that we have proposed:

1. We have changed the name of the product from Alphagan-P™ to ALPHAGAN® P as initially proposed in our August 2, 2000 submission, Appendix 2.

2. We have added the wording ALPHAGAN® P ... is a "relatively selective" alpha-2 adrenergic agonist for ophthalmic use. This statement is supported by the data on page 1 295 of NDA 21-262 and is consistent with the ALPHAGAN® insert (NDA 20-613). Please see Appendix 3.

1 page(s) of revised draft labeling has been redacted from this portion of the review.

8. In the Adverse Reactions Section,



We hope the enclosed is satisfactory for your review and approval. If you have any questions, please call me at 714-246-6088.

Sincerely,

Lewis Gryziewicz
Director
Regulatory Affairs

LG/JI

Desk Copy: Lori Gorski, Project Manager DAAOP

ALLERGAN

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

50 years GROWTH & INNOVATION

December 12, 2000

Wiley Chambers, MD
Deputy Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration HFD-550
Attention: Document Room
Building 2
9201 Corporate Blvd.
Rockville, MD 20850

RE Brimonidine-Purite™ Ophthalmic Solution 0.15%
New Drug Application 21-262
Response to FDA Questions on CMC – Mock Up Label [redacted]

Reference is made to our original New Drug Application 21-262 submitted on June 29, 2000. Reference is also made to the fax received from Dr. Libaniel Rodriguez on November 8, 2000 requesting mock – up labeling and making reference to [redacted] (copy attached).

Enclosed are four copies of the mock – up labeling for the carton and bottle label for the [redacted] fill sizes. We have been informed that the supplier of the adhesive has communicated with the Agency regarding [redacted]

We hope the enclosed is satisfactory for your review and approval. If you have any questions, please call me at 714-246-6088.

Sincerely,

Lewis Gryziewicz
Director
Regulatory Affairs

LG/JI

Desk Copy: Lori Gorski, Project Manager, DAAOP

ALLERGAN

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December 12, 2000

Wiley Chambers, MD
Deputy Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration HFD-550
Attention: Document Room
Building 2
9201 Corporate Blvd.
Rockville, MD 20850

RE Brimonidine-Purite™ Ophthalmic Solution 0.15%
New Drug Application 21-262
Response to FDA Questions on Pharmacology/Toxicology

Reference is made to our original New Drug Application 21-262 submitted on June 29, 2000. Reference is made to the fax received from Lori Gorski on December 8, 2000 regarding pharmacology/toxicology questions, copy attached.

October 25, 2000 Questions

FDA Question:

Volume 22 page 2 shows a bibliography in the Index. However, the report does not have any bibliography. Please provide or clarify.

Allergan Response

The bibliography for this reference was erroneously omitted from the NDA. It is included in Attachment 1.

FDA Question:

Also, volume 22 page 5 suggests an increase still birth at 100 PPM and above dose of chlorite. Where is the data to support this statement? Please provide data and location in the NDA to support that less than 100 PPM is safe for reproductive safety as stated in page 5 volume 22.

The report in question is a literature reference. Allergan does not have the data that supports the reference.

ORIGINAL

Reproductive toxicity studies conducted with Purite are discussed on page 15 034 of NDA 21-262, included in Attachment 2 for ease of review.

Please note that the referenced studies incorporated Purite into the drinking water of the subject animals. Based on the data presented the no effect dose of Purite corresponds to at least 2,000 times the human topical dose of Purite received by humans subjected to the intended clinical regimen of Brimonidine-Purite™.

We hope the enclosed is satisfactory for your review and approval. If you have any questions, please call me at 714-246-6088.

Sincerely,

Lewis Gryziewicz
Director
Regulatory Affairs

ALLERGAN

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

50 years Growth & Innovation

November 27, 2000

Wiley Chambers, MD
Deputy Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration HFD-550
Attention: Document Room
Building 2
9201 Corporate Blvd.
Rockville, MD 20850

BC

RE Brimonidine-Purite™ Ophthalmic Solution 0.15%
New Drug Application 21-262
Response to FDA Questions on CMC

Reference is made to our original New Drug Application 21-262 submitted on June 29, 2000. Reference is also made to the fax received from Dr. Libaniel Rodriguez on October 25, 2000 (Item number 2) requesting the most up to date stability information (copy attached) and to our November 9, 2000 response indicating that an updated stability report would be available by the end of November.

Enclosed is an 18-Month Interim stability report for the primary registration batches of Brimonidine-Purite™ Ophthalmic Solution 0.15%. Based upon the evaluation of the room and accelerated stability data, a [redacted] expiry dating is justified for Brimonidine-Purite™ Ophthalmic Solution 0.15% when the product is stored at 25°C (77° F); excursions permitted to 15°-[redacted] C (59°-[redacted] F). Container orientation studies indicate little or no significant difference between samples stored in the upright versus inverted positions.

We hope you find the enclosed satisfactory for your review and approval. If you have any questions, please call me at 714-246-6088.

Sincerely,

Lewis Gryziewicz
Director
Regulatory Affairs

LG/JI

Desk Copy: Libaniel Rodriguez, Ph.D., Review Chemist, DAAOP

DUPLICATE

ALLERGAN

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

50 years GROWTH & INNOVATION

December 8, 2000

Wiley Chambers, MD
Deputy Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration HFD-550
Attention: Document Room
Building 2
9201 Corporate Blvd.
Rockville, MD 20850

NDA ORIG AMENDMENT

Bc

RE Brimonidine-Purite™ Ophthalmic Solution 0.15%
New Drug Application 21-262
Response to FDA Questions on CMC

Reference is made to our original New Drug Application 21-262 submitted on June 29, 2000. Reference is also made to the fax received from Dr. Libaniel Rodriguez on December 1, 2000 requesting information on the drug substance (copy attached).

Below are FDA questions followed by Allergan Response:

FDA Question

1. Please clarify the roles of [redacted] in the synthesis of brimonidine tartrate drug substance

Allergan Response

The bulk drug substance, brimonidine tartrate is synthesized/manufactured at both [redacted] Both companies have been qualified by Allergan and approved by the FDA to manufacture the Active Pharmaceutical Ingredient (API) brimonidine tartrate.

