CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-490/S007

20-613/S018

21-262/S006

CORRESPONDENCE

HFD-550/HOLMES

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-613

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

JUN [illegible]

JUN 25 1999

Dear Mr. Buxbaum:

Reference is made to your Proposed Pediatric Study Requests submitted on September 29, 1998, and April 30, 1999, for Alphagan (brimonidine tartrate ophthalmic solution), 0.2% to NDA 20-613. We also refer to our letter dated January 14, 1999.

We acknowledge receipt of your submission dated March 4, 1999.

To obtain needed pediatric information on brimonidine tartrate for the treatment of elevated intraocular pressure, the Food and Drug Administration (FDA) is hereby issuing to you an official Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act. FDA requests that you submit information from the following study:

Type of Study:
The study should be a randomized, double-masked, parallel comparison trial.

Indication/Objective:
The primary objective of the study should be to evaluate the safety and the clinical response on elevated intraocular pressure between treatment groups. Enrolled patients should include male and female pediatric patients with a clinical diagnosis of glaucoma or elevated intraocular pressure.

Age Groups:
There should be at least 5 pediatric patients per arm per strata. The strata should consist of approximately 1 year intervals between the ages of 2 and 7 years (i.e., between 2 years and 3 years, between 3 years and 4 years, etc.).

Drug Information:
Brimonidine tartrate ophthalmic solution, 0.2% should be compared to an appropriate control treatment.

Drug Specific Safety Concerns:
In addition to monitoring adverse events, vital signs, intraocular pressure, visual acuity, dilated ophthalmoscopy, and corneal diameter should be performed at baseline and end of therapy. Particular attention should be made to evaluate the drug products' effects on safety evaluations of pulse, blood pressure, and alertness.

Statistical Analysis:
At least 30 patients per arm should be evaluated. The study should be of at least 12 weeks duration and should include a minimum of four evaluations including baseline and end of treatment.

Labeling:
Information collected in the study should permit the determination of appropriate labeling instructions.

Format of Reports To Be Submitted:
At the completion of this study, a full study report providing the analyses outlined in this request should be provided, with complete analysis, assessment, and interpretation of the study.

Timeframe:
This report must be submitted by August 1, 2001.

Please notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Please clearly mark your submission **"PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission.

Please submit the protocol for the above study to an investigational new drug application (IND) and clearly mark your submission **"PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY"** in large font, bolded type at the beginning of the cover letter of the submission. Please notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission **"PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission.

The report of this study should be submitted as a supplement to your approved NDA, with the proposed labeling you believe would be warranted based on the data derived from this study. When submitting the report, please clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS-PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or mail/messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, Maryland 20855-2773.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your applications. Submissions of proposed changes to this request should be clearly marked **"PROPOSED CHANGES IN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits to the pediatric population.

If you have any questions, please contact Joanne Holmes, M.B.A., Clinical Reviewer, at (301) 827-2090.

Sincerely,

/S/ 6/25/1999

Robert DeLap, M.D., Ph.D.
Director
Office of Drug Evaluation V
Center for Drug Evaluation and Research

cc:
NDA 20-613
HFD-550 Div Files
HFD-550/Proj Mgr/Gorski /S/ 5/20/99
HFD-550/PedRep/Ludwig /S/
HFD-550/PedRep/Dunbar /S/ 5/27/99
HFD-550/DepDir/Chambers /S/ 6/24/99
HFD-550/MO/Boyd /S/ 6/24/99
HFD-550/SCSO/Zeccola /S/ 5/20/99
HFD-550/ClinRev/Holmes /S/
HFD-105/ADRA/Walling
HFD-105/DeLap
HFD-600/Office of Generic Drugs
HF-2/Lumpkin
HFD-6/KRoberts
HFD-104/DMurphy

Drafted by: jh/May 20, 1999
Revised:

PEDIATRIC WRITTEN REQUEST LETTER
INFORMATION REQUEST (IR)

SE5-006/PM

ALLERGAN

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

August 14, 2001

Wiley Chambers, M.D.
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
9201 Corporate Blvd., Building 2
Rockville, MD 20850

Re: NDA 20-613 / ALPHAGAN® (brimonidine tartrate ophthalmic solution) 0.2%
Cross-Refer: NDA 20-490 / ALPHAGAN® (brimonidine tartrate ophthalmic solution) 0.5%, [redacted] / ALPHAGAN® P (brimonidine tartrate ophthalmic solution) 0.15%,
SUBMISSION OF PEDIATRIC STUDY REPORT – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED

Dear Dr. Chambers:

Reference is made to the June 25, 1999 Written Request received from the Agency for pediatric information on brimonidine tartrate ophthalmic solution and the May 17, 2001 letter from the Agency amending the timeframe of the Written Request in response to our request, copies attached.

