

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-398

APPROVABLE LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-398

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

Dear Mr. Gryziewicz:

Please refer to your new drug application (NDA) dated September 17, 2001, received September 18, 2001, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for COMBIGAN™ (brimonidine tartrate/timolol maleate ophthalmic solution) 0.2%/0.5%.

We acknowledge receipt of your submissions dated March 30, 2005, May 15, June 29, July 26, August 4, October 3, and 27, and December 1, and 8, 2006.

The June 29, 2006, submission constituted a complete response to our March 14, 2005, action letter.

We completed our review of this application, as amended, and it is approvable. However, the submitted studies fail to demonstrate that the benefits of the proposed combination outweigh the risks. In the clinical studies, the contribution of each component was smaller than expected and the magnitude of the observed effect was not sufficient to outweigh the risks of the components' contribution. Before the application may be approved, it will be necessary for you to address this deficiency.

An alternative dosing regimen could provide a useful product if it could be demonstrated that the safety profile of the proposed combination product is better than that of the individual agents taken as currently permitted in the approved labeling; the combination's IOP-lowering ability is inferior (approximately 1 mmHg) to that of brimonidine and timolol given concomitantly.

Study 190342-23T submitted in this amendment was designed to address this deficiency. Although Study 190342-023T demonstrates that the safety profile of the proposed combination product is numerically superior to that of the individual agents taken as currently permitted in their approved labeling in the incidence of oral dryness adverse events, the difference in oral dryness rates alone, particularly at the magnitude observed, is not sufficient to offset the combination's inferior IOP-lowering ability compared to that of brimonidine and timolol given concomitantly.

The Agency considers that there is preliminary evidence that the proposed combination has an improved safety profile in subjects over the age of 40. To confirm this hypothesis, a new trial similar to 190343-023T in a population of subjects whose age ≥ 40 is recommended; both the dry mouth and sleepiness endpoints would be expected to show significance and the magnitude would be expected to be at least that observed in the patients ≥ 40 years old in study 190343-023T. There is no evidence presented to date that subjects under age 40 benefit from an improved safety profile with the fixed combination versus concurrent therapy.

We will continue to work with you on the proposed labeling.

When you respond to the above deficiency, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

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

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Alison Rodgers, Regulatory Project Manager, at (301) 796-0797.

Sincerely,

{See appended electronic signature page}

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

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/s/

Janice Soreth
12/20/2006 01:13:25 PM



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Public Health Service

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Rockville, MD 20857

NDA 21-398

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Attention: Lewis Gryziewicz
Director, Regulatory Affairs
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P.O. Box 19534
Irvine, California 92623-9534

Dear Mr. Gryziewicz:

Please refer to your new drug application (NDA) dated September 17, 2001, received September 18, 2001, pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Combigan (brimonidine tartrate-timolol maleate ophthalmic solution) 0.2%/0.5%.

We acknowledge receipt of your submission dated September 13, 2004, which constituted a complete response to our June 5, 2002, action letter.

We completed our review of this application, as amended, and it is approvable. However, the submitted studies fail to demonstrate that the benefits of the proposed combination outweigh the risks. In the clinical studies, the contribution of each component was smaller than expected and the magnitude of the observed effect was not sufficient to outweigh the risks of the components' contribution. Before the application may be approved, it will be necessary for you to address this deficiency.

Additionally, a patent certification must be submitted to the application in reference to the primary source data for timolol maleate.

We will continue to work with you on the proposed labeling.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of the other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65.

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

NDA 21-398

Page 2

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

Sincerely,

{See appended electronic signature page}

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

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/s/

Wiley Chambers
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Allergan, Inc.
Attention: Lewis Gryziewicz
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2525 Dupont Drive
P.O. Box 19534
Irvine, CA 92623-9534

Dear Mr. Gryziewicz:

Please refer to your new drug application (NDA) dated September 17, 2001, received September 18, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Combigan (brimonidine tartrate-timolol maleate ophthalmic solution) 0.2%/0.5%.

We acknowledge receipt of your submissions dated October 2, and December 7, 2001, and January 15, 16, 18, 31, February 22, and May 1, 2002 (two).

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

1. The submitted studies fail to demonstrate that the benefits of the proposed combination outweigh the risks. In the clinical studies, the contribution of each component was smaller than expected and the magnitude of the observed effect was not sufficient to outweigh the risks of the components' contribution. It is recognized that there may be study design issues (patient population, baseline characteristics, timing of drug administration, etc.) accounting for these observations; however, an additional study correcting these design issues would be necessary to confirm that hypothesis.

An alternative dosing regimen could provide a useful product if it could be demonstrated that the benefits and risks of the proposed combination product are equivalent to the benefits and risks of the individual agents taken as currently permitted in the approved labeling. Each of the principal ingredients (timolol and brimonidine) which make up this combination product is available as an individual agent, and labeling of each product permits the administration of both individual products to the same patient for treatment of the same indication. Evidence has been submitted in this application to support that the risks of the proposed combination are equivalent to the risks when both of the individual agents are taken concurrently as currently permitted in the approved labeling. However, an additional study is needed to demonstrate that the benefits of the proposed combination are equivalent to benefits of timolol administered in the morning and evening and brimonidine administered three times daily, approximately 8 hours apart as currently labeled.

This deficiency could be addressed by an adequate, well-controlled clinical study of at least two weeks duration in patients who are pharmacologically naïve to intraocular pressure (IOP) lowering medications. In addition to baseline diurnal IOP measurements, at least one additional set of diurnal measurements would need to be performed after at least 10 days of drug administration. The diurnal IOP measurements should be performed prior to planned morning drug administration, two hours after morning drug administration and ten hours after morning drug administration (e.g., 8 am, 10am, and 6 pm). The clinical study must be masked and have at least three arms: a) the proposed combination given twice a day with placebo given three times a day, b) timolol given twice a day and brimonidine given three times a day and c) placebo given twice a day and brimonidine given three times a day. The clinical study would need to demonstrate equivalence between the proposed combination and the concomitant individual components. It would also need to demonstrate assay validation by demonstrating a difference between the proposed combination and brimonidine administered as a single agent. Equivalence with respect to IOP lowering is considered to be a demonstration of a 95% confidence interval within 1.5 mmHg for all time points and within 1 mmHg for the majority of time points measured.

2. An expiry period of 24 months has not been supported. An expiry is acceptable at this time. Data to support a 24-month expiry period should be submitted.

We will continue to work with you on the proposed labeling.

Under 21 CFR 314.50(d)(5)(vi)(b), we request that you update your NDA by submitting all safety information you now have regarding your new drug.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

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

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NDA 21-398

Page 3

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

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Wiley A. Chambers, M.D.
Deputy Director
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and Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
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/s/

Wiley Chambers
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