FDA Question

2. For release testing of the drug substance, who is responsible for the release testing and what tests are performed?

Allergan Response

[redacted] will manufacture and test the API to meet pre-shipment specifications. Refer to NDA 20-613, Volume 2, page 058 for [redacted] page 24 and 25. Copies are in Appendix 1. Final analytical and release of brimonidine tartrate bulk drug substance will be conducted at the following Allergan sites:

Allergan Inc.
2525 Dupont Drive
Irvine, CA 92713-9534

Allergan America
Puerto Rico Road 345, KM. 1.5
P.O.Box 60
Hormigueros, Puerto Rico 00660

Allergan Waco
8301 Mars Drive
Waco, TX 76712

Please refer to NDA 20-613, Volume 2, page 021 and volume 1, page 1 of the [redacted] supplement. Copies are included in Appendix 2.

FDA Question

3. What acceptance tests are performed on the drug substance at the drug product manufacturing site upon receipt?

Allergan Response

At the drug product manufacturing site (s), the tests listed in the NDA are performed to ensure the identity, strength, quality, and purity of the brimonidine tartrate drug substance. Please refer to NDA 21-262, Volume 2, pages 005 and 006. Copies included in Appendix 3.

We hope the enclosed is satisfactory for your review and approval. If you have any questions, please call me at 714-246-6088.

Sincerely,

Lewis Gryziewicz
Director
Regulatory Affairs

LG/JI

Desk Copy: Libaniel Rodriguez, Ph.D., Review Chemist, DAAOP

LERGAN

NDA ORIG AMENDMENT

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

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BC

November 21, 2000

Wiley Chambers, MD
Deputy Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration HFD-550
Attention: Document Room
Building 2
9201 Corporate Blvd.
Rockville, MD 20850

RE Brimonidine-Purite™ Ophthalmic Solution 0.15%
New Drug Application 21-262
Response to FDA Questions on CMC

Reference is made to our original New Drug Application 21-262 submitted on June 29, 2000. Reference is made to the fax received from Dr. Libaniel Rodriguez on October 25, 2000 regarding CMC questions and to our response of November 9, 2000.

Concerning question 4 of the October 25, 2000 fax, our response indicated that Allergan would conduct a Ruggedness study to evaluate the resolution in method AP-L262. We have completed the study and are submitting our updated response to question 4 at this time.

FDA Question

[redacted]

Allergan Response

[redacted]

IGINAL

We hope the enclosed is satisfactory for your review and approval. If you have any questions, please call me at 714-246-6088.

Sincerely,

Lewis Gryziewicz
Director
Regulatory Affairs

LG

Desk Copy: Libaniel Rodriguez, Ph.D., Review Chemist, DAAOP

ALLERGAN

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

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November 9, 2000

Wiley Chambers, MD
Deputy Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration HFD-550
Attention: Document Room
Building 2
9201 Corporate Blvd.
Rockville, MD 20850

...DOCUMENT

BC

RE Brimonidine-Purite™ Ophthalmic Solution 0.15%
New Drug Application 21-262
Response to FDA Questions on CMC

Reference is made to our original New Drug Application 21-262 submitted on June 29, 2000. Reference is made to the fax received from Dr. Libaniel Rodriguez on October 25, 2000 regarding CMC questions, copy attached. Reference is also made to the fax received from Dr. Libaniel Rodriguez on October 13, 2000 regarding CMC questions and to our October 17, 2000 reply that did not contain a response to question 2 regarding physical appearance.

October 25, 2000 Questions

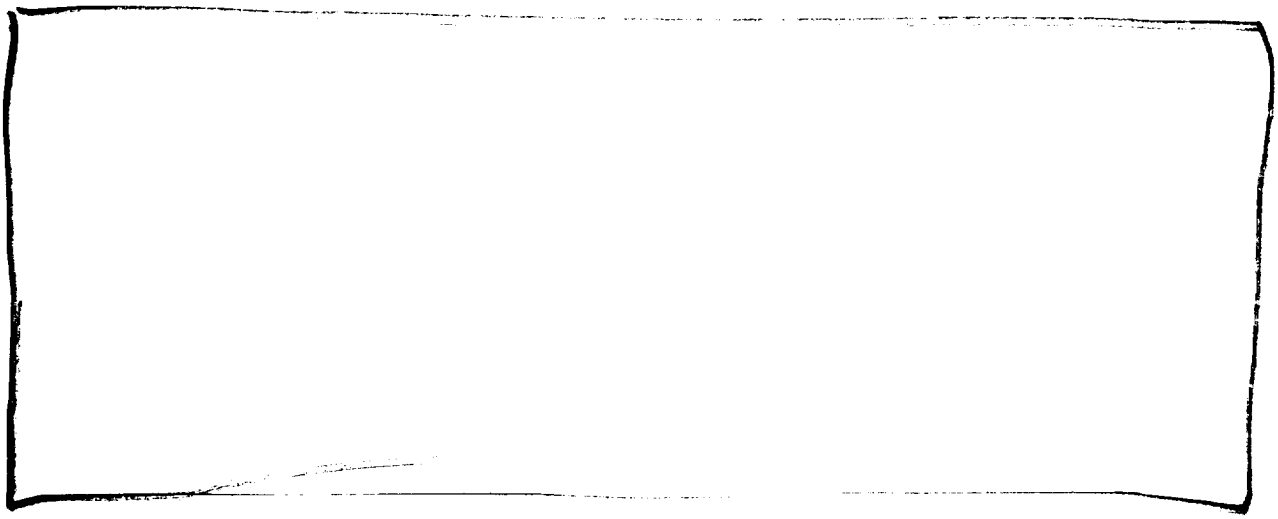
FDA Question:

[redacted]

Allergan Response

[redacted]

DUPLICATE



FDA Question:

2. ***Submit all updated stability including the six months of elevated temperature data in the upright and inverted positions for batch 11394.***

Allergan Response

Stability data for batch 11394 at [redacted] in the upright and inverted positions is found on pages 12 259 – 12 272. Allergan is preparing an updated stability report containing 18 months stability data at [redacted] This report should be finalized by the end of November.