At this time, and in accordance with 21 CFR 201.57(f)(9), we are submitting an archival and a review copy of a Supplemental Pediatric Study Report to the above-referenced NDAs and requesting that a pediatric exclusivity determination be made.

In support of the proposed new wording to the pediatric use section of the package insert a clinical safety and tolerability study, 190342-015 was conducted. This study was a multi-center, randomized, double-masked, parallel group study completed worldwide which compared ALPHAGAN® TID to TRUSOPT® TID. A total of 76 patients between the ages of 2 and 7 years were enrolled and 63 patients completed the study.

The results of this study support the hypothesis that ALPHAGAN® 0.2% ophthalmic solution is a therapeutic option in pediatric glaucoma patients aged 2 and older.

ORIGINAL

Letter to W. Chambers, M.D.
ALPHAGAN®/ALPHAGAN® P Pediatric Supplement
Page 2

Submission of this study report fulfills the requirements of section 505A of the Federal Food, Drug, and Cosmetic Act entitling Allergan to an additional six months of marketing exclusivity for ALPHAGAN® (brimonidine tartrate ophthalmic solution) 0.2% and ALPHAGAN® P (brimonidine tartrate ophthalmic solution) 0.15%. This will prevent other companies from submitting any applications for brimonidine tartrate ophthalmic solution 0.2% under sections 505(b)(2) or 505(j) of the Act during the FDA review period (up to 90 days) for assuring conformance with the Written Request. Once FDA determines that the clinical study was conducted in accordance with the Written Request, the exclusivity for ALPHAGAN® will be extended to March 6, 2002 and the exclusivity for ALPHAGAN® P will be extended to September 16, 2004.

Section 2, Proposed Draft Labeling, Section 11, SAS Data sets, and Section 12, Case Report Forms were sent electronically in the archival copy filed to NDA 20-613.

We trust that the enclosed information is satisfactory for your review and approval and request that it be included in the files for NDA 20-490, NDA 20-613, and NDA 21-262. Should you have any questions, please contact me at (714) 246-6088.

Sincerely,

Lewis Gryziewicz
Director
Regulatory Affairs

cc: G. Buehler, Director, OGD

LG:tp

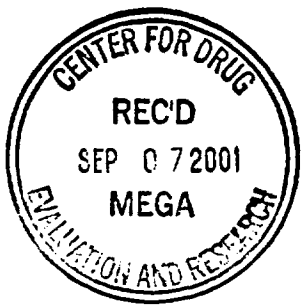
SES-007/BL
NDA SUPPL AMENDMENT

ALLERGAN

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

September 6, 2001

Wiley Chambers, M.D.
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 Control Room
9201 Corporate Blvd., Building 2
Rockville, MD 20850



Re: NDA 20-490/ALPHAGAN® (brimonidine tartrate ophthalmic solution) 0.5%
Amendment to Labeling Supplement
SUBMISSION OF PEDIATRIC STUDY REPORT – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED

Dear Dr. Chambers:

Reference is made to our August 14, 2001 submission of a Supplemental Pediatric Study Report requesting a pediatric exclusivity determination to NDA 20-490. Reference is also made to an August telephone conversation between Lori Gorski, Project Manager, DAAOP, and myself during which Ms. Gorski requested Allergan submit proposed labeling for ALPHAGAN 0.5%.

At this time Allergan is submitting an archival and review copy of the proposed labeling for ALPHAGAN 0.5%.

Please note that Allergan has not marketed ALPHAGAN 0.5% since its approval in 1997 and has no immediate plans to market the product. Labeling was not included in the original SNDA submission for this reason.

We have enclosed a disk copy of the proposed labeling in the desk copy sent to Ms. Gorski.

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
enc

DUPLICATE

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-490/S-007
NDA 20-613/S-018
NDA 21-262/S-006

PRIOR APPROVAL SUPPLEMENTS

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 supplemental drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Product number	Product Name
20-490/S-007	Alphagan (brimonidine tartrate ophthalmic solution) Ophthalmic Solution 0.5%
20-613/ S-018	Alphagan (brimonidine tartrate ophthalmic solution) Ophthalmic Solution 0.2%
21-262/S-006	Alphagan P (brimonidine tartrate ophthalmic solution) Ophthalmic Solution 0.15%

Review Priority Classification: Priority (P)

Date of Supplements: August 14, 2001

Date of Receipt: August 15, 2001

These supplements propose a change in the wording of the pediatric section of the package inserts.

Unless we notify you within 60 days of our receipt date that the applications are not sufficiently complete to permit a substantive review, the applications will be filed under section 505(b) of the Act on October 14, 2001, in accordance with 21 CFR 314.101(a).

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.

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

{See appended electronic signature page}

Mary Jane Walling
Associate Director for Regulatory Affairs,
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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

/s/

Lori Gorski
9/7/01 09:48:00 AM
Lori Gorski has signed for Mary Jane Walling

ALLERGAN

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

September 12, 2001

DUPLICATE

SE5-016

NEW CORRESP

RECEIVED

SEP 1 9 2001

MEGA/CDER

Wiley Chambers, M.D.
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 Control Room
9201 Corporate Blvd., Building 2
Rockville, MD 20850

Re:NDA 20-613/ALPHAGAN® (brimonidine tartrate ophthalmic solution) 0.2%
Cross-Refer: NDA 20-490/ALPHAGAN® (brimonidine tartrate ophthalmic solution) 0.5%, NDA 21-262/ALPHAGAN® (brimonidine tartrate ophthalmic solution) 0.15%
Amendment to Labeling Supplement
SUBMISSION OF PEDIATRIC STUDY REPORT – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED

Dear Dr. Chambers:

Reference is made to our August 14, 2001 submission of a Supplemental Pediatric Study Report requesting a pediatric exclusivity determination to the above referenced NDAs. Reference is also made to a September 12, 2001 telephone conversation between Wiley Chambers, Deputy Director, Lucious Lin, Medical Officer, and Lori Gorski, Project Manager, representing DAAOP, and Peter Kresel, Scott Whitcup, and myself during which FDA suggested Allergan re-evaluate the demographics of the patients enrolled in the study

At this time Allergan is submitting additional tables of Demographic data for Clinical Study 190342-015. The Written Request dated June 25, 1999 states "There should be at least 5 pediatric patients per arm per strata. The strata should consist of approximately 1 year intervals ...". The enclosed data shows that grouping patients in strata of 1.2 years from age 2 through 7 results in at least 5 patients per arm per strata. We have also included a table that stratifies all of the patients enrolled in the study by age to assist in your review.

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

Sincerely,

Lewis Gryzlewicz
Director
Regulatory Affairs

Desk copy: 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

SE5-018/IBM

NDA SUPPL AMENDMENT
RECEIVED
OCT 2 2 2001
MEGA/CDER

October 19, 2001

Wiley Chambers, M.D.
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 Control Room
9201 Corporate Blvd., Building 2
Rockville, MD 20850

Re:NDA 20-613/ALPHAGAN® (brimonidine tartrate ophthalmic solution) 0.2%
Cross-Refer: NDA 20-490/ALPHAGAN® (brimonidine tartrate ophthalmic solution) 0.5%, NDA 21-262/ALPHAGAN® (brimonidine tartrate ophthalmic solution) 0.15%
Response to FDA Questions

Dear Dr. Chambers:

Reference is made to our August 14, 2001 submission of a Supplemental Pediatric Study Report requesting a pediatric exclusivity determination to the above referenced NDAs and to an October 18, 2001 fax from FDA, Attachment 1.

In response to FDA's question, it is difficult to conduct visual acuity testing in the children in the study age group, ages 2 – 7. The children are either too young to be adequately tested or are sometimes uncooperative.

Listing 15, pages 4 059 – 4 070, gives the visual acuity for patients that were tested. From that table Allergan has prepared the list in Attachment 2 of patients who do not have visual acuity scores. Attachment 3 highlights, from the Demographic Listing, the patients and their ages. Attachment 4 contains the list of Protocol Deviations from the study report highlighting those for whom visual acuity is not available.

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
enc

DUPLICATE

ALLERGAN

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

November 7, 2001

Wiley Chambers, M.D.
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 Control Room
9201 Corporate Blvd., Building 2
Rockville, MD 20850

Re:NDA 20-613/ALPHAGAN® (brimonidine tartrate ophthalmic solution) 0.2%
Cross-Refer: NDA 20-490/ALPHAGAN® (brimonidine tartrate ophthalmic solution) 0.5%, NDA 21-262/ALPHAGAN® (brimonidine tartrate ophthalmic solution) 0.15%
Response to FDA Questions

Dear Dr. Chambers:

Reference is made to our August 14, 2001 submission of a Supplemental Pediatric Study Report requesting a pediatric exclusivity determination to the above referenced NDAs and to a November 5, 2001 fax from FDA, [redacted]

A list of patients who do not have visual acuity scores [redacted] The General Comments from the Data Listings in the Clinical Study Report [redacted] We have highlighted the reasons given for each patient for not having a visual acuity score for that patient.