FDA Question:

3. ***Please revise the individual unspecified or unknown impurity acceptance criterion to*** [redacted]

Allergan Response

The individual unspecified or unknown impurity regulatory specification has been changed to [redacted] A complete specification sheet for Brimonidine-Purite™ Ophthalmic Solution 0.15% is found in Attachment 1.

FDA Question:

4. ***A response factor at 1.1 does not reflect baseline resolution. Based on the results submitted with method*** [redacted] ***(vol. 14, p.064), this parameter could be amended to > 2.0. Please submit the amended method.***

Allergan Response

FDA Question:

5. ***Provide data for poly-ethylene glycol in stability batch***

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

Allergan Response

Technical Report PA-2000-418, "Drop Size Results for Brimonidine Tartrate 0.15% Solution with Purite and CMC" is found in Attachment 4.

FDA Question:

7. ***Submit the modified method for particulate matter which include corrective actions (vol.11, pages 11-12).***

Allergan Response

Analytical method "Light Obscuration Particle Count Test For Quantitating Particles in Ophthalmic Solutions" is found in Attachment 5.

October 13, 2000 Question-Physical Appearance

FDA Question

2. ***The label insert has the drug substance as an "off-white, pale yellow to pale pink powder". The Merck Index has brimonidine as yellow crystals. Please provide a more narrow range for the color of the pure drug substance.***

Allergan Response

Allergan agrees to change the physical appearance specification for brimonidine tartrate to "White to off-white to pale yellow powder".

We hope the enclosed is satisfactory for your review and approval. If you have any questions, please call me at 714-246-6088.

Sincerely,

Lewis Gryziewicz
Director
Regulatory Affairs

LG/JI

Desk Copy: Libaniel Rodriguez, Ph.D., Review Chemist, DAAOP

ALLERGAN

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

50 years
GROWTH & INNOVATION

November 2, 2000

Wiley Chambers, M.D.
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products
9201 Corporate Boulevard
Rockville, MD 20850-3202

Re: Brimonidine-Purite™ Ophthalmic Solution 0.15%
New Drug Application 21-262
Four Month Safety Update

...ENT
SU

Dear Dr. Chambers:

Reference is made to our original New Drug Application 21-262 submitted June 29, 2000. As per 21 CFR 314.50(d)(5)(vi)(b) Allergan is submitting at this time the four month safety update for Brimonidine-Purite™ Ophthalmic Solution 0.15%.

Allergan is submitting integrated safety data for 12 months dosing in our pivotal phase 3 clinical trials for Brimonidine-Purite™ Ophthalmic Solution 0.15%.

The information included in this submission is that detailed in our August 28, 2000 proposal. As per a conversation between Lori Gorski, Project Manager, Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products (DAAOP) and myself Allergan is including Case Report Forms for all patients who discontinued from the two pivotal studies. Case Report Forms for all patients who discontinued from the study after the initial 3 month analysis are provided electronically in the archival copy of this submission.

We have updated the Adverse Reactions section of the labeling to include the adverse event incidences for 12 months of dosing. We have also updated the Pharmacokinetics subsection of the Clinical Pharmacology section of the label to reflect the results of Study PK-98-130 in response to the October 27, 2000 fax from DAAOP.

Brief updates on other studies ongoing with brimonidine tartrate are also included.

DL...E

In addition to the clinical information provided in this submission, a nonclinical toxicology report, entitled "Brimonidine-Purite™ [redacted] A 1-Month Ocular Toxicity Study in Rabbits" was submitted to NDA 21-262 on October 17, 2000 along with revised stability specifications as part of the response to the Agency questions from Dr. L. Rodriguez, chemistry reviewer. The study report supports the safety of degraded Brimonidine-Purite™ Ophthalmic Solution 0.15% and allows for a shelf life specification of [redacted]

Should you have any questions, please contact me at (714) 246-6088.

Sincerely,

Lewis Gryziewicz
Director
Regulatory Affairs

Desk copy: Lori Gorski, Project Manager, DAAOP

ALLERGAN

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

50 years GROWTH & INNOVATION

October 19, 2000

Wiley Chambers, MD
Deputy Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration HFD-550
Attention: Document Room
Building 2
9201 Corporate Blvd.
Rockville, MD 20850

RE Brimonidine-Purite™ Ophthalmic Solution 0.15%
New Drug Application 21-262
Request for Clarification on Statistical Information

Reference is made to our original New Drug Application 21-262 submitted on June 29, 2000. Reference is also made to the fax received from Ms. Lori Gorski on October 17, 2000 regarding clarification on the statistical information (copy attached). Archival and review copies are enclosed.

FDA Request

*1. **Provide patients randomization code in SAS data set.***

Allergan Response

The following information was transmitted to Ms Lori Gorski as an e mail on October 18, 2000. "The randomization files are available in the CDRom we sent to the FDA for both 007 and 008 studies. Our original documentation regarding RAW SAS data sets neglected to mention the RANDOM files. But, they do reside together with all RAW SAS data sets in each study in transport format. The file name is RANDOM".

FDA Request

*2. **Provide SAS file 'lib.sas'.***

Allergan Response

Four (4) lib.sas electronic files are enclosed.

FDA Request

2. ***Provide SAS programs for primary analysis.***

Allergan Response

Sixty four (64) SAS programs for primary efficacy analysis are included.

We hope the enclosed is satisfactory for your review and approval. If you have any questions, please call me at 714-246-6088.

Sincerely,

for

Lewis Gryziewicz
Director
Regulatory Affairs

LG/JI

Desk Copy: Lori Gorski, Project Manager, DAAOP, HFD-550 (2 copies of same Diskette (word and pdf format) and hard copy).

ALLERGAN

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

October 17, 2000

Wiley Chambers, MD
Deputy Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration HFD-550
Attention: Document Room
Building 2
9201 Corporate Blvd.
Rockville, MD 20850

AMENDMENT
Bc

RE Brimonidine-Purite™ Ophthalmic Solution 0.15%
New Drug Application 21-262
Response to FDA Questions on CMC

Reference is made to our original New Drug Application 21-262 submitted on June 29, 2000. Reference is also made to the faxes received from Dr. Libaniel Rodriguez on October 10, 2000 and October 13, 2000 regarding CMC questions (copies attached) and the request over the telephone regarding the safety data for [redacted]cap (see Appendix 1 for the USP/NF biological and physicochemical tests).

October 10, 2000 QUESTIONS

FDA Question

1. ***The acceptance criteria values that you proposed in your submission of October 6, 2000 in response to question number 2 of our fax dated September 11, 2000 are not acceptable. Values shown in the table below, based on the submitted stability data are recommended.***

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

We hope the enclosed is satisfactory for your review and approval. If you have any questions, please call me at 714-246-6088.

Sincerely,

Lewis Gryziewicz
Director
Regulatory Affairs

LG/JI

Desk Copy: Dr Libaniel Rodriguez, Review Chemist, DAAOP

ALLERGAN

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

50 years GROWTH & INNOVATION

October 9, 2000

Wiley Chambers, MD
Deputy Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration HFD-550
Attention: Document Room
Building 2
9201 Corporate Blvd.
Rockville, MD 20850

RE Brimonidine-Purite™ Ophthalmic Solution 0.15%
New Drug Application 21-262
Response to FDA Questions on CMC

Reference is made to our original New Drug Application 21-262 submitted on June 29, 2000. Reference is also made to the fax received from Dr. Libaniel Rodriguez on September 26, 2000 regarding CMC questions, copy attached.

As suggested by the FDA, wherever applicable we have cited the exact location of the data within the submission. Below are the FDA queries followed by Allergan's response:

[redacted]

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

However, the start date for these new inverted studies was erroneously set at the same start date as that for the upright studies which had begun 4 months earlier. Thus, six months after the upright stability study was initiated both the [redacted] were automatically terminated by our [redacted] Therefore, only 2 months of elevated temperature data exist for the [redacted] for two of the three primary batches studied. The elevated temperature study for the third batch (11394) was initiated after we were aware of the new guidance and is in complete compliance with it.

Please note that we currently have performed two years of room temperature stability testing demonstrating that no difference in product characteristics can be discerned comparing each orientation in the three batches tested.

5. ***Submit particulate matter result for the*** [redacted]

Allergan Response

Particulate matter result for the [redacted] is in Appendix 2

[redacted]

Allergan Response

The requested data can be found in Appendix 3.

We hope the enclosed is satisfactory for your review and approval. If you have any questions, please call me at 714-246-6088.

Sincerely,

Lewis Gryziewicz
Director
Regulatory Affairs

LG/JI

Desk Copy: Dr Libaniel Rodriguez, Review Chemist, DAAOP

LLERGAN

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

50 years GROWTH & INNOVATION

October 6, 2000

NDA ORIG AMENDMENT

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
OCT 1 0 2000
MEGA DOC RM

Wiley Chambers, MD
Deputy Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration HFD-550
Attention: Document Room
Building 2
9201 Corporate Blvd.
Rockville, MD 20850

BC

RE Brimonidine-Purite™ Ophthalmic Solution 0.15%
New Drug Application 21-262
Response to FDA Questions on CMC – Item Number 2

Reference is made to our original New Drug Application 21-262 submitted on June 29, 2000. Reference is also made to the fax received from Dr. Libaniel Rodriguez on September 11, 2000 regarding CMC questions. Allergan responded to the Agency queries on October 3, 2000 except for item number 2 regarding the acceptance criteria for the impurities.

FDA Question

2. ***Acceptance criteria for the impurities should be adjusted to reflect actual data.***

Allergan Response

The release specifications remain unchanged. The updated specifications are shown in the attached tables and will support the proposed expiration dating period of [redacted] when stored at controlled room temperature.

Attached are two Tables, the first Table reflects the changes (bolded) and the second Table is the listing of the current specifications.

ORIGINAL

We hope the enclosed is satisfactory for your review and approval. If you have any questions, please call me at 714-246-6088.

Sincerely,

Lewis Gryziewicz
Director
Regulatory Affairs

LG/JI

Fax: Libaniel Rodriguez, Review Chemist, DAAOP

ALLERGAN

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

50 years GROWTH & INNOVATION

October 3, 2000

Wiley Chambers, MD
Deputy Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration HFD-550
Attention: Document Room
Building 2
9201 Corporate Blvd.
Rockville, MD 20850

RE Brimonidine-Purite™ Ophthalmic Solution 0.15%
New Drug Application 21-262
Response to FDA Questions on Microbiology

Reference is made to our original New Drug Application 21-262 submitted on June 29, 2000. Reference is also made to the telephone message received from Dr. Vinayak Pawar on September 22, 2000 regarding microbiology questions.

Below are the FDA questions followed by Allergan Response:

FDA Question

1. ***Which components are gamma sterilized and which are [redacted] sterilized.***

Allergan Response

The bottles and tips are gamma sterilized. The caps are [redacted] sterilized.

FDA Question

2. ***The bioburden prior to sterilization [redacted] What is the size of the lot?***

Allergan Response

Reference is made to [redacted] Validation Report PRTC – 94029. There is a typographical error in this protocol. The lot average bioburden of the report should read [redacted] We apologize for the oversight.

FDA Question

3. ***For the Package Integrity Test [redacted] were the bottles filled with preserved or unpreserved product?***

Allergan Response

[redacted]

FDA Question

4. For Environmental Monitoring we list results and refer to alert and action levels listed in the protocol, but never list the alert and action levels. What are they?

Allergan Response

Below are Alert and Action Levels for environmental monitoring.

Surface Testing Alert and Action Levels are:

[redacted]

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

[redacted]

We hope the enclosed is satisfactory for your review and approval. If you have any questions, please call me at 714-246-6088.

Sincerely,

Lewis Gryziewicz
Director
Regulatory Affairs

LG/JI

Fax: Vinayak Pawar, Ph.D., Microbiology Reviewer, DAAOP

ALLERGAN

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

50 years GROWTH & INNOVATION

October 2, 2000

Wiley Chambers, MD
Deputy Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration HFD-550
Attention: Document Room
Building 2
9201 Corporate Blvd.
Rockville, MD 20850

RE Brimonidine-Purite™ Ophthalmic Solution 0.15%
New Drug Application 21-262
Response to FDA Questions on CMC

Reference is made to our original New Drug Application 21-262 submitted on June 29, 2000. Reference is also made to the fax received from Dr. Libaniel Rodriguez on September 11, 2000 regarding CMC questions, copy attached.

Below are the FDA queries followed by Allergan's response:

1. ***Provide supporting information for the use of the [redacted] similar to the information provided for the [redacted]***

Allergan Response

[redacted]

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

7. ***Clarify whether the quantitative and qualitative composition of the inks used for the brimonidine purite drug product label are the same as those used for ALPHAGAN.***

Allergan Response

Allergan confirms that the quantitative and qualitative composition of the inks used for the Brimonidine Purite drug product label are the same as those used for ALPHAGAN.

We hope the enclosed is satisfactory for your review and approval. If you have any questions, please call me at 714-246-6088.

Sincerely,

Lewis Gryziewicz
Director
Regulatory Affairs

LG/JI

Desk Copy: Libaniel Rodriguez, Review Chemist, DAAOP

ALLERGAN

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

50 years GROWTH & INNOVATION

October 2, 2000

Wiley Chambers, MD
Deputy Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration HFD-550
Attention: Document Room
Building 2
9201 Corporate Blvd.
Rockville, MD 20850

AMENDMENT
Bm

RE Brimonidine-Purite™ Ophthalmic Solution 0.15%
New Drug Application 21-262
Response to FDA Questions - Clinical

Reference is made to our original New Drug Application 21-262 submitted on June 29, 2000. Reference is also made to the fax received from Ms. Lori Gorski on September 29, 2000 regarding Clinical questions, copy attached.

FDA Question

Please provide clarification on the following clinical information for NDA 21-262, Brimonidine Purite. Please provide information on investigator 0642-Mark Weiss, M.D., who withdrew from study 008. The reason for his withdrawal cannot be found. Please provide this information, or a location in the NDA where the information can be found.

Allergan Response

The reason for the withdrawal of Dr Mark Weiss, M.D. from study 190342-008 is explained in the attached letter received from Dr Weiss where he states that for unforeseen personal commitments he would not be able to devote the time needed to this study.

We hope the enclosed is satisfactory for your review and approval. If you have any questions, please call me at 714-246-6088.

Sincerely,

Lewis Gryziewicz
Director
Regulatory Affairs

LG/JI

cc: Ms Lori Gorski, Project Manager, DAAOP

Enc.

ALLERGAN

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

NDA ORIG AMENDMENT

September 26, 2000

Wiley Chambers, MD
Deputy Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration HFD-550
Attention: Document Room
Building 2
9201 Corporate Blvd.
Rockville, MD 20850

BP

RE Brimonidine-Purite™ Ophthalmic Solution 0.15%
New Drug Application 21-262
Request for Clarification on Pharm/Tox Information

Reference is made to our original New Drug Application 21-262 submitted on June 29, 2000. Reference is also made to the fax received from Ms. Lori Gorski on September 26, 2000 regarding Clarification on Pharmacology/Toxicology information.

Enclosed are copies of Histology Tables 44 through 51. These tables were inadvertently left out from the original NDA. We apologize for the inconvenience.

We hope the enclosed is satisfactory for your review and approval. If you have any questions, please call me at 714-246-6088.

Sincerely,

Lewis Gryziewicz
Director
Regulatory Affairs

LG/JI

cc: Lori Gorski, Project Manager, DAAOP

DUPLICATE

ALLERGAN

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

50 years
Growth & Innovation

September 5, 2000

NDA ORIG AMENDMENT

Wiley Chambers, MD
Deputy Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration HFD-550
Attention: Document Room
Building 2
9201 Corporate Blvd.
Rockville, MD 20850

BM

RE Brimonidine-Purite™ Ophthalmic Solution 0.15%
New Drug Application 21-262
Response to FDA Request

Reference is made to our original New Drug Application 21-262 submitted on June 29, 2000. Reference is also made to the fax received from Ms Lori Gorski on August 29, 2000 regarding clinical study 005 item number 1 of the fax, copy attached.

Enclosed are the requested tables which show the mean diurnal IOP at each timepoint for each study. A per protocol analysis of the data was performed. However, please note that no patients were excluded from the per protocol analysis, therefore the population for an intent-to-treat analysis would be the same.

We have also enclosed the same information for clinical study 004 for your convenience and possible use. If you have any questions, please call me at 714-246-6088.

Sincerely,

Lewis Gryziewicz
Director
Regulatory Affairs

LG/JI

DUPLICATE

Desk Copy: Lori Gorski, Project Manager, DAAOP

ALLERGAN

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

50 years
GROWTH & INNOVATION

August 28, 2000

NEW CORRES

Wiley Chambers
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic,
And Ophthalmic Drug Products
9201 Corporate Boulevard
Rockville, MD 20850-3202

NC

Re: Brimonidine-Purite™ Ophthalmic Solution 0.15%
New Drug Application 21-262

Dear Mr. Chambers:

Reference is made to our original New Drug Application 21-262 submitted June 29, 2000. As per 21 CFR 314.50(d)(5)(vi)(b) we are submitting our proposal for the Four Month Safety Update in order to reach agreement with the Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products (DAAOP) on the content of the safety update.

Attached is the list of tables we propose to include in the Four Month Safety Update. The tables will include data through 12 months of dosing. Note that we are proposing to not include Case Report Forms for any patients in the submission.

Please contact me directly at (714) 246-6088 to discuss our proposal.

Sincerely,

Lewis Gryziewicz
Director
Regulatory Affairs

Desk copy: Lori Gorski, Project Manager, DAAOP

DUPLICATE

- Summary of All Adverse Events Tabulated by Descending Order of Frequent Reports Number and Percent of Patients
- Summary of All Adverse Events - Pairwise Comparisons
- Summary of Adverse Events by Body System Number and Percent of Patients
- Summary of Adverse Events by Body System - Pairwise Comparisons
- Summary of All Adverse Events by Body System and Severity Number and Percent of Patients
- Summary of Treatment-Related Adverse Events Tabulated by Descending Order of Frequent Reports Number and Percent of Patients Reported
- Summary of Treatment-Related Adverse Events - Pairwise Comparisons
- Summary of Treatment-Related Adverse Events by Body System Number and Percent of Patients
- Summary of Treatment-Related Adverse Events by Body System - Pairwise Comparisons
- Summary of Treatment Related Adverse Events by Body System and Severity Number and Percent of Patients
- Number and Percent of Patients Discontinued Due to Adverse Events
- Number and Percent of Patients with Serious Adverse Events
- Patients with Serious Adverse Event
- Heart Rate, Systolic Blood Pressure, Diastolic Blood Pressure

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50 years
GROWTH & INNOVATION

August 16, 2000

Wiley Chambers, MD
Acting Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration HFD-550
Attention: Document Room
Building 2
9201 Corporate Blvd.
Rockville, MD 20850

RE Brimonidine-Purite™ Ophthalmic Solution 0.15%
New Drug Application 21-262

Reference is made to our New Drug Application 21-262 submitted June 29, 2000 and to an August 15, 2000 telephone call from Mike Puglisi, Project Manager, Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Product (DAAOP) requesting a copy of the USP test report for purple resin colorant submitted in the September 1997 Annual Report to NDA 20-613.

Enclosed please find an archival and review copy of the requested report. Please add this to the file for NDA 21-262. Thank you.

Should you have any additional questions, please contact me at (714) 246-6088.

Sincerely,

Lewis Gryziewicz
Director
Regulatory Affairs

LG/JI

Desk Copy: Mike Puglisi, Project Manager, Division of Anti-Inflammatory Analgesic, & Ophthalmic Drug Products

DUPLICATE

ALLERGAN

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

August 11, 2000

Wiley Chambers, M.D.
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products
9201 Corporate Boulevard
Rockville, MD 20850-3202

Re: Brimonidine-Purite™ Ophthalmic Solution 0.15%
New Drug Application 21-262

Dear Dr. Chambers:

Reference is made to our original New Drug Application 21-262 submitted June 29, 2000 and to a facsimile dated August 7, 2000 from Lori Gorski, Project Manager, Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products (DAAOP) requesting additional information for the NDA review, copy attached.

1. *Study 008. There seems to be an inconsistancy in the patients who were reported as discontinued in the study. There are several patients listed as discontinued in the Listing of Adverse Events (Volume 91, page 001) that were omitted from the Listing of Discontinued Patients (Volume 51, page 89). For example patients 2983-E06, 1587-H06, 2122-T01, 2450-S01, 2893-F04, etc. Please clarify.*

When an adverse event is recorded on the case report form, the investigator completes the "Action Regarding the Study Drug" field which has four options: none, reduced, interrupted, and discontinued. The Adverse Event Case Report Form also has a box that the investigator can check if patient was discontinued from the study due to an adverse event. The column in Appendix 16.4, Listing 8 that is referenced in your facsimile has a column listing "Action". This is the action regarding study drug, not regarding the patient's exit from the study. We have revised Appendix 16.4, Listing 8 for both studies 190342-007 and 190342-008 to clarify the heading of this column to "Action Regarding Study Drug" and included an additional column with heading "Discontinued From Study Due to the AE".

We have compared the Appendix 16.4, Listing 8 and Appendix 16.2.1, Listing 1, Discontinued Patients with Exit Reasons. A narrative explanation is included in our response that discusses any patient who listed "Discontinued" in the "Action" column of Listing 8 and did not appear in Listing 1. Primarily, our review found that the investigator checked "discontinued" for Action Regarding Study Drug in error. The Action to Study Drug should have been marked as "interrupted" or "none" during the first 3 months of treatment. The patients were not exited from the study within the first 3 months of treatment.

2. *Study 008. A listing showing the principle investigators along with the number of subjects enrolled and the subject ID series cannot be located for this study. (e.g. similar to the one provided for study 007, Volume 49 page 001). It appears to have been inadvertently left out of section 16.1.4, Volume 73, page 001.*

Enclosed please find the List of Investigators for Study 190342-008. This was inadvertently omitted from section 16.1.4.

Should you have any additional questions, please contact me at (714) 246-6088.

Sincerely,

Lewis Gryziewicz
Director
Regulatory Affairs

Desk copy: Lori Gorski, Project Manager, DAAOP

ALLERGAN

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

August 8, 2000

Wiley Chambers
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products
9201 Corporate Boulevard
Rockville, MD 20850-3202

Re: Brimonidine-Purite™ Ophthalmic Solution 0.15%
New Drug Application 21-262

AMENDMENT
BZ

Dear Dr. Chambers:

Reference is made to our original New Drug Application 21-262 submitted June 29, 2000 and to a facsimile dated July 27, 2000 from Lori Gorski, Project Manager, Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products requesting additional information for the NDA review, copy attached.

Statistical – Please provide a written description of the statistical methodology used in the data analysis.

The Statistical Analysis Plan for the pivotal phase 3 protocols is located in the NDA in Section 8 on page 75 108. The corresponding page in Section 10 is 139 108. For ease of review we have included a copy of the Statistical Analysis Plan in Attachment 1. The Statistical Analysis Plans for the two phase 3 studies are identical.

[redacted]

The letter of cross reference for [redacted] is found in the NDA on page 11 179, for [redacted] on page 11 180, and for [redacted] on page 11 460. Copies of the letters are found in Attachment 2 for ease of review.

Clinical Issues

1. Study 008 Volume 70 Section 14.2

This section contains several sets of data tables with the same headings which contain different data. Examples include tables 13.2 and 14.2, tables 15.2 and 16.2, tables 17.2 and 18.2. Please provide clarification.

DUPLICATE

Replacement versions of the Tables 14.2, 16.2, and 18.2 are found in Attachment 3 with headings that are more descriptive, allowing for greater differentiation from Tables 13.2, 15.2, and 17.2. We have added the phrase "In Mean Changes from Baseline" to the ends of the titles for Tables 14.2, 16.2, and 18.2.. The data in the tables is identical to that submitted in the original NDA.

2. *Study 008 Volume 70 Section 14.2 (Intent-to-treat LOCF Analysis section)*

The diurnal IOP with a 95% confidence interval of between-group differences for hour 7 and 9 at baseline cannot be located in the provided tables. All other time points have been provided.

3. *Study 007 Volume 46 Section 14.2*

Same comment as #2.

Tables containing diurnal IOP with a 95% confidence interval of between-group differences for hour 7 and 9 at baseline for the intent-to-treat LOCF and per protocol analysis groups for both studies are included in Attachment 4 of this submission.

4. *Please provide a table listing discontinued patients by investigator, patient number, treatment arm and reason for discontinuation for study 007 and 008. This information cannot be located.*

This information can be found in the NDA in Section 8 page 51 089 for Study 190342-007 and 75 144 for Study 190342-008. The corresponding pages in Section 10 are 115 089 and 139 144. The tables are included in Attachment 5 for ease of review.

Also, as per my August 7, 2000 conversation with Lori Gorski, Project Manager, DAAOP, please find as Attachment 6 the carton labeling for the product.

Should you have any questions, please contact me directly at (714) 246-6088.

Sincerely,

Lewis Gryziewicz
Director
Regulatory Affairs

Desk copy: Lori Gorski, Project Manager, DAAOP

ALLERGAN

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

50 years
GROWTH & INNOVATION

August 2, 2000

NEW CORRESP
NC

Wiley Chambers, MD
Deputy Director
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration HFD-550
Attention: Document Room
Building 2
9201 Corporate Blvd.
Rockville, MD 20850

RE: NDA 21-262
Brimonidine - Purite™ Ophthalmic Solution 0.15%
Trade Name

Dear Dr. Chambers,

Allergan hereby submits a new tradename for NDA 21-262:

ALPHAGAN® P

We are assigning the P suffix to indicate Purite™ the preservative of the product. We trust this name is acceptable for your review and approval.

Sincerely,

Lewis Gryziewicz
Director
Regulatory Affairs

LG/JI

cc: Lori Gorski, Project Manager, Division of Anti-Inflammatory, Analgesic & Ophthalmologic Drug Products

ALLERGAN

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

July 27, 2000

Central Document Room
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD 20850

Re: Brimonidine-Purite™ Ophthalmic Solution 0.15%
New Drug Application 21-262

Dear Sir or Madam:

Reference is made to our original New Drug Application 21-262 submitted June 29, 2000. Reference is also made to a telephone conversation between Dr. Randy Levin, Associate Director, Electronic Review and myself during which Dr. Levin requested that I submit a copy of the electronic files for the two pivotal studies to the Central Document Control Room.

As requested, please find a copy of the electronic files for the two pivotal studies. This submission differs from that sent June 29, 2000 to Michael Puglisi, Consumer Safety Officer, Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products (DAAOP) with respect to the derived dataset programs. Incorrect versions of some of these programs were previously sent. As such I am sending a replacement copy to DAAOP.

Should you have any questions, please contact me directly at (714) 246-6088.

Sincerely,

Lewis Gryziewicz
Director
Regulatory Affairs

√ Desk copy: Lori Gorski, Project Manager, DAAOP, HFD-550
Letter only: Randy Levin, Associate Director, Electronic Review, CDER, HFD-1

NDA 21-262

JUL 21 2000

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

Dear Mr. Gryziewicz:

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:	Brimonidine-Purite (brimonidine tartrate ophthalmic solution) Ophthalmic Solution, 0.15%
Therapeutic Classification:	Standard (S)
Date of Application:	June 29, 2000
Date of Receipt:	June 30, 2000
Our Reference Number:	NDA 21-262

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 August 29, 2000, in accordance with 21 CFR 314.101(a).

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 your request for deferral of the pediatric study data until August 2001.

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
5600 Fishers Lane
Rockville, Maryland 20857

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

If you have any questions, call Lori M. Gorski, Project Manager, at (301) 827-2090.

Sincerely,

/S/ - 7/21/00

Leslie Vaccari
Chief, Project Management Staff
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

cc:
NDA 21-262
HFD-550/Div. Files
HFD-550/CSO/Gorski /S/ 7/20/00
HFD-550/MO/Harris 7/21/00
HFD-550/SCSO/Vaccari
DISTRICT OFFICE /S/ 7/21/00
HFD-550/Chambers
Drafted by: /July 7, 2000
Initialed by:

ACKNOWLEDGEMENT (AC)

ALLERGAN

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

50 years GROWTH & INNOVATION

July 21, 2000

NEW CORRESP

CENTER FOR DRUG REC'D JUL 24 2000 MEGA EVALUATION AND RESEARCH

Wiley Chambers, MD
Deputy Director
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration HFD-550
Attention: Document Room
Building 2
9201 Corporate Blvd.
Rockville, MD 20850

NC

RE: NDA 21-262
Brimonidine - Purite™ Ophthalmic Solution 0.15%

Dear Dr. Chambers,

Reference is made to the telephone conversation between Ms Jeanette Injejikian, Allergan Regulatory Affairs and Ms Lori Gorski, Project Manager from the Agency on July 6, 2000 requesting the trade name for NDA 21-262.

At this time Allergan submits the following trade name:

ALPHAGAN® NP

We are assigning the NP suffix to indicate New Preservative. We trust this name is acceptable for your review and approval.

Sincerely,

Lewis Gryziewicz
Director
Regulatory Affairs

DUPLICATE

LG/JI

cc: Lori Gorski, Project Manager, Division of Anti-Inflammatory, Analgesic & Ophthalmologic Drug Products

ALLERGAN

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

June 29, 2000

Central Document Room
Food and Drug Administration
12229 Wilkins Ave
Rockville, MD 20850

REF.: Brimonidine-Purite™ Ophthalmic Solution 0.15%
Original New Drug Application (NDA 21-262)

Dear Sir or Madam:

Allergan, Inc., hereby submits a review and an archival copy of the above-referenced New Drug Application (NDA), Brimonidine-Purite™ Ophthalmic Solution 0.15% which, applied topically to the eye, three times per day, has been shown to be safe and effective in lowering intraocular pressure (IOP) in patients with open-angle glaucoma (OAG) and/or ocular hypertension (OHT). Brimonidine-Purite™ is a new formulation of brimonidine tartrate, which is the active drug substance of ALPHAGAN® (brimonidine tartrate ophthalmic solution) 0.2% (NDA 20-613).

This NDA includes the results of 5 completed studies in support of the safety and efficacy of Brimonidine-Purite™ Ophthalmic Solution 0.15% for use in controlling IOP in glaucoma or ocular hypertensive patients. The presentation of the clinical data in this NDA is in accordance with the instructions given by the Medical Reviewers during the pre-NDA meeting held January 24, 2000. Brimonidine-Purite™ at 0.15% concentration combines efficacy with the possibility of increased safety and tolerability by delivering the lowest effective dose of brimonidine tartrate. The data from the two pivotal studies (190342-007, 190342-008) demonstrate that Brimonidine-Purite™ Ophthalmic Solution 0.15% is effective as a first-line therapy for reducing elevated intraocular pressure in patients with open-angle glaucoma and/or ocular hypertension. Both the overall mean pressure reductions at morning and afternoon trough, and peak, as well as the percentage of patients that receive benefit from treatment were clinically significant. The safety profile demonstrates that Brimonidine-Purite™ Ophthalmic Solution 0.15% is safe for use three times per day.

Brimonidine tartrate is a selective alpha-2 adrenoreceptor agonist. Structurally, brimonidine is similar to p-aminoclonidine, however, it is a more selective alpha-2 adrenoreceptor agonist than is p-aminoclonidine. The alpha-2 adrenoreceptor selectivity of brimonidine was characterized by radioligand binding and functional assays. The potent ocular hypotensive effect of brimonidine was demonstrated in rabbits, cats, and three species of primates (i.e., owl, cynamolgus, and capuchin monkeys). Brimonidine significantly lowered the IOP in both ocular normotensive and ocular hypertensive rabbits and primates.

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Mechanistic studies in rabbits and primates, including humans, indicate that the ocular hypotensive effects of brimonidine result from the suppression of aqueous humor production and from enhanced uveoscleral outflow. The ocular hypotensive effects in rabbits are mediated through stimulation of a peripheral alpha-2 adrenoreceptor whereas both the ocular hypotensive and cardiovascular effects in primates are mediated by an imidazoline receptor in the brain. Brimonidine, at pharmacological doses, did not cause vasoconstriction in a xenograph model of human retinal microvasculature. These pharmacological data were previously submitted to the Agency in approved NDA 20-613.

A number of single dose, repeat dose, mutagenicity, carcinogenicity, and reproductive studies were conducted and previously submitted to the Agency in approved NDA 20-613. Brimonidine-Purite™ Ophthalmic Solution 0.15%, NDA 21-262 contains additional studies which confirm previous observations. The study results support the ocular and systemic safety of brimonidine. The safety of Brimonidine-Purite™ has been well characterized in repeated-dose, topical ocular studies up to 6 months duration in rabbits. The safety of Purite™ (preservative) has been established independently from brimonidine in acute, repeated-dose, mutagenicity, and special toxicity studies conducted on lens care or eye drop solutions containing as much as 150 ppm Purite. No ocular toxicity was observed in 3-4 day ocular studies in rabbits comparing Brimonidine-Purite™ 0.2% to ALPHAGAN® 0.2% given up to 4 times daily. Brimonidine-Purite™ 0.1% and 0.2%, given ocularly 3 times daily into one eye for 6 months, were well tolerated in rabbits with no apparent ocular toxicity. No toxicologically significant findings were noted after multiple ocular installations of brimonidine in rabbits and monkeys and from reproduction and fertility studies following systemic dosing. Brimonidine does not exhibit any mutagenic or carcinogenic potential.

Systemic brimonidine exposure during ophthalmic administration of Brimonidine-Purite™ 0.1% and 0.2% was assessed in a human pharmacokinetic study. Plasma brimonidine concentrations were generally very low, with a Cmax of 47.4 pg/ml in plasma. After reaching peak concentration, plasma concentrations generally declined with a mean terminal $t_{1/2}$ of approximately 2 hours.

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The proposed product, Brimonidine- Purite™ Ophthalmic Solution 0.15% contains 0.15% w/v of brimonidine tartrate as the active pharmaceutical ingredient and Purite™ at 50ppm (0.005% w/v) as the preservative. The inactive ingredients include sodium carboxymethylcellulose (CMC), boric acid, sodium borate, sodium chloride, potassium chloride, calcium chloride, magnesium chloride and purified water. The target pH of 7.1-7.3 is provided by the borate buffer. All ingredients except the active drug and Purite™ are USP/NF compendial grade materials. The drug substance is manufactured at [redacted]
These manufacturing sites of the API have been inspected and approved by the FDA under approved NDA 20-613 for ALPHAGAN® (brimonidine tartrate ophthalmic solution) 0.2%. The product, in a multi-dose container, will be manufactured, packaged, and labeled by Allergan, Waco, Texas. The proposed expiration dating for this product is [redacted] with storage at 25°C (77°F); excursions permitted to 15-[redacted]C (59-[redacted] F).

Allergan, Inc. has manufactured three validation lots of the drug product at its manufacturing facility at Allergan, Waco, Texas. The site is ready for a Pre-Approval Inspection.

Allergan is requesting a deferral of submission of pediatric data for this NDA. Allergan is currently conducting a clinical trial of ALPHAGAN® (brimonidine tartrate ophthalmic solution) 0.2% in pediatric patients under [redacted] and plans to submit a clinical study report for this trial by August 1, 2001.

We confirm that the electronic and the hard copy of the complete submission of NDA 21-262 for Brimonidine-Purite™ Ophthalmic Solution 0.15% are identical.

Allergan, Inc. concludes that all the available data from clinical, toxicological, pharmacokinetic and pharmacology studies performed on this product have indicated that Brimonidine -Purite™ (brimonidine tartrate ophthalmic solution) 0.15% is safe and effective for its intended use.

Should you have any questions, please contact me at 714-246-6088.

Sincerely,

Lewis Gryziewicz
Director
Regulatory Affairs

LG/JI