As stated in our October 19, 2001 letter, many of the patients in the study are too young to cooperate to conduct visual acuity testing. The inclusion criteria for the study allowed patients whose vision allowed them to fixate on and follow a light or test object (fix and follow) to be enrolled in the study. Visual acuity scores are not recordable on the LEA symbols acuity chart for patients whose visual acuity is determined by the ability to fix or follow, count fingers, hand motion, or perceive light.

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
enc

ALLERGAN

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

November 16, 2001.

Wiley Chambers, M.D.
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 Control Room
9201 Corporate Blvd., Building 2
Rockville, MD 20850

Re:NDA 20-613/ALPHAGAN® (brimonidine tartrate ophthalmic solution) 0.2%
Cross-Refer: NDA 20-490/ALPHAGAN® (brimonidine tartrate ophthalmic solution) 0.5%, NDA 21-262/ALPHAGAN® (brimonidine tartrate ophthalmic solution) 0.15%
Response to FDA Draft Labeling

Dear Dr. Chambers:

Reference is made to our August 14, 2001 submission of a Supplemental Pediatric Study Report to the above referenced NDAs and to the draft labeling dated October 30, 2001 from FDA.

Allergan would like to propose the following changes to the text in the Pediatric Use section proposed by FDA:

FDA-proposed language:

[redacted]

Allergan proposal:

In a well-controlled clinical study conducted in pediatric glaucoma patients (ages 2 to 7 years) the most commonly observed adverse events with brimonidine tartrate ophthalmic solution 0.2% dosed three times daily were somnolence (25% - 83%) and decreased alertness. In pediatric patients 7 years of age or older, somnolence appears to occur less frequently (25%).

Based on the results of our clinical study, 100% of the reports of somnolence in ages 2-6 years occurred in patients who weighed ≤ 20 Kg. In the 2 reports of somnolence in age 7, one child weighed 21 Kg and the other weighed 26.6 Kg. In the ALPHAGAN group, all children (ages 2-5), 6/8 children (age 6), and 2/8 children (age 7), weighed ≤ 20 Kg. Quite often, medication dose in children is determined by weight, not by age.

Of the two 7-year-old patients who experienced somnolence, one patient weighed 21 Kg. The second patient, weighting 26.6 Kg, experienced somnolence on the first day of dosing. The mother and the investigator stated that it could be related to the drug or the long time spent in the hospital. The mother returned to the office one and a half weeks later claiming to have spoken to another ophthalmologist for a second opinion. That physician told her the child did not have glaucoma and the mother decided that she did not want her child participating in the study. The investigator states that no somnolence was related during the study period and the doctor would not have stopped the study medication due to the report of mild somnolence. The doctor states that the reason for discontinuation should be "parent choice". This patient had no medical or ophthalmic history (other than congenital glaucoma). The patient was taking no concomitant medications other than timolol 0.5%.

The data clearly demonstrate a direct relationship between weight and somnolence. Since weight is the determining factor for adverse events in pediatric patients, it is appropriate to include this statement in the labeling.

We have added the pH information to the labels and agree with the other text proposed by FDA.

A floppy disk containing electronic versions of the labeling are included in the desk copy sent to Lori Gorski.

Should further discussion be required, please contact me at (714) 246-6088.

Sincerely,

Lewis Gryziewicz
Director
Regulatory Affairs

Desk copy: 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

December 11, 2001

Wiley Chambers, M.D.
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 Control Room
9201 Corporate Blvd., Building 2
Rockville, MD 20850

Re:NDA 20-613/ALPHAGAN® (brimonidine tartrate ophthalmic solution) 0.2%
Cross-Refer: NDA 20-490/ALPHAGAN® (brimonidine tartrate ophthalmic solution) 0.5%, NDA 21-262/ALPHAGAN® P (brimonidine tartrate ophthalmic solution) 0.15%
Response to FDA Draft Labeling

Dear Dr. Chambers:

Reference is made to our August 14, 2001 submission of a Supplemental Pediatric Study Report to the above referenced NDAs, to the FDA draft labeling dated October 30, 2001 and the November 16, 2001 Allergan response, and to the December 6, 2001 draft labeling from FDA, copy attached. Reference is also made to a December 10, 2001 telephone conversation between Lori Gorski, Project Manager, DAAOP and myself to discuss the labeling.

Allergan accepts the December 6, 2001 FDA proposal with the exception that we will delete the phrase "(beginning after 4 weeks of treatment)" from the labeling. This was agreed to during the telephone conversation with Ms. Gorski. The label text will read as follows:

> In a well-controlled clinical study conducted in pediatric glaucoma patients (ages 2 to 7 years) the most commonly observed adverse events with brimonidine tartrate ophthalmic solution 0.2% dosed three times daily were somnolence (25% - 83%) and decreased alertness. In pediatric patients 7 years of age or older (>20kg), somnolence appears to occur less frequently (25%). Approximately 16% of patients on brimonidine tartrate ophthalmic solution discontinued from the study due to somnolence.

Labeling incorporating the revised text is enclosed in Attachment 2. A floppy disk containing electronic versions of the labeling is included in the desk copy sent to Lori Gorski.

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

Sincerely,

Lewis Gryziewicz
Director
Regulatory Affairs

Desk copy: Lori Gorski, Project Manager, DAAOP
enc

NDA SUPPL AMENDMENT
SES-002 | BL

ALLERGAN

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

December 13, 2001

RECEIVED
DEC 17 2001
MEGA/CDER

Wiley Chambers, M.D.
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 Control Room
9201 Corporate Blvd., Building 2
Rockville, MD 20850

Re:NDA 20-613/ALPHAGAN® (brimonidine tartrate ophthalmic solution) 0.2%
Cross-Refer: NDA 20-490/ALPHAGAN® (brimonidine tartrate ophthalmic solution) 0.5%, NDA 21-262/ALPHAGAN® P (brimonidine tartrate ophthalmic solution) 0.15%
Response to FDA Draft Labeling

Dear Dr. Chambers:

Reference is made to our August 14, 2001 submission of a Supplemental Pediatric Study Report to the above referenced NDAs, the FDA draft labeling dated October 30, 2001 and the November 16, 2001 Allergan response, and the December 6, 2001 draft labeling from FDA and our December 11, 2001 response. Reference is also made to a December 13, 2001 telephone conversation between Lucious Lim, MD, Medical Officer, DAAOP and myself discussing the labeling.

Allergan agrees to make the change that Dr. Lim requested during the telephone conversation. We agree to amend the labeling to read "... (50% - 83% in patients ages 2 to 6 years) ...". The label text will read as follows:

> In a well-controlled clinical study conducted in pediatric glaucoma patients (ages 2 to 7 years) the most commonly observed adverse events with brimonidine tartrate ophthalmic solution 0.2% dosed three times daily were somnolence (50% - 83% in patients ages 2 to 6 years) and decreased alertness. In pediatric patients 7 years of age or older (>20kg), somnolence appears to occur less frequently (25%). Approximately 16% of patients on brimonidine tartrate ophthalmic solution discontinued from the study due to somnolence.

DUPLICATE

Labeling incorporating the revised text is enclosed. A floppy disk containing electronic versions of the labeling is included in the desk copy sent to Lori Gorski.

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

Sincerely,

Lewis Gryziewicz
Director
Regulatory Affairs

Desk copy: Lori Gorski, Project Manager, DAAOP
enc

December 17, 2001

Wiley Chambers, M.D.
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 Control Room
9201 Corporate Blvd., Building 2
Rockville, MD 20850

Re:NDA 20-613/ALPHAGAN® (brimonidine tartrate ophthalmic solution) 0.2%
Cross-Refer: NDA 20-490/ALPHAGAN® (brimonidine tartrate ophthalmic solution) 0.5%
Response to FDA Draft Labeling

Dear Dr. Chambers:

Reference is made to our August 14, 2001 submission of a Supplemental Pediatric Study Report to the above referenced NDAs, the FDA draft labeling dated October 30, 2001 and the November 16, 2001 Allergan response, the December 6, 2001 draft labeling from FDA and our December 11, 2001 response, the December 13, 2001 FDA comments and our December 13, 2001 response. Reference is also made to the December 17, 2001 telephone conversation between Lori Gorski, Project Manager, DAAOP and myself discussing the labeling.

Allergan has incorporated the information on osmolality and pH into the labeling as requested by Ms. Gorski during our telephone conversation. The following phrase is added to the labeling for ALPHAGAN 0.2% and ALPHAGAN 0.5%:

It has an osmolality of 280 – 330 mOsml/kg and a pH of 5.6 – 6.6.

Labeling incorporating the revised text is enclosed. A floppy disk containing electronic versions of the labeling is included in the desk copy sent to Lori Gorski.

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

Sincerely,

Lewis Gryziewicz
Director
Regulatory Affairs

Desk copy: Lori Gorski, Project Manager, DAAOP
